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Screening to Prevent Osteoporotic Fractures: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review evidence about screening to prevent osteoporotic fractures for the U.S. Preventive Services Task Force (USPSTF).

Data Sources: PubMed, the Cochrane Library, Embase, and trial registries from November 1, 2009, through October 1, 2016, and surveillance of the literature through March 23, 2018; bibliographies from retrieved articles.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We selected studies with a majority of adults age 40 years or older conducted in countries with a very high human development index. For screening studies, we required that studies include a majority of participants without prevalent low-trauma fractures. For treatment studies, we required that studies include a majority of participants with increased fracture risk. We selected studies of screening tests (fracture risk prediction instruments, bone measurement testing, or a combination of fracture risk prediction instruments and bone measurement testing) that were feasible for primary care settings and available in the United States. We selected studies of treatment approved by the U.S. Food and Drug Administration for synthesis of benefits and harms. We excluded studies of poor quality and of fracture risk prediction instruments without external validation.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for included studies using predefined criteria.

Data Synthesis: One fair-quality trial demonstrated reduction in hip fractures when comparing screening with no screening (2.6% v 3.5%, Hazard rate [HR] 0.72; 95% confidence interval [CI], 0.59 to 0.89). The study reported no other statistically significant benefits (osteoporotic or clinical fractures, mortality) or harms (anxiety, quality of life). We included 168 articles of fair or good quality; 105 articles assessed screening accuracy and 65 articles assessed benefits and harms of treatment. Using centrally measured dual-energy X-ray absorptiometry (DXA) as the reference standard for identifying osteoporosis, the pooled estimate of accuracy as measured by the area under the curve (AUC) for clinical risk assessment instruments for women ranges from 0.65 to 0.76 and for men from 0.76 to 0.80. AUCs for the accuracy of calcaneal quantitative ultrasound in identifying central DXA–measured osteoporosis for women is 0.77 (95% CI, 0.72 to 0.82, 7 studies) and for men is 0.80 (95% CI, 0.67 to 0.94, 3 studies). The AUCs of machine-based tests, including centrally measured DXA (areal bone mineral density and trabecular bone score) and calcaneal quantitative ultrasound, for predicting fractures ranged from 0.59 to 0.86 (21 studies). The AUCs for instruments predicting fractures, some of which incorporate machine-based tests, have similar accuracy (pooled AUC range for the Fracture Risk Assessment Tool: 0.62 to 0.79; 24 studies). Available but limited evidence in studies including participants with a wide spectrum of baseline bone mineral density from normal to osteoporosis suggests no benefit from repeating a bone measurement test between 4 and 8 years after the initial screen. Evidence from placebo-controlled trials demonstrates the following benefits. For women, the risk of vertebral fractures can be reduced by bisphosphonates, parathyroid hormone, raloxifene, and denosumab by 36 percent to 68 percent. Relative risks (RRs) range from 0.32 (parathyroid hormone or denosumab) to 0.64 (raloxifene). The risk of nonvertebral fractures can

be reduced by 16 percent to 20 percent by bisphosphonates and denosumab (RR, 0.84 and 0.80, respectively). The risk of hip fractures can be reduced by 40 percent by denosumab (RR, 0.60). Evidence from bisphosphonates does not demonstrate benefit for hip fractures. Evidence is very limited for men. The risk of morphometric vertebral fractures can be reduced by 67 percent by zoledronic acid (RR, 0.33). No studies demonstrate reductions in risk of clinical vertebral fractures or hip fractures for men. Evidence on variations in effectiveness for subgroups is also limited; a single trial each for five drugs suggests no differences in effectiveness by age, baseline bone mineral density, prior fractures, or a combination of risk factors. Bisphosphonates are not consistently associated with discontinuations, serious adverse events, gastrointestinal events, or cardiovascular events. No included studies reported cases of osteonecrosis of the jaw or atypical femur fracture, although evidence from excluded studies (including active comparisons, case series, and secondary prevention populations) suggests an increased but rare risk of these outcomes. Raloxifene increases the risk of deep vein thrombosis (0.7% vs. 0.3%, RR, 2.14; 95% CI, 0.99 to 4.66; I^2=0%, 3 studies, N=5,839) and hot flashes (11.2% vs. 7.6%, RR, 1.42; 95% CI, 1.22 to 1.66; I^2=0%, 5 trials; N=6,249) when compared with placebo.

Limitations: The evidence is limited on the direct question of the benefits and harms of screening for elevated osteoporotic fracture risk. The indirect evidence pathway rests on studies evaluating (1) the accuracy of screening approaches in identifying osteoporosis and predicting fractures and (2) the benefits of treatment among those with osteoporosis or at high risk for fractures. Other limitations of the evidence base relate to underlying heterogeneity in baseline risk, prior fractures, prior treatment, and duration of followup.

Conclusions: Evidence from one trial of screening to prevent osteoporotic fractures suggests a reduction in hip fractures. The accuracy of clinical risk assessment tools for identifying osteoporosis or predicting fractures generally ranges from very poor (0.50) to good (0.90). Treatments reduce the risk of vertebral and nonvertebral fractures. Studies do not consistently demonstrate an increased risk of harms for drugs, although studies of raloxifene suggest a trend toward higher risk of deep vein thrombosis. Rare harms, such as osteonecrosis of the jaw and atypical femur fractures were not reported in this body of evidence but they may occur. The evidence is limited for subpopulations characterized by age, sex, baseline bone mineral density, and baseline fracture risk.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF or Task Force) will use this report to update its 2011 recommendation on screening for osteoporosis.[1] This report evaluates the evidence on the accuracy, reliability, and harms of screening approaches, appropriate screening intervals, and the benefits and harms of pharmacotherapy.

This report focuses on populations without known comorbidities or medication use associated with secondary osteoporosis because the detection and management of secondary osteoporosis falls outside the purview of the Task Force. The report also excludes younger populations (<40 years of age) because increasing age is the single most important risk for osteoporosis and fragility fractures. Further, a diagnosis of osteoporosis among those under age 40 is extremely rare in the absence of an underlying medical comorbidity or use of medications associated with bone loss. The scope of this review includes screening strategies related to fracture risk assessment, with or without bone mineral density testing; other types of screening (e.g., functional assessment, safety evaluations, vision examinations, nutrition assessments) are not included. Because the focus of this review is on primary prevention of osteoporotic fractures, the management of osteoporosis in populations characterized primarily by prevalent fractures and comparative effectiveness of osteoporosis treatments are also outside the scope of this review.

Condition Background

Condition Definition

Osteoporosis is a skeletal disorder characterized by loss of bone mass, microarchitectural deterioration of bone tissue, and decline in bone quality leading to increased bone fragility and risk of fractures.[2-4] Although bone mass (expressed by bone mineral density [BMD]) is only one factor contributing to fracture risk, and new tools measuring bone quality are under development, osteoporosis has been defined operationally on the basis of BMD assessments or the history of a fragility fracture.[5]

The World Health Organization (WHO) defines osteoporosis as a bone density at the hip or spine that is 2.5 standard deviations or lower (T-score $\leq$-2.5) than the mean bone density of a reference population of young healthy women, presumably at peak bone mass. This definition was established originally for postmenopausal women using BMD of the proximal femur, but guidelines from the International Society for Clinical Densitometry indicate that they can also be used for men 50 years or older.[6] The WHO definition is currently used for lumbar spine, distal radius, and total hip.[7] Of note, U.S. bone density machines report T-scores using a reference group matched on race and sex, whereas the WHO uses a reference group of young white women only using normative data from the National Health and Nutrition Examination Survey (NHANES) reference database.[8] Low bone mass, sometimes referred to as osteopenia, is

operationally defined as a T-score between -1 and -2.5.

Osteoporotic fractures, also known as fragility, "low-energy," or "low-trauma" fractures, are those sustained from a fall from standing height or lower and that would not give rise to a fracture in most healthy individuals.[9] Osteoporotic fractures occur as a result of bone fragility resulting from bone loss or structural changes.[10] Major osteoporotic fractures include fractures of the hip, spine, wrist, or shoulder. Because osteoporosis itself is asymptomatic, preventing osteoporotic fractures is the main goal of any osteoporosis screening strategy.

Prevalence and Burden of Disease

In the United States, the prevalence rates of osteoporosis and low bone mass at the femoral neck or lumbar spine among the noninstitutionalized population 50 years of age or older (adjusted by age, sex, and race and ethnicity) was estimated to be 10.3 percent and 43.9 percent, respectively, based on the NHANES.[11] In 2010, these estimates equated to 10.2 million older adults with osteoporosis and 43.4 million with low bone mass.

In the group that is 50 years of age or older, the prevalence of osteoporosis is greater in women (15.4%) than men (4.3%). The prevalence also varies by race and ethnicity: 10.2 percent in non-Hispanic whites, 4.9 percent in non-Hispanic blacks, and 13.4 percent in Mexican Americans. Prevalence increases dramatically with age: 50 to 59 years, 5.1 percent; 60 to 69 years, 8.0 percent; 70 to 79 years, 16.4 percent; and 80 years or older, 26.2 percent.

Researchers applying the NHANES data to 2020 and 2030 Census population projections estimated that the population that is 50 years of age or older with osteoporosis or low bone mass is forecast to increase from an estimated 53 million in 2010 to 63.9 million in 2020 and 70.6 million in 2030.[11]

In 2005, approximately 2 million osteoporotic fractures occurred in the United States.[12] Most fractures (71%) occur among women, and more than three-quarters of the total costs of incident fractures (more than $16.9 billion) were among women. Hip fractures account for a large portion of the mortality and morbidity related to osteoporotic fractures. Estimates based on Medicare claims data from 1986 to 2005 suggest an annual rate of hip fractures of 957.3 per 100,000 in women and 414.4 per 100,000 in men.[13] The excess mortality due to hip fracture in the first year after fracture ranges from 8 percent to 36 percent, more than twice that of age and sex matched controls.[14] Men have greater excess mortality compared to women at all ages, for unclear reasons. The greatest risk of death occurs in the first 3 to 6 months after fracture and may be due to post-operative events associated with corrective hip surgery, comorbid medical conditions, or inadequate treatment of risk factors for fracture including osteoporosis.[14, 15] The extent to which these factors contribute to excess mortality is unclear. Mortality from hip fracture decreases over time, but does not return to that of age- and sex-matched controls.[15]All types of fractures are associated with higher rates of mortality.[16-19]

Etiology and Natural History

Osteoporosis may occur either without a known cause or secondary to another condition. Bone loss is associated with certain medical conditions: various endocrine conditions of the pituitary, thyroid, parathyroid, or reproductive organs; eating disorders; disorders of the gastrointestinal or biliary tract; renal disease; bone marrow disorders; and cancer.[20] Secondary osteoporosis can also result after organ transplantation. It can also arise from chronic use of medications with known deleterious effects on bone mass, such as glucocorticosteroids, immunosuppressants, antiepileptic medications, heparin, gonadotropin-releasing hormone agonists, and some long-acting progesterone agents used as contraceptives.

Although osteoporosis is related to an increased risk of fracture,[3] most fractures occur in those with nonosteoporotic T-scores.[21-23] Similarly, fragility fractures can occur in persons with normal bone mass.[24] Older adults have much higher fracture rates than younger adults with the same bone density because of concurrent increasing risk from declining bone quality and an increasing tendency to fall.[25]

Clinical Risk Factors

For both men and women, advancing age was found to be a more critical determinant of fracture than bone mass.[26] Additional risk factors include menopausal status in women,[27] previous osteoporotic fracture, long-term glucocorticoid therapy, low body weight (less than 58 kg [127 lbs.]), parental history of hip fracture, cigarette smoking, excess alcohol consumption, and use of anti-convulsants or benzodiazepines.[28, 29]

A systematic review and meta-analysis identified risk factors associated with osteoporotic fractures in men.[30] The review found statistically significant associations between fractures and increasing age, low body mass index, excessive alcohol intake (daily intake or greater than 10 servings per week), current smoking, chronic corticosteroid use, history of prior fractures, history of falls within the past year, hypogonadism, history of cerebrovascular accident, and history of diabetes. A large multiethnic study, the National Osteoporosis Risk Assessment Cohort, compared fracture risk among races and ethnicities, and found that Black women and Asian American women had a lower risk of fracture when compared with white women, whereas Hispanic and Native American women had risks similar to white women.[31] Genetic, anthropometric, lifestyle, comorbidities all contribute to fracture risk and the relative contribution of these factors to fracture risk is likely to differ between races and ethnicities.[31]

Rationale for Screening

The rationale for screening for osteoporosis is to identify those at risk of fracture and provide treatment to increase bone mass and prevent further losses. These actions can prevent fractures and related morbidity. Screening for osteoporosis traditionally involves bone measurement testing (e.g., bone density). More recently, fracture risk assessment (with or without bone measurement testing) have been proposed as alternative strategies to identify individuals who may benefit from treatment. Numerous risk assessment instruments have been developed to

either (1) identify low bone density or (2) predict the risk of fracture.[2, 3] These instruments vary in the number and weight assigned to risk factors, but the USPSTF 2010 systematic review found that instruments with fewer risk factors often had similar or higher areas under the curve than instruments with more risk factors.[2, 3] Several instruments had not been developed using prospective cohorts or validated in men. The most studied risk assessment instrument is the Fracture Risk Assessment Tool (FRAX), which WHO developed in 2008. FRAX uses an algorithm for predicting the 10-year probability of hip fracture or major osteoporotic fractures (hip, spine, wrist, shoulder) using clinical risk factors and bone mineral density at the femoral neck when available. It was derived from nine cohorts in Europe, the United States, Japan, and Canada and has been applied to men.[9, 32] Country-specific versions of FRAX are available that have been calibrated for use in each country using country-specific fracture incidence and mortality data. For the US non-Hispanic white population, the FRAX model was calibrated using national mortality data and fracture incidence rates from the population of Olmsted County, Minnesota between 1989 and 1991.[33] For non-white US populations, race-specific fracture incidence and mortality was used to calibrate the model. In response to declining fracture incidence, the US FRAX model was recalibrated in 2009. In countries or settings without access to bone density testing, the FRAX score (without BMD) can be used to make treatment decisions.

Bone density can be measured using various methods and at various bone sites. Dual-energy X-ray absorptiometry (DXA) measures bone mass at either central (e.g., hip and lumbar spine) or peripheral bone sites; both central and peripheral DXA can identify patients with low bone mass at increased fracture risk.[2, 34] Centrally measured DXA serves as the standard machine-based test for identifying osteoporosis because trials of treatment for osteoporosis to prevent fracture have been conducted with study populations assessed with centrally measured DXA.[2] Other machine-based tests include quantitative ultrasound (QUS), peripheral DXA, quantitative computed tomography (QCT), and radiograph absorptiometry. Further, the lack of a single population-based reference for determining T-scores, required because of technical differences among tests, has limited the ability to use noncentrally measured DXA tests for diagnostic and treatment decisions.

QUS is used at peripheral bone sites, such as the heel, and it avoids the risk of radiation inherent in DXA. However, QUS does not actually measure BMD, so it cannot be used in risk prediction instruments that use BMD. Peripheral DXA and QUS use portable devices and may be more accessible than central DXA measurement. QCT provides a volumetric measure of bone density, which may improve detection of osteoporosis compared to areal BMD by DXA.[35, 36] However, reproducibility is poor in community settings, and few data are available on how T-scores generated from QCT predict fracture risk compared with those based on DXA.[7] The most recent version of FRAX allows providers to enter bone mineral density from Mindways QCT (Mindways Software, Austin, Texas).[37] Finally, radiograph absorptiometry, which uses computerized processing of radiographs from peripheral sites such as hand or heel, and dental radiographs can also be used to assess low bone mass.[38]

Current Drug Therapies

The U.S. Food and Drug Administration (FDA) has approved various medications from different

drug classes to prevent osteoporosis (adults with T-scores between -1.0 and -2.5) and to treat osteoporosis (adults with T-scores <-2.5 or history of fragility fractures regardless of bone mass). These drugs work either to inhibit osteoclastic bone resorption (antiresorptive agents) or to stimulate osteoblastic new bone formation (anabolic agents).[39] Drugs classified primarily as antiresorptive include bisphosphonates, estrogens, selective estrogen receptor modulators, calcitonin, and denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL) approved by the FDA in 2010. In addition, in 2013 the FDA approved the first combination estrogen-estrogen agonist/antagonist (Duavee®) to prevent osteoporosis in postmenopausal women. The FDA-approved therapeutic agent with an anabolic mechanism of action are teriparatide (human recombinant parathyroid hormone [PTH] fragment [1-34 N-terminal amino acid sequence]) and abaloparatide (synthetic peptide analog of human PTH-related protein). Abaloparatide is indicated for women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.[40]

Emerging Drug Therapies

A human recombinant PTH (full length 1 to 84 sequence) has been studied for use in osteoporosis. It is approved for use in Europe, but in the United States it is available only for patients with chronic hypoparathyroidism. In addition, alternative PTH fragments and delivery mechanisms, including intermittent, transdermal, oral, and inhalational, are under investigation.[41] Several other potential targets for increasing bone mass have been identified and several drug candidates are in phase III trials.[42] These new drugs include romosozumab and blosozumab, which are sclerostin human monoclonal antibodies that enhance the wingless-int signaling pathway to prevent the inhibition of bone formation. The sponsors of odanacatib, a cathepsin-K inhibitor that is involved in bone resorption, stopped a Phase III trial after evidence of increased risk of stroke.[43]

Adjunctive Therapies

Typical adjunctive treatments, in addition to medication for preventing or treating osteoporosis, include adequate dietary intake of calories (to avoid underweight), calcium, and vitamin D, with supplemental calcium or vitamin D (or both) if dietary intake is insufficient. Additionally, exercise of various types may reduce the risk of fracture, for example through small increases in bone density and beneficial changes in bone architecture; they may also decrease the risk of falls.[44]

Current Clinical Practice

Screening and primary prevention of osteoporosis in asymptomatic adults without known risks for secondary osteoporosis is within the scope of practice for most primary care providers (e.g., internal medicine, family medicine). It may also be in scope for gynecologic practices that serve as primary care providers for women during perimenopause. Recommendations for screening developed by various organizations and specialty societies continue to differ. This is especially true with respect to who should be screened, how to screen (i.e., bone density testing vs. fracture

risk assessment), when to start or stop screening, and the frequency of screening (see **Table 1**).

Although all currently approved medications for osteoporosis are labeled for use based on BMD or history of fragility fracture, a shift toward treatment based on absolute fracture risk has received increasing consideration. A systematic review of osteoporotic fracture risk assessment guidelines using FRAX identified 120 such guidelines.[45] Of these, 38 did not provide a rationale for the use of fracture probabilities in setting intervention thresholds. The authors categorized the others as offering fixed-probability threshold (N=58, a group that includes the USPSTF 2011 recommendation), an age-dependent threshold (N=22), or a combination (N=2). Of the guidelines referencing fixed-probability thresholds, over half (N=39) reference an absolute fracture risk of 20 percent or greater for major osteoporotic fractures as the threshold for treatment in those with low bone mass. In the United States, this threshold, along with a threshold of 3 percent or greater absolute fracture risk for hip fractures, is based on a cost-effectiveness analysis of treatment relying on 2005 cost data.[46] The 2011 USPSTF recommendation,[1] along with a small minority of other guidelines (Scottish Intercollegiate Guidelines Network,[47] the Michigan Quality Improvement Consortium,[48] the American Academy of Family Physicians,[49] and the Institute for Clinical Systems Improvement)[50] uses a fixed-probability FRAX threshold as a gateway to further assessment with bone density testing rather than treatment. Specifically, the 2011 USPSTF recommendation relied on the U.S. FRAX tool for identifying risk in women younger than 65 and establishes a threshold for bone density testing for women at an absolute fracture risk of 9.3 percent or greater, which is the 10-year probability of a major osteoporotic fracture for a 65-year old white woman of average body mass index of 25 kg/m^2 with no other risk factors.

In 2006, the National Committee for Quality Assurance introduced the Healthcare Effectiveness Data and Information Set measure assessing the percentage of women 65 to 85 years of age who report ever having received a bone density test to screen for osteoporosis. The rate of receipt of bone density tests rose in the ensuing decade.[51] In 2006, 64.4 percent of women 65 to 85 years of age in a Medicare health maintenance organization plan and 71.3 percent in a Medicare preferred provider organization reported ever having a bone density test. By 2014, these numbers had risen to 74.2 percent and 78.5 percent, respectively. At the same time, some studies have identified inappropriate use of bone mineral density screening. Overuse is defined as a diagnostic test or treatment that is commonly used but that offers limited benefits or carries risks that outweigh its benefits)[52] For BMD tests, the Good Stewardship Working Group defines overuse as DXA screening in women under age 65 years or men under 70 years with no risk factors. Findings from the National Ambulatory Medical Care Survey indicated that overuse of DXA in primary care accounted for $527 million in expenditures;[53] a study in a large regional health care system suggested that about one-half of women under age 65 without risk factors received DXA screening over a 7-year period.[54] The Choosing Wisely® Campaign, which is endorsed by multiple medical societies, lists bone density testing as a test that should be considered carefully before ordering in women younger than 65 and in men younger than 70 with no risk factors.

Previous Review and USPSTF Recommendations

In 2011, the USPSTF recommended screening for osteoporosis in women age 65 or older and in

younger women whose fracture risk is equal to or greater than that of a 65-year old white women who has no additional risk factors (B grade). The USPSTF also concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

Use and Accuracy of Fracture Risk Instruments for Identifying Patients for Further Evaluation

Modeling studies raise concerns regarding the clinical value of the USPSTF-recommended fracture risk threshold for bone density testing in younger women. In 2011, the USPSTF recommended screening with DXA in women 55 to 64 years of age whose fracture risk is equal to or greater than that of a 65-year old white woman who has no additional risk factors, which is equivalent to a FRAX calculated risk of ≥9.3 percent for major osteoporotic fracture. **Table 2** reflects fracture risk probabilities by age, race, and sex for men and women in the United States at mean height and weight, with no other risk factors.[55] Notably, FRAX calculates the risk of a fracture, not the risk of osteoporosis defined operationally by a T-score ≤ -2.5.

The 2011 USPSTF recommendation used FRAX as a risk stratification tool for screening for osteoporosis for women younger than 65 to try to identify higher-risk women who may benefit from earlier screening (women older than 65 are to be routinely screened). The use of FRAX in younger women is then intended to lead to cascade of interventions that results in lower future risk of fractures. An implicit assumption of the recommendation is that FRAX is a reasonable risk stratification tool for osteoporosis. Studies published after the recommendation do not support the assumption that FRAX predicts osteoporosis as defined by T-score accurately. A retrospective application of the FRAX threshold of ≥9.3 percent to a series of women 50 to 64.5 years of age undergoing DXA found sensitivity and specificity of 37 and 74 percent, respectively, for the detection of osteoporosis.[56] The study found that lowering the FRAX risk threshold to 5.5 percent would increase the sensitivity from 37 to 80 percent while reducing the specificity from 74 to 27 percent.

Another study compared FRAX, Osteoporosis Self-Assessment Tool (OST), and the Simple Calculated Osteoporosis Risk Estimate (SCORE) among 5,165 Women's Health Initiative participants 50 to 64 years of age from 1994 to 2012. The study found that the FRAX threshold of ≥9.3 percent was modestly better than chance, and inferior to OST and SCORE in identifying women with osteoporosis (femoral neck T-score ≤-2.5).[57] Using the same database, the authors also examined the sensitivity and specificity of FRAX, SCORE, and OST in predicting the incidence of major osteoporotic fracture. The findings of low sensitivity and specificity and thus very low area under the curve scores ranging from 0.52 to 0.56 suggested that none of these tools are suitable for predicting fractures in younger postmenopausal women.[58]

Clinical Considerations for the Update

Numerous comments received during workplan development for the current update noted the limitations of focusing on screening for osteoporosis with BMD alone. Commenters requested that the analytic framework include consideration of the full spectrum of risk beyond bone mineral density measurement, and focus on screening for osteoporotic fracture risk rather than

osteoporosis. As a result, the analytic framework was expanded to address the full spectrum of risk related to osteoporotic fractures beyond low BMD. The current update also reviews continuing uncertainties regarding the overarching question of effectiveness and harms of screening and treatment, risk assessment thresholds, efficacy of screening and treatment for subgroups, and screening intervals.

Chapter 2. Methods

Key Questions and Analytic Framework

The investigators, U.S. Preventive Services Task Force (USPSTF) members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope, key questions (KQs), and analytic framework (**Figure 1**) that guided the literature search and review. The KQs are as follows.

Key Questions

1. Does screening (clinical risk assessment, bone density measurement, or both) for osteoporotic fracture risk reduce fractures and fracture-related morbidity and mortality in adults?

2a. What is the accuracy and reliability of screening approaches to identify adults who are at increased risk for osteoporotic fracture?

2b. What is the evidence to determine screening intervals and how do these vary by baseline fracture risk?

3. What are the harms of screening for osteoporotic fracture risk?

4a. What is the effectiveness of pharmacotherapy for the reduction of fractures and related morbidity and mortality?

4b. How does the effectiveness of pharmacotherapy for the reduction of fractures and related morbidity and mortality vary by subgroup, specifically in postmenopausal women, premenopausal women, men, younger age groups (age <65 years), older age groups (age ≥65 years), baseline bone mineral density, and baseline fracture risk?

5. What are the harms associated with pharmacotherapy?

We include two contextual questions to help inform the report. We do not show these questions in the analytic framework because they were not analyzed using the same rigorous systematic review methodology as the studies that met the report's inclusion criteria. At the title and abstract and full-text article review stages, reviewers categorized studies not included to answer KQs that related to the specific contextual questions.

Contextual Questions

1. What is the evidence from modeling studies about different fracture risk thresholds for identifying patients for further evaluation or treatment?
2. What is the evidence from modeling studies about the effectiveness of screening strategies (screening, risk assessment, or bone measurement) that use (a) different ages at which to start and stop screening and (b) different screening intervals?

Contextual Question 1 is addressed in the introduction. Contextual Question 2 is addressed in the Results section (for screening intervals, along with other included evidence on screening intervals) and in the discussion section (for starting and stopping ages).

Search Strategies

We searched PubMed, the Cochrane Library, and Embase for English-language articles published from November 1, 2009, through October 1, 2016, with active surveillance through March 23, 2018. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, screening tests, interventions, outcomes, and study designs. **Appendix A** describes the complete search strategies. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, Drugs@FDA.gov, Cochrane Clinical Trials Registry, and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. We included citations from the previous report and from other systematic reviews in our handsearch yield.

Study Selection

Newly Identified Studies

We selected studies on the basis of inclusion and exclusion criteria developed for each KQ for identifying populations, interventions, comparators, outcomes, timing, settings, and study designs (PICOTS) (**Appendix B**). **Appendix C** lists studies excluded at the full-stage review stage. We imported all citations identified through searches and other sources into EndNote X7.

Two investigators independently reviewed titles and abstracts. We dually and independently reviewed the full text of abstracts marked for potential inclusion by either reviewer. Two experienced team members then resolved disagreements.

Population

We included studies that focused on adults age 40 years or older. For screening questions (KQs 1–3), we required studies to have included a majority of participants without history of low trauma fractures, endocrine disorders likely to be related to metabolic bone disease, or chronic use of glucocorticoid medications. If information on the proportion of low trauma fractures was unavailable in the report, we sent an inquiry to the author. In cases of nonresponse, we planned to include these studies and noted lack of information on prevalent fracture rates. For treatment questions (KQs 4–5), we also required that a majority of included participants had an increased fracture risk (as defined by the study [typically bone mineral density (BMD) status).

Interventions

For screening questions (KQs 1–3), we searched for studies on risk assessment tools, bone measurement testing, or a combination of risk assessment and bone measurement testing. Eligible risk assessment tools included any paper-based or electronic instrument that compiled and compared various demographic or clinical characteristics for individuals to establish an absolute or categorical risk estimate. Eligible bone measurement testing included dual-energy X-

ray absorptiometry (DXA, central or peripherally measured), quantitative ultrasound, dental tests, vertebral fracture assessment, and trabecular bone score (**Appendix B**). All tests and instruments needed to be feasible for primary care settings (i.e., could be ordered, administered, or interpreted by primary care providers) and be available in the United States; we excluded tests and instruments that were not commercially available. We required instruments to have been externally validated. For tests and instruments that included bone measurement testing (imaging and nonimaging machine-based tests), we required that the investigators measure bone mineral density in participants before the occurrence or identification of the fracture.

For treatment questions (KQs 4–5), we limited eligible interventions to pharmacotherapy approved by the U.S. Food and Drug Administration (FDA) for treating or preventing osteoporosis. These include (a) antiresorptive therapies, specifically bisphosphonates, estrogen agonists/antagonists, hormone therapy, and Receptor Activator of Nuclear Factor κ B ligand (RANKL) inhibitors and (b) anabolic therapies, specifically, parathyroid hormone. We did not summarize the evidence on calcitonin because it is no longer a first-line therapy for osteoporosis.

Comparators

For the overarching question on the benefits and harms of screening and health outcomes (KQ 1 and KQ 3), we included studies that compared screened with unscreened groups. For questions on screening accuracy and screening intervals (KQ 2), we included studies that evaluated fracture risk assessments or bone tests. For treatment benefits (KQ 4), we included studies comparing treatment with placebo. For treatment harms (KQ 5), we included studies comparing treatment with placebo or no treatment.

Outcomes

For KQ 1 and KQ 4, we included data on fractures, fracture-related morbidity, fracture-related mortality, or all-cause mortality. Fractures included major osteoporotic fractures defined as fractures of the hip, distal radius, proximal humerus, and vertebrae (clinically presenting). We also included and recorded separately morphometric (asymptomatic) vertebral fractures. For KQ 2, eligible outcomes included test characteristics (e.g., accuracy, reliability) for bone measurement tests and accuracy and reclassification for fracture risk assessment instruments. For KQ 3, we looked for evidence on outcomes such as unnecessary radiation, labeling, anxiety, false-positive results. We focused our systematic review on studies of risk assessment tools and bone measurement tests that predicted future fracture risk as an outcome, rather than identification of osteoporosis defined operationally by BMD. For KQ 5, eligible harms included serious adverse drug events, discontinuation attributed to adverse events, cardiovascular events, hot flashes, esophageal cancer, gastrointestinal events, osteonecrosis of the jaw, atypical fractures of the femur, and rashes.

Timing

Outcomes for KQ 1 studies had to be measured 6 months or more following screening. Although we had planned to limit the KQ 4 and KQ 5 studies outcomes to those measured 6 months or more after the initiation of treatment, we also included harms (KQ 5) measured at shorter

intervals for completeness of reporting. All timings were considered for KQ 2 and KQ 3 (although studies for fracture prediction, we required that assessments of outcomes occur after fracture risk assessment or machine-based tests).

Settings

We required the overarching screening question (KQ 1) to be in primary care settings or other settings similar to primary care. For all other questions, we also included studies in specialist settings. For all KQs, we limited our search to studies conducted in the United States or in countries with very high human development indexes.[59]

Study Designs

For screening questions (KQs 1–3), we included randomized controlled trials (RCTs), controlled clinical trials, and systematic reviews of trials. For questions on screening accuracy and screening intervals (KQs 2 and 3), we also included systematic reviews of observational studies and observational studies other than case series and case reports. For treatment questions (KQ 4 and KQ 5), we included systematic reviews, RCTs, and controlled trials published since any recent relevant review. For harms (KQ 5), we also included observational studies published since any recent relevant review.

Studies in the 2010 USPSTF Review

We applied, dually and independently, the inclusion and exclusion criteria described above to all studies included in the 2010 USPSTF review. (Note that the review was published in 2010,[2, 3] and the recommendation statement in 2011[1]). We resolved disagreements by discussion and consensus; if necessary, we sought adjudication of conflicts from other experienced team members.

We also conducted a check of the quality ratings of studies included in 2010 to ensure that studies met our current quality rating criteria. If the reviewer did not agree with this earlier assessment, we re-rated the quality of the study through dual review. Among included studies from the 2010 report, one reviewer checked for errors in previously generated abstraction tables and updated them as needed.

Data Abstraction and Quality Rating

We abstracted pertinent information from each newly included study; details included methods and patient PICOTS. A second investigator checked all data abstractions for completeness and accuracy. Two investigators independently evaluated the quality (internal validity) of each study, corresponding to USPSTF predefined methods criteria.[60] The criteria by which the USPSTF requires individual study quality to be assessed differ by study design, but ultimately each study is to receive a rating corresponding to good, fair, or poor quality. We selected several tools for developing quality ratings, with specific tools corresponding to the design of the study that was being evaluated.

For studies with treatment outcomes (KQs 1, 3, 4, and 5), we rated quality as good, fair, or poor based on a tool developed by the Cochrane Collaboration for assessing the risk of bias of RCTs.[61] When relevant, we also applied supplementary items developed by the RTI-University of North Carolina Evidence-based Practice Center for evaluating additional bias concerns relevant to cohort and case control study designs.[62]

For screening studies (KQ 2) assessing diagnostic test accuracy, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool;[63] for diagnostic prediction model studies, we used a preliminary version of the in-development Prediction Model Study Risk of Bias Assessment Tool (PROBAST).[64] Based on these two tools, we evaluated each study as low, unclear, or high risk of bias. Low corresponds to good quality, high to poor quality, and unclear identifies studies for which we could not make a determination on the risk of bias.

The quality of existing systematic reviews that we integrated into this review were evaluated using ROBIS,[63, 65] a tool designed to evaluate the risk of bias of systematic reviews. Using this tool, each systematic review was rated as low, unclear or some concerns, or high risk of bias. As with the PROBAST and QUADAS tools, low risk of bias corresponds to good quality, high to poor quality, and unclear represents uncertainty. **Appendix C** describes the quality rating criteria for each tool. We did not review the quality of individual studies contained within any good-quality systematic reviews that we included.

We resolved disagreements by discussion and consensus. We rated studies with fatal flaws as poor quality. For RCT and cohort studies included to answer KQ 1, 3, 4, or 5, "fatal flaws" that could result in poor-quality (i.e., high risk of bias) ratings included the following: groups assembled initially were not close to being comparable or were not maintained throughout the study; unreliable or invalid measurement instruments were used or not applied equally among groups (including not masking outcome assessment); and key confounders were given little or no attention. For RCTs, intention-to-treat analysis was lacking. For case-control studies pertaining to KQ 3 or 5, fatal flaws included major selection or verification (diagnostic workup) bias, a response rate less than 50 percent, or inattention to confounding variables. For KQ 2 screening studies, fatal flaws in at least one domain could lead to poor-quality ratings. Such flaws include cross-sectional design for risk prediction (i.e., predictors measured at same time as incident fracture in cases) and spectrum bias resulting from subgroups created through convenience groupings (such as quintiles) that do not represent a clinically rational categorization of participants.

Data Synthesis and Analysis

In Chapter 3 on results, we describe the yield from newly identified included studies and studies identified in the previous review that continue to meet current inclusion and quality criteria. We then present a synthesis of the last update and current findings.

When at least three similar studies were available, we conducted quantitative synthesis of AUCs and event rates in studies with random-effects models using the inverse-variance weighted method (DerSimonian and Laird). For studies presenting multiple doses of medications, we

selected the dose closest or equal to the FDA-approved dose, unless otherwise specified. We conducted sensitivity analyses using restricted maximum likelihood estimates to explore whether DerSimonian and Laird random-effects models underestimate variance for small meta-analyses.[66]

For all quantitative syntheses, we calculated the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) to assess statistical heterogeneity in effects between studies.[67, 68] An I^2 from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and 75 percent to 100 percent represents considerable heterogeneity.[61] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). However, as precision and the number of subjects increase, I^2 may become inflated toward 100 percent, and may not reflect clinically relevant heterogeneity.[69] All quantitative analyses were conducted using OpenMetaAnalyst.[70] We additionally conducted sensitivity analyses using Comprehensive Meta Analysis.[71]

We interpret AUCs close to 0.50 as being no better than chance; AUCs of 1.0 represent perfect test accuracy.

The discussion chapter summarizes conclusions from the previous 2010 review, the 2011 USPSTF statement, and the implications of the new synthesis for previous conclusions. In addition, we assess the overall summary of the body of evidence for each KQ using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results among studies (similar magnitude and direction of effect); and applicability of the results to the population of interest.

Expert Review and Public Comment

A draft report was reviewed by content experts, representatives of federal partners, USPSTF members, and AHRQ Medical Officers, and was revised based on comments, as appropriate, to include suggested citations that met our inclusion criteria. Additionally, we updated the report to add details on a newly published trial of screening[72] and summarized the accuracy of clinical risk assessment instruments on identifying osteoporosis in younger women.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 5,207 unique records and assessed 842 full texts for eligibility (**Figure 2**). We excluded 674 studies for various reasons detailed in **Appendix C** and included 168 published articles of good or fair quality in our main analyses. One article was included for key question (KQ) 1, 103 articles were relevant for KQ 2a, 2 articles were relevant for KQ 2b, one article was relevant for KQ 3, 25 articles were relevant for KQ 4, and 50 articles were relevant for KQ 5. In addition to the previous report,[2, 3] we drew from reference lists and data from other systematic reviews.[73-76] Details of quality assessments of included studies and studies excluded based on poor quality are provided in **Appendix D**. **Appendix E** lists the inclusion and exclusion status of studies included in the previous review. **Appendix F** presents details for included studies in Evidence Tables. **Appendix G** describes ongoing trials, and **Appendix H** presents forest plots for meta-analyses.

Key Question 1. Does Screening (Clinical Risk Assessment, Bone Density Measurement, or Both) for Osteoporotic Fracture Risk Reduce Fractures and Fracture-Related Morbidity and Mortality in Adults?

We found one eligible study. The Screening for Osteoporosis in Older Women for the Prevention of Fracture (SCOOP) trial randomized 12,483 women ages 70 to 85 years to screening with the FRAX or usual care.[72] In this fair-quality trial, participants in the intervention arm who were identified as high risk based on FRAX-generated 10-year hip fracture risk were invited to undergo DXA testing. The investigators recalculated the FRAX risk for those who undertook DXA screening and communicated the results to the participant's general practitioner, who then offered treatment as appropriate.[72] At 5 years followup, the study found no difference in the primary outcome of any osteoporotic fracture in the intervention arm when compared with the usual care arm (12.9% vs. 13.6%; HR, 0.94; 95% CI, 0.85 to 1.03). The study also did not find any difference in the overall incidence of all clinical fractures (15.3% vs. 16.0%; HR:0.94; 95% CI, 0·86 to 1·03) or mortality (8.8% vs. 8.4%; HR 1.05, 95% CI, 0.93 to 1.19). However, the study reported a statistically significant difference in hip fracture incidence (2.6% vs. 3.5%; HR 0.72; 95% CI, 0.59 to 0.89).

Key Question 2a. What Is the Accuracy and Reliability of Screening Approaches to Identify Adults Who Are at Increased Risk for Osteoporotic Fracture?

This section is organized as follows: evidence on the accuracy of (1) clinical risk assessment tools for identifying osteoporosis, (2) bone measurement tests screening for identifying low bone mass and osteoporosis, (3) fracture risk prediction instruments for predicting fracture, and (4) bone measurement tests for predicting fracture. Each section includes an overview of the

evidence, followed by findings. We then discuss calibration of fracture risk prediction instruments and other measures of test performance, specifically, reclassification.

Accuracy of Clinical Risk Assessment Tools for Identifying Osteoporosis: Overview of the Evidence

Thirty-eight studies (comprising 41 publications)[56, 57, 77-115] provide information on the accuracy of 16 clinical risk assessment instruments in identifying osteoporosis (bone mineral density [BMD] T-score ≤-2.5) (summary in **Table 3**; details in **Appendix F Tables 1-5**). We restricted inclusion to validated instruments. Studies were conducted in the United States (14 studies), Canada (5 studies), the United Kingdom (2 studies), Australia (2 studies), Republic of Korea (3 studies), Italy (3 studies), Spain (2 studies), Hong Kong (2 studies), Belgium (1 study), Denmark (1 study), Singapore (1 study), Portugal (1 study), and one study conducted data in the United States and Hong Kong. Thirty-seven reported area under the curve (AUC) and 34 reported sensitivity or specificity. A smaller subset reported on positive (19 studies) or negative (17 studies) predictive values. The evidence base is characterized by heterogeneity in included risk factors (ranging from 2 to 17), clinical (19 in clinics, 19 in community settings,) and geographic settings, measurement of osteoporosis (studies measured osteoporosis at spine, total hip, femoral neck, other sites [thoracic vertebra, lumbar vertebra, arms, ribs, or legs], or combinations of sites), thresholds used to calculate sensitivity and specificity, reference ranges, and baseline osteoporosis rates (4.4%[110] to 47.4%[88]). Studies on five instruments (Mscore,[112] Male Osteoporosis Risk Estimation Score (MORES),[85, 110, 114, 115] Male Osteoporosis Screening Tool (MOST),[97] Osteoporosis Screening Test [OST], and FRAX[114]) reported results in men-only samples, with OST reported separately in predominantly Asian (Osteoporosis Screening Tool for Asians [OSTA])[96, 98, 104, 105]and other populations (OST).[77, 97, 98, 108, 111, 112] One study reported results for men and women for FRAX and OST.[106] All other studies reported results in women-only samples. Although the range of mean ages in included studies varied from 50.5[109] to 78.2,[106] among those reporting a mean age (33 studies), the mean in most studies (22 studies, 67%) ranged between 60 and 70 years.

Accuracy of Clinical Risk Assessment Instruments in Identifying Osteoporosis: Findings

Overall Findings

As in the previous update, we found a wide range of AUCs (**Table 3**). When possible, we pooled AUCs for instruments reporting results from three or more populations (**Appendix H Figures 1-7**). With the exception of one meta-analysis, all demonstrated high I^2 (>83%), suggesting that the variability between studies can be explained by heterogeneity rather than chance. Pooled estimates of AUCs ranged from 0.65 (Osteoporosis Risk Assessment Instrument [ORAI]; 10 studies; 16,780 participants) to 0.76 (Osteoporosis Self-Assessment Tool for Asians [OSTA]; four studies; 2,962 participants) in women. AUCs from individual studies have a wider range from 0.32[88] to 0.873[107]. AUCs appear to be higher in studies recruiting men, ranging from 0.62[98] to 0.89.[111] The pooled estimate for OST is 0.76 (seven studies; 7,798 participants) and for MORES is 0.80 (three studies; 4,828 participants). Instruments with more risk factors do not report higher AUCs than instruments with fewer risk factors.

Findings in Younger Women

We also evaluated the accuracy of clinical risk assessment instruments in younger women, drawing on studies of populations under age 65 years, subgroup analysis of those under age 65 years, and studies with a mean age under 60 years.

FRAX. Three studies of younger women (<65 years) evaluated the accuracy of FRAX in identifying major osteoporotic fractures.[56, 57, 113] Of these, two specified the USPSTF recommended threshold of 9.3 percent for a 10-year risk of major osteoporotic fractures[56, 57] and one did not.[113] AUCs range from 0.58 to 0.67. As noted previously in Chapter 1, one of these studies also compared the accuracy of FRAX with those of other instruments (OST and SCORE) and found that that the FRAX threshold of ≥9.3 percent was modestly better than chance, and inferior to OST and SCORE in identifying women with osteoporosis (femoral neck T-score ≤−2.5).[57]

OST. Five studies evaluated the performance of OST in women (three in populations under age 65 years,[57, 102, 113] one in a subgroup of women under age 65 years,[79] and one in a population ranging from ages 40 to 69 years, with a mean age of 54.2 years[99]). AUCs ranged from 0.64[99] to 0.77.[79, 102]

SCORE. Four studies reported on the performance of SCORE in younger women (one in a population under age 65 years,[57] two in subgroup analyses of women younger than 65 years of age,[79, 100] and one in a population with a mean age of 50.5.[109] AUCs ranged from 0.68[109] to 0.85.[100]

ORAI. Four studies reported on the performance of SCORE in younger women (two in subgroup analyses of women younger than 65 years of age,[79, 100] and two in population with mean ages of 50.5[109] and 54.2 years,[99] respectively. AUCs ranged from 0.62[99] to 0.82.[100]

Other instruments. Two studies reported on the performance of the NOF guidelines and OSIRIS and reported AUCs of 0.69[100] and 0.63[99] respectively.

Appendix F Tables 1-7 provides additional details on sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). As noted above, fewer studies reported these statistics than AUCs. Reported thresholds varied considerably within instruments; we present ranges for the most commonly reported threshold. Even with a common threshold, results varied widely; as an example, for the ORAI instrument, sensitivity ranged from 50 percent to 100 percent, specificity from 10 percent to 75 percent, PPV from 20 percent to 98 percent, and NPV from 25 percent to 94 percent. These wide ranges reflect the underlying heterogeneity described above.

Accuracy of Bone Measurement Tests Used to Identify Low Bone Mass and Osteoporosis: Overview of the Evidence

Eleven studies provide information on the accuracy of bone measurement tests for screening for low bone mass or osteoporosis (summary in **Table 4**; details in **Appendix F Table 6**). Of these,

five are new inclusions[94-96, 101, 116] and six[87, 93, 97, 111, 117, 118] were previously described in the 2010 review.[3] The previous review also relied on a systematic review that found a pooled AUC of 0.76 (95% CI, 0.72 to 0.79) overall, and specifically for postmenopausal women, 0.75 (95% CI, 0.66 to 0.82).[119, 120]

Seven of 11 studies included fewer than 250 patients.[87, 93, 101, 111, 116-118] Three studies, including the largest (N=6,572)[97] focused on men in the United States,[111] Hong Kong,[96] or both countries.[97] Studies of women were set in Belgium,[116, 118] Hong Kong,[95] Spain,[94] Canada,[101] and the United Kingdom.[87, 93, 117] Studies varied widely in the degree of restrictiveness of participant inclusion and exclusion. Two studies reported no exclusion criteria.[87, 101] In contrast, two studies set in Hong Kong reported an extensive list of inclusion and exclusion criteria.[95, 96] All were of low or unclear risk of bias.

Studies evaluated quantitative ultrasound (QUS),[87, 93, 95-97, 101, 111, 116, 117] peripheral DXA,[93, 94] digital X-ray absorptiometry (DXR),[116] and radiographic absorptiometry.[116] No studies on vertebral fracture assessment or dental tests met our inclusion criteria.

Accuracy of Bone Measurement Tests Used to Identify Low Bone Mass and Osteoporosis: Findings

Studies in women focusing on comparisons of calcaneal QUS against a centrally measured DXA BMD T-score cutoff of -2.5 or less reported AUCs varying from 0.69 (N=202, Belgium) to 0.90 (N=174, Canada). For women, seven studies of 1,969 women yielded a pooled estimate of 0.77 for the AUC (95% CI, 0.72 to 0.81, I^2=82.1%) (**Appendix H Figure 8**). We were unable to replicate reported confidence intervals in three studies,[87, 101, 117] and used our estimate, based on reported populations and AUCs. Sensitivity analysis without these three studies yielded similar results (AUC, 0.74; 95% CI, 0.70 to 0.78; I^2:65%; 4 studies, N=1352). Studies in women also reported on the use of peripheral DXA, with AUC ranging from 0.67 to 0.80;[93, 94] DXR with an AUC of 0.84 (95% CI, 0.79 to 0.89);[116] and radiographic absorptiometry with an AUC of 0.80 (95% CI, 0.74 to 0.85).[116]

All studies in men focused on comparisons of calcaneal QUS to a centrally-measured DXA BMD T-score cutoff of -2.5 or less.[96, 97, 111] AUC estimates ranged from 0.70 (N=4,658 Caucasian men in the United States) to 0.93 (N=128 African American men). For all men in the three studies (N=5,142), the pooled AUC estimate was 0.80 (95% CI, 0.67 to 0.94; I^2, 98%) (**Appendix H Figure 9**).

Accuracy of Fracture Risk Prediction Instruments: Overview

We identified five systematic reviews[75, 76, 119, 121, 122] addressing the accuracy of tools to predict fracture in adults. Our synthesis is based on the good-quality Marques et al systematic review[76] supplemented by 13 eligible observational studies with low risk of bias or unclear bias not included in the Marques et al review (summary in **Table 6**; details in **Appendix F Table 8**)[58, 102, 123-133] The Marques et al review used a search through late 2014, and selected studies for inclusion based on similar criteria to our review and consistent with the previous evidence review in support of this USPSTF recommendation.[3]

Marques et al included 45 articles that assessed 13 different risk prediction instruments; of these, 10 had been evaluated by only one or two studies. The three risk prediction tools evaluated by three or more studies and for which a quantitative synthesis was performed included FRAX (k=26), the Garvan Fracture Risk Calculator (FRC) (k=6), and the QFracture prediction tool (k=4).

Marques et al identified other fracture risk prediction instruments, but studies on these instruments reported no measures of discrimination (e.g., AUC, sensitivity, specificity) for populations external to the development cohort. This includes the Cummings Risk Score,[134] Fracture and Mortality Index,[135, 136] a simple clinical score,[137] and simplified system for fracture risk assessment.[138] Of the studies that we identified as eligible that had not been included in the Marques et al review, four studies were published after the Marques et al search dates,[58, 124, 129, 133] and nine were studies we identified as eligible but were either not identified or not included by Marques et al[102, 123, 125-128, 130-132] These additional studies reported on FRAX, Garvan FRC, and QFracture in addition to five risk instruments not reported in Marques et al The evidence tables for studies we identified are in **Appendix F**; these tables do not contain the studies that were included in the Marques et al review.

In updating the Marques et al meta-analysis, we identified one study[139] included in the original pooled AUC estimate that was not from an external validation population, and one study[140] that used a cross-sectional design, which has a high risk of bias for risk prediction. We have excluded these two studies from this update. The previous review[3] included several studies not included in this update. Two studies evaluating risk prediction instruments used cross-sectional designs. This includes a study[141] assessing age, body size, and estrogen use, ORAI, and body weight as risk prediction instruments, and a study[142] assessing FRAX and Garvan FRC. Three studies[143-145] of clinical risk scoring algorithms, the Dubbo Osteoporosis Epidemiology Score, the Established Populations for the Epidemiologic Study of the Elderly, and the Fracture Index did not report outcomes for an external validation population. One study[146] evaluated a risk prediction model focused exclusively on risk prediction in nursing home residents using the Minimum Data Set.

Accuracy of Fracture Risk Prediction Instruments: Discrimination Findings

In **Table 5** we characterize and report the accuracy of fracture risk prediction at 10 years for 11 instruments as measured by the AUC measure of discrimination. These findings are stratified by sex, site of fracture, and whether BMD was used in the risk prediction. Where possible, we pool AUCs. The rest of this section details findings by risk prediction instrument.

FRAX

FRAX was developed and validated in 11 different cohorts (230,486 participants including men and women) and uses age, sex, weight, height, prior fracture, parental history of fracture, and five other clinical risk factors.[32] It can be used with or without femoral neck BMD to predict the 10-year risk of hip and MOF. FRAX is calibrated for use in different countries based on country-specific data. Studies included were conducted in the following countries: Australia, Canada, Denmark, Finland, France, Hong Kong, Japan, Netherlands, New Zealand, Spain, the United States, and in a multinational European and U.S. cohort.

The discriminative ability of FRAX for predicting future fracture varied by sex, site of fracture prediction, and whether BMD was used in the risk prediction. In men, pooled estimates of AUC from 3 to 44 studies and 13,970 to 15,842 participants ranged from 0.62 to 0.76 (depending on the model) (**Appendix H, Figures 10-13**). Within that range, pooled estimates were higher for 13 prediction models that included BMD and for the models predicting hip fracture. Pooled estimates for women based on between 10 and 17 studies with between 62,054 and 190,795 participants ranged somewhat higher (0.67 to 0.79) but they shared a similar pattern (**Appendix H Figures 14-17**). Pooled estimates for the prediction of MOF based on three studies (66,777 participants), including men and women, but that did not report findings by sex, were similar (AUC without BMD, 0.67 [95% CI, 0.66 to 0.67; I^2, 47.1%]; AUC with BMD, 0.69 [95% CI, 0.69 to 070, I^2, 70.3%]) (**Appendix H, Figures 18-19**). Two studies reported AUC for hip fracture with and without BMD from combined cohorts of men and women; estimates from these two studies[147, 148] were similar to estimates from the women-only cohorts.

The original FRAX validation study[32] also reported AUCs; however, the AUCs reflected the risk of fracture at age 70, not a 10-year fracture risk, and did not report on MOF. Thus, we did not include these AUCs in our pooled estimates. In this validation study, the range of AUCs in the validation cohorts for prediction of hip fracture at age 70 (both sexes combined) was 0.70 to 0.81 with BMD and 0.57 to 0.77 without BMD. For nonhip osteoporotic fractures, the range was 0.55 to 0.77 with BMD and 0.54 to 0.81 without BMD.

Garvan Fracture Risk Calculator

The Garvan FRC, originally developed in cohorts of Australian men and women,[139] uses age, sex, weight, prior nontraumatic fracture after age 50, and a fall within the past year as risk to predict risk of hip or MOF at either 5 or 10 years. BMD at the hip is an optional input to the risk prediction. We focus on estimates for 10-year fracture risk prediction, for comparison with other instruments that predict 10-year risk. Studies included were conducted in Australia, Canada, Netherlands, New Zealand, and Norway.

The discriminative ability of the Garvan FRC varied by sex, site of fracture prediction, and whether BMD was used in the risk prediction. Two studies reported AUC estimates in men.[129, 149] The AUC for hip fracture without BMD was 0.65 (95% CI, not reported [NR]; 1,285 men).[129] With BMD, the AUC for hip fracture was 0.74 (95% CI, NR; 1,285 men) in one study[129] and 0.85 (95% CI, NR; 1,606 men) in the other study.[149] Estimates of AUC for nonvertebral fractures were 0.61 and 0.57 with and without BMD, respectively (95% CI, NR for either).[129] Only one of the two studies reported AUC for MOF; the estimate was 0.70 (95% CI, NR; 1,606 men).[149]

In women, we calculated pooled AUC estimates for models with BMD of 0.68 (95% CI, 0.64 to 0.71; I^2=848%; three studies, 6,534 women) for MOF (**Appendix H Figure 20**) and 0.73 (95% CI, 0.66 to 0.79; I^2=97.3%; four studies, 7,809 women) for hip fracture (**Appendix H Figure 21**). One study[124] reported an AUC of 0.69 (95% CI, NR; 506 women); a different study[129] reported an AUC of 0.62 (95% CI, NR; 1,637 women) for nonvertebral fracture, both for prediction without BMD. Estimates of AUC for models without BMD ranged from 0.58 to 0.68 depending on site of fracture based on estimates from three studies.[124, 126, 129]

QFracture

QFracture predicts fracture risk in men and women over a 1- to 10-year period using age, sex, weight, height, parental fracture, previous fall, and between 11 and 13 clinical risk factors depending on sex.[150] A 2012 update to the instrument added previous fall, ethnicity, and 10 additional clinical risk factors.[130] BMD is not used to predict risk with QFracture. Studies included were conducted in France and the U.K. The AUC for MOF ranged from 0.69 to 0.74 in men and from 0.79 to 0.82 in women.[76] For hip fracture, AUC estimates were 0.86 to 0.89 in men and was 0.89 in women.[76]

Other Fracture Risk Assessment Instruments

The remaining eight fracture risk assessments include the Women's Health Initiative algorithm,[151] OST,[152] SCORE,[153] Fracture and Immobilization Score,[154] Fracture Risk Score,[155] FRC,[156] ORAI,[157] and Osteoporosis Index of Risk (OSIRIS).[158] Of these, all but the Fracture Risk Calculator[156] were developed using only cohorts of women, and the prediction time range from 3 to 10 years. The only assessments evaluated in U.S. populations are the Women's Health Initiative algorithm, OST, SCORE, and the Fracture Risk Calculator. Several of these instruments (OST, SCORE, ORAI, OSIRIS) were initially developed for the prediction of low bone mass or osteoporosis and later applied to the prediction of incident fracture. The Fracture Risk Calculator, OST, and the Women's Health Initiative algorithm were evaluated in two external validation populations; the rest of the instruments have been evaluated only in one external validation population. Across all these instruments, AUC estimates for MOF in women ranged from 0.53 to 0.73[58, 102, 126, 128] and from 0.80 to 0.85 for hip fracture.[151, 159, 160]

Last, the Canadian Association of Radiologist and Osteoporosis Canada uses age, sex, prior fragility fracture, use of glucocorticoid steroids, and BMD to predict the 10-year risk of MOF in men and women age 50 or older.[161] This instrument computes a 10-year absolute fracture risk and then categorizes risk as high (>20%), moderate (between 10% and 20%), and low (<10%). An external validation study using 10,039 participants reported a sensitivity of 0.54 (95% CI, 0.52 to 0.56) for predicting fracture among women in the high-risk category and a sensitivity of 0.31 (95% CI, 0.24 to 0.38) for men.[131] The reported specificities were 0.75 (95% CI, 0.74 to 0.75) and 0.86 (0.85 to 0.87) for women and men, respectively.

Accuracy of Bone Measurement Tests Used to Predict Fracture: Overview of the Evidence

The 2010 review,[3] based on evidence from 11 studies, found that DXA and QUS had similar AUC estimates for the prediction of fracture outcomes among samples of both women and men. Among postmenopausal women, for all types of fractures combined, AUC estimates based on DXA ranged from 0.59 to 0.66, and estimates based on QUS were approximately 0.66.
In our updated review, we included 23 studies of low or unclear risk of bias (reported in 24 articles), two of which were included in the 2010 review,[162, 163] evaluating the performance of various bone measurement tests for predicting fractures (summary in **Table 6**; details in **Appendix F Table 7**).[133, 144, 147, 148, 154, 155, 162-179] We do not discuss two studies further because they did not have usable data for our analysis of fracture outcomes; Henry et al did not report AUC estimates,[155] and Ensrud et al did not present risk estimates separately for BMD alone.[178]

We rated one other study as high risk of bias and did not include it in our update.[180] We did not include eight other studies from the 2010 review because they did not meet our inclusion criteria for one or more reasons, such as measuring bone density after the occurrence or identification of fracture or not reporting an AUC estimate.

Of the 21 studies we report on, two were conducted in the United States,[133, 163] one in Scotland,[162] four in Japan,[154, 164, 169, 177] three in Canada,[147, 148, 165, 166] two in Hong Kong,[167, 176] two in Australia,[144, 168, 171] one in Finland,[170] two in France,[172, 173] one in Denmark,[174] one in Sweden,[179]one in New Zealand,[87] and one in Spain.[175]

The Canadian Manitoba study of men and women age 50 years or older was the largest study (N=39,603).[148]

One study only reported data on men and women combined.[147] All others included separate reporting on women and men; 14 reported on postmenopausal women and four reported on men. These studies generally had few exclusion restrictions.

All studies reported on centrally measured DXA. Four studies also reported on calcaneal QUS tests, and one study also reported on dual X-ray and laser (DXL). No studies on vertebral fracture assessment or dental tests met our inclusion criteria. The various bone measurement tests evaluate bone density using different technologies; this results in different measures of bone "strength" that are not comparable across technologies. For example, QUS yields measures of broadband attenuation (BUA), speed of sound (SOS), or a quantitative ultrasound index (QUI). Studies also differ by the number and location of the incident fracture site being predicted (any osteoporotic fracture, vertebral, or hip), and the reference sites (spine, hip, or femoral neck) used to determine DXA-measured BMD. The length of followup for fracture surveillance following bone measurement testing ranged from approximately 4 years to up to 15 years.

Accuracy of Bone Measurement Tests Used to Predict Fracture: Findings

Because of differences across studies in the combination of the type of imaging test, sex of the participants, and location of an incident facture being predicted, few studies reported on the same combination of parameters (**Table 6**). In general, we did not find differences in AUC by type of bone test or sex.

Regarding type of bone test, AUC estimates for fracture prediction based on centrally measured DXA BMD, trabecular bone score, or a combination of both were as follows: any osteoporotic fracture (0.63 to 0.74), vertebral or spine fracture (0.61 to 0.75), and hip (0.64 to 0.85). The AUC estimate of hip fracture based on DXL was 0.61.[179] The range of AUC estimates for fracture prediction based on QUS parameters (BUA, SOS, or QUI) were similar: any osteoporotic fracture (0.64 to 0.72) and, measured in men in one study, hip (0.84). Two studies[163, 168] measured a combination of DXA and QUS (BUA parameter) and found that this approach did not appreciably increase AUC: any osteoporotic fracture (0.69 to 0.73), vertebral (0.72 in women) and (0.75 in men) in one study,[168] and hip (0.78 to 0.85).

Regarding sex of the study participants, AUC estimates for fracture predictions based on DXA

BMD in postmenopausal women ranged from 0.64 to 0.82. For QUS, AUC estimates ranged from 0.66 to 0.72. AUC estimates based on combinations of DXA and QUS reported in one study ranged from 0.72 to 0.81, differing by the location of the fracture.[168] Four studies evaluating the performance of bone measurement tests for predicting fractures in men examined the same bone measurement screening tests used for women.[163, 167, 168, 174] AUC estimates based on DXA BMD in men ranged from 0.64 to 0.85, and for QUS, ranged from 0.64 to 0.84.[163, 167] AUC estimates based on combinations of DXA and QUS, reported in two studies, ranged from 0.69 to 0.85.[163, 168]

Regarding fracture site, for both men and women, AUC point estimates of 0.80 or better were associated only with predictions of future hip fracture. These results were found in eight of 12 studies that evaluated this outcome. These include studies of women based on results of DXA of the total hip (0.81 to 0.82),[165, 166] middle phalanges of the second, third, and fourth fingers on the nondominant hand (0.83),[174] and the femoral neck (0.85 and 0.82).[176, 177] Similar results among women were based on a combination of DXA of the femoral neck and QUS (0.81).[168] One study of men found similar results, based on DXA of the femoral neck (0.85), QUS (0.84), and a combination of the two (0.85),[163] but these findings were not replicated in one study based on DXA of the middle phalanges (0.64).[174] AUC point estimates in two studies combined hip fracture results for men and women, based on DXA of the femoral neck (0.80[148] and 0.76[147]). AUC accuracy in predicting hip fracture were lower in one study of women (0.77) than in two other studies, possibly the authors adjusted the results for age, falls, and fracture history,[168] whereas the other two studies reported unadjusted outcomes. The reasons that the prediction for women in yet another study was lower (0.64) are unknown.[171]

Calibration of Fracture Risk Prediction Instruments

We identified 14 studies of low or unclear risk of bias reporting eligible calibration outcomes in countries with an incidence of hip fracture similar to that found in the United States (i.e., in the moderate range).[102, 125, 147-149, 154, 170, 171, 175, 177, 181-185] Eleven reported calibration outcomes for FRAX (various versions);[125, 147, 148, 170, 171, 175, 177, 181-185] four reported outcomes for other risk models.[102, 149, 154, 171] We identified no published studies that met our eligibility criteria that provided results of calibration for the U.S. version of FRAX or of other risk assessment instruments in U.S. populations. Ten calibration studies conducted outside of the United States in countries with hip fracture incidence dissimilar to the US were not included in the evidence synthesis.[102, 123, 125, 127, 129-131, 181, 183, 184]

Other Measures of Test Performance: Reclassification of Risk Overview

Several studies compared overall proportions of individuals classified at risk for various fracture risk prediction instruments without presenting reclassification data.[131, 138, 178, 186, 187] Others present reclassification rates[188-190] or net reclassification improvement (NRI).[127, 129, 149, 164, 168, 191, 192] We describe results for studies presenting only reclassification rates in greater detail in the text below. We present details regarding NRI in text below and in **Table 7**. In instances in which studies report NRI as a percentage, we follow guidance on net reclassification to present these results as unitless measures rather than as a percentage of the cohort reclassified. Guidance suggests that these results cannot be interpreted as percentages because of the implicit weighting

by event rates when summing two fracture numbers with two different denominators to arrive at the NRI.[193]

Other Measures of Test Performance: Findings

FRAX

Five studies evaluate reclassification for FRAX.[123, 127, 149, 189, 190] One study examined reclassification in the context of FRAX with and without BMD in a sample of 36,730 women and 2,873 men age 50 years or older from the Manitoba Bone Density Program database (Canada).[123] The study reported no differences in AUCs for men or women for any outcomes other than major osteoporotic fractures. It reported the addition of BMD to FRAX, against an intervention threshold of a 10-year risk ≥20 percent of a MOF, resulting in a reclassification of 8.5 percent of the cohort. Of these individuals, 2.8 percent moved to the higher risk category (≥20% risk of MOF) and 5.7 percent moved to the lower risk category (<20%). For those in the intermediate category of risk (10% to 19% risk of MOF), adding BMD to FRAX produced a reclassification of 7.5 percent to the low-risk category (<10% risk of MOF) and 2.7 percent to high risk (≥20% risk of MOF). Of those categorized as low risk, adding BMD to FRAX led to a reclassification of 6.2 percent to moderate risk and 0.1 percent to high risk.[123] A large study of 94,489 women age 50 years or older with BMD measured during 1997–2003 in Kaiser Permanente Northern California also found no differences in AUC with or without BMD.[187] An exploration of reclassification when adding BMD to fracture risk assessment used an 81 percent sensitivity threshold (identified as the optimal level from the receiver operating characteristic curve, corresponding to a 10-year risk for hip fracture of 1.2% in the model without BMD). This reclassification resulted in an NRI of 0.055.

Three studies reporting on the same cohort of participants in Manitoba, focused on issues specific to the measure of BMD in FRAX, specifically the inclusion of information on lumbar spine BMD in addition to femoral neck BMD. Two were developed and validated using a split-sample cohort.[189, 190] One study developed a hybrid system for FRAX that incorporated femoral neck BMD to assess nonvertebral fracture risk and lumbar spine BMD for clinical vertebral fracture risk.[190] The study found that in 37,032 women, against an intervention threshold of >20 percent risk of a major MOF, the use of the hybrid model resulted in a reclassification of 7.6 percent of the cohort. Of these individuals, 0.1 percent moved to the higher risk category (>20% risk of MOF) and 7.5 percent moved to the lower risk category (≤20%). For those in the moderate category of risk (10% to 20% risk of MOF), the hybrid model resulted in a reclassification of 0.5 percent of the cohort to the low-risk category (<10% risk of MOF) and 7.5 percent to high risk. Of those categorized as low risk, the hybrid model produced a reclassification of 6.1 percent of the cohort to moderate risk.[190]

The difficulties in applying this hybrid model in clinical practice led to further testing of ways to incorporate lumbar spine measurement. A second study evaluated reclassification after adding information on an offset (the difference between lumbar spine and femoral neck T-scores) to FRAX.[189] In a sample of 18,215 women in the validation cohort, adding the lumbar spine offset against an intervention threshold of ≥20 percent risk of a MOF, resulted in a reclassification of 13.1 percent of the cohort. Of these individuals, 3.8 percent moved to the higher risk category

(≥20% risk of MOF) and 9.3 percent moved to the lower risk category (<20% risk of MOF). For those in the moderate category of risk (10% to 19% risk of MOF), adding the lumbar spine offset to FRAX resulted in a reclassification of 8.8 percent to the low-risk category (<10% risk of MOF) and 3.8 percent to high risk) (≥20% risk of MOF). Of those categorized as low risk, the addition of lumbar spine offset to FRAX led to a reclassification of 4.9 percent to moderate risk (10% to 19% risk of MOF).[189]

A third study compared FRAX with T-scores from the femoral neck, lumbar spine, minimum site (femoral neck or lumbar spine), weighted mean, and an offset (the difference between the lumbar spine and femoral neck T-scores) in 20,477 men and women.[127] It found that the use of lumbar spine or minimum site resulted in both reclassification and miscalibration, while the use of weighted mean or offset did not. Specifically, the authors report that the change in accuracy was negative for lumbar spine (-4.4%) and minimum site (-11.8%), and unchanged for weighted mean (0.1%) and offset (0.3%) (details on calculation of change of accuracy not reported).

Fracture Risk Calculator

One study evaluated adding BMD to the FRC in men 65 years and older using the Osteoporotic Fractures in Men Study database of 5,893 men in the United States who participated in the baseline visit (March 2000–April 2002).[191] Against the National Osteoporosis Foundation's (NOF) intervention threshold (10-year 3% risk of a hip fracture), the addition of BMD resulted in an NRI of 0.085. Using the NOF intervention threshold of a 20 percent 10-year risk of MOF, the addition of BMD resulted in an NRI of 0.04. In 17 of 20 examined quintiles of expected fracture probabilities to observed fractures (with BMD, without BMD, hip fracture, MOF), the ratio (of expected to observed fractures) was within 20 percent of the ideal 1.0 ratio.

Garvan FRC (Dubbo Nomogram in Earlier Studies)

Two studies, both drawing from the Dubbo Osteoporosis Epidemiology Study (Australia), evaluated the performance of fracture risk prediction models that included calcaneal QUS (measured through BUA) with the Garvan FRC,[168, 192] which includes femoral neck BMD, age, history of falls, and prior fracture. One study included 899 participants between ages 62 and 89 years (445 men and 454 women) who had both QUS and DXA BMD measurements.[168] Participants been followed for a median of 13 years. The second study restricted analysis to nonosteoporotic participants (BMD T-score >−2.5).[192] The sample comprised 312 women and 390 men ages 62 to 90 years, followed for a median of 12 years. Both studies reported that the addition of BUA to the femoral neck BMD model improved AUC for women for hip fractures and any fractures,[168, 192] and for vertebral fractures in nonosteoporotic women only.[192] Both studies found that adding BUA to the model did not improve AUCs. In the larger sample of all women, adding BUA to the model resulted in an NRI of 0.073 for any fracture, 0.111 for hip fracture, and 0.052 for vertebral fracture.[168] In nonosteoporotic women, adding BUA to the model resulted in an NRI of 0.164 for any fractures and 0.338 for hip fracture.[192] The importance of these differences is difficult to evaluate in the context of small sample sizes and lack of information on the potential for miscalibration.

One study of 4,152 women and 1,606 men, ages 55 to 95 years at baseline in the Canadian

Multicentre Osteoporosis Study compared the performance of the instrument with (1) the World Health Organization (WHO) criteria of a T-score of ≤−2.5 indicating high risk and (2) Canadian guidelines (defining low risk = 0–10%, moderate = 10–20%, and high >20%, and derived from age, minimum T-score [lumbar spine, total hip, femoral neck, trochanter], glucocorticoid use and history of fracture after age 40).[149] Comparisons with the WHO criteria suggested no differences with an NRI of 0.067 (95% CI, –0.06 to 0.194) among men and 0.015 in women (95% CI, −0.026 to 0.056). Comparisons with the Canadian guidelines suggested improvements in prediction for men (NRI, 0.192 [95% CI, 0.063 to 0.322) and worsening for women (NRI, −0.055 [95% CI, −0.095 to −0.015).[149] The study did not present AUCs for these comparisons.

One study examined the performance of the Garvan tool with and without BMD in predicting nonvertebral osteoporotic and hip fractures. The study included 1,637 women and 1,355 men older than age 60 years from Tromsø (Norway).[129] The study recorded all incident fragility fractures between 2001 and 2009. AUCs for the model with BMD were higher than the models without BMD but with body weight for men and women. Models that included body weight rather than BMD resulted in an NRI of −0.106 in women and −0.172 in men for nonvertebral osteoporotic fractures. For hip fractures, models that included weight rather than BMD resulted in an NRI of −0.133 for women and −0.175 for men.

Trabecular Bone Score

One study evaluated reclassification arising from adding trabecular bone score to spine BMD in a sample of 665 Japanese women age 50 years or older who completed the baseline study and at least one followup survey over 10 years.[164] The study reported no significant differences in AUC, but reported an NRI of 0.235 (95% CI, 0.15 to 0.54); no risk categories were specified for the NRI. This finding can potentially be explained by chance (given the small sample size) or miscalibration.

Key Question 2b. What Is the Evidence to Determine Screening Intervals for Osteoporosis and Low Bone Density?

Overview

Although the previous USPSTF recommendation suggested that a minimum of 2 years may be needed to measure a change in BMD reliably, it also noted continued clinical uncertainty about the optimal interval for rescreening to improve fracture prediction.[1] Two good-quality studies address screening intervals for osteoporosis and low bone density; of these, one[194] was reported in the 2010 review.[3] These longitudinal cohort studies examined the effect of repeat BMD testing on prediction of fracture risk (**Table 8**).[194, 195]

We also identified three studies for Contextual Question 2 that used data from large cohort studies to estimate the optimal screening interval to identify osteoporosis or fracture.[196-198]

Findings

The Study of Osteoporotic Fractures (N=4,124), in which women (mean age at baseline: 72;

mean T-score: −1.37; 95% CI, −1.40 to −1.34) who had a repeat BMD an average of 8 years after baseline DXA measurement, found no significantly different AUCs for either hip, nonspine, or spine fractures for women with information on change in BMD or combined baseline BMD and change in BMD compared with women with information on baseline BMD alone.[194] The study followed participants for a mean of 5 years after the second DXA measurement. The Framingham Osteoporosis study cohort included male participants (41%) with a similar mean age (74.8) and 74.7 percent of the sample having T-score >−2.5, but a shorter screening interval (3.7 years vs. 8 years), and followed patients for a median of 9.6 years after repeat BMD study (N=802).[194, 195] The authors of the Framingham Osteoporosis study reported similar results to the Study of Osteoporotic Fractures: AUCs for fractures among men with information on change in BMD or combined baseline and change in BMD did not differ from men with information on baseline BMD alone.[195] The study reported a net gain in the percentage of participants with a hip fracture reclassified as high risk (defined by FRAX, NRI, 3.9% [95% CI, −2.2% to 9.9%]) with a second BMD, and a net loss for those without a hip fracture reclassified as low risk with repeat BMD (NRI, −2.2% [95% CI, −4.5% to 0.1%). The study reported a higher rate of reclassification for major osteoporotic fractures (NRI, 9.7% [95% CI, 3.4 to 15.7] vs. −4.6% [95% CI, −6.7 to −2.6]) than for hip fractures.

Additional contextual evidence comes from a small number of publications that have attempted to identify appropriate screening intervals based on the time in which 10 percent of patients transition to osteoporosis. A publication using healthy postmenopausal women age 65 years or older from the Study of Osteoporotic Fractures evaluated the time for 10 percent of women to develop osteoporosis across the various BMD categories; it found that baseline T-score is the most important determinant of BMD testing intervals, with results suggesting that the times for 10 percent of women to develop osteoporosis are as follows: 16.8 years (95% CI, 11.5 to 24.6) for women with normal BMD (T-score, −1.00 or higher), 17.3 years (95% CI, 13.9 to 21.5) for women with mild osteopenia (T-score, −1.01 to −1.49), 4.7 years (95% CI, 4.2 to 5.2) for women with moderate osteopenia (T-score, −1.50 to −1.99), and 1.1 years (95% CI, 1.0 to 1.3) for women with advanced osteopenia (T-score, −2.00 to −2.49).[196] Within a given T-score range, the estimated time for 10 percent of women to transition from osteopenia to osteoporosis was longer for women with younger age and for those taking estrogen at baseline. For women with moderate osteopenia at baseline, the estimated BMD testing interval was 5.6 years (95% CI, 4.9 to 6.4) for women age 67 years compared with 3.2 years (95% CI, 2.6 to 3.9) for women age 85 years. Also for women with moderate osteopenia, the estimated BMD testing interval for past or never-users of estrogen was shorter, 4.3 years (95% CI, 3.9 to 4.8), than for women with current estrogen use, 6.9 years (95% CI, 5.7 to 8.4). Using an absolute risk-based prognostic model with a sample of nonosteoporotic women and men over the age of 60 from the Dubbo Osteoporosis Epidemiology study, the study found that current age and BMD T-score could be used to estimate the optimal time to repeat BMD testing for both men and women.[197] For example, the time for women 60 years of age with a normal BMD to reach a 10 percent risk of sustaining a fracture or developing osteoporosis was 8.9 years (90% CI 6.7 to 10.6); it was 2.7 years (90% CI, 2.3 to 3.1) for women 80 years of age.

A third study provides contextual evidence for identifying the time to transition to fracture (rather than osteoporosis) in younger postmenopausal women ages 50 to 64 years. In a study of women from the Women's Health Initiative with a baseline BMD, investigators estimated the

time for 1 percent of women to sustain a hip or clinical vertebral fracture and for 3 percent of women to sustain a major osteoporotic fracture.[198] Women were followed for up to 11 years after the initial BMD. Similar to findings of studies estimating time to transition to osteoporosis, the study found that age and baseline T-score were associated with the estimated time for 1 percent of women to transition to fracture. For women without osteoporosis at baseline ($t > -2.50$), the estimated times for 1 percent of women to transition to hip or clinical vertebral fracture were 12.8 years (95% CI, 8 to 20.4) for ages 50 to 54 years, 11.7 years (95% CI, 6.9 to 20) for ages 55 to 59 years, and 7.6 years (95% CI, 4.8 to 12.1) for ages 60 to 64 years. For all women with osteoporosis at baseline ($t \leq -2.50$), the time interval for 1 percent of women ages 50 to 64 years to transition to hip or clinical vertebral fracture was 3.0 years (95% CI, 1.3 to 7.1). There were similar findings for major osteoporotic fracture.

Key Question 3. What Are the Harms of Screening for Osteoporotic Fracture Risk?

One trial (SCOOP, previously described in KQ1)[72] assessed the impact of screening on anxiety (based on State-Trait Anxiety Inventory) and quality of life (based on the EuroQol- 5 Dimension tool and the Short-Form Health Survey 12 [physical and mental health]) and found no differences between participants who were allocated to screening vs. usual care (variance not reported, P values >0.10 for all outcomes).

Key Question 4a. What Is the Effectiveness of Pharmacotherapy for the Reduction of Fractures and Related Morbidity and Mortality?

We present summary results in text below. **Appendix F** includes detailed evidence for alendronate (**Appendix F Table 9**), zoledronic acid (**Appendix F Table 10**), risedronate (**Appendix F Table 11**), etidronate (**Appendix F Table 12**), raloxifene (**Appendix F Table 13**), denosumab (**Appendix F Table 14**), and parathyroid hormone (**Appendix F Table 15**). **Appendix H** includes forest plots for meta-analyses.

Bisphosphonates: Overview of the Evidence

Alendronate

Seven fair- to good-quality studies examined fracture outcomes in patients receiving alendronate versus placebo. All studies were conducted in postmenopausal women receiving daily or weekly alendronate. The duration of the studies ranged from 1 to 3 years.[199-205] Three studies reported fractures at baseline,[199, 202, 205] three studies reported no fractures at baseline,[199, 200, 203] and one study did not specify.[201] Two studies reported on the Fracture Intervention Trial (FIT).[200, 205] The FIT had two arms, one with vertebral fractures at baseline, which was excluded for wrong population,[206] and no fractures at baseline.[200] One study looked at a subset of women with low bone mass from both arms of the FIT.[205]

We excluded several studies that were included in previous reviews, most commonly for wrong study population (i.e., specialty versus primary care population) or wrong outcome (change in

BMD rather than fractures),[207-215] and one study for high risk of bias.[216]

Zoledronic Acid

Two trials of zoledronic acid (N=1,550) met our eligibility criteria.[217, 218] Two studies in the previous review, both from the Horizon Pivotal Fracture Trial, were not included because more than 50 percent of the study population had a fracture at baseline.[219, 220] In addition, we excluded one study from a recent comparative effectiveness review[221] because it drew from a nonprimary care population.[222]

One study of fair quality was a phase 2 study in postmenopausal women ages 45 to 80 years with low bone density (T-score <-2) and no prior vertebral fractures. It was conducted in 24 centers across 10 countries with 1 year of followup.[217] A second and more recent study (good-quality) was also a multicenter trial conducted in Europe, South America, Africa, and Australia. This study examined men ages 50 to 85 years with T-score <1.5 or prevalent fractures with 2 years of followup.[218] Both studies evaluated zoledronic acid against placebo infusion.[217, 218] In the phase 2 trial, cumulative doses of 4 mg yearly were included in the analysis of benefits;[217] in the more recent study, zoledronic acid 5 mg was administered intravenously at baseline and 1 year.[218]

Risedronate

Four trials evaluating risedronate met eligibility criteria.[223-226] All were conducted in postmenopausal women with low bone mass or osteoporosis, and we rated them as fair quality. Three of these studies were included in the main analysis[223-225] of the previous review; one study was included in its sensitivity analysis because the proportion of prevalent vertebral fracture exceeded 20 percent.[226] We did not include one study from the previous review[227] in this update because the study population had mean T-score of -0.7 and was otherwise not at an increased risk for fracture. Approximately one-third of study subjects in two studies[223, 226] had prevalent or prior vertebral fracture at baseline. One study[224] excluded subjects with prior fractures and one study[225] did not report the proportion of study subjects with prior or prevalent fracture. All studies evaluated a dose of 5 mg per day for 2 years compared with placebo; followup for fracture outcome ascertainment was 2 to 3 years after baseline. Two trials were conducted in multiple centers in several European countries,[225, 226] one trial[223] was conducted at multiple centers in North America, Europe, Australia and New Zealand, and one trial[224] was conducted at two centers (one in the United States and one in Denmark).

One trial[223] was powered to detect an effect on hip fracture outcomes. The other three trials were powered to detect an effect on BMD. For these trials, therefore, fracture outcomes reported in these trials were reported as safety events as opposed to efficacy end points.[224-226]

Etidronate

Two fair-quality trials of etidronate (n=206) met eligibility criteria.[228, 229] We excluded one trial of etidronate for wrong population that had been included in the 2010 review.[230] Both included trials were conducted in postmenopausal women with no prior fractures[228] or with unknown prior fracture history.[229] One study enrolled women who were 6 to 60 months postmenopausal[229] and

one enrolled women 1 to 10 years postmenopausal.[228] The mean baseline T-scores for the studies ranged between -1.3 and -1.1. The mean age of participants was <55 years in both trials. Both trials evaluated cyclical etidronate 400 mg for 2 years with change in BMD as the primary outcome. Both included studies were set in Europe.[228, 229]

Ibandronate

We identified no studies or trials that assessed the benefits of ibandronate for preventing fractures.

Bisphosphonates: Findings

Vertebral Fracture

This analysis includes 11 trials (10 from the previous report and one from the new evidence).[199, 200, 203, 204, 217, 218, 224-226, 228, 229] All studies reported on the reduction in radiographic vertebral fractures, except for one study reporting clinical vertebral fractures [225] and one study that did not specific fracture type.[204] Among women, bisphosphonates reduced vertebral fractures compared with placebo (2.1% vs. 3.8%; RR, 0.57 [95% CI, 0.41 to 0.78]; I^2, 0%; 5 trials, N=5,433) (**Appendix H Figure 22**).[199, 200, 224, 226, 229] Five trials recorded zero vertebral fractures and did not contribute to the pooled estimate in the primary analysis.[203, 204, 217, 225, 228]

Results based on alternative methods for pooling were nearly identical with and without zero event trials.

As noted in the 2010 review, the largest trial, FIT, a 4-year trial of alendronate, contributed 82 percent of the total number of patients (N=4,432 of 5,433) and vertebral fractures (171) in the analysis (1.9% vs. 3.5%; RR, 0.55 [95% CI, 0.38 to 0.80]).[200] Drugs other than alendronate had small samples and few fractures.

One new trial reported on the effectiveness of zoledronic acid in 1,199 men with mean femoral neck T-scores of -2.23 (intervention) and -2.24 (control). Men were eligible to participate if they had a bone mineral density T score of –1.5 or less (based on the device-specific reference values for men). The authors found a reduced risk of morphometric vertebral fractures in the treatment arm (1.5% vs. 4.6%; RR, 0.33 [95% CI, 0.16 to 0.70]).[218]

Nonvertebral Fracture

Ten trials reported on nonvertebral fractures.[200, 201, 204, 217, 218, 223-226, 229] Of these, one reported no fracture outcomes with either alendronate or placebo.[204] Studies were generally not powered to examine this outcome and did not always clarify the definition or source of the fracture. Also, they often reported these fracture results along with other adverse events.

Among women, a pooled analysis of trials reporting total nonvertebral fractures a reduced risk of fractures in the treatment arm (8.9% vs. 10.6%; RR, 0.84 [95% CI, 0.76 to 0.92]; I^2, 0; eight trials, N=16,438) (**Appendix H Figure 23**).[200, 201, 217, 224-226, 229] One trial recorded zero

nonvertebral fractures and did not contribute to the primary analysis.[204]

One new trial reported on the effectiveness of zoledronic acid in 1,199 men, with mean femoral neck T-score values of -2.23 (intervention) and -2.24 (control). The authors found a reduced risk of nonvertebral fractures in the treatment arm but the effect was not statistically significant (0.9% vs. 1.3%; RR, 0.65 [95% CI, 0.21 to 1.97]).[218]

Hip Fractures

Four studies reported on hip fractures.[200, 201, 223, 224] All had been identified in the 2010 review. We excluded one study because we were unable to find the reported data.[225] One trial recorded no hip fractures and did not contribute to the primary analysis.[224]

Among women, the pooled analysis suggested a lower risk but wide confidence intervals (0.7% vs. 0.96%; RR, 0.70 [95% CI, 0.44 to 1.11]; I^2, 0%; 3 trials, N=8,988) (**Appendix H Figure 24**). The two large trials dominating this meta-analysis, FIT[200] and the study by McClung et al[223] also found no statistically significant effects. Only one trial was powered for detecting differences in hip fractures;[223] other studies may have been underpowered for this outcome. Results based on alternative methods for pooling were nearly identical with and without zero event trials; the confidence interval for the Peto odds ratio approaches but does not cross the line of no difference.

Results based on alternative methods for pooling were nearly identical with and without zero event trials.

No studies reported on hip fractures in men.

Raloxifene: Overview of the Evidence

One large good-quality RCT, included in the 2010 review,[3] the Multiple Outcomes of Raloxifene (MORE) trial, reported in two articles, measured fracture outcomes among postmenopausal women at increased risk for fracture who were receiving raloxifene, a selective estrogen receptor modulator.[231, 232] A second large good-quality RCT, the Raloxifene Use for the Heart (RUTH) study, also reported in the 2010 review,[3] does not meet our inclusion criterion of participants being at increased risk for fracture.[3, 233, 234] We identified no new studies measuring fracture outcomes.

Raloxifene: Findings

The MORE trial (N=7,705) measured outcomes in women with BMD T-scores ≤-2.5, with or without previous vertebral fractures (37% with previous fractures).[231, 232] Although the approved Food and Drug Administration (FDA) raloxifene dosage is 60 mg/day, some study results report a combined treatment group (60 mg/day or 120 mg/day). After 4 years, raloxifene (60 mg/day) reduced radiographic vertebral fracture (7.5% vs. 12.5%; RR, 0.64 [95% CI, 0.53 to 0.76]) compared with placebo. Treatment with raloxifene (combined dosage amount group) did not yield differences in nonvertebral or hip fracture.

The RUTH trial (N=10,101) was designed primarily to evaluate coronary heart disease (CHD) and breast cancer outcomes among postmenopausal women with CHD or multiple risk factors for CHD and is therefore excluded from this review.[233, 234] Baseline BMD T-scores were not an inclusion criteria and are not reported. We note, however, that as was found in the MORE trial, raloxifene (60 mg/day) reduced clinical vertebral fractures (HR, 0.65 [95% CI, 0.47 to 0.89]) compared with placebo, but did not reduce nonvertebral or hip fractures.

Estrogen

The 2010 review discussed the results of the Women's Health Initiative (WHI). Because the women enrolled in this trial had not been identified to be at high risk for osteoporosis (other than that all were postmenopausal), the trial did not meet inclusion criteria for this update. A recently completed review on the benefits and harms of estrogen therapy, with and without progestin, in primary care populations provides important contextual information.[235] It incorporated information from WHI and other similar trials. Women using only estrogen had lower risks for total osteoporotic fractures (HR, 0.72; 95% CI, 0.64 to 0.80) when compared with women taking placebo. Women on estrogen plus progestin therapy also had lower risks for fractures (RR, 0.80; 95% CI, 0.68 to 0.94) with women on placebo. Additionally, we found one high risk-of-bias safety trial that included an estrogen only arm in comparison with a placebo arm (N=193). It reported a lower incidence but not statistically significant difference in clinical fractures over 2 years (7% vs. 8%; RR, 0.87 [95% CI, 0.29 to 2.66]).[216]

Denosumab: Overview of the Evidence

Three fair-quality phase 2 or phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trials of denosumab (N=8,565) met eligibility criteria.[236-238] All were conducted in postmenopausal women with low bone mass or osteoporosis. One of these trials excluded women with any fractures since age 25.[237] A second reported a 24 percent rate of prevalent fractures[238] and the third excluded women with more than one vertebral fracture or any osteoporotic fracture in the past 2 years but did not report the rate of prevalent fractures.[236] All evaluated subcutaneous denosumab against placebo for a minimum of 24 months; doses in the later studies were established as 60 mg every 6 months.[184, 237, 238] One study was set in the United States,[236] the second in the United States and Canada,[237] and the third was a multicenter study that included sites in Europe, North America, Latin America, Australia, and New Zealand.[238] A fourth dose-response study (N=226), also of postmenopausal osteoporotic women, was set in Japan.

Denosumab: Findings

Three studies were not powered to look at fractures as benefits and found no statistically significant differences in fractures (clinical, osteoporotic, or vertebral fracture).[236, 237, 239] The fourth study was powered to evaluate vertebral, nonvertebral, and hip fractures (N=7,868).[238] This large study demonstrated a statistically significant difference in incident vertebral fractures (2.3% vs. 7.2%; RR, 0.32 [95% CI, 0.26 to 0.41]), nonvertebral fractures (6.1% vs. 7.5%; RR, 0.80 [95% CI, 0.67 to 0.95]), hip fractures (0.7% vs. 1.1%; RR, 0.60 [95% CI, 0.37 to 0.97]). The study also reported a reduction in new clinical vertebral fractures and multiple new vertebral

fractures.

Parathyroid Hormone: Overview of the Evidence

Two fair-quality studies[36, 240] which were also included in the prior systematic review by Nelson et al examined vertebral and nonvertebral fracture outcomes in patients receiving parathyroid hormone (an anabolic agent) versus placebo. One of these trials, the Treatment of Osteoporosis with Parathyroid Hormone (TOP) Study[36] was conducted in postmenopausal women receiving daily PTH injections for 18 months versus placebo. Nineteen percent had a prior vertebral fracture. A second study[240] was conducted among 437 men with a mean age of 59 years who were randomized to either placebo or one of two treatments arms of teriparatide (20 µg [the FDA-approved dose] or 40 µg daily) for an average of 11 months (treatment ranged from less than two months to 15 months). Prevalent fracture rates were not reported, nor was the reference range for the T-score (mean femoral neck T-score:-2.7). One new RCT[241] among 40 postmenopausal women treated with teriparatide or placebo has been published since the systematic review by the 2010 review,[3] but did not meet our inclusion criteria because of a high risk of bias.

Parathyroid Hormone Findings

Vertebral Fractures in Women

The TOP Study[36] (N=2,532) evaluated effects of parathyroid hormone compared with placebo on risk of fractures in postmenopausal women with BMD T-score ≤-3.0 and no prevalent vertebral fractures or a T-score <-2.5 and one to four prevalent fractures (19% had prior vertebral fracture). Among women without a baseline fracture, parathyroid hormone produced a significant (0.7% vs. 2.1%; RR, 0.32 [95% CI, 0.14 to 0.75]) reduction in new radiographic vertebral fractures with parathyroid hormone.

Nonvertebral Fractures in Women

In an analysis of all participants with and without baseline fractures (N=2,532), there was no difference in risk of new nonvertebral fracture between the treatment and placebo arms (5.6% vs. 5.8%; RR, 0.97 [95% CI, 0.71 to 1.33]).

Vertebral Fractures in Men

No studies met our inclusion criteria to assess the effects of parathyroid hormone on vertebral fractures in men.

Nonvertebral Fractures in Men

In a fair-quality randomized, placebo-controlled trial (N=437), Orwoll and colleagues[240] evaluated the effects of teriparatide at a dose of 20 µg (the FDA-approved dose, N=151 men) or 40 µg (N=139 men) and placebo (N=147) on risk of fractures in men with osteoporosis (mean baseline BMD femoral neck T-scores, -2.7). Reported findings show a reduction in nonvertebral

fractures in both treatment groups compared with placebo, but the number of fractures was small and results did not reach statistical significance. Additionally, outcome assessments were limited by early termination of the study (mean duration of treatment was 11 months) because of a finding of osteosarcomas in routine animal toxicology studies.

Key Question 4b. How Does the Effectiveness of Pharmacotherapy for the Reduction of Fractures and Related Morbidity and Mortality Vary by Subgroup?

Bisphosphonates

We found no relevant results in included studies for subgroup analysis for zoledronic acid, etidronate, and ibandronate.

Alendronate

One study reported on a subset of osteopenic women (femoral neck T-score between -1.6 and -2.5) from both arms of the FIT.[205] This subset of women had a relative risk of vertebral fracture of 0.59 (95% CI, 0.41 to 0.83, calculated; 2.7% vs. 4.6% rate of vertebral fractures for treatment vs. placebo); this figure is similar to findings from the parent FIT studies included in this update.[200]

Risedronate

One trial[223] conducted among women age 70 or older, after a mean of 2.3 years follow up, reported an incidence of hip fracture of 3.9 percent in the placebo group and 2.8 percent in the treatment group (RR, 0.7; 95% CI, 0.6 to 0.9). In a post-hoc subgroup analysis of women ages 70 to 79 years without vertebral fracture at baseline, the incidence of hip fracture was 1.6 percent and 1.0 percent in the placebo and treatment groups, respectively (RR, 0.6; 95% CI, 0.3 to 1.2). Low numbers of fracture events could potentially explain the poor precision of estimates in women age 70 to 79 years.

Raloxifene

Subgroups of women, with and without a baseline vertebral fracture, did not different significantly in vertebral fracture outcomes, as reported in one article from the MORE study.[242]

Estrogen

Although we found no eligible evidence on estrogen, a recently updated review on hormone replacement therapy in primary care populations, unselected for osteoporosis or fracture risk, offers contextual information.[235] The systematic review reported that some subgroup analyses indicated that time since menopause and age might modify the cardiovascular effects of hormone therapy. Younger women taking only estrogen had lower risks for myocardial infarction than older women relative to women using placebo. Younger women on estrogen only also had a reduced risk for all-cause mortality, whereas older women had an increased risk. Women who

initiated estrogen plus progestin therapy closer to menopause did not have the elevated risk for myocardial infarction that women experienced who had started this therapy more than 20 years after menopause.

Denosumab

One trial of 7,808 osteoporotic women between the ages of 60 and 90 years reported variations in benefits by age, baseline BMD, and the combination of age and baseline BMD.[243-245] The overall findings for the trial demonstrated effectiveness in reducing vertebral, nonvertebral, and hip fractures.[238] Subgroup analysis for age demonstrated no statistically significant differences by age, when comparing women less than age 75 with women age 75 years or older (2.0% vs. 6.5%; RR, 0.30 [95% CI, 0.22 to 0.41] vs. 0.36 [3.1% vs. 8.6%; 95% CI, 0.25 to 0.53]; p for test of interaction = 0.48).[243] Similarly, the trial demonstrated no statistically significant differences by baseline femoral neck T-score, when comparing those with T-scores at or lower than -2.5 with those with T-scores higher than -2.5 (3.1% vs. 9.9%; RR, 0.31 [95% CI, 0.22 to 0.44] vs. 1.9% vs. 5.6%; 0.34 [95% CI, 0.24 to 0.47]; p for test of interaction = 0.64).[243] The trial reported no statistically significant differences when comparing combined risk.[244]

Parathyroid Hormone

The two eligible trials did not compare subgroups. However, one trial reported results in women without a baseline fracture and in women with a prior fracture.[36] Women on parathyroid hormone who had a prior fracture had a lower risk of new fractures (4.2% vs. 8.9%; RR, 0.47; [95% CI, 0.22 to 0.98]) than women on placebo, as did women without a prior fracture (0.7% vs. 2.1%; RR, 0.32 [95% CI, 0.14 to 0.75]).

Key Question 5. What Are the Harms Associated With Pharmacotherapy?

We present summary results in text below. **Appendix F** includes detailed evidence for alendronate (**Appendix F Table 16**), zoledronic acid (**Appendix F Table 17**), risedronate (**Appendix F Table 18**), etidronate (**Appendix F Table 19**), ibandronate (**Appendix F Table 20**), raloxifene (**Appendix F Table 21**), denosumab (**Appendix F Table 22**), and parathyroid hormone (**Appendix F Table 23**). **Appendix H** includes forest plots for meta-analyses.

Bisphosphonates: Overview of the Evidence

The 2010 review relied largely on systematic reviews to present evidence on harms.[3] To ensure that we captured all relevant evidence, we relied on our searches, handsearches from included systematic reviews, particularly from a recent systematic review on the efficacy and effectiveness of drugs for osteoporosis.[221]

Alendronate

Sixteen fair- and good-quality studies reported on harms: 14 studies in postmenopausal women[199-204, 246-253] and 2 studies in combined populations of women and men.[254, 255] We

excluded several studies that were included in previous reviews for wrong study population,[215, 256-261] wrong intervention,[262] wrong comparator,[263-265] wrong outcome,[266] wrong setting,[267, 268] and wrong study design,[269] an older review that has been subsequently updated,[270] and high risk of bias.[216, 265, 271-273] Nine studies reported on discontinuations because of adverse effects.[199-202, 204, 246, 252-254] Five studies reported serious adverse effects.[202, 250, 252-254] Death was reported as a harm in two studies.[200, 250] Several gastrointestinal (GI) events were reported, including abdominal pain, reflux, ulcers, and esophagitis. The most commonly reported across studies was any upper GI adverse events.[200, 202, 204, 250-255] Three studies reported cardiovascular outcomes, including chest pain,[246] myocardial infarction,[249] and atrial fibrillation.[248]

Zoledronic Acid

Four fair- or good-quality studies reported on harms: three studies in postmenopausal women[217, 274, 275] and one in men.[218] We excluded several studies that were included in previous reviews for wrong study population,[219, 220, 222, 276-280] wrong study design,[281] wrong comparator,[282] and an older review that has been subsequently updated.[270]

Only one study reported on discontinuation of zoledronic acid due to adverse events,[217] while three studies reported serious adverse events.[217, 218, 275] Three studies reported on osteonecrosis of the jaw[218, 274, 275] and two on atrial fibrillation.[274, 275] Three studies examined myalgia and arthralgia.[218, 274, 275]

Risedronate

Six trials met eligibility criteria for harms. These include four trials previously described.[223-226] Two additional trials were also conducted among postmenopausal women, and we rated them as fair quality.[202, 283] One trial, conducted at multiple sites in Europe and Brazil, assessed 5 mg of risedronate for 3 months compared with placebo.[202] Nearly half of the study population had prior fractures. The other trial assessed 5 mg of risedronate for 36 weeks, and was conducted in Japan.[283] Women with prevalent fracture were not excluded from this study and the mean number of prevalent fractures at baseline was 0.3 (standard deviation [SD], 0.8) in the placebo group and 0.2 (SD, 0.5) in the risedronate group.

Etidronate

Two fair-quality studies reported on harms (N=206).[228, 229] Both reported on the rates of discontinuation and GI adverse events.[228, 229] One trial reported on serious adverse events and infection as an adverse event.[228]

Ibandronate

Seven fair-quality studies of ibandronate reported on harms (N=2,115).[284-290] All were conducted in postmenopausal women with no prior fractures[285, 286, 289, 290] or with unknown prior fracture history.[285, 287, 288] These studies differed in the menopausal categories of women enrolled: at least 1 year postmenopausal (two studies),[284, 285] at least 3 years postmenopausal (one study),[287] at least 5 years postmenopausal (two studies),[288, 290] at least 10 years postmenopausal (one

study),[286] and 1 to 10 years postmenopausal (one study).[289] The mean baseline T-scores for the seven studies ranged from -3.2 to 1.03. The mean age of participants ranged between ages 54 and 67 years. Included trials evaluated varying dosages and time periods. One trial evaluated 50 to 150 mg monthly for 3 months,[287] one evaluated 0.25 mg to 2.0 mg every 3 months over a 1-year period,[290] and one evaluated daily dosages of 0.25 to 50 mg over a 1-year period. Four publications reported on studies that evaluated ibandronate over a 2-year period, including two trials that evaluated daily dosages of 0.5 to 2.5 mg,[285, 288] one that evaluated intermittent dosages of 20 mg,[288] one that evaluated weekly dosages of 5 to 20 mg,[289] and one that evaluated monthly dosages of 150 mg.[284] Six of the included trials were set in Europe[284, 286-290] and one in the United States and Canada.[285] Four trials[284-287] reported on the discontinuation of participants by treatment group and two studies reported only the number of discontinuations overall.[289, 290] Four trials[284-287] reported on serious adverse events by treatment group and two studies reported only serious adverse events overall.[289, 290] Six studies evaluated the risk of GI adverse events.[285-290] Only one trial reported on infection;[286] two reported on deaths.[287, 288]

Bisphosphonates: Findings

Discontinuations Due to Adverse Events

The 2010 review reported no differences in risk of discontinuation between study arms for any bisphosphonate drug. Our updated analysis of 20 trials and 17,369 participants found that the pooled risk was not significantly different for any individual drug or overall (RR, 0.99; 95% CI, 0.91 to 1.07; I^2, 0%) (**Appendix H Figure 25**). Alternate methods of pooling that account for the contribution of a single trial[202] to two arms yielded very similar results (11.5% vs. 11.8%; RR, 0.98; 95% CI, 0.89 to 1.08; I^2, 0%).

Serious Adverse Events

The 2010 review did not summarize the evidence on overall serious adverse events. Our pooled estimate of effect of 17 trials and 11,745 participants showed no statistically significant differences for any individual drug or overall (RR, 0.98; 95% CI, 0.92 to 1.04; I^2, 0%) (**Appendix H Figure 26**). Alternate methods of pooling that account for the contribution of a single trial[202] to two arms yielded identical results (21.0% vs. 23.4%; RR, 0.97; 95% CI, 0.89 to 1.07; I^2, 0%).

Gastrointestinal Adverse Events

The 2010 review reported a higher risk of mild upper GI events for etidronate and pamidronate than placebo but not for other drugs. The review noted a higher risk of esophageal ulceration for etidronate when including individuals without osteoporosis in the control group, but not otherwise; it also reported no differences in esophageal ulcerations for any other drug. Finally, it noted that the FDA has called for further research on the risk of esophageal adenocarcinoma.

Our updated analysis found that studies vary widely in the definition and reporting of GI adverse events. Some studies specify upper GI events overall, with no additional detail, whereas other studies provide details on individual complaints such as dyspepsia and abdominal pain. We

pooled 13 trials with 20,485 participants that reported upper GI events and found no differences for any individual drug or overall (RR, 1.01; 95% CI, 0.98 to 1.05; I^2, 0%) (**Appendix H Figure 27**). Alternate methods of pooling that account for the contribution of a single trial[202] to two arms yielded very similar results (35.3% vs. 35.6%; RR, 1.01; 95% CI, 0.98 to 1.05; I^2, 0%), as did an analysis that included a wider variety of outcomes in addition to upper GI events (all GI adverse events, abdominal pain, severe GI events, and esophagitis (RR, 1.02; 95% CI, 0.98 to 1.05; I^2, 0%). We found no differences by study arms in individual study reports of ulcers[200, 202, 251, 254, 255] and no reports of esophageal adenocarcinoma.

Cardiovascular Events

The 2010 review noted no clear evidence of an association between bisphosphonate use and atrial fibrillation. Our review found one study of alendronate reporting a higher incidence of atrial fibrillation in women in the intervention arm, but the association was not statistically significant (2.5% vs. 2.2%; RR, 1.14 [95% CI, 0.83 to 1.56]),[248] and one study of zoledronic acid in men with a similarly nonsignificant association but higher incidence of atrial fibrillation (1.2% vs. 0.8%; RR, 1.45; 95% CI, 0.46 to 4.56).[218] Two studies of women reported no cases of atrial fibrillation.[274, 275] A case control study using a Danish registry studied the association of bisphosphonates and atrial fibrillation and reported a relative risk of 0.75 (95% CI, 0.49 to 1.16; 3.2% vs. 2.9%) for new users.[247] Two ineligible systematic reviews[291, 292] sought additional data from two sets of investigators not included in their published results.[236, 293] Estimates of effect for both studies spanned the null (RR, 1.11, 95% CI, 0.69 to 1.90 for data from Karam et al and RR, 0.99, 95% CI, 0.45 to 2.16 for unpublished data from Leiwecki et al).

Osteonecrosis of the Jaw

The 2010 review noted that the FDA published a case series listing osteonecrosis of the jaw, but that most cases occurred in cancer patients. The 2010 review noted that the FIT found one case each in the active and placebo arms. In our update, three studies (one in men and two in women) reported that they found no cases of osteonecrosis of the jaw.[218, 274, 275] We also identified several additional studies of osteonecrosis of the jaw that did not meet our inclusion criteria; the study populations had a high proportion of subjects with prevalent vertebral fractures or secondary causes of osteoporosis.[278, 281, 282, 294-298]

A systematic review, which also did not meet our inclusion criteria because it included populations outside the purview of this report, reported a higher incidence of osteonecrosis of the jaw with intravenous bisphosphonates and with greater duration (these findings are not restricted to primary prevention populations only).[299] The review noted, however, that the incidence of osteonecrosis of the jaw ranged between 1.04 and 69 per 100,000 patient-years for oral bisphosphonate and between 0 and 90 per 100,000 patient-years for intravenous bisphosphonates. The authors note that the incidence is marginally higher than the estimated incidence in the general population of <0.001 percent. In comparison, the authors note that the incidence in the oncology patient population ranges from 0 to 12,222 per 100,000 patient-years.

Atypical Fractures of the Femur

The FDA added a warning label to bisphosphonates regarding the potential risk of atypical femur fractures; the communication also noted the rarity of the condition (fewer than 1% of all hip and femur fractures), the lack of evidence establishing causality, and the fact that atypical femur fractures have been reported primarily in patients taking bisphosphonates. No included studies in our review reported atypical femur fracture outcomes. Although we identified several additional studies reporting on atypical femur fractures, they did not meet inclusion criteria (wrong population,[300, 301] wrong comparator,[302, 303] wrong intervention,[304] wrong design).[263]

Two excluded systematic reviews, published in 2013[302] and 2015[303] respectively, included a partially overlapping set of studies. Both reported an increased risk of atypical femur fractures, with odds ranging from 1.70 (95% CI, 1.22 to 2.37)[302] to 1.99 (95% CIs, 1.28 to 3.10).[303] Both reviews reported very high heterogeneity (I^2 exceeding 80 percent), but only one review explored heterogeneity in greater detail.[302] Specifically, Gedmintas et al explored subgroup analyses by outcome definition and found a continued high risk with more restrictive and validated measurement of outcomes, but with varying precision and heterogeneity. These results suggest an increased risk for atypical femur fractures, but the extent and applicability of this risk to a primary prevention population is unclear.

Kidney Failure

The FDA added a warning label to Reclast (zoledronic acid) in 2011 to note contraindication in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.[305] No included studies in our review reported kidney failure outcomes.

Raloxifene: Overview of the Evidence

As was true for benefits of raloxifene, harms reported in the 2010 review were based on results from two studies, the MORE and RUTH trials.[3] We include findings from six studies, with only the MORE study reported in multiple articles.[231, 232, 242, 246, 306-313] As noted previously, we do not include the RUTH trial as evidence because it did not meet our inclusion criterion that participants be at increased risk for fracture.

Raloxifene: Findings

Pooled estimates of women followed from 1 to 4 years found no increased risk of discontinuation of treatment because of adverse events (12.6% vs. 11.2%; RR, 1.12; 95% CI, 0.98 to 1.28; I^2, 0%, 6 trials, N=6,438) (**Appendix H Figure 28**). The pooled analysis suggests a higher rate of deep vein thromboses in the intervention arm (0.7% vs. 0.3%; RR, 2.14; 95% CI, 0.99 to 4.66; I^2, 0%, 3 trials, N=5,839) (**Appendix H Figure 29**). However, among these studies, the large MORE trial found an increased risk after 4 years (0.8% vs. 0.3%; RR, 2.52; 95% CI, 1.11 to 5.71), whereas the other two included studies were much smaller and followed women for only 2 years.[307, 308] In contrast, the 2010 review found a statistically significant increase in thromboembolic events (RR, 1.60; 95% CI, 1.15 to 2.23). Similar to the 2010 review, we found no association between raloxifene and CHD, stroke, or endometrial cancer, an increased risk for

hot flashes, (11.2% vs. 7.6%; RR, 1.42; 95% CI, 1.22 to 1.66; I^2, 0%, 5 trials; N=6,249; **Appendix H Figure 30**) and no statistically significant increased risk of leg cramps (8.0% vs. 4.8%; RR, 1.41; 95% CI, 1.41; 0.92 to 2.14; I^2, 67%, 3 trials; N=6,000) (**Appendix H Figure 31**).

Estrogen

The 2010 review discussed the results of the WHI. As noted, the WHI did not meet inclusion criteria for our update. A recently completed review on the benefits and harms of estrogen therapy, with and without progestin, in primary care populations provides important contextual information.[235] Compared with women on placebo, women on estrogen, over a 5-year followup, experienced a higher rate of gallbladder events, stroke, and venous thromboembolism. The risk for urinary incontinence was increased during a followup of 1 year. Compared with women on placebo, women on estrogen plus progestin were found to have a higher risk of invasive breast cancer, CHD, probable dementia, gallbladder events, stroke, and venous thromboembolism. The risk for urinary incontinence was increased during a followup of 1 year. Additionally, one high risk-of-bias safety trial compared an estrogen only arm with a placebo arm (N=193) and found no statistically significant differences in discontinuations attributable to adverse events (10% vs. 10%; RR, 0.98 [95% CI, 0.37 to 2.58]), serious adverse events (12% vs. 10%; RR, 1.19 [95% CI, 0.46 to 305]), or upper gastrointestinal events over 2 years (30% vs. 22%; RR, 1.37 [95% CI, 0.77 to 2.44]).[216]

Denosumab: Overview of the Evidence

Four studies reported on harms.[209, 236-239, 314] All were conducted in postmenopausal women with low bone mass or osteoporosis and were phase 2 or phase 3 studies for the FREEDOM trial.

Denosumab: Findings

Pooled estimates of effect from three trials with 8,451 participants suggest no differences in the rates of discontinuation due to adverse events (2.4% vs. 2.1%; RR, 1.14 [95% CI, 0.85 to 1.52]; I^2, 0%) (**Appendix H Figure 32**) or serious adverse events (23.8% vs. 23.9%; RR, 1.12; 95% CI, 0.88 to 1.44; I^2, 14.1%) (**Appendix H Figure 33**). Although treatment arms had higher rates of serious infections than control arms, confidence intervals for the pooled estimate were wide (4.0% vs. 3.3%; RR, 1.89; [95% CI, 0.61 to 5.91]; I^2, 40.09%) (**Appendix H Figure 34**). A Peto odds ratio estimate, to account for zero events in one trial, also resulted in an estimate of effect with wide confidence intervals (Peto odds: 2.12; 95% CI, 0.72 to 6.14). A detailed analysis of serious infections identified these differences as arising from a higher rate of cellulitis and erysipelas in the denosumab arm (RR, 14.96 [95% CI, 1.98 to 113.21]).[314] Two trials evaluated the risk of rash or eczema. Both reported a higher incidence in the treatment arm (RR for eczema, 1.81 [95% CI, 1.34 to 2.44; 3.0% vs. 1.7%][238] and rash, 2.82 [95% CI, 1.04 to 7.64; 8.5% vs. 3.0%][237]). The studies reported wide confidence intervals spanning the null for GI events[236, 237] and cardiac or cardiovascular events.[236, 238] Although the large FREEDOM trial reported fewer deaths in the treatment arm, the difference in rates did not reach statistical significance (1.8% vs. 2.3%; RR, 0.78 [95% CI, 0.57 to 1.06]).[238] One study reported no occurrences of osteonecrosis of the jaw events.[239]

Parathyroid Hormone: Overview of the Evidence

Two fair-quality studies[36, 240] reported adverse events in women and men receiving parathyroid hormone compared to placebo. The TOP Study[36] was conducted in postmenopausal women receiving daily PTH injections for 18 months versus placebo. Another RCT[240] was conducted among 437 men who were randomized to either placebo or one of two dosages of teriparatide (20 or 40 µg daily) for an average of 11 months (treatment ranged from <2 months to 15 months).

Parathyroid Hormone: Findings

Harms in Women

The TOP Study[36] reported adverse events and discontinuation of study participants in the treatment and placebo groups. Among 2,532 postmenopausal women, the treatment group had higher rates of discontinuation due to adverse events when compared with the placebo group (30.2% vs. 24.6%; RR, 1.22 [95% CI, 1.08 to 1.40]). Other reported adverse events, which were related largely to nausea and headache, were higher in the treatment group (22.6% vs. 9.1%; RR, 2.47 [95% CI, 2.02 to 3.03]).

Harms in Men

In an RCT among 437 men,[240] both the 20-microgram and 40-microgram treatment groups had a higher proportion of withdrawals than the placebo group (9.2% vs. 12.9% vs. 4.8%). The risk of withdrawals was statistically significant higher in the 40-microgram treatment group than the placebo group (RR, 2.72 [95% CI, 1.17 to 6.3]), although the number of withdrawals was small among all three groups. Cancers were reported in two groups (3/147 in the placebo group and 3/151 in the 20- µg treatment group), but none was reported as osteosarcomas. Evidence on harms associated with PTH is limited due to sparse data from two RCTs and incomplete descriptions of the criteria for an adverse event and therefore, inconsistent reporting of adverse events.

Chapter 4. Discussion

This chapter begins with a summary of review findings for each key question (KQ); **Table 9** provides additional details. Our synthesis also addressed two contextual questions on the (1) different fracture risk thresholds for identifying patients for further evaluation or treatment and (2) the effectiveness of screening strategies using different ages to start and stop screening and screening intervals (see Methods for detailed contextual questions). The introduction chapter includes information on contextual question 1; we address contextual question 2 after the summary of findings for the various KQs in this chapter. Following those sections, we present limitations of the evidence and our update review, and then end with conclusions.

Summary of Review Findings

Effectiveness of Screening Approaches (Key Question 1)

One trial (SCOOP) addressed the gap identified in the 2010 review on the effectiveness of screening on morbidity and mortality associated with osteoporotic fracture risk. The trial found evidence of benefit for a secondary outcome only—the incidence of hip fractures. For all other outcomes (osteoporosis-related fractures, clinical fractures, and mortality), the trial did not report benefits. The discrepancy in results between the hip fracture outcomes and other outcomes, coupled with the lack of the significance of the primary outcome, points to the need for caution in interpreting the results. A few potential explanations include changes in usual care standards and the threshold used to identify those at risk. Identification and treatment in the usual care may have changed over time with the release of guidelines during the trial recruitment[315] and observation[316] periods, and as a result, differences between the intervention and usual care arms may have been diminished. SCOOP investigators also note that the use of the 10-year risk of hip fracture (rather than the risk of any major osteoporotic fracture) as the threshold for further intervention may have increased the likelihood of effectiveness of the screening in preventing hip rather than other fractures, given that risks of hip and other fractures are correlated but not identical[72]. The authors also note a potential bias toward selection of healthy participants. However, participants also had a higher risk of parental history of fractures than nonparticipants, and the effect of these differences in baseline characteristics on outcomes is unclear.

Women in the intervention arm received universal screening, whereas women in the usual care arm received risk-based identification and treatment. However, the factors described above (under-treatment, under-reporting, the absence of primary care guidelines at the start of the trial, and the release of guidelines during the trial) imply that usual care could have varied across facilities and may have changed somewhat over the period of the trial. These variations could explain the results of the SCOOP trial.

Results from studies that did not meet our quality or design criteria are consistent with the SCOOP trial in demonstrating reductions in hip fractures and no effects on major osteoporotic fractures, but confidence in these results is limited. Results from one high risk-of-bias RCT of 4,800 women ages 45 to 54 years in Aberdeen, Scotland, indicated no difference in the rate of

incident major osteoporotic fractures (MOF) (3.96% [47/1841] vs. 4.03% [50/1241]; RR, 1.00, 95% CI, 0.983 to 1.02)[317] but the study's attrition exceeded 40 percent.[317] A cohort study with a nonconcurrent control (which did not meet our design criteria), evaluated the effectiveness of screening for osteoporosis on reducing hip fractures in 3,107 women and men age 65 years or older.[78] This study was part of a nested study on bone density within the Cardiovascular Health Study. Participants in two of four counties were offered DXA screening while the remaining received usual care. The study reported an adjusted hazard of hip fracture of 0.64 (2.32% [33/1,422] vs. 4.09% [69/1,685]; 95% CI, 0.41 to 0.99) for the screened group compared with the usual care group.

Accuracy and Reliability of Screening Approaches (Key Question 2a)

Our findings are consistent with the 2010 review on this topic:[3] Nelson et al concluded that the accuracy of screening approaches is moderate. We did not observe differences by sex; predictions of hip fractures were more accurate than prediction of fractures at other sites or composite fracture outcomes (i.e., major osteoporotic fractures).

Using centrally measured dual-energy X-ray absorptiometry (DXA) as the reference standard for identifying osteoporosis, the pooled estimate of accuracy as measured by the area under the curve (AUC) for clinical risk assessment instruments for women ranges from 0.65 to 0.76 and for men from 0.76 to 0.80. Studies of machine-based tests for screening to identify osteoporosis generally compared calcaneal quantitative ultrasound to central dual energy X-ray absorptiometry (DXA); pooled areas under the curve (AUCs) ranged from 0.77 for women to 0.80 for men.

Studies of machine-based tests to predict fractures used a variety of machine-based tests (areal bone mineral density [BMD] with central DXA, trabecular bone score, and quantitative ultrasound [QUS]) and did not show differences by sex, type of test, or age. For these tests, predictions of hip fractures had higher range of accuracy (AUC of 0.80 to 0.85) in eight of twelve studies than predictions of fractures at other sites (AUC, 0.54 to 0.77).

The evidence base for fracture risk prediction instruments is dominated by studies of Fracture Risk Assessment Tool (FRAX) but also includes studies of other prediction instruments. Instruments differ by the number of risks included but they commonly include age, sex (if developed for use with both sexes), weight or body mass index (BMI), and a variety of medical conditions or historical events (e.g., prior fracture or fall). Some of the evaluated instruments can incorporate BMD results into the risk prediction, most commonly BMD of the femoral neck. Pooled analysis of FRAX AUCs in men ranged from a low of 0.62 for predicting major osteoporotic fractures without the inclusion of BMD to a high of 0.76 for predicting hip fractures with BMD included. Pooled AUCs in women for FRAX similarly range from a low of 0.67 for predicting major osteoporotic fractures without the inclusion of BMD to a high of 0.79 for predicting hip fractures with BMD. Garvan, QFracture, and Fracture Risk Calculator were the only other instruments validated for use in men. We identified no published studies that met our eligibility criteria that assessed calibration of the U.S. version of FRAX or calibration of other risk assessment instruments in U.S. populations. Overall, the accuracy of clinical risk assessment tools for identifying osteoporosis or predicting fractures generally ranges from very poor (0.50)

to good (0.90). **Table 10** recapitulates results for the instruments for which we found evidence on the accuracy of identifying osteoporosis as well as the accuracy of predicting fractures. FRAX predicts fractures over a 10-year time horizon, though not all studies reported 10 complete years of participant followup for reporting accuracy. The other instrument (SCORE, ORAI, OSIRIS, OST) were not developed as fracture risk prediction instruments; the length of followup reported by studies who evaluated these instruments as risk prediction instruments ranged from 3 to 10 years.

Evidence to Determine Screening Intervals for Osteoporosis and Low Bone Density (Key Question 2b)

The 2010 review noted the paucity of evidence on this topic,[3] with a single study indicating no advantage to repeated measures (8 years apart).[194] A second study, identified by our update, does not alter this conclusion: it also suggests similar accuracy in predicting fractures with repeat BMD (3.7 years apart) when compared with baseline BMD.[195] Both studies included participants with a wide spectrum of baseline BMD from normal to osteoporosis. However, three studies that developed prognostic models suggested that the optimal screening interval varies by baseline BMD.[196-198] Age and hormone replacement therapy use also influence optimal screening intervals.[196, 197]

Harms of Screening (Key Question 3)

One trial addresses the gap identified in the previous report on the harms of screening. The study found no evidence of harms on anxiety or quality of life.

Benefits of Pharmacotherapy (Key Question 4a)

Our findings about medications align with those of the 2010 review. For women, the risk of vertebral fractures can be reduced by bisphosphonates, parathyroid hormone, raloxifene, and denosumab. The risk of nonvertebral fractures can be reduced by bisphosphonates and denosumab. The risk of hip fractures can be reduced by denosumab (relative risk [RR]: 0.60). Two of three studies of bisphosphonates that reported hip fractures were not powered to detect effects on hip fractures; the pooled evidence did not demonstrate a statistically significant benefit. Evidence is very limited for men. The risk of morphometric vertebral fractures can be reduced by zoledronic acid (RR, 0.33).[218] One study, which was underpowered, found no statistically significant reductions in risk of clinical vertebral fractures or nonvertebral for men.[218] The study of parathyroid hormone in men also demonstrated a trend toward benefit in nonvertebral fractures, consistent with the finding in women, but was not statistically significant, possibly because it was stopped early.[240] We found no studies reporting on hip fractures, fracture-related morbidity, or mortality.

Variation in Benefits of Pharmacotherapy in Subgroups (Key Question 4b)

One trial each offered further analyses on subgroups for alendronate, risedronate, raloxifene, denosumab, and parathyroid hormone. We found no evidence from included studies on differences in effectiveness by age, baseline BMD, prior fractures, or a combination of risk factors.

Harms of Pharmacotherapy (Key Question 5)

Although several trials reported on harms, they varied substantially in definitions. We found no consistent evidence of harms with bisphosphonates (discontinuation due to adverse events, serious adverse events, gastrointestinal events, and cardiovascular events). We found no bisphosphonate trials with reported cases of osteonecrosis of the jaw, atypical femur fractures, or kidney failure, although evidence from excluded studies of populations, designs, and comparators outside the purview of this review suggests a rare but increased risk with bisphosphonates for some harms. Specifically, raloxifene produced a higher risk of deep vein thrombosis (0.7% vs. 0.3%; pooled RR, 2.14; 95% confidence interval [CI], 0.99 to 4.66; I^2=0%, 3 trials, N=5,839) and hot flashes (11.2% vs. 7.6%; pooled RR, 1.42; 95% CI, 1.22 to 1.66; I^2=0%, 5 trials; N=6,249), but not discontinuations or leg cramps. One trial of parathyroid hormone reported a higher risk of discontinuation due to adverse events (29.7% vs. 24.6%; RR, 1.22; 95% CI, 1.08 to 1.40) for women; the trial in men did not report a higher risk of discontinuation. We found no statistically significantly increased of discontinuations, serious adverse events, or serious infections with denosumab. The evidence on harms in men was very limited—but consistent, when available—with harms for women.

Contextual Considerations

We addressed Contextual Question 1 in the introduction chapter, in the section on the use and accuracy of fracture risk instruments for identifying patients for further evaluation. Below we discuss Contextual Question 2 on the effectiveness of screening strategies using different ages to start and start screening and screening intervals.

Effectiveness of Screening Strategies Using Different Ages to Start and Stop Screening

Initiation of Screening: Women

Although the USPSTF and other guidelines recommend screening in average-risk women age 65 years or older, debate continues as to whether to recommend a standard age for mass screening. Studies suggest that mass screening and treatment of postmenopausal women under 60 years of age is likely to be very inefficient.[3, 318] One study concluded that women with a negative screening between the ages of 50 and 64 years are unlikely to benefit from frequent screenings because the population is less likely to experience a fracture before age 65.[198] No studies have

examined the long-term benefits of early treatment initiation.[318] A modeling study examining the initiation of screening women at ages 55, 60, 65, 70, 75, and 80 years found that all screening strategies (e.g., DXA, prescreen with QUS before DXA; prescreened with Simple Calculated Osteoporosis Risk Estimation [SCORE] before DXA) were more effective than no screening in increasing quality-adjusted life-years (QALY).[319] No screening was more expensive and less effective than multiple screening strategies starting at age 65 or older. However, no single strategy emerged clearly as best at willingness-to-pay thresholds of $50,000 per QALY or $100,000 per QALY, suggesting that differences between strategies are likely to be small.

Initiation of Screening: Men

No standard osteoporosis screening schedules for average-risk men exist,[196] leading to continued uncertainty about starting and stopping ages. A study[320] that examined the effectiveness of the DXA, Osteoporosis Self-Assessment Tool (OST), Vertebral Fracture Risk Assessment, and no screening found that all screening strategies, regardless of test used, screening initiation age (e.g., 50, 60, 70, or 80 years), or repeat screening interval (5 years or 10 years) were more effective than no screening in increasing QALYs. A study of community-dwelling 70-year old white men with no history of fractures found that selective DXA using an OST prescreen was most cost-effective relative to universal DXA screening at the lowest OST cutoff score of -2. Selective DXA using the OST was also more effective and less costly than no DXA screening among men age 84 or older.[321]

Discontinuation of Screening

Currently, no evidence examines the age to stop BMD testing and no guidelines recommend cessation of screening at a specific age for women or men.[318] Cost-effectiveness studies suggest benefits from continuing to screen women in older age groups.[322, 323] Using a Markov model with women ages 70 to 80 years, one study showed greater cost-effectiveness when screening all women compared with screening women with at least one risk factor.[322] Another modeling study found that universal DXA is more cost-effective with increasing age because the prevalence of low BMD (femoral neck T-score of <2.5 or less) increases substantially with age, as does associated fracture risk.[323]

Effectiveness of Screening Strategies Using Different Screening Intervals

The effectiveness of using different screening intervals to identify osteoporosis was discussed under the results for KQ 2b.

Limitations and Future Research

Limitations

One eligible study addresses the direct question of the benefits and harms of screening for

osteoporotic fractures. Given the limited direct evidence, strong links along the indirect evidence pathway are necessary. A major constraint in ensuring these strong links is that the operational definitions of osteoporosis (i.e., BMD T-scores) and the resulting thresholds for screening and treatment that are established based on these definitions capture only one aspect of osteoporotic fracture risk. Although osteoporotic fractures can arise from loss of bone mass, microarchitectural deterioration of bone tissue and decline in bone quality also contribute to fracture risk and are not captured by BMD measurement.[29] As a consequence, screening approaches that rely on BMD measurement wholly or in part may not be the most accurate approaches for predicting risk of osteoporotic fractures.

Another important limitation of this evidence base is that it focuses on one of many approaches to averting osteoporotic fractures. The task of screening for and subsequently treating low bone density is only one aspect of fracture prevention: preventing falls is another critical component[24, 29, 324] and is addressed by another USPSTF recommendation.[325] A comprehensive approach may rely on screening, counseling, medication, physical therapy, and other interventions to prevent falls and improve physical function in older adults.

Clinical risk assessment instruments that can potentially capture a wider array of factors beyond BMD measurement also have serious constraints on utility for treatment decisions. No trials thus far have established efficacy of treatment based on identifying risk using clinical risk assessment tools: individuals enrolled in treatment trials are typically enrolled on the basis of their BMD level, not on fracture risk.

In the absence of strong evidence linking screening approaches to fracture risk, uncertainties persist in understanding who requires screening and how often. In particular, evidence on effectiveness of screening and treatment by age, baseline BMD, and baseline fracture risk continues to be lacking. Long-term studies on harms continue to be lacking. Evidence is limited on the value of repeat BMD screening. These gaps are particularly evident for younger postmenopausal women. Few studies compare strategies[57, 58, 113] in this age group. One study shows that a FRAX threshold of 9.3% for a 10-year major osteoporotic fracture performs no better than chance in identifying osteoporosis[57] and is inferior to OST and SCORE. All three performed poorly in predicting fractures.[58]

Other limitations of the evidence base pertain to the underlying heterogeneity of included studies. Screening studies differ in the strictness of their inclusion criteria, particularly with regard to baseline fractures, baseline BMD, and prior treatment. They also differ in the length of followup and in their applicability to U.S. primary care populations. Studies of 10-year fracture risk did not always observe participants for 10 years. Further, most instruments were not calibrated for U.S. populations. The majority of both treatment and screening studies focused on women, and reported very limited results on the outcomes of screening and treatment in men. Some treatment studies included mixed populations of subjects with and without a history of prior osteoporotic fracture.

Future Research

Identifying the optimal screening strategy to reduce osteoporotic fractures requires accounting for variations in patient baseline characteristics, multiple potential pathways into screening, and the multiple cascade of interventions that follow screening. Randomized controlled trials cannot fully address all these components, but decision analyses may offer some clarity. Decision analyses may also help frame a comprehensive approach to integrating multiple strategies relevant to preventing osteoporotic fractures beyond screening for osteoporotic risk, such as counseling and interventions for falls prevention and improvement in physical function.

Innovations in the measurement of bone quality that are followed by studies of implementation in and translation to primary care settings will help improve accuracy of screening approaches. Measurements of bone density other than central DXA require better evidence of accuracy and applicability in the context of treatments that target patients with centrally measured BMD. Evidence is lacking on the harms of screening, even for routine and widely available screening approaches.

Treatment trials focusing on or including men will help to fill gaps in our understanding of the benefits and harms of treatment in men. Notably, no randomized controlled trial of osteoporosis treatment in men has demonstrated reduction of hip fracture or clinical vertebral fractures. Evidence on an array of harms is not consistently available for long-term outcomes or for all medications.

Reanalyses of existing trials or new studies employing prospective observational data or fracture registries can help fill gaps on how treatment benefits and harms might vary by differences in baseline risk, including age and BMD status.

The evidence on optimal screening intervals is also scant. The present recommendation to repeat DXA screening at 2 years is based on the amount of time to observe a reliable change in BMD, although further research is necessary to determine the optimal interval of repeat screening associated with reduced fracture risk.

Ongoing and Unpublished Studies

An ongoing, pragmatic trial in the United Kingdom (U.K.) is randomizing more than 11,000 women ages 70 to 85 years to screening or usual care. Women in the screening arm will have a 10-year fracture risk calculated using FRAX based on information obtained through questionnaires. The investigators propose to compare the probability of a hip fracture with age-based BMD testing and osteoporosis treatment thresholds established from existing U.K. cost-effectiveness data. No further action will be taken for women below these thresholds in the treatment arm; women with fracture risks above these thresholds will be offered BMD testing, followed by recalculation of their fracture risk and treatment as needed. Women will be followed for 5 years. The study is powered to detect an 18 percent reduction in fractures.[326]

Additionally, a search of trial registries yielded information about several completed and ongoing trials that have yet to publish results, but these trials can be expected to expand the

evidence base on treatments (**Appendix G**). These include parathyroid hormone (3 trials, women, United States, N>90 [N not reported for 1 trial]), risedronate (2 trials, women, South Korea and United States, N=1,150), raloxifene (2 trials, women, multisite and United States respectively, N not reported), zoledronic acid (1 trial, women, United States, N=1000) and denosumab (1 trial, men and women, United States, N=212)

Conclusions

Evidence from one trial of screening to prevent osteoporotic fractures suggests a reduction in hip fractures. The accuracy of screening ranges from very poor to good. Treatments reduce the risk of vertebral and nonvertebral fractures in women, and studies do not consistently demonstrate an increased risk of harms for drugs. Studies of raloxifene suggest a trend toward higher risk of deep vein thrombosis. Rare harms, such as osteonecrosis of the jaw and atypical femur fractures were not reported in this body of evidence but they may occur. The evidence is limited or not available for other regimens and outcomes among the populations included in this review.

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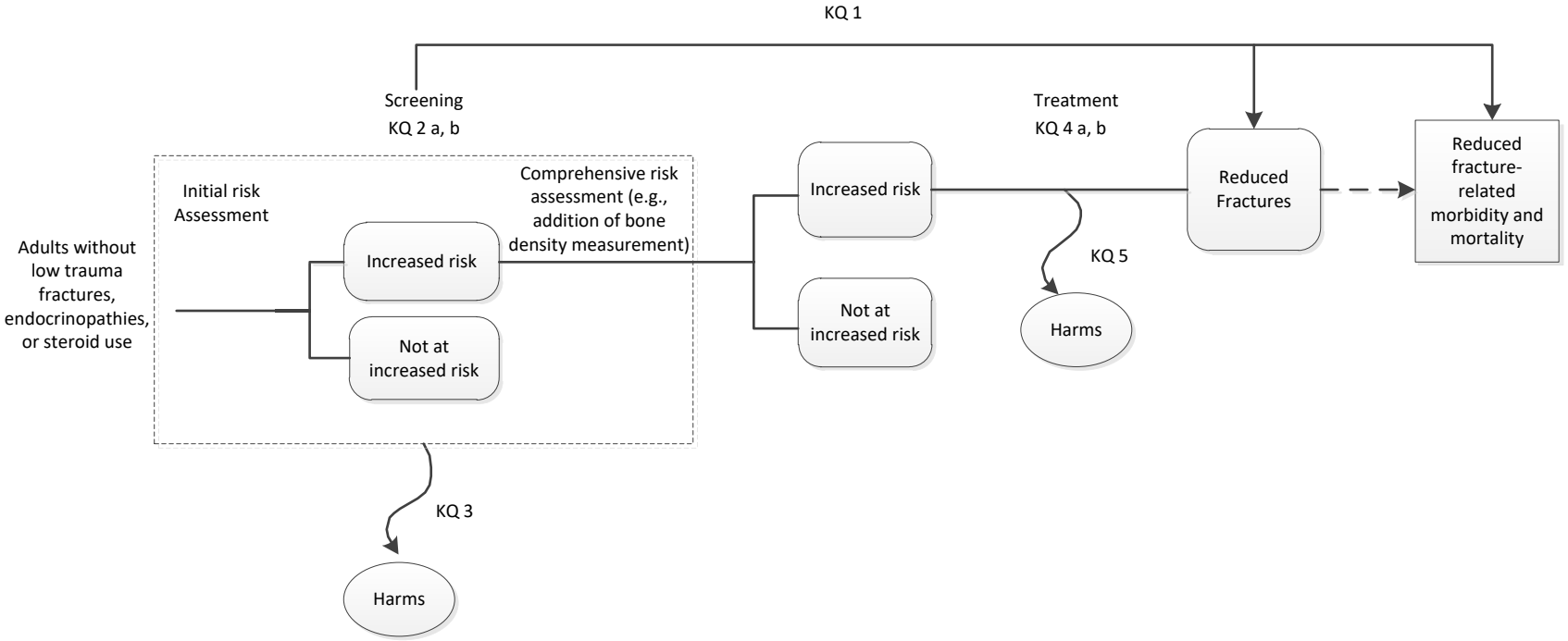
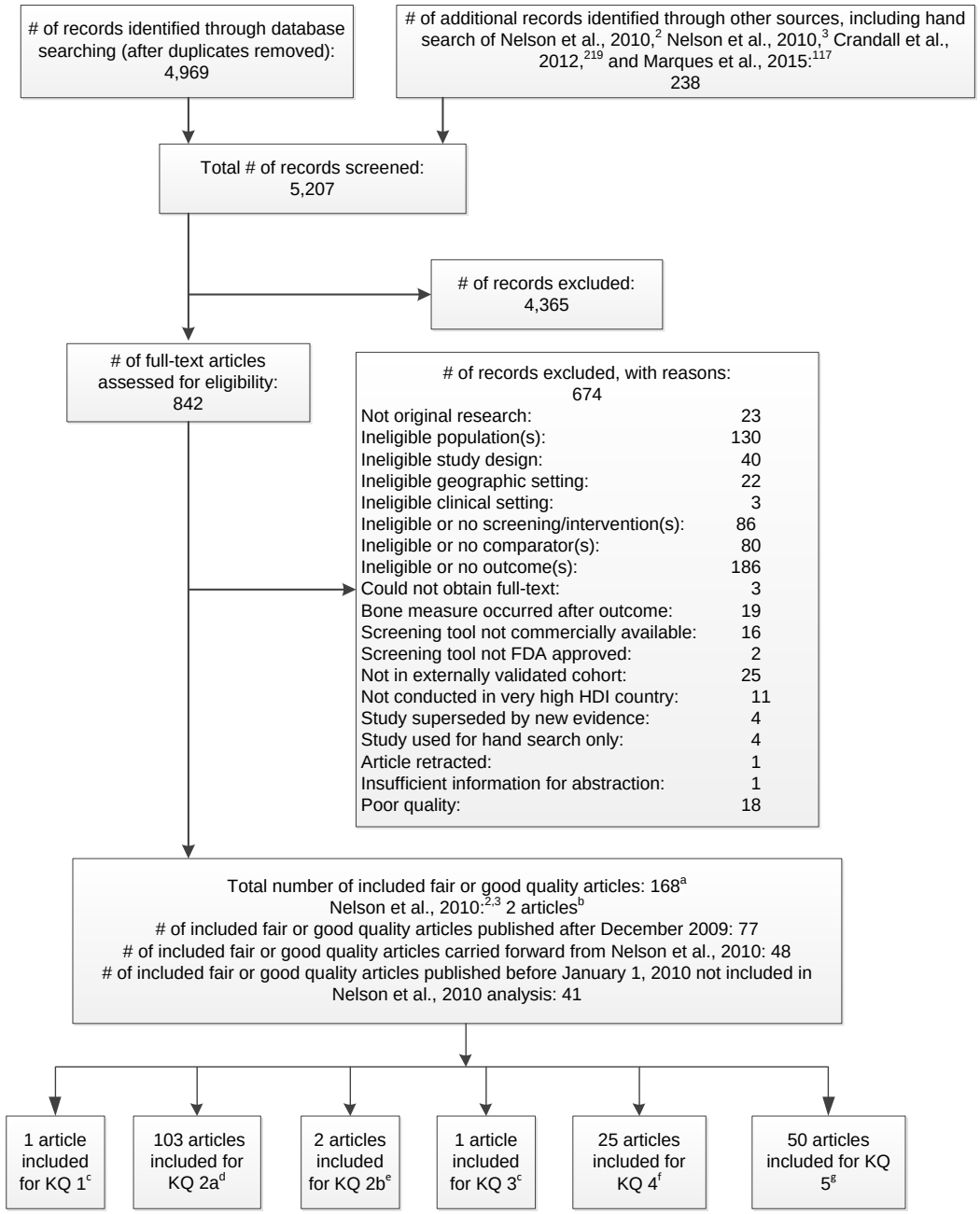
Figure 1. Analytic Framework



Abbreviations: KQ=key question

Figure 2. PRISMA Tree



a: Due to overlap in studies across populations and results sections, only article counts are reported. Citation counts by KQ are not unique; studies may contribute to multiple KQ.
b: Not included in individual study counts at the bottom level of the diagram.
c: KQ1 and KQ 3: 1 study (1 article)
d: KQ 2a Accuracy of Clinical Risk Assessment Tools for Identifying Osteoporosis: 38 studies (41 articles); Accuracy of Bone Measurement Tests Used to Identify Low Bone Mass and Osteoporosis: 11 studies (11 articles); Accuracy of Fracture Risk Prediction Instruments: 5 systematic reviews supplemented by 13 studies; Accuracy of Bone Measurement Tests Used to Predict Fracture: 23 studies (24 articles); Calibration of Fracture Risk Prediction Instruments: 14 studies (14 articles); Reclassification Risk: 10 studies (10 articles)
e: KQ 2 b: 2 studies (2 articles)
f: KQ 4a: Alendronate: 7 studies (7 articles); Zolendronic Acid: 2 studies (2 articles); Risedronate: 4 studies (4 articles); Etidronate: 2 studies (2 articles); Ibandronate: 0 studies; Raloxifine: 1 study (2 articles); Estrogen: 0 studies; Denosumab: 4 studies (5 articles); Parathyroid Hormone: 2 studies (2 articles). KQ 4b: 4 studies (5 articles)
g: Alendronate: 16 studies (16 articles); Zolendronic Acid: 4 studies (4 articles); Risedronate: 6 studies (6 articles); Etidronate: 2 studies (2 articles); Ibandronate: 7 studies (7 articles); Raloxifine: 6 studies (12 articles); Estrogen: 0 studies; Denosumab: 4 studies (5 articles); Parathyroid Hormone: 2 studies (2 articles)
FDA= Food and Drug Administration; HDI= human development index; KQ= key question

Abbreviations: FDA=Food and Drug Administration; HDI=human development index; KQ=key question.

Table 1. Recommendations About Screening and Treatment of Osteoporosis From Various Professional and Health Organizations

Organization, Year	Population	Recommendations
AACE, 2016[327]	Postmenopausal women	Screening • Evaluate all postmenopausal women age 50 years or older for osteoporosis risk • Include a detailed history, physical exam, and clinical fracture risk assessment with FRAX in the initial evaluation for osteoporosis • Consider BMD testing based on clinical fracture risk profile • When BMD is measured, use DXA measurement (spine and hip) • Osteoporosis should be diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders or a T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius even in the absence of a prevalent fracture • Osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX country-specific threshold Evaluation • Evaluate for causes of secondary osteoporosis and prevalent vertebral fractures, consider using bone turnover markers Treatment for patients with • Osteopenia or low bone mass and a history of fragility fracture of the hip or spine • T-score of -2.5 or lower in the spine, femoral neck, total hip, or 33% radius • T-score between -1.0 and -2.5 if the FRAX 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% in the United States or above the country-specific threshold in other countries or regions
AAFP, 2011[328]	Postmenopausal women Men	Same recommendations as the 2011 USPSTF recommendations (recommended screening for osteoporosis in women age 65 years or older and in younger women whose fracture risk is equal to or greater than that of a 65-year old white woman who has no additional risk factors, insufficient evidence to assess the balance of benefits and harms of screening for osteoporosis in men)
ACOG, 2012 (reaffirmed in 2014)[329]	Women	1. Recommend BMD testing by DXA: • for all women age 65 years or older • for younger women if they are postmenopausal and have other risk factors for fracture and/or a 10-year FRAX risk of fracture of ≥9.3% • at intervals not more frequent than every 2 years 2. Recommend FDA-approved therapies for women with BMD diagnostic of osteoporosis or women with osteopenia and 10-year FRAX probability of major osteoporosis risk ≥20% or hip fracture risk ≥3%
ACPM, 2009[330]	Women age 65 years or older Men age 70 years or older	1. Recommend BMD testing with DXA for all women age 65 years or older years and men age 70 years or older, and not more frequently than every 2 years 2. Younger postmenopausal women and men ages 50–69 years should undergo screening if they have at least one major or two minor risk factors for osteoporosis 3. Osteoporosis risk assessment tools that estimate absolute fracture risk can be useful supplements to BMD testing, improving the sensitivity and specificity of either approach (BMD or risk assessment) alone; risk assessment can also be used if BMD testing is not readily available or feasible

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Organization, Year	Population	Recommendations
ACR, 2016[331]	Asymptomatic BMD screening or individuals with established or clinically suspected low BMD, patients with T-scores less than -1.0 with additional risk factors, premenopausal females with risk factors, and males 20–50 years of age with risk factors	Rate appropriateness and relative radiation levels of various tests for identifying low bone density and fracture risk
Endocrine Society, 2012[332]	Higher-risk men	Recommend BMD testing by central DXA in 1. men age 70 years or older 2. men ages 50–69 years with risk factors (e.g., low body weight, prior fracture as an adult, smoking)
ISCD, 2015[65]	Men and postmenopausal women	Indications for BMD testing: 1. women age 65 or older 2. postmenopausal women under 65 years of age with risk factors for low bone mass 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 years or older 5. men under 70 years of age with clinical risk factors for low bone mass 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
NOF, 2014[5]	Men age 50 or older and postmenopausal women	1. Recommend BMD testing with DXA for • women age 65 years or older and men age 70 years or older • postmenopausal women and men ages 50–69 years based on risk factor profile • postmenopausal women and men age 50 years or older who have had an adult-age fracture 2. Recommend pharmacologic treatment in those with T-scores <-2.5, in postmenopausal women and mean age 50 years or older with T-scores between -1.0 and -2.5 and a 10-year FRAX probability of major osteoporosis-related fracture ≥20% or hip fracture probability ≥3%

Table 1. Recommendations About Screening and Treatment of Osteoporosis From Various Professional and Health Organizations

Organization, Year	Population	Recommendations
NICE, 2012[333]	Persons presenting in any health care setting	1. Consider assessment of fracture risk: • In all women age 65 years or older and all men age 75 years or older • in women under 65 years of age and men under 75 years of age in the presence of risk factors, for example: a. previous fragility fracture b. current use or frequent recent use of oral or systemic glucocorticoids c. history of falls d. family history of hip fracture e. other causes of secondary osteoporosis f. low BMI (<18.5 kg/m^2) g. smoking h. alcohol intake of more than 14 units per week for women and more than 21 units per week for men. 2. Do not routinely assess fracture risk in people under 50 years of age unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause, or previous fragility fracture), because they are unlikely to be at high risk 3. Consider measuring BMD with DXA in people whose absolute fracture risk (via FRAX or QFracture) is in the region of an intervention threshold for a proposed treatment, and recalculate FRAX with BMD value
North American Menopause Society, 2010[334]	Postmenopausal women	1. Measure height and weight annually and assess chronic back pain, kyphosis, and clinical risk factors 2. Recommend BMD testing with DXA in postmenopausal women with medical causes of bone loss and all women age 65 years or older 3. Recommend BMD testing with DXA for postmenopausal women age 50 years or older with risk factors of previous fracture, thinness, history of hip fracture in parent, current smoking, rheumatoid arthritis, or excessive alcohol intake 4. Vertebral fracture must be confirmed by lateral spine radiographs or vertebral fracture assessment visualization of fracture at the time of BMD testing 5. Recommendations of calcium intake of 1,200 mg/day for adults age 50 years or older, and vitamin D3 of 800 to 1,000 IU/day 6. Recommend pharmacologic treatment in postmenopausal women who have had an osteoporotic vertebral or hip fracture, postmenopausal women who have BMD values consistent with osteoporosis (i.e., T-scores ≤−2.5) at the lumbar spine, femoral neck, or total hip region, and postmenopausal women who have a T-score from −1.0 to −2.5 and a 10-year risk, based on the FRAX calculator, of at least 20% for major osteoporotic fracture (spine, hip, shoulder, and wrist) or at least 3% for hip fracture 7. Recommend repeating BMD testing 1–2 years after treatment 8. For untreated postmenopausal women, repeat DXA testing is not useful until 2–5 years have passed 9. Recommend bisphosphonates as the first-line drugs for treating postmenopausal women with osteoporosis 10. Recommend SERM raloxifene for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis 11. Recommend teriparatide (PTH 1-34) for postmenopausal women with osteoporosis who are at high risk of fracture with therapy indicated for no more than 24 months

Table 1. Recommendations About Screening and Treatment of Osteoporosis From Various Professional and Health Organizations

Organization, Year	Population	Recommendations
Scientific Advisory Council of Osteoporosis Canada, 2010[335]	Men and women older than 50 years of age	1. Measure height annually and assess for vertebral fracture 2. Assess history of falls 3. Perform biochemical testing in select patients to rule out secondary causes of osteoporosis 4. Perform lateral thoracic and lumbar spine radiography or DXA if clinical evidence suggests fracture 5. Use the 2010 version of the Canadian Association of Radiologists and Osteoporosis Canada tool or Canadian version of FRAX to assess absolute risk of fracture; offer treatment to individuals with a 10-year risk of >20% for major osteoporotic fractures
UKNSC, 2013[336]	Postmenopausal women	Systematic population screening not recommended because no RCT has assessed the clinical and cost effectiveness of any current approach to screening for osteoporosis
WHO, 2008[337]	Men and women 40–90 years of age	DXA and an assessment tool for case-finding high-risk individuals (FRAX) should be used to evaluate fracture risks for men and women. Recommend treatment with FDA-approved medication to lower risk in three high-risk groups: 1. history of fracture of the hip or spine 2. BMD in the osteoporosis range (T-score of -2.5 or lower) 3. BMD in the low bone mass or osteopenia range with a higher risk of fracture defined by FRAX score for a. major osteoporotic fracture 10-year probability of 20% or higher OR b. hip fracture 10-year probability 3% or higher

Abbreviations: AACE=American Association of Clinical Endocrinologists; AAFP=American Association of Family Physicians; ACOG=American College of Obstetricians and Gynecologists; ACPM=American College of Preventive Medicine; ACR=American College of Radiology; BMD=bone mineral density; BMI=body mass index; DXA=dual-energy X-ray absorptiometry; FDA=U.S. Food and Drug Administration; FRAX=Fracture Risk Assessment Tool; ISCD=International Society of Clinical Densitometry; IU/day=international unit per day; NICE=National Institute for Health and Care Excellence; NOF=National Osteoporosis Foundation; PTH=parathyroid hormone; QFracture=third tool: Promising Developments in Osteoporosis Treatment; RCT=randomized controlled trial; SERM=selective estrogen-receptor modulator; T-score=number of units (standard deviations) that bone density is above or below the average; UKNSC=United Kingdom National Screening Committee; USPSTF=United States Preventive Services Task Force; WHO=World Health Organization.

Table 2. FRAX-Generated 10-Year Fracture Risk Probabilities by Age, Race, and Sex for U.S. Populations of Average Height and Weight

Race, Height, Weight	BMD	Age 50, MOF	Age 50, Hip	Age 55, MOF	Age 55, Hip	Age 60, MOF	Age 60, Hip	Age 65, MOF	Age 65. Hip	Age 70, MOF	Age 70, Hip	Age 75, MOF	Age 75, Hip	Age 80, MOF	Age 80, Hip
Causasian woman	Without BMD	3.4	0.2	5.2	0.3	6.9	0.5	8.4	1	10	2	13	3.8	18	6.3
Ages 50-55: height	With BMD T-score 0.0	3.4	0.1	5	0.1	6	0.1	6.5	0.2	6.9	0.3	7.3	0.6	8.6	1
163.8 cm, weight 76.1 kg	With BMD T-score -1.75	4.8	0.5	7.1	0.7	8.6	0.9	9.6	1.2	10	1.8	12	2.7	14	3.8
Ages 60-80: height 160.3 cm, weight 73.9 kg	With BMD T-score -3.25	9.6	3.9	13	4.3	16	5.1	18	6	21	7.7	24	10	27	12
Black woman	Without BMD	1.3	0.1	2.1	0.1	2.9	0.2	3.5	0.4	4.3	0.8	5.5	1.5	7.6	2.5
Ages 50-55: height	With BMD T-score 0.0	1.5	0	2.1	0	2.6	0.1	2.8	0.1	3	0.1	3.2	0.3	3.8	0.4
163.5 cm, weight 88.3 kg	With BMD T-score -1.75	2.1	0.2	3	0.3	3.8	0.4	4.2	0.5	4.6	0.7	5.2	1.1	6.5	1.6
Ages 60-80: height 160. 6 cm, weight 80.7 kg	With BMD T-score -3.25	4.2	1.6	5.7	1.8	7.1	2.2	8.2	2.6	9.4	3.3	11	4.3	13	5.2
Causasian man	Without BMD	2.6	0.1	3.7	0.2	4.5	0.3	4.9	0.6	5.6	1.1	6.5	2.1	8.4	3.5
Ages 50-55: height	With BMD T-score 0.0	2.8	0.1	3.9	0.1	4.4	0.2	4.5	0.3	4.6	0.5	4.8	0.9	5.5	1.3
178.3 cm, weight 92.9 kg	With BMD T-score -1.75	4.6	0.8	6.2	1	7.2	1.3	7.6	1.6	8	2.1	8.4	2.9	9.4	3.7
height 174.6 cm, weight 89.0 kg	With BMD T-score -3.25	10	5.5	13	6.1	14	6.3	15	6.7	16	7.4	16	8.5	17	9.1
Black man	Without BMD	1.1	0	1.5	0.14	1.9	0.1	2.1	0.3	2.3	0.5	2.8	0.9	3.7	1.5
Ages 50-55: height	With BMD T-score 0.0	1.2	0	1.6	0.1	1.9	0.1	1.9	0.1	1.9	0.2	2	0.4	2.4	0.6
176.7 cm, weight 92.1 kg	With BMD T-score -1.75	2.4	0.4	2.6	0.4	3	0.5	3.1	0.7	3.3	0.9	3.5	1.2	4.1	1.6
Ages 60-80: height 174.4 cm, weight 87.8 kg	With BMD T-score -3.25	4.5	2.4	5.5	2.6	6.1	2.6	6.3	2.7	6.5	3	6.9	3.5	7.6	3.9

Abbreviations: BMD=bone mineral density; FRAX=Fracture Risk Assessment Tool; MOF=major osteoporotic fracture; U.S.=United States.

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
ABONE[82, 86]	66. to 68.4	All women	White and Chinese	General population; Canada Singapore	Age, body size, no estrogen use for at least 6 months	Ranges from 0.70 to 0.72 (femoral neck); 2; 2,500	≥2: 83.3 (78.5-88.0); 1; 2,365	≥2: 47.7 (45.6-49.8); 1; 2,365	Not reported	Not reported
AMMEB[88, 89]	65	All women	NR	General practices; Italy	Age, BMI, age at menarche, postmenopausal period	Ranges from 0.63 to 0.71; 2; 1,520	NR	NR	NR	NR
DOEScore[103]	70.5	All women	98.6% Caucasian; 1.4% Aboriginal (overall cohort, NR for included sample)	Population-based cohort; Dubbo, Australia	Age, body weight, and history of fracture	Any site: 0.75 (95% CI, 0.691 to 0.809); 1; 410	>10: 82% (NR); 1; 410	>10: 52% (NR); 1; 410	NR	>10: 55% (NR); 1; 410
FRAX without BMD for 10-year risk of hip fracure[94]	61	All women	100% Caucasian	General practice, Spain	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	Any site: 0.82 (NR); 1; 505	NR	NR	NR	NR
FRAX without BMD for 10-year risk of hip fracure[106]	78.2	45.1% women	Not reported	General practice; Australia	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	Any site: 0.70 (95% CI, 0.64 to 0.75); 1; 626	Hip≥3% 92.2 (NR); 1; 626	Hip≥3% 37.7 (NR); 1; 626	Hip≥3% 17.1 (NR); 1; 626	Hip≥3% 97.1 (NR); 1; 626

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
FRAX without BMD for 10-year risk of major osteoporotic fracure[56, 57, 94, 113]	57 to 57.7	All women	72% white, 17% black, 8% Hispanic in one study[57]; 97%–100% white in 2 studies;[56, 94] NR[113]	General practice; USA, Spain; Population-based cohort, Canada	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	Ranges from 0.58[56] to 0.82[56], 2 had thresholds specified as ≥9.3% risk[56,57] two did not specify[113]; 4; 22,141	MOF ≥9.3% Ranges from 33.3% to 37%; 2; 3,321	MOF ≥9.3% Ranges from 74% to 86.4% (85.1–87.7); 2; 3,321	MOF ≥9.3% 13.7 (10.4–17.0); 1; 2,857	Not reported
FRAX without BMD for 10-year risk of major osteoporotic fracure[114]	64.2	All men	88.5% white, 8.5% black, 2.9% Mexican-American	Community-based sample, USA	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	0.79 (95% CI, 0.74 to 0.84); 1; 1,498	FRAX MOF risk ≥9.3% 39% (27-51); 1; 1,498	FRAX MOF risk ≥9.3% 89% (87-91); 1; 1,498	FRAX MOF risk ≥9.3% 14% (9-20)	FRAX MOF risk ≥9.3% 97% (96-98)
FRAX without BMD for 10-year risk of major osteoporotic fracure[106]	78.2	45.1% women	Not reported	General practice; Australia	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	Any site: 0.68 (95% CI, 0.63 to 0.74); 1; 626	MOF≥6.5% 89.6 (NR); 1; 626	MOF≥6.5% 35 (NR); 1; 626	MOF≥6.5% 16.8 (NR); 1; 626	MOF≥6.5% 96.2 (NR); 1; 626
Gnudi et al, 2005[91]	64.3	All women	100% white	Women requiring a DXA scan at "a center," Italy	Age at menarche, weight, years since menopause, previous fracture, weight, fracture in subject's mother, arm help to get up from sitting	Any site: 0.74 (95% CI, 0.70 to 0.79); 1; 478	Predicted probability of low BMD at 0.132[c]: 95.5%; 1; 478	Predicted probability of low BMD at 0.132[c]: 27.7%; 1; 478	Predicted probability of low BMD at 0.132[c]; 0.156 91.2%; 1; 478	Predicted probability of low BMD at 0.132[c]: 43.9%;1; 478

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
Mscore[112]	60.9 to 68.4	All men	Caucasian and African-American subgroups	Clinic-based	2 models: Age and weight (reduced Mscore) or Age, weight, gastrectomy, COPD, two or more prior fractures (Mscore)	Femoral neck: Age-weight model: Caucasian 0.81 (95% CI, 0.69 to 0.92); 1; 197 African-American[e] 0.99 (95% CI, 0.98 to 1.01); 1; 134 5-variable model Caucasian 0.84 (95% CI, 0.74 to 0.95); 1; 197 NR for African-American	Age-weight model <9 Caucasian 85%; 1; 197 African-American[e] 93%; 1; 134 5-variable model<9 Caucasian 88%; 1; 197 NR for African-American	Age-weight model <9 Caucasian 58%; 1; 197 African-American[e] 79%; 1; 134 5-variable model<9 Caucasian 57%; 1; 197 NR for African-American	Age-weight model <9 Caucasian 18%; 1; 197 African-American[e] 34%; 1; 134 5-variable model<9 Caucasian 16%; 1; 197 NR for African-American	Age-weight model <9 Caucasian 97%; 1; 197 African-American[e] 99%; 1; 134 5-variable model<9 Caucasian 98%; 1; 197 NR for African-American
MORES[85, 110, 115]	63 to 70.2	All men	NR	1 clinic sample, 2 population-based samples	Age, weight, history of COPD	Pooled AUC (total hip or hip in combination with other measures)[d]: 0.80 (95% CI, 0.71 to 0.88); 3; 4,828	≥6: 66-95%; 3; 4,828	≥6: 61-70%; 3; 4,828	≥6 (hip) 10-11%, 2; 1,844	≥6 (hip) 99-100%; 2; 1,844

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
MOST[97]	65 and older	All men	71% Caucasian 29% Chinese	Cohort of community-dwelling, ambulatory men; US and Hong Kong	QUI, body weight	US Any site: 0.80 (95% CI, 0.78 to 0.82), 1; 4,658 Hong Kong Any site: 0.83 (95% CI, 0.80 to 0.86); 1; 1,914	NR	NR	NR	NR
NOF guidelines[82, 88, 89, 100]	57.3 to 69.2	All women	Predominantly white	Majority of studies general population or general practice; USA Canada Italy	Age, weight, personal history of fracture with minimal trauma >40 years, family history of fracture, current cigarette smoking	Lowest T score: 0.60; 2; 1,520	≥1: 96-100%	≥1: 10-18%; 2; 2,567	≥1: 37%; 2; 202	≥1: 100%; 2; 202
ORAI[79, 80, 82-84, 86-90, 92-94, 99, 100, 103, 109]	50.5 to 70.5	All women	White participants in majority of studies	Half of studies conducted in general practice or population settings Countries: USA Australia Belgium Canada Denmark England Italy Singapore Spain	Age, weight in pounds, current estrogen use	Pooled AUC for any site: 0.65 (95% CI, 0.60 to 0.71); 10;16,780	≥9: 50-100%; 9; 7,830	≥9: 10-75%; 9 7,830	≥9: 20-98%; 4; 3,079	≥9: 25-94%; 4; 3,079

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
OSIRIS[72, 80, 87, 93, 94, 99]	54.1 to 61.5	All women	Predominantly Causasian	All clinic-based, all in Europe	Age, weight, HRT use, history of low trauma fracture	Pooled AUC (any site): 0.68 (95% CI 0.64 to 0.72) 5; 5,649	<1: 64%; 1; 4,035	<1: 69%; 1; 4,035	<1: 50%; 2; 2,701	<1: 80%; 2; 2,701
OST[77, 97, 98, 108, 111, 112]	64 to 68	All men	Predominantly Caucasian	4 clinic-based, 2 community-based; 5 in US and 1 in Portugal	Age and weight	Pooled AUC (any site or femoral neck): 0.76 (95%CI, 0.71 to 0.80); 6; 7798	<2: 61.8% to 87.6%; 5; 5,366	<2: 36.1 to 74%; 5; 5,366	<2: 9.7 to 38%; 5; 5,366	<2: 89.2 to 9%; 5; 5,366
OST[57, 83, 87-90, 92-94, 99, 101, 10272, 80, 109, 113]	51 to 62	All women	Predominantly Caucasian	9 clinic-based and 6 community based; 3 in US, 4 in Canada, 8 in Northern/ Western Europe	Age and weight	Pooled AUC (any site): 0.65 (95% CI, 0.60 to 0.69); 13; 44,323; without outlier,[88, 89] pooled AUC: 0.71, 95% CI, 0.70 to 0.72; 11; 42,802	<2: 69% to 95.3% 7 studies; 11,486 participants	< 2: 34% to 71%; 11; 42,802	<2: 2% to 41%; 4; 9,566	<2: 86% to 100%; 3; 6,709
OST[106]	78	45.1% men	Predominantly Caucasian	Clinic-based, Australia	Age and weight	Any site: 0.76 (95% CI, 0.71 to 0.82); 1; 626	≤0: 90.9%	≤0: 39.9%	≤0: 17.5%	≤0: 96.9%
OSTA[96, 98, 104]	63.4 to 54	All men	Asian	Community-based, Hong Kong and S. Korea	Age and weight	Any site: AUCs range from 0.627 to 0.72; 2; 1,911	Varies by study, no common cutoff	Varies by study, no common cutoff	Varies by study, no common cutoff	Varies by study, no common cutoff
OSTA[86, 89, 95, 103, 104, 107]	59.1 to 70.5	All women	Caucasian and Asian	1 clinic-based and 4 community-based studies; Australia, Singapore, Hong Kong, South Korea	Age and weight	Pooled AUC: 0.76 (95% CI, 0.63 to 0.90); 4; 2,962	≤-1: 41% to 97%; 5; 3,414	≤-1: 24% to 67.1%; 5; 3,414	≤-1: 24% to 49.4%; 3; 2,557	≤-1: 87% to 98%; 2; 2,147

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
SCORE[57, 79-82, 84, 86, 87, 90, 93, 94, 100, 109]	57.7 to 69.2	All women	Predominantly white	4 clinic-based, 7 community-based US: 4; UK: 2; Spain: 1; Singapore: 1; Belgium: 1; Denmark: 1; Canada: 1	Age, weight, and estrogen replacement therapy, the SCORE instrument includes race/ethnicity, history of rheumatoid arthritis, and history of nontraumatic fractures after age 45	Pooled AUC (any site): 0.70 (95% CI, 0.69 to 0.71); 8; 15,362	≥6: 54% to 100%; 6; 7,455	≥6: 17.9% to 72%; 6; 7,455	≥6: 89.1% to 100%; 3; 4,440	≥6: 19% to 41%; 3 studies; 4,440

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
SOF[81]	69.3	All women	93.5% white	OPRA study, Group Health participant; US	Prior fracture after age 50; age 60-64 with t-score <−2.5 or age 65 or older with z-score <−0.43; and 5 or more risk factors (first-degree relative with hip fracture, current weight less than at age 25, dementia, using corticosteroids or seizure medication or benzodiazepines, had a fracture age 50+, not taking HRT, on feet <4 h/day, heart rate >80 beats/min, was >5′7 at age 25, 80+ years old; subtract 1 point each for race (African American); walk for exercise; can rise from chair without arms	Any site: 0.54 (SE 0.03); 1; 416	≥ 5: 32.6 (26.6, 38.6); 1; 416	≥ 5: 76.0 (63.5, 88.6); 1; 416	NR	NR

Table 3. Characteristics and Accuracy of Clinical Risk Assessment Tools in Identifying Osteoporosis

Instrument	Mean Age	Sex	Race/ethnicity	Clinical and Geographic Setting	Components	Pooled AUC (95% CI) or Range of AUCs;[a] No. of Studies; No. of Participants	Threshold,[b] Range of Sensitivity; No. of Studies; Participants	Threshold,[b] Range of Specificity; No. of Studies; No. of Participants	Threshold,[b] Range of Positive Predictive Values; No. of Studies; No. of Participants	Threshold,[b] Range of Negative Predictive Values; No. of Studies; No. of Participants
SOFSURF[87, 90, 103]	59.7 to 70.5	All women	Mostly white	Population-based cohort; Dubbo, Australia Scanning clinics; UK	Age, weight, smoking and history of postmenopausal fracture	NR in 2 studies;[90, 103] Any site: 0.717 (95% CI, 0.777 to 0.670); 1; 208[87]	Varies by study, no common cutoff	Varies by study, no common cutoff	Varies by study, no common cutoff	Varies by study, no common cutoff

[a] Presented for any site when available (femoral neck, lumbar spine, total hip); if not available, presented for femoral neck.
[b] Sensitivity, specificity, NPV, and PPV presented for the most commonly reported threshold across studies.
[c] Study presents multiple predicted probabilities of low BMD; the study notes that the threshold offered the highest number of DXA-deferred cases and the lowest number of low-BMD missed cases.
[d] Studies present results for three different sites of BMD measurement: total hip,[110] total hip or femoral neck,[85] or thoracic vertebra, lumbar vertebra, arms, ribs, pelvis, or legs.[115]
[e] The African-American sample includes data from 95 new subjects and 39 subjects from development cohort and is therefore not a pure validation cohort.

Abbreviations: ABONE=assessing age, body size, and estrogen use; AMMEB=Age, years after Menopause, age at MEnarche, Body mass index; 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 Score; DXA=Dual-energy X-ray absorptiometry; FN=Femoral neck; FRAX=Fracture Risk Assessment tool; HRT=hormone replacement therapy; MOF=Melton Osteoporotic Fracture study; MORE=Multiple Outcomes of Raloxifene Trial; MOST=Male Osteoporosis Screening Tool; NOF=National Osteoporosis Foundation; NR=not reported; OPRA=osteoporosis population-based risk assessment; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; OSTA=Osteoporosis Self-assessment Tool for Asians; QUI=ultrasound index; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SE=standard error; SOF=Study of Osteoporotic Fractures; SOFSURF=Study of Osteoporotic Fractures Simple Useful Risk Factors; UK=United Kingdom; US=United States; USA=United States of America.

Table 4. Characteristics and Accuracy of Machine-Based Tests in Identifying Osteoporosis

Imaging Test	Site of Test	Sex	Age Range (Years)	Gold Standard Test	Site of Gold Standard	Number of Studies	Number of Participants	Summary of Accuracy
QUS	Calcaneus	Women	Mean age ranges from 59–63	DXA ≤-2.5	Lumbar spine, femoral, or total hip	7[87, 93, 95, 101, 116-118]	1,969	AUCs range from 0.69 to 0.898, pooled estimate: 0.77 (95% CI, 0.72 to 0.81)
QUS	Calcaneus	Men	Mean age ranges from 61–63	DXA ≤-2.5	Lumbar spine, femoral, or total hip	3[96, 97, 111]	5,142	AUCs vary from 0.696 to 0.93, pooled estimate: 0.80 (95% CI, 0.67 to 0.94)
Peripheral DXA	Calcaneus	Women	61 (SD ranges from 4 to 8)	DXA	Lumbar spine, femoral, or total hip	2[93, 94]	712	AUC ranges from 0.67 to 0.803 (variance NR)
DXR	Nondominant metacarpals	Women	61 (range 50–75)	DXA	Lumbar spine or total hip	1[116]	221	AUC: 0.84 (95% CI, 0.79 to 0.89)
RA	Nondominant phalanges	Women	61 (range 50–75)	DXA	Lumbar spine or total hip	1[116]	221	AUC: 0.80 (95% CI, 0.74 to 0.85)

Abbreviations: AUC=area under the curve; CI=confidence interval; DXA=dual energy X-ray absorptiometry; DXR=digital X-ray radiogrammetry; NR=not reported; QUS=quantitative ultrasound; RA=radiographic absorptiometry; SD=standard deviation; SE=standard error.

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

Risk Prediction Tool	Risks Included	Bone Tests Included	Sex	Age Range (Years)	Prediction Time (Years)	AUC without BMD[b]	AUC with BMD[b]	Countries Covered by Included Studies
FRAX®[c32]	Age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoid steroid use, rheumatoid arthritis, secondary osteoporosis, alcohol use	Hip BMD[d] optional	Men and women	40 to 90	10[c]	<u>*Men*</u> *MOF:* 0.62 (95% CI, 0.61 to 0.64, I^2=40.5%, 3 studies, 13,970 men)[123, 174, 338] *Hip*: 0.73 (95% CI, 0.68 to 0.77, I^2=96.7%, 3 studies, 13,970 men)[123, 174, 338] <u>*Women*</u> *MOF:* 0.67 (95% CI, 0.65 to 0.68, I^2=99.2%, 17 studies, 158,897 women)[58, 123-126, 128, 133, 171-174, 176-178, 184, 339, 340] *Hip*: 0.76 (95% CI, 0.72 to 0.81, I^2=99.8%, 12 studies, 190,795 women)[123, 125, 133, 170, 171, 174, 176-178, 184, 187, 340] <u>*Both Sexes*</u> MOF: 0.67 (95% CI, 0.66 to 0.67, I^2=47.1%, 3 studies, 66,777)[127, 147, 148] *Hip:* 0.77 (95% CI, 0.73 to 0.79, 6,697 participants)[147] 0.79 (95% CI, 0.78 to 0.82, 39,603 participants)[148]	<u>*Men*</u> *MOF:* 0.67 (95% CI, 0.66 to 0.68, I^2=0%, 4 studies, 15,842 men)[123, 132, 174, 338] *Hip*: 0.76 (95% CI, 0.72 to 0.80, I^2=96.7%, 3 studies, 13,970 men)[123, 174, 338] <u>*Women*</u> *MOF:* 0.70 (95% CI, 0.68 to 0.71, I^2=92.1%, 12 studies, 62,054 women)[123-126, 171, 172, 174-178, 339] *Hip*: 0.79 (95% CI, 0.76 to 0.81, I^2=99.1%, 10 studies, 161,984 women)[123-125, 170, 171, 174, 176-178, 187] <u>*Both Sexes*</u> *MOF*: 0.69 (95% CI, 0.69 to 0.70, I^2=70.3%, 3 studies, 66,777)[127, 147, 148] *Hip:* 0.80 (95% CI, 0.77 to 0.83, 6,697 participants)[147] 0.83 (95% CI, 0.82 to 0.85, 39,603 participants)[148]	<u>*Men*</u> Canada, Denmark, U.S., Japan <u>*Women*</u> Australia, Canada, Denmark (2), Finland, France (2), Hong Kong, Japan, Multinational European and U.S. Cohort, Netherlands, New Zealand, Spain (3), U.S. (4) <u>*Both Sexes*</u> Canada (3)

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

Risk Prediction Tool	Risks Included	Bone Tests Included	Sex	Age Range (Years)	Prediction Time (Years)	AUC without BMD[b]	AUC with BMD[b]	Countries Covered by Included Studies
Garvan nomogram/ FRC[139]	Age, sex, weight, previous nontraumatic fracture since age 50, fall within past 12 months	Hip BMD[e] optional[f]	Men and Women	60 to 96	10[g]	<u>*Men*</u> *Hip:* 0.65 (95% CI, NR, 1,285 men)[129] *Nonvertebral:* 0.61 (95% CI, NR, 1,355 men)[129] <u>*Women*</u> *MOF*: 0.66 (95% CI, 0.61 to 0.72, 600 women)[126] *Any OF:* 0.65 (95% CI, NR, 506 women)[124] *Hip:* 0.68 (95% CI, NR, 1,369 women)[129] *Nonvertebral:* 0.58 (95% CI, NR, 1,637 women)[129]	<u>*Men*</u> *MOF*[h]: 0.70 (95% CI, NR, 1,606 men)[149] *Hip*[h]: 0.79 (95% CI, NR, 1,346 men)[129] 0.85 (95% CI, NR, 1,606 men)[149] *Nonvertebral:* 0.67 (95% CI, NR, 1,346 men)[129] <u>*Women*</u> *MOF*[h]: 0.68 (95% CI, 0.64 to 0.71, I^2=84.8%, 3 studies,[126, 149, 171] 6,174 women) *Any OF*: 0.69 (95% CI, NR, 506 women)[124] *Hip*[h]: 0.73 (95% CI, 0.66 to 0.79, I^2=97.3%, 4 studies,[124, 129, 149, 171] 7,449 women) *Nonvertebral:* 0.62 (95% CI, NR, 1,646 women)[129]	<u>*Men*</u> Canada, Norway <u>*Women*</u> Australia, Canada, Netherlands, New Zealand, Norway

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

Risk Prediction Tool	Risks Included	Bone Tests Included	Sex	Age Range (Years)	Prediction Time (Years)	AUC without BMD[b]	AUC with BMD[b]	Countries Covered by Included Studies
QFracture[150]	Age, sex, weight, height, smoking, parental fracture or osteoporosis, previous fall, glucocorticoid steroid use, rheumatoid arthritis, alcohol use, hormone replacement therapy[i], asthma, endrocrine disease, cardiovascular disease, menopausal symptoms[i], malapsorptive gastrointestinal disease, liver disease, type II diabetes, tricyclic antidepressant use (or other antidepressant use[i]), ethnicity[i], previous fracture[i], dementia[i], kidney disease[i], epilepsy[i], Parkinson's disease[i], living in a nursing home[i], COPD[i], cancer[i], lupus[i], anti-convulsant use[i], type I diabetes[i]	None	Men and women	30 to 85[k]	1 to 10	*2009 version of instrument:* <u>Men</u> *MOF[j]:* 0.69 (95% CI, 0.68 to 0.69, 633,764 men)[150] 0.74 (95% CI, NR, 1,108,219 men)[341] *Hip:* 0.86 (95% CI, 0.85 to 0.86, 633,764 men)[76, 150] 0.86 (95% CI, NR, 1,108,219 men)[341] <u>Women</u> *MOF[j]:* 0.79 (95% CI, 0.79 to 0.79, 642,153 women)[76, 150] 0.82 (95% CI, NR, 1,136,417 women)[341] *Hip:* 0.89 (95% CI, 0.89 to 0.89, 642,153 women)[150] 0.89 (95% CI, NR, 1,136,417 women)[76, 341] *2012 version of instrument:* <u>Men</u> *MOF[j]*: 0.71 (95% CI, 0.70 to 0.72, 778,810 men)[130] *Hip:* 0.88 (95% CI, 0.87 to 0.88, 778,810 men)[130] <u>Women</u> *MOF[j]:* 0.79 (95% CI, 0.79 to 0.79, 804,563 women)[130] *Hip:* 0.89 (95% CI, 0.89 to 0.90, 804,563 women)[130]	NA	<u>*Men and Women*</u> France, U.K. <u>*Men and Women*</u> U.K.

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

Risk Prediction Tool	Risks Included	Bone Tests Included	Sex	Age Range (Years)	Prediction Time (Years)	AUC without BMD[b]	AUC with BMD[b]	Countries Covered by Included Studies
WHI[151]	Age, weight, height, self-reported health, previous fracture after age 55, race/ethnicity, physical activity, smoking, parental hip fracture after age 40, diabetes treated with medications, glucocorticoid steroid use	Hip BMD optional[m]	Women	50 to 79	5	*Hip:* 0.80 (95% CI, 0.77 to 0.82, 10,750 women)[151] 0.82 (95% CI, NR, 13,353 women)[160]	*Hip:* 0.80 (95% CI, 0.75 to 0.85, 10,750 women)[151]	Denmark, U.S.
OST[152]	Age, weight (score calculated as 0.2 X [weight in kg-age])	None	Women	45 to 88	NA[n]	*MOF* (3-year risk): 0.56 (95% CI, 0.52 to 0.60, 8,254 women)[102] 0.71 (95% CI, 0.68 to 0.75, 3,614 women)[128] *MOF* (10-year risk): 0.52 (95% CI, 0.52 to 0.53, 62,492 women)[58]	NA	Canada, Denmark, U.S.
SCORE[153]	Age, weight, race, rheumatoid arthritis, prior nontraumatic fracture, prior estrogen use	None	Women	45 and older	NA[n]	*MOF* (10-year risk):0.53 (95% CI, 0.53 to 0.54, 62,492 women)[58] *MOF* (3-year risk): 0.70 (95% CI, 0.66 to 0.74, 3,614 women)[128]	NA	Denmark, U.S.
FRISC[154]	Age, weight, menopausal status, secondary osteoporosis, prior fracture, back pain, dementia	Lumbar BMD	Women	40 to 79	1, 3, 5 or 10	NA	*MOF*: 0.73 (95% CI, NR, 400 women)[154] *Long bone and vertebral fracture*[o]: 0.69 (95% CI, 0.64 to 0.73, 765 women)[169]	Japan (2)
FRISK[155]	Age, weight, height, prior fracture, prior falls	Lumbar and Hip BMD, optional	Women	60 and older	5 or 10	*MOF*: 0.62 (95% CI, 0.56 to 0.67, 600 women)[126, 155]	*MOF*: 0.66 (0.60 to 0.71, 600 women)[126]	Australia

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

Risk Prediction Tool	Risks Included	Bone Tests Included	Sex	Age Range (Years)	Prediction Time (Years)	AUC without BMD[b]	AUC with BMD[b]	Countries Covered by Included Studies
FRC[156]	Age, sex, BMI, prior fracture, parental fracture, smoking, alcohol use, glucocorticosteroid use, rheumatoid arthritis, secondary osteoporosis, race/ethnicity	BMD[p] optional	Men and women[q]	45 to 75	10[q]	*MOF*: 0.66 (95% CI, NR, 893 men)[191] *Hip*: 0.71 (95% CI, NR, 893 men)[191] *Hip*: 0.83 (95% CI, 0.82 to 0.84, 94,489 women)[159]	*MOF*: 0.70 (95% CI, NR, 893 men)[191] *Hip*: 0.79 (95% CI, NR, 893 men)[191] *Hip*: 0.85 (95% CI, 0.84 to 0.86, 94,489 women)[159]	U.S. (2)
ORAI[157]	Age, weight, current estrogen use	No	Women	45 or older	NA[n]	*MOF* (3-year risk): 0.71 (95% CI, 0.68 to 0.75, 3,614 women)[128] *Any OF* (3-year risk): 0.69 (95% CI, 0.66 to 0.72, 3,614 women)[128]	NA	Denmark
OSIRIS[158]	Age, weight, current hormone therapy use, prior fracture	No	Women	60 to 80	NA[n]	*MOF* (3-year risk): 0.70 (95% CI, 0.66 to 0.74, 3,614 women)[128] *Any OF* (3-year risk): 0.68 (95% CI, 0.65 to 0.72, 3,614 women)[128]	NA	Denmark

[a] Studies summarized in this table include instruments predicting fracture risk over a specified time horizon (e.g., 5 or 10 years). Additional studies predicting fracture by a certain age are summarized in the narrative.
[b] Updated pooled estimates are provided where possible; otherwise, range of AUC estimates from relevant studies is provided.
[c] FRAX has been updated several times since its initial release. Studies included in this review do not consistently report which version was used; thus, findings reflect various versions of FRAX released from the initial version through the current version. Further, although FRAX predicts 10 year fracture risk, the range of actual followup used by studies reporting accuracy of fracture risk prediction varied from 2 years to 10 years.
[d] Based on DXA at the femoral neck with T-scores based on NHANES reference values for women 20-29 years of age.
[e] Based on DXA, site unspecified, reference values for T-scores unspecified.
[f] Either BMD or body weight is used in the nomogram.
[g] This instrument can be used for either 5- or 10-year fracture risk prediction.
[h] One of the studies included[171] uses a broader definition of major osteoporotic fractures and one study[149] reports discrimination using Harrell's C statistic.
[i] Risk factors only used in prediction of fracture for women.
[j] Risk factor not included in the original QFracture, but is present in the 2012 update to QFracture.
[k] Original instrument was validated for up to 85 years of age; 2012 updated version included up to 100 years of age.
[l] Two studies[130, 150] did not include fractures of the proximal humerus in their definition of major osteoporotic fracture.
[m] Based on DXA of the proximal femur, reference values for T-scores unspecified.
[n] These instruments were initially developed to predict osteoporosis, not incident fracture. Studies have evaluated their use for fracture prediction with length of followup over 3 years or over 10 years as indicated.
[o] Only five risk factors from the original FRISC model were used for this estimate: age, weight, prior fracture, lumbar BMD, back pain.
[p] Based on DXA of the total hip and hip subregions, T-scores based on NHANES reference values for men.

Table 5. Characteristics and Accuracy of Fracture Risk Prediction Models in Predicting Fracture[a]

[q] Originally developed on a cohort of only women for 5-year risk prediction, with a smaller set of clinical risk factors. Subsequent validation studies included added risk factors, included 10-year risk predictions, and applied the model to a cohort of only men.

Abbreviations: AUC=area under the curve; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; COPD=chronic obstructive pulmonary disease; DXA=dual-energy X-ray absorptiometry; FRAX=Fracture Risk Assessment Tool; FRC=Fracture Risk Calculator; FRISC=Fracture and Immobilization Score; FRISK=Fracture Risk Score; lb=pound(s); MOF=major osteoporotic fracture defined as fractures of the proximal femur, distal radius, proximal humerus, and clinical vertebral fractures; NA=not applicable; NHANES=National Health and Nutrition Examination Survey; NR=not reported; OF=osteoporotic fracture; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; WHI=Women's Health Initiative.

Table 6. Summary of Imaging Tests Predicting Fracture

Imaging Test	Type of Incident Fracture	Site of Test	Sex	Age Range at Baseline (Years)	Number of Studies	Number of Participants	Summary of Accuracy (AUC)
DXA/DXA aBMD	Any osteoporotic or nonspine	Lumbar spine	Women	44-95	3[162, 165, 166, 144]	33,839	Unadjusted: 0.64-0.77 Adjusted: 0.66[a]
			Men	65-≥75	1[167]	1,921	Adjusted: 0.71[b]
		Total hip	Women	46-95	2[165, 166, 173]	29,963	Unadjusted: 0.66-0.68
			Men	65-≥75	1[167]	1,921	Adjusted: 0.72[b]
		Femoral neck	Women	40-95	10[144, 154, 162, 165, 166, 168, 171, 172, 175-177]	41,294	Unadjusted: 0.59-0.76 Unadjusted by baseline T-score range: -1: 0.54, ≤ -1 > -2.5: 0.57, ≤ -2.5: 0.63 Adjusted 64[a]-0.71[c]
			Men	60-≥75	3[163, 167, 168]	7,972	Unadjusted: 0.68 Adjusted: 0.71[c]-0.72[b]
			Combined	≥50	2[147, 148]	46,300	Unadjusted: 0.66-0.68
		Middle phalanges	Women	40-90	2[133, 174]	12,830	Unadjusted: 0.71 Adjusted: 0.68[d]
			Men	40-90	1[174]	5,206	Unadjusted: 0.64
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	50-95	3[164-166, 169]	30,837	Unadjusted: 0.61-0.69
		Total hip	Women	50-95	2[165, 166, 168]	29,861	Unadjusted: 0.71 Adjusted: 0.77[c]
		Femoral neck	Women	50-95	2[165, 166, 168]	29,861	Unadjusted: 0.71 Adjusted: 0.70[c]
			Men	≥60	1[168]	445	Adjusted: 0.75[c]
	Hip	Thoracolumbar vertebra, spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.65
		Total hip	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.81
			Men	≥60	1[168]	445	Adjusted: 0.77[c]
		Femoral neck	Women	40-95	7[165, 166, 168, 170, 171, 176, 177]	38,322	Unadjusted: 0.64-0.86 Adjusted: 0.75[d]
			Men	≥65	1[163]	5,606	Unadjusted: 0.85
			Combined	≥50	2[147, 148]	46,300	Unadjusted: 0.76-0.80
		Middle phalanges	Women	40-90	2[174]	12,830	Unadjusted: 0.83
			Men	40-90	1[174]	5,206	Unadjusted: 0.64
DXA TBS	Any osteoporotic	Spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.63
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	53-61; 50-95	2[164-166]	30,072	Unadjusted: 0.66-0.68
	Hip	Spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.68
	Any osteoporotic	Spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.66
		DXA BMD total hip + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.69

Table 6. Summary of Imaging Tests Predicting Fracture

Imaging Test	Type of Incident Fracture	Site of Test	Sex	Age Range at Baseline (Years)	Number of Studies	Number of Participants	Summary of Accuracy (AUC)
DXA aBMD & TBS		DXA BMD femoral neck + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.69
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	53-61; 50-95	2[164-166]	30,072	Unadjusted: 0.70-0.71 Adjusted: 0.72[d]-0.73[e]
		DXA BMD total hip + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.73
		DXA BMD femoral neck + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.73
	Hip	Spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.69
		DXA BMD total hip + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.82
		DXA BMD femoral neck + TBS spine	Women	50-95	1[165, 166]	29,407	Unadjusted: 0.81
QUS (BUA)	Any osteoporotic	Heel	Women	44-56	1[162]	775	Adjusted: 0.72[a]
			Men	65-≥75; ≥65	2[163, 167]	1,921 + 5,606	Unadjusted: 0.68 Adjusted: 0.65[b]
	Hip	Heel	Men	≥65	1[163]	5,606	Unadjusted: 0.84
QUS (SOS)	Any osteoporotic	Heel	Men	65-≥75	1[167]	1,921	Adjusted: 0.64[b]
QUS (QUI)	Any osteoporotic or nonspine	Heel	Men	65-≥75	1[167]	1,921	Adjusted: 0.66[b]
QUS (BUA) & DXA BMD	Any osteoporotic or nonspine	QUS: Heel DXA: Femoral neck	Women	≥60	1[168]	454	Adjusted: 0.73[c]
		QUS: Heel DXA: Femoral neck	Men	≥65; ≥60	2[163, 168]	5,606	Unadjusted: 0.69 Adjusted: 0.71[c]
	Vertebral	QUS: Heel DXA: Femoral neck	Women	≥60	1[168]	454	Adjusted: 0.72[c]
			Men	≥60	1[168]	445	Adjusted: 0.75[c]
	Hip	QUS: Heel DXA: Femoral neck	Women	≥60	1[168]	454	Adjusted: 0.81[c]
			Men	≥65; ≥60	2[163, 168]	5,606 + 445	Unadjusted: 0.85 Adjusted: 0.78[c]

[a] Adjusted for age, height, weight, menopausal status, neck BMD (QUS only).
[b] Adjusted for age and fracture history.
[c] Adjusted for age, falls, and fracture history.
[d] Adjusted for age.
[e] Adjusted for age and prevalent vertebral deformity.

Abbreviations: aBMD=areal bone mineral density; AUC=area under the curve; BUA=broadband ultrasound attenuation; DXA=dual-energy X-ray absorptiometry; DXL=dual X-ray and laser; QUI=quantitative ultrasound index (combines BUA and SOS); QUS=quantitative ultrasound measured at the calcaneus in all studies; SOS=speed of sound; TBS=trabecular bone score.

Table 7. Reclassification of Risk With Osteoporosis Tools or Instruments

Tool or Instrument	Author, Year of Publication	Population	N	Follow up Period	Fracture Rate	Clinical Threshold or Tool Used for Reclassification	Results
FRAX with BMD	Pressman et al, 2011[187]	Participants >50 years of age with BMD in Kaiser Permanente Northern California, USA	94,489 women	Mean: 6.6 years	Hip fracture: 1.7% (1,579/94,489)	Youden's Index (81% sensitivity threshold [identified as the optimal level from the NRI curve for the model without BMD, corresponding to a 10-year probability of 1.2% risk of hip fracture])	NRI: 0.055
FRAX with lumbar spine BMD inputs	Leslie et al, 2012[127]	All individuals age 50 years of age and older with valid DXA measurements from the lumbar spine and femoral neck in Manitoba, Canada	20,477 men and women	Mean: 8 years	Osteoporotic fracture: 9% (1,845/20,477)	FRAX with femoral neck BMD	NRI for FRAX with weighted mean (lumbar spine or femoral neck): 0.02 NRI for FRAX with offset spine–hip T-score difference): 0.02 FRAX with minimum site (lumbar spine or femoral neck): 0.028 NRI for FRAX with lumbar spine T-score: 0.01
FRC with BMD	Ettinger et al, 2012[191]	Participants age ≥65 years in the Osteoporotic Fractures in Men Study database, United States	5,893 men	Mean: 8.4 years	Incident hip fracture: 2.6% (156/5,873) Incident major osteoporotic fracture: 5.7% (335/5,873)	NOF 10-year 3% probability of a hip fracture	NRI: 0.085
						NOF 10-year 20% probability of a major osteoporotic fracture	NRI: 0.04
Dubbo nomogram with calcaneal QUS	Chan et al, 2012[168]	Participants ages 62–89 years from the Dubbo Osteoporosis Epidemiology Study, Australia	454 women	Median: 13 years	33.9% (154/454)	Dubbo nomogram with femoral neck BMD	NRI for hip fractures: 0.111 for hip fracture NRI for vertebral fractures: 0.052 NRI for any fractures: 0.073
			445 men	Median: 13 years	16.9% (75/445)	Dubbo nomogram with femoral neck BMD	NRI for hip fractures: −0.055 for hip fracture NRI for vertebral fractures: 0.038 NRI for any fractures: no improvement

Table 7. Reclassification of Risk With Osteoporosis Tools or Instruments

Tool or Instrument	Author, Year of Publication	Population	N	Followup Period	Fracture Rate	Clinical Threshold or Tool Used for Reclassification	Results
Dubbo nomogram with calcaneal QUS	Chan et al, 2013[192]	Participants ages 62–90 years with BMD T-score >−2.5 at femoral neck from the Dubbo Osteoporosis Epidemiology Study, Australia	312 women	Median: 12 years	26% (80/312)	Dubbo nomogram with femoral neck BMD	NRI for hip fractures: 0.338 for hip fracture NRI for vertebral fractures: −0.09 NRI for any fractures: 0.164
			390 men	Median: 12 years	14% (53/390)	Dubbo nomogram with femoral neck BMD	NRI for hip fractures: −0.003 for hip fracture NRI for vertebral fractures: 0 NRI for any fractures: 0.035
Dubbo nomogram	Langsetmo et al, 2011[149]	Participants ages 55–95 years at baseline in the Canadian Multicentre Osteoporosis Study	4,152 women	Mean: 8.6 years	14.04% (583/4,152)	WHO criteria of a T-score of ≤-2.5 for high risk	NRI: 0.015 in women (95% CI, -0.026 to 0.056)
						Canadian guidelines: low risk = 0%–10%, moderate = 10%–20%, and high = >20%	NRI: -0.055 (95% CI, -0.095 to -0.015)
			1,606 men	Mean: 8.3 years	7.2% (116/1,606)	WHO criteria of a T-score of ≤-2.5 for high risk	NRI: 0.067 (95% CI, -0.06 to 0.194)
						Canadian guidelines: low risk = 0%–10%, moderate = 10%–20% and high = >20%	NRI: 0.192 (95% CI, 0.063 to 0.322)
Garvan nomogram with body weight	Ahmed et al, 2014[129]	Participants age 60 years and older from Tromsø, Norway	1,637 women 1,355 men	Mean: 6.9 years Mean: 7.1 years	Nonvertebral osteoporotic fractures: 21.7% (356/1,637) Hip fractures: 5.4% (88/1,637)	Garvan nomogram with BMD	NRI for nonvertebral osteoporotic fractures: −0.106 (SE: 0.04) NRI for hip fractures: −0.172 (SE: 0.052)
					Nonvertebral osteoporotic fractures: 8.6% (117/1,355) Hip fracture: 3.5% (47/1,355)	Garvan nomogram with BMD	NRI for nonvertebral osteoporotic fractures: −0.133 (SE: 0.072) NRI for hip fractures: −0.175 (SE: 0.10)

Table 7. Reclassification of Risk With Osteoporosis Tools or Instruments

Tool or Instrument	Author, Year of Publication	Population	N	Followup Period	Fracture Rate	Clinical Threshold or Tool Used for Reclassification	Results
Lumbar spine trabecular bone score	Iki et al, 2014[164]	Japanese women age 50 years and older	665	Median: 10 years	13.8% (92/665)	Appears to be continuous (no risk categories specified)	NRI: 0.235 (95% CI, 0.15 to 0.54)

Abbreviations: BMD=bone mineral density; CI=confidence interval; DXA=dual energy X-ray absorptiometry; FRAX=Fracture Risk Assessment tool; FRC=Fracture Risk Calculator; N=number; NOF=National Osteoporosis Foundation; NRI=net reclassification improvement; QUS=quantitative ultrasound; SE=standard error; USA=United States of America; WHO=World Health Organization.

Table 8. Using Repeat BMD Testing to Predict Fracture Risk

Study	Study Cohort, Country	Inclusion / Exclusion Criteria	Mean Length of Followup, Years (Range)	N	Participant Characteristics	Bone Measurement Test	Fracture Site	AUC for Baseline BMD (95% CI)	AUC for BMD% Change (95% CI)	AUC for BMD Baseline and % Change (95% CI)
Berry, 2013[195]	Framingham Osteoporosis Study, USA	Included participants with at least two BMD measurements. Excluded those with fracture prior to second test.	3.7 (2.4 to 6.0)	802	Mean age: 74.8 (SD 4.5) Percent women: 61	DXA, BMD	Hip fracture[1]	0.71 (0.65 to 0.78)	0.68 (0.62 to 0.75)	0.72 (0.66 to 0.79)
							MOF fracture[1]	0.74 (0.69 to 0.79)	0.71 (0.66 to 0.76)	0.74 (0.69 to 0.79)
Hillier, 2007[194]	Study of Osteoporotic Fractures, USA	Included participants with at least two BMD measurements. Excluded those with fracture prior to second test.	8.0 (6.3 to 9.8)	4,124	Mean age: 74 (SD 4) Percent women: 100	DXA, BMD	Hip fracture[2]	0.73 (CI, NR)	0.68 (CI, NR)	0.74 (CI, NR)
							Nonspine fracture[2]	0.65 (CI,NR)	0.61 (CI, NR)	0.65 (CI, NR)
							Spine fracture[2]	0.67 (CI, NR)	0.62 (CI, NR)	0.68 (CI, NR)

[1] Adjusted for age, sex, BMI, weight loss, and history of fracture measured at the time of the second BMD.
[2] Adjusted for age and weight change.

Abbreviations: AUC=area under the curve; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DXA=dual energy X-ray absorptiometry; MOF=major osteoporotic fracture defined as fractures of the proximal femur, distal radius, proximal humerus, and clinical vertebral fractures; N=number; NR=not reported; SD=standard deviation; USA=United States of America.

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ1: Effectiveness of screening	Women	1; 12,483	Osteoporotic fratures: 12.9% vs. 13.6%; HR, 0.94; 95% CI, 0.85 to 1.03 All clinical fractures: 15.3% vs. 16.0%; HR:0.94; 95% CI, 0·86 to 1·03 Mortality: 8.8% vs. 8.4%; HR 1.05, 95% CI, 0.93 to 1.19 Hip fractures: 2.6% vs. 3.5%; HR 0.72; 95% CI, 0.59 to 0.89	Single study, consistency unknown/precise for hip fractures, imprecise for other outcomes	No evidence of reporting bias	Fair	Potential for contamination	Low for benefit for hip fractures, insufficient for other outcomes	Unclear whether findings apply to men or younger women
KQ 2a Accuracy of clinical risk assessment instruments for identifying osteoporosis	Women[a]	27; 55,898	AUCs range from 0.32 to 0.87 for all included instruments (pooled AUCs range from 0.65 to 0.76)	Inconsistent/ precise	No evidence of reporting bias	Fair	Heterogeneity in included studies	Moderate	Unclear whether findings apply to subgroups defined by age or race
KQ 2a Accuracy of clinical risk assessment instruments for identifying osteoporosis	Men	11; 14,052	AUCs range from 0.62 to 0.89 for all included instruments (pooled AUCs range from 0.76 to 0.80])	Inconsistent/ imprecise	No evidence of reporting bias	Fair	Heterogeneity in included studies	Low	Unclear whether findings apply to subgroups defined by age
KQ 2a Accuracy of machine-based tests for identifying osteoporosis	Women	7; 1,969	BMD tests for identifying osteoporosis: AUCs range from 0.67 to 0.94 for all included machine-based tests[b] (pooled AUC for calcaneal QUS: 0.77 [95% CI, 0.72 to 0.81])	Inconsistent/ precise	No evidence of reporting bias	Fair	Heterogeneity in included studies	Moderate	Unclear whether findings apply to subgroups defined by age or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ 2a Accuracy of machine-based tests for identifying osteoporosis	Men	3; 5,142	BMD tests for identifying osteoporosis for calcaneal QUS: 0.80 [95% CI, 0.67 to 0.94])	Inconsistent/ imprecise	No evidence of reporting bias	Fair	Ultrasound imaging only; heterogeneity in size, estimate of effect, and applicability of included studies	Low	Unclear whether findings apply to subgroups defined by age
KQ 2a Accuracy of machine-based tests for fracture prediction	Women	Varies by type of imaging test and site of test	Centrally measured DXA BMD, TBS, or a combination of both predicting fractures from 14 studies, N=46,036: AUCs range from 0.59 to0.86 For other machine-based tests or combination of tests, 2 studies with N=712 QUS alone predicting fractures: AUCs range from 0.66 to 0.72. QUS + DXA BMD predicting fractures: AUCs range from 0.72 to 0.81.	Inconsistent/ precise	No evidence of reporting bias	Fair	Inconsistent control for baseline variables	Moderate	Unclear whether findings apply to nonwhite subgroups
KQ 2a Accuracy of machine-based tests for fracture prediction	Men	3; 7,972	Centrally measured DXA BMD or TBS predicting fractures: AUCs range from 0.68 to 0.85 QUS alone predicting fractures: AUCs range from 0.64 to 0.84. QUS + DXA BMD predicting fractures: AUCs range from 0.69 to 0.85.	Inconsistent/ precise	No evidence of reporting bias	Fair to good	Inconsistent control for baseline variables	Moderate	Unclear whether findings apply to nonwhite, non-east Asian subgroups

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ 2a Accuracy of machine-based tests for fracture prediction	Women and Men combined	2; 46,300	Centrally measured DXA BMD predicting fractures: AUCs range from 0.66 to 0.80	Inconsistent/ precise	No evidence of reporting bias	Fair to good	None identified	Moderate	Findings limited to Canadian samples, unclear whether results are applicable to other populations
KQ 2a Accuracy of fracture risk prediction instruments	Women	Varies by instrument	AUCs for fracture risk prediction instruments range from 0.53 to 0.89, and vary by instrument, type of fracture, and whether BMD is used in the prediction. Within this range, prediction of hip fractures and predictions that use BMD report higher AUCs. Pooled AUC for FRAX prediction of hip fractures without BMD: 0.76 (95% CI, 0.72 to 0.82, I^2=99.8%, 12 studies, 190,795 women) and with BMD: 0.79 (95% CI, 0.76 to 0.81, I^2=99.1%, 10 studies, 161,984 women) Pooled AUC for FRAX prediction of MOF without BMD: 0.67 (95% CI, 0.65 to 0.68, I^2=99.2%, 17 studies, 158,897 women) and with BMD: 0.70 (95% CI, 0.68 to 0.71, I^2=92.1%, 12 studies, 62,054 women)	Inconsistent/ precise	No evidence of reporting bias	Fair	Some studies did not follow subjects for the entire duration of the prediction interval (i.e., 10 years). Heterogenous study populations, that may have included subjects with osteoporosis, with prior fracture, or receiving treatment.	Moderate	Other than FRAX, most instruments have not been calibrated for use in U.S. populations. Unclear whether findings apply to nonwhite subgroups.

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ 2a Accuracy of fracture risk prediction instruments	Men	Varies by instrument	AUCs for fracture risk prediction instruments range from 0.62 to 0.88, and vary by instrument, type of fracture, and whether BMD is used in the prediction.Within this range, prediction of hip fractures and predictions that use BMD report higher AUCs Pooled AUC for FRAX prediction of hip fractures without BMD: 0.73 (95% CI, 0.68 to 0.77, I^2=96.7%, 3 studies, 13,970 men) and with BMD: 0.76 (95% CI, 0.72 to 0.80, I^2=96.7%, 3 studies, 13,970 men) Pooled AUC for FRAX prediction of MOF without BMD: 0.62 (95% CI, 0.61 to 0.64, I^2=40.5%, 3 studies, 13,970 men) and with BMD: 0.67 (95% CI, 0.66 to 0.68, I^2=0%, 4 studies, 15,842 men)	Inconsistent/ precise	No evidence of reporting bias	Fair	Some studies did not follow subjects for the entire duration of the prediction interval (i.e., 10 years). Heterogenous study populations, that may have included subjects with osteoporosis, with prior fracture, or receiving treatment.	Moderate	Other than FRAX, most instruments have not been calibrated for use in U.S. populations. Unclear whether findings apply to nonwhite subgroups.
KQ 2b	Women and men (1 study each)	2; 4,926	Similar accuracy of predicting fracture with repeat BMD when compared with baseline BMD alone	Consistent/ precise	No evidence of reporting bias	Fair	Limited number of studies, follow up period inadequate for women, small N for men, inconsistent screening intervals	Insufficient	Unclear whether all findings apply to subgroups by age, sex, or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ3: Harms of screening	Women	1; 12,483	Anxiety: p value for repeated measures: 0.154 (variance NR) Quality of life: p value for repeated measures for Euroquol 5-Dimension and SF 12>0.10 (variance NR)	Single study, consistency and precision unknown	No evidence of reporting bias	Fair	Potential for contamination and reporting bias	Insufficient	Unclear whether findings apply to men or younger women
KQ 4a	Women and men	Varies by outcome	Bisphosphonates for women RR for vertebral fractures: 0.57 (95% CI, 0.41–0.78), 5 trials, N=5,433, 2.1% vs. 3.8% RR for nonvertebral fracures:0.84 (95% CI, 0.76 to 0.92); 8 trials, N=16,438, 8.9% vs. 10.6% RR for hip fractures: 0.70 (95% CI, 0.44 to 1.11); 3 trials, N=8,988, 0.7% vs. 0.96% Zoledronic acid for men RR for morphometric vertebral fracures: 0.33 (95% CI, 0.16 to 0.70); 1 trial, N=1,199, 1.5% vs. 4.6% RR for nonvertebral fractures, 0.65 (95% CI, 0.21 to 1.97), 1 trial, N=1,199, 0.9% vs. 1.3% RR for clinical fractures (vertebral or nonvertebral), 0.57 (95% CI, 0.21 to 1.52), 1 trial, N=1,199, 1.0% vs. 1.8%	Consistent/ precise for vertebral and nonvertebral fractures, consistent and imprecise for hip outcomes	No evidence of reporting bias	Fair	Evidence dominated by one big study for each drug	Moderate for benefit for bisphosphonates for vertebral and nonvertebral fractures, low for hip fractures	Unclear whether all findings apply to subgroups by age, sex, or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
	Women	1; 7,705	Raloxifene RR for vertebral fractures: 0.64 (95% CI, 0.53 to 0.76), 7.5% vs. 12.5% RR for nonvertebral fractures: 0.93 (0.81–1.06[c], 12.1% vs. 12.9%	Consistency unknown (single trial)/precise for vertebral fractures, imprecise for nonvertebral fractures	No evidence of reporting bias	Good	Single large trial	Moderate for benefit for vertebral fractures, low for nonvertebral fractures	Unclear whether findings apply to other sub-populations defined by age, sex, or race
	Women	Varies by outcome	Denosumab RR for vertebral fractures: 0.32 (95% CI, 0.26 to 0.41), 2 trials, 8,020 participants, 2.3% vs. 7.2% in trial with events RR for nonvertebral fractures: 0.80 (95% CI, 0.67 to 0.95), 1 trial, 7,808 participants, 6.1% vs. 7.5% RR for hip fractures: 0.60 (0.37 to 0.97), 1 trial, 7,808 participants, 0.7% vs. 1.1%	Consistency unknown (single trial for most outcomes)/ precise	No evidence of reporting bias	Fair	Single large trial for most outcomes	Low for benefit for vertebral, nonvertebral, and hip fractures	Unclear whether findings apply to subgroups by age, sex, or race
	Women and men	2; 2,830	Parathyroid hormone For women (1 trial, N=2,532) RR for vertebral fractures: 0.32 (95% CI: 0.14 to 0.75), 0.7% vs. 2.1%, RR for nonvertebral fractures: 0.97 (95% CI, 0.71 to 1.33), 5.6% vs. 5.8% For men (1 trial, N=298) RR for nonvertebral fractures: 0.65 (95% CI, 0.11 to 3.83), 1.3% vs. 2.0%	Consistency unknown (single trial/ precise for women for vertebral fractures Consistency unknown (single trial)/ imprecise for men for vertebral fractures	No evidence of reporting bias	Fair	Single trial each for men and women; small trial in men	Low for benefit for vertebral fractures for women, insufficient for men for vertebral fractures	Unclear whether findings apply to subgroups by age, sex, or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ 4b	Women	4; N varies by drug	Similar results by subgroup for Alendronate for baseline BMD (1 trial, N=3,737) Risedronate for age (1 trial, N=2,648) Raloxifene (prior fractures, 1 trial, N=5,114) Denosumab for age, baseline BMD, and a combination of risk factors (1 trial, N=7,868)	Consistency unknown (single trial)/ precise	No evidence of reporting bias	Fair	Single trial for each drug	Low for no differences	No information on variations by menopausal status

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
KQ 5	Women and men	Varies by outcome	Bisphosphonates[d] RR for discontinuations: RR, 0.99 (95% CI, 0.91 to 1.07) 20 trials, N=17,369[e], 11.5% vs. 11.8% RR for serious adverse events: RR, 0.98 (95% CI, 0.92 to 1.04), 17 trials, N=11,745[e], 21.0% vs. 23.4% RR for upper GI events: 1.01 (95% CI, 0.98 to 1.05); 13 trials, N=20,485[e], 35.3% vs. 35.6% No statistically significant differences for cardiovascular outcomes No reports of osteonecrosis of the jaw No reports of atypical femur fracture No reports of kidney failure 3 trials combining results for men and women or included men only had results consistent with trials of women only for discontinuations, serious adverse events, and upper GI events	Consistent/ precise for discontinuations, serious adverse events, and upper gastrointestinal events; inconsistent and imprecise for cardiovascular outcomes, osteonecrosis and atypical femur fractures	No evidence of reporting bias	Fair	Evidence dominated by one big study for each drug	Moderate for no harms bisphosphonates for discontinuation, serious adverse events, and upper gastrointestinal events; insufficient for cardiovascular events, osteonecrosis and atypical femur fractures	Unclear whether findings for all drugs apply to sub-populations defined by age, sex, or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
	Women	Varies by outcome	Raloxifene RR for discontinuations: RR, 1.12 (95% CI, 0.98 to 1.28); 6 trials, N=6,438, 12.6% vs. 11.2% RR for deep vein thrombosis: 2.14 (95% CI, 0.99 to 4.66); 3 trials, N=5,839, 0.7% vs. 0.3% RR for hot flashes: 1.42 (95% CI, 1.22 to 1.66); 5 trials; N=6,249, 11.2% vs. 7.6% RR for leg cramps: 1.41 (95% CI: 0.92 to 2.14); 3 trials; N=6,000, 8.0% vs. 4.8%	Inconsistent/ precise for deep vein thrombosis, leg cramps, and hot flashes; consistent/ imprecise for discontinuation	No evidence of reporting bias	Good	Single large trial dominating results	Low for harm for deep vein thrombosis and hot flashes; low for no harm discontinuation and leg cramps	Unclear whether findings apply to other sub-populations defined by age, sex, or race
	Women	Varies by outcome	Denosumab RR for discontinuations: 1.14 (95% CI, 0.85 to 1.52), 2.4% vs. 2.1% RR for serious adverse events: 1.12 (95% CI, 0.88 to 1.44), 23.8% vs. 23.9% RR for serious infections: 1.89 (95% CI, 0.61 to 5.91), 4.0% vs. 3.3%	Inconsistent/ imprecise for discontinuations, consistent/ imprecise for serious adverse events and serious infections	No evidence of reporting bias	Fair	Single large trial dominating results	Insufficient for discontinuation; low for no harm for serious adverse events and serious infections	Unclear whether findings apply to subgroups by age, sex, or race

Table 9. Summary of Evidence

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence: For Outcome	Applicability
	Women and men	2; 2,830	Parathyroid hormone For women (1 trial, N=2,532) RR for discontinuations: 1.23 (1.08-1.40), 30.2% vs. 24.6% For men (1 trial, N=298 for 20 µg [FDA approved dose] vs. placebo) RR for discontinuations: 1.94 (0.81-4.69), 9.2% vs. 4.8% RR for cancers: 0.97 (0.2-4.74), 2.0 vs. 2.0%	Consistency unknown (single trial)/precise Consistency unknown (single trial)/ imprecise for men	No evidence of reporting bias	Fair	Single trial each for men and women; small trial in men	Low for harm for women for discontination; insufficient for men for discontinuations and serious adverse events	Unclear whether findings apply to subgroups by age or race

[a] One study (not included in strength of evidence ratings; N=282) evaluated the accuracy of FRAX and OST in a mixed population with 45.1% women. AUCs ranged from 0.68 to 0.76 and is consistent with findings in men and women separately.
[b] Included studies evaluated calcaneal quantitative ultrasound, peripheral dual energy X-ray absorptiometry, digital X-ray radiogrammetry, and radiographic absorptiometry.
[c] Data available only for combined group of participants receiving dosages of 60 mg/day or 120 mg/day. Recommended dosage is 60 mg/day.
[d] Pooled estimates include men, women, and combined estimates (one study did not provide adverse events by sex).[254]
[e] Sum of N in trials in meta-analysis, after accounting for the duplication in patients in the placebo arm for a 3-arm study.[202]

Abbreviations: AUC=area under the curve; BMD=bone mineral density; CI=confidence interval; DXA=dual-energy X-ray absorptiometry; EPC=Evidence-based Practice Center; FDA=Food and Drug Administration; FRAX=Fracture Risk Assessment Tool; KQ=key question; MOF=major osteoporotic fractures; N=number; QUS=quantitative ultrasound; RR=relative risk; TBS=trabecular bone score; U.S.=United States.

Table 10. Accuracy of Clinical Risk Prediction Instruments With Evidence on Identifying Osteoporosis and Predicting Fractures

Instrument	Risk Factors	Sex	Accuracy in Identifying Osteoporosis (at Femoral Neck or Any Skeletal Site as Indicated); N of Studies; N of Participants	Accuracy in Predicting Fractures
FRAX without BMD	Age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoid steroid use, rheumatoid arthritis, secondary osteoporosis, alcohol use	Men and women	Men: *MOF*: 0.79 (0.74 to 0.84); 1; 1,498 *Hip*: NR Women: *MOF*: Ranges from 0.58 to 0.82; (any site or hip) 4; 22,141 *Hip*: 0.82 (any site); 1; 505 Both sexes† (any site): *MOF*: 0.68 (95% CI, 0.63 to 0.74); 1; 626 *Hip*: 0.70 (95% CI, 0.64 to 0.75); 1; 626	<u>*Men*</u> *MOF:* 0.62 (95% CI, 0.61 to 0.64); 3; 13,970 *Hip*: 0.73 (95% CI, 0.68 to 0.77); 3; 13,970 <u>*Women*</u> *MOF:* 0.67 (95% CI, 0.65 to 0.68); 17; 158,897 *Hip*: 0.76 (95% CI, 0.72 to 0.81); 12; 190,795 <u>*Both Sexes*</u> *MOF*: 0.67 (95% CI, 0.66 to 0.67); 3; 66,777 *Hip:* 0.77 (95% CI, 0.73 to 0.79); 1; 6,697 0.79 (95% CI, 0.78 to 0.82); 1; 39,603
SCORE	Age, weight, race, rheumatoid arthritis, prior nontraumatic fracture, prior estrogen use	Women	Pooled AUC (any site): 0.70, (95% CI, 0.69 to 0.71); 8; 15,362	MOF (10-year risk): 0.53 (95% CI, 0.53 to 0.54); 1; 62,492 MOF (3-year risk): 0.70 (95% CI, 0.66 to 0.74);1; 3,614
ORAI	Age, weight, current estrogen use	Women	Pooled AUC (any site): 0.65 (95% CI, 0.60 to 0.71); 10; 16,780	MOF(3-year risk): 0.71 (95% CI, 0.68 to 0.75); 1; 3,614 Any OF (3-year risk): 0.69 (95% CI, 0.66 to 0.72); 1; 3,614
OSIRIS	Age, weight, current hormone therapy use, prior fracture	Women	Pooled AUC (any site): 0.68 (95% CI 0.64 to 0.72); 5; 5,649	MOF (3-year risk): 0.70 (95% CI, 0.66 to 0.74); 1; 3,614 Any OF (3-year risk): 0.68 (95% CI, 0.65 to 0.72); 1; 3,614
OST	Age, weight	Women	Pooled AUC (any site): 0.65 (95% CI, 0.60 to 0.69); 13; 44,323; without outlier,[88, 89] pooled AUC: 0.71, 95% CI, 0.70 to 0.72; 11; 42,802	MOF (3-year risk): 0.56 (95% CI, 0.52 to 0.60, 8,254 women) 0.71 (95% CI, 0.68 to 0.75, 3,614 women) MOF (10-year risk): 0.52 (95% CI, 0.52 to 0.53, 62,492 women)

† Study population was 45.5% women.

Abbreviations: AUC=area under the curve; BMD=bone mineral density; CI=confidence interval; FRAX=Fracture Risk Assessment Tool; MOF=major osteoporotic fracture defined as fractures of the proximal femur, distal radius, proximal humerus, and clinical vertebral fractures; OF=osteoporotic fracture; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool.

Osteoporosis Search April 16, 2015

Pubmed

	Search String	Results
#1	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]	197432
#5	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh] Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	19932
#7	Search "Mass Screening"[Mesh] OR "Risk Assessment"[Mesh]	281086
#8	Search (#5 AND #7)	1279
#9	Search (#5 AND #7) Filters: Systematic Reviews	85
#11	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2263475
#12	Search (#8 AND #11)	818
#13	Search (#9 OR #12)	859
#14	Search ("Osteoporosis"[Mesh] OR "Bone Density"[Mesh] OR "Calcaneus"[Mesh])	74931
#18	Search ("Osteoporosis"[Mesh] OR "Bone Density"[Mesh] OR "Calcaneus"[Mesh])Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	8672
#20	Search (("Ultrasonography"[Mesh]) OR "Tomography, X-Ray Computed"[Mesh]) OR ("Densitometry"[Mesh] OR "Absorptiometry, Photon"[Mesh])	573915
#21	Search (#18 AND #20)	2718
#22	Search (#18 AND #20) Filters: Systematic Reviews	33
#23	Search (#21 AND #11)	1336
#24	Search (#22 OR #23)	1354
#25	Search (("Osteoporosis"[Mesh] OR "Bone Density"[Mesh]))	70305
#29	Search (("Osteoporosis"[Mesh] OR "Bone Density"[Mesh])) Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	8207
#31	Search (((((("Diphosphonates"[Mesh]) OR "Alendronate"[Mesh] OR "risedronic acid"[Supplementary Concept]) OR "Etidronic Acid"[Mesh]) OR "ibandronic acid"[Supplementary Concept]) OR "pamidronate"[Supplementary Concept]) OR "zoledronic acid"[Supplementary Concept] OR Bone Density Conservation Agents[mesh] "Calcium Carbonate"[Mesh] OR "Estrogen Receptor Modulators"[Mesh] OR "Selective Estrogen Receptor Modulators"[Mesh]	5166
#32	Search (("Calcitonin"[Mesh]) OR (("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh]) OR "Estradiol Congeners"[Mesh])) OR ((((("Parathyroid Hormone"[Mesh]) OR "Tamoxifen"[Mesh]) OR "Teriparatide"[Mesh] OR "Raloxifene"[Mesh]) OR "Testosterone"[Mesh]) OR "RANK ligand inhibitor" OR "estropipate" [Supplementary Concept] OR "bazedoxifene" [Supplementary Concept]	206284
#33	Search (#31 OR #32)	207691
#34	Search (#29 AND #33)	977
#35	Search (#34 and #11)	534
#36	Search (#29 AND #33) Filters: Systematic Reviews	27
#41	Search #35 OR #36	552
#42	Search (#41 OR #24 OR #13)	2439

Cochrane

Osteoporosis AND (screening OR treatment) = 40

Embase

Osteoporosis AND (screening OR treatment) = 233

ClinicalTrials.gov

Osteoporosis AND (screening OR treatment) = 285

Drugs@FDA.gov

Osteoporosis AND (screening OR treatment)

HSRProj

"osteoporosis" = 19

Cochrane Clinical Trials Registry

Osteoporosis AND (screening OR treatment) = 1068

WHO ICTRP

Osteoporosis AND (screening OR treatment) = 23

Official "Risk Assessment" Add in for Earlier Work (October 16, 2015)

	Search String	Results
#1	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]	202036
#2	Search "Mass Screening"[Mesh] OR screen	237370
#3	Search "Risk Assessment"[Mesh]	190623
#4	Search (#3 NOT #2)	183589
#5	Search (#1 AND #4)	3743
#6	Search (#1 AND #4) Filters: Humans	3719
#7	Search (#1 AND #4) Filters: Humans; English	3416
#8	Search (#1 AND #4) Filters: Humans; English; Adult: 19+ years	2450
#9	Search (#1 AND #4) Filters: Publication date from 2001/01/01 to 2009/12/31; Humans; English; Adult: 19+ years	1207

Osteoporosis Update Search October 16, 2015

Pubmed

Full Results for All Screening or Risk Assessment (Not narrowed by study type)

	Search String	Results
#1	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]	202036
#8	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]Filters: Humans	176314
#9	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]Filters: Humans; English	131410
#10	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]Filters: Humans; English; Adult: 19+ years	83026
#11	Search "Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	22192
#13	Search "Mass Screening"[Mesh] OR "Risk Assessment"[Mesh]	289991
#14	Search (#11 AND #13)	1388

Updates for April Search

	Search String	Results
#15	Search ((“Osteoporosis”[Mesh] OR “Bone Density”[Mesh] OR “Calcaneus”[Mesh]))	76720
#18	Search ((“Osteoporosis”[Mesh] OR “Bone Density”[Mesh] OR “Calcaneus”[Mesh]))Filters: Humans; English; Adult: 19+ years	35637
#19	Search (“2015”[Date - Entrez] : “3000”[Date - Entrez]) Filters: Humans; English; Adult: 19+ years	32504
#21	Search ((“Ultrasonography”[Mesh]) OR “Tomography, X-Ray Computed”[Mesh]) OR (“Densitometry”[Mesh] OR “Absorptiometry, Photon”[Mesh])	590335
#22	Search (#18 AND #19 AND #21)	58
#23	Search (#18 AND #19 AND #21) Filters: Systematic Reviews	0
#25	Search ((“Controlled Clinical Trial” [Publication Type] OR “Randomized Controlled Trial” [Publication Type] OR “Meta-Analysis” [Publication Type] OR “Cohort Studies”[Mesh]) OR “Case-Control Studies”[Mesh] OR “Sensitivity and Specificity”[Mesh])	2344296
#26	Search (#18 AND #19 AND #25)	111
#28	Search (((“Osteoporosis”[Mesh] OR “Bone Density”[Mesh])))	71994
#31	Search (((“Osteoporosis”[Mesh] OR “Bone Density”[Mesh]))) Filters: Humans; English; Adult: 19+ years	33693
#32	Search (#31 AND #19) Filters: Humans; English; Adult: 19+ years	190
#34	Search (((((((“Diphosphonates”[Mesh]) OR “Alendronate”[Mesh] OR “risedronic acid”[Supplementary Concept]) OR “Etidronic Acid”[Mesh]) OR “ibandronic acid”[Supplementary Concept]) OR “pamidronate”[Supplementary Concept]) OR “zoledronic acid”[Supplementary Concept] OR Bone Density Conservation Agents[mesh] “Calcium Carbonate”[Mesh] OR “Estrogen Receptor Modulators”[Mesh] OR “Selective Estrogen Receptor Modulators”[Mesh])) OR (((“Calcitonin”[Mesh]) OR ((“Hormone Replacement Therapy”[Mesh] OR “Estrogen Replacement Therapy”[Mesh]) OR “Estradiol Congeners”[Mesh])) OR ((((“Parathyroid Hormone”[Mesh]) OR “Tamoxifen”[Mesh]) OR “Teriparatide”[Mesh] OR “Raloxifene”[Mesh]) OR “Testosterone”[Mesh]) OR “RANK ligand inhibitor” OR “estropipate” [Supplementary Concept] OR “bazedoxifene” [Supplementary Concept] OR “denosumab” [Supplementary Concept])	210994
#35	Search (#32 AND #34)	22
#36	Search (#35 AND #25)	15
#37	Search (#32 AND #34) Filters: Systematic Reviews	0

PubMed = 117 = **98 NEW**

Cochrane

Osteoporosis AND (screening OR treatment) = 0 NEW

Embase

Osteoporosis AND (screening OR treatment) = 65 = 44 NEW

ClinicalTrials.gov

Osteoporosis AND (screening OR treatment) = 3 = 0 NEW
(Citations provided separately – not part of database)

Drugs@FDA.gov

Will do targeted searches for “harms” as indicated

HSRProj

"osteoporosis" = 1 = 0

Cochrane Clinical Trials Registry

Osteoporosis AND (screening OR treatment) = 48 = 44 New

WHO ICTRP

Osteoporosis AND (screening OR treatment) = 0
Total Unduplicated Database = 186

TBS Add on (December 21, 2015)

	Search String	Results
#102	Search "trabecular bone score"	113
#105	Search ("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh])	293426
#106	Search (#102 AND #105)	17
#107	Search (#102 AND #105) Filters: Systematic Reviews	0
#108	Search (#102 AND #105) Schema: all Filters: Systematic Reviews	0
#109	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2376092
#110	Search (#102 AND #109)	32
#114	Search (#102 AND #109) Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	28

7 new

Supplemental Denosumab Search (July 29, 2016)

	Search String	Results
#1	Search denosumab	1631
#4	Search "Osteoporosis"[Mesh] OR "Bone Density"[Mesh]	74955
#5	Search (#1 AND #4)	566
#6	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2474527
#7	Search (#5 AND #6)	116
#8	Search (#5 AND #6) Filters: Humans	116
#9	Search (#5 AND #6) Filters: Humans; English	114
#10	Search (#5 AND #6) Filters: Humans; English; Adult: 19+ years	98

Supplemental Pharmaceutical Search and Deduplication (8/1/2016)

	Search String	Results
#1	Search "Fractures, Bone"[Mesh]	157410
#2	Search (("Osteoporosis"[Mesh] OR "Bone Density"[Mesh]))	74997
#3	Search (#1 NOT #2)	140422
#7	Search (#1 NOT #2) Filters: Publication date from 2009/11/01; Humans; English; Adult: 19+ years	15369
#10	Search (("Calcitonin"[Mesh]) OR (("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh]) OR "Estradiol Congeners"[Mesh])) OR ((((("Parathyroid Hormone"[Mesh]) OR "Tamoxifen"[Mesh]) OR "Teriparatide"[Mesh] OR "Raloxifene"[Mesh]) OR "Testosterone"[Mesh]) OR "RANK ligand inhibitor" OR "estropipate" [Supplementary Concept] OR "bazedoxifene" [Supplementary Concept] OR "denosumab" [Supplementary Concept]	218717
#11	Search (((((("Diphosphonates"[Mesh]) OR "Alendronate"[Mesh] OR "risedronic acid"[Supplementary Concept]) OR "Etidronic Acid"[Mesh]) OR "ibandronic acid"[Supplementary Concept]) OR "pamidronate"[Supplementary Concept]) OR "zoledronic acid"[Supplementary Concept] OR Bone Density Conservation Agents[mesh] "Calcium Carbonate"[Mesh] OR "Estrogen Receptor Modulators"[Mesh] OR "Selective Estrogen Receptor Modulators"[Mesh]	5443
#12	Search (#10 OR #11)	220200
#13	Search (#7 AND #12)	119
#14	Search (#7 AND #12) Filters: Systematic Reviews	7
#15	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2477337
#18	Search (#13 AND #15)	45
#19	Search (#14 OR #18)	47

Update to Full Search (10/1/2016)

	Search String	Results
#1	Search ("Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh])	216915
#5	Search ("Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh]) Filters: Publication date from 2016/01/01; Humans; English; Adult: 19+ years	519
#6	Search ("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh])	308814
#7	Search (#5 AND #6)	31
#8	Search (#5 AND #6) Filters: Systematic Reviews	2
#9	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2505387
#10	Search (#7 AND #9)	24
#11	Search (#8 OR #10)	24
#13	Search ("Osteoporosis"[Mesh] OR "Bone Density"[Mesh] OR "Calcaneus"[Mesh])	80677
#16	Search ("Osteoporosis"[Mesh] OR "Bone Density"[Mesh] OR "Calcaneus"[Mesh])Filters: Humans; English; Adult: 19+ years	37386
#17	Search ("Osteoporosis"[Mesh] OR "Bone Density"[Mesh] OR "Calcaneus"[Mesh])Filters: Publication date from 2016/01/01; Humans; English; Adult: 19+ years	202
#19	Search (("Ultrasonography"[Mesh]) OR "Tomography, X-Ray Computed"[Mesh]) OR ("Densitometry"[Mesh] OR "Absorptiometry, Photon"[Mesh]))	622542
#20	Search (#17 AND #19)	80
#21	Search (#17 AND #19) Filters: Systematic Reviews	0
#22	Search (#20 AND #9)	44
#24	Search (("Osteoporosis"[Mesh] OR "Bone Density"[Mesh]))	75586
#28	Search (("Osteoporosis"[Mesh] OR "Bone Density"[Mesh])) Filters: Publication date from 2016/01/01; Humans; English; Adult: 19+ years	198
#30	Search (((((("Diphosphonates"[Mesh]) OR "Alendronate"[Mesh] OR "risedronic acid"[Supplementary Concept]) OR "Etidronic Acid"[Mesh]) OR "ibandronic acid"[Supplementary Concept]) OR "pamidronate"[Supplementary Concept]) OR "zoledronic acid"[Supplementary Concept] OR Bone Density Conservation Agents[mesh] "Calcium Carbonate"[Mesh] OR "Estrogen Receptor Modulators"[Mesh] OR "Selective Estrogen Receptor Modulators"[Mesh]	5478

	Search String	Results
#31	Search ((("Calcitonin"[Mesh]) OR (("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh]) OR "Estradiol Congeners"[Mesh])) OR ((((("Parathyroid Hormone"[Mesh]) OR "Tamoxifen"[Mesh]) OR "Teriparatide"[Mesh] OR "Raloxifene"[Mesh]) OR "Testosterone"[Mesh]) OR "RANK ligand inhibitor" OR "estropipate" [Supplementary Concept] OR "bazedoxifene" [Supplementary Concept] OR "denosumab" [Supplementary Concept])	219684
#32	Search (#30 OR #31)	221184
#33	Search (#28 AND #32)	19
#34	Search (#28 AND #32) Filters: Systematic Reviews	0
#36	Search (#33 AND #9)	12
#38	Search (#11 OR #22 OR #36)	71

Total New Unduplicated Database Additions = 76

TBS Add on (10/1/2016)

	Search String	Results
#1	Search "trabecular bone score"	160
#2	Search ("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh])	308814
#3	Search ("trabecular bone score") AND (("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh]))	22
#4	Search ("trabecular bone score") AND (("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh])) Filters: Systematic Reviews	0
#5	Search ("trabecular bone score") AND (("Mass Screening"[Mesh] OR "Risk Assessment"[Mesh])) Schema: all Filters: Systematic Reviews	0
#6	Search (("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])	2505387
#7	Search ("trabecular bone score") AND ((("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh]))	43
#8	Search ("trabecular bone score") AND ((("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])) Filters: Humans	43
#9	Search ("trabecular bone score") AND ((("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])) Filters: Humans; Adult: 19+ years	41
#10	Search ("trabecular bone score") AND ((("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])) Filters: Humans; English; Adult: 19+ years	40
#11	Search ("trabecular bone score") AND ((("Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh] OR "Sensitivity and Specificity"[Mesh])) Filters: Publication date from 2015/01/01; Humans; English; Adult: 19+ years	14

Total New Unduplicated Database Additions = 12

Appendix B. Screening for Osteoporosis: Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
1. Was the article published in English?	X1	Not published in English	Study must be published in English	Study not published in English
2. Does the title/abstract represent original research?	X2	Not original research	Published or unpublished original research	Nonsystematic review article, letter, or editorial; articles in which results are reported elsewhere; articles with no original data
3. **KQs 1–3:** Does the study report on general primary care men and women age ≥40 years without history of low trauma fractures; or endocrine disorders likely to be related to metabolic bone disease, such as premature ovarian failure, hypogonadism, untreated hyperthyroidism, hyperparathyroidism, adrenal insufficiency or Cushing's syndrome; or chronic use of glucocorticoids medications (>5 mg/d oral prednisone (or equivalent) for 3 months or longer)? **KQs 4, 5:** Does the review report on adults age ≥40 years with increased fracture risk?	X3	Wrong population	**KQs 1–3:** General primary care men and women age ≥40 years without history of low trauma fractures; or endocrine disorders likely to be related to metabolic bone disease, such as premature ovarian failure, hypogonadism, untreated hyperthyroidism, hyperparathyroidism, adrenal insufficiency or Cushing's syndrome; or chronic use of glucocorticoids medications (>5 mg/d oral prednisone (or equivalent) for 3 months or longer) **KQs 4, 5:** Majority are adults with increased fracture risk	**KQs 1–5:** • Majority of study population has underlying medical condition likely to be related to metabolic bone disease or is already receiving treatment for osteoporosis or has experienced a low-trauma facture • Nonhuman populations • Majority of study population comprises adults younger than age 40 years **KQs 4, 5:** Majority are adults with no increased fracture risk
4. Does the study use of a study design of interest?	X4	Wrong study design	**KQs 1–3:** • Randomized, controlled trials • Controlled clinical trials • Systematic reviews of trials **KQs 2, 3:** Observational studies other than case series and case reports **KQ 4:** Systematic reviews and randomized controlled trials, controlled trials published since any recent, relevant review **KQ 5:** Systematic reviews and randomized controlled trials, controlled trials, and observational studies published since any recent, relevant review	**KQ 1:** Nonrandomized, controlled trials; noncontrolled clinical trials, or nonsystematic reviews of trials **KQs 2, 3:** Case series, case reports **KQs 4, 5:** Nonsystematic reviews, case series, case reports ***KQ 4:*** *Case control studies*[a]
5. Does the study include countries with a human development index (HDI) similar to the United States?	X5	Wrong geographical setting	**KQs 1, 4, 5:** U.S. adult population or comparable populations (i.e., those categorized as "Very High" on the Human Development Index, as defined by the United Nations Development Programme)[b] **KQs 2, 3:** Include all geographic settings	**KQs 1, 4 5:** Settings not comparable or applicable to U.S. adult population **KQs 2, 3:** Include all geographic settings at this time

Appendix B. Screening for Osteoporosis: Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
6. Is the study conducted in a clinical setting of interest?	X6	Wrong clinical setting	**KQ 1:** Primary care or primary care–like settings **KQs 2–5:** Primary care or primary care–like settings, specialists	**KQ 1:** Inpatient, medical specialty (e.g., endocrinology), or nursing home settings **KQs 2–5:** Inpatient or nursing home settings
7. Does the study include an intervention of interest?	X7	Wrong or no intervention	**KQs 1–3:** Externally validated and publicly available risk assessment instruments for low bone mass, osteoporosis, or fracture risk (interventions available in the United States) *Risk assessment tools are any paper-based or electronic approach/instrument that compiles/consolidates various demographic or clinical characteristics of an individual and compares an individual's characteristics against a threshold or guideline to make a subsequent decision for testing or treatment. Examples include age, body weight criterion, Brown's clinical risk assessment, "clinical guidelines," "case identification algorithm," Elderly Falls Screening Test, Fracture absolute risk assessment, Garvan Fracture Risk Calculator, Male Osteoporosis Risk Estimation Score (MORES), NOF guidelines, Nomograms, Osteoporosis Self-Assessment Tool; Osteoporosis Self assessment Tool for Asians (OSTA); modified OSTA, ORAI, OSIRIS, QFracture algorithm, Simple Calculated Osteoporosis Risk Estimate (SCORE)*[a] *Eligible bone measurement testing includes DXA (central or peripherally measured) and quantitative ultrasound, also include dental bone tests and trabecular bone score*[a]	**KQs 1–3:** • Not externally validated or publicly available risk assessment or bone measurement testing *specifically for osteoporosis or fracture risk*[a] • Test not widely for routine clinical use in the United States **KQs 2, 3:** Non-FDA approved tests for screening; biomarkers of bone metabolism, quantitative CT, MRI, hip structural analysis, structural engineering models, finite element analysis

Appendix B. Screening for Osteoporosis: Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
7. Does the study include an intervention of interest? (continued)			***KQs 4, 5:*** *Pharmacotherapy for the treatment or prevention of osteoporosis (including bisphosphonates, estrogen agonists/antagonists, hormone therapy, parathyroid hormone, and RANK Ligand Inhibitors)* -Note: Bazedoxifine alone is not FDA approved, calcitonin is no longer used as first-line therapy[a]	**KQs 4, 5:** Interventions other than those described in the inclusion criteria
8. Does the study include a comparator of interest?	X8	Wrong or no comparator	**KQ 1 (control interventions):** No screening group **KQs 2, 3 (control interventions):** *Other risk assessment/testing approach, threshold, or interval; DXA screening at hip or lumbar spine reporting T-scores based on NHANES III US White Female reference ranges*[a] **KQ 4 (control interventions):** Placebo **KQ 5 (control interventions):** Placebo or no treatment	**KQ 1 (control interventions):** Lack of a no screening group (active comparator) **KQ 2 (control interventions):** Not an active comparator; n*o comparator, DXA screening at peripheral sites, other non-central DXA imaging tests (e.g., quantitative ultrasound), T-scores based on non-NHANES or local reference ranges*[a] **KQ 3:** None **KQs 4, 5 (control interventions):** Active comparator

Appendix B. Screening for Osteoporosis: Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
9. Does the study include an outcome of interest?	X9	Wrong or no outcome	**All KQs:** Fractures, fracture-related morbidity, fracture-related mortality, or all-cause mortality. *Fractures include "major osteoporotic fractures," which include fractures of the hip, wrist (including distal radius), humerus, and spine/vertebral (clinically presenting). Morphometric spine/ vertebral fractures will also be included but recorded separately if possible.*[a] **KQ 2:** • Screening test characteristics *(e.g., Youden's index, sensitivity, specificity, area under the receiver operating characteristic curve or AUC, positive predictive value, negative predictive value, diagnostic odds ratio, likelihood ratio)*[a] *and reliability (test-retest measures such as Kappa)*[a] *of risk assessment (for fractures)*[a]*, bone mass measurement (for fractures or identification of osteoporosis)*[a]*, or both (for fractures)*[a] • Fracture risk prediction characteristics (overall model performance *[Brier score, R-squared] extended measures of discrimination [concordance statistic c, discrimination slope], calibration [calibration-in-the-large, calibration slope, "goodness-of-fit" test or Hosmer-Lemeshow test], reclassfication [reclassification table, reclassification calibration, net reclassification improvement, integrated discrimination improvement]), and clinical usefulness (net benefit, decision curve analysis)*[a] • Risk assessment instruments for identifying osteoporosis: AUC for ROC curves for identifying BMD ≤−2.5	Exclude if: **KQ 1 *and KQ 4*:** • Nonvalidated fractures (*i.e., self-reported*)[a], fracture-related morbidity, or fracture-related mortality • Bone measurement testing (T-scores, z-scores) **KQ 2:** Outcomes *other than screening test or risk prediction characteristics*[a] ***KQs 3, 5:*** *No health outcomes excluded for harms*[a]

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
9. Does the study include an outcome of interest? (continued)			**KQ 3:** Harms (e.g., unnecessary radiation, labeling, anxiety, false-positive results) **KQ 5:** Harms (e.g., cardiovascular events, hot flashes, esophageal cancer, gastrointestinal events, osteonecrosis of the jaw, atypical fractures of the femur, rashes)	

[a] Italicized text represents additional clarification to operationalize inclusion and exclusion criteria.
[b] Very high human development index countries include Norway, Australia, Switzerland, Denmark, Netherlands, Germany, Ireland, United States, Canada, New Zealand, Singapore, Hong Kong, China (SAR), Liechtenstein, Sweden, United Kingdom, Iceland, Korea (Republic of), Israel, Luxembourg, Japan, Belgium, France, Austria, Finland, Slovenia, Spain, Italy, Czech Republic, Greece, Estonia, Brunei Darussalam, Cyprus, Qatar, Andorra, Slovakia, Poland, Lithuania, Malta, Saudi Arabia, Argentina, United Arab Emirates, Chile, Portugal, Hungary, Bahrain, Latvia, Croatia, Kuwait, Montenegro (http://hdr.undp.org/en/content/table-1-human-development-index-and-its-components).

Appendix C. Reasons for Exclusion

X1: not published in English
X2: not original research
X3: wrong population
X4: wrong study design
X5: wrong geographic setting
X6: wrong clinical setting
X7: wrong or no intervention
X8: wrong or no comparator
X9: wrong or no outcome
X10: article retracted
X11: bone measurement after outcome
X12: exclude not commercially available
X13: not FDA approved
X14: not in externally validated cohort
X15: not in very high HDI country
X16: study superseded by new evidence
X17: only used for hand search
X18: full text article not accessible
X19: insufficient information for abstraction
X20: poor quality

1. Menostar: a low-dose estrogen patch for osteoporosis. Obstet Gynecol. 2005 Feb;105(2):432-3. PMID: 15684177. Exclusion Code: X2.
2. Bone health may get higher visibility with new approach to fracture risk assessment that considers multiple factors. Dis Manag Advis. 2007 Sep;13(9):104-5, 97. PMID: 17907656. Exclusion Code: X2.
3. Discontinuing denosumab treatment does not increase fracture risk. Bonekey Rep. 2013;2:269. doi: 10.1038/bonekey.2013.3. PMID: 24422041. Exclusion Code: X9.
4. Abendroth K, Mohrke W. Number and incidence of hip fractures in Germany from 2000 to 2013 : Is hip fracture prevention by osteoporosis therapy derivable from these epidemiological data?. [German]. In Osteologie Exclusion Code: X18.
5. Abou-Raya S, Abou-Raya A, Khadrawi T. A randomized controlled trial of early initiation of osteoporosis assessment and management in the acute setting of the fracture clinic. In Ann Rheum Dis Exclusion Code: X9.
6. Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab. 2010 Dec;95(12):5258-65. doi: 10.1210/jc.2010-1571. PMID: 20843943. Exclusion Code: X20.
7. Abrahamsen B, Vestergaard P, Rud B, et al. Ten-year absolute risk of osteoporotic fractures according to BMD T score at menopause: the Danish Osteoporosis Prevention Study. J Bone Miner Res. 2006 May;21(5):796-800. doi: 10.1359/jbmr.020604. PMID: 16734396. Exclusion Code: X7.
8. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum. 2001 Jan;44(1):202-11. doi: 10.1002/1529-0131(200101)44:1<202::aid-anr27>3.0.co;2-w. PMID: 11212161. Exclusion Code: X3.
9. Adami S, Bianchi G, Brandi ML, et al. Validation and further development of the WHO 10-year fracture risk assessment tool in Italian postmenopausal women: project rationale and description. Clin Exp Rheumatol. 2010 Jul-Aug;28(4):561-70. PMID: 20497630. Exclusion Code: X4.
10. Adami S, Libanati C, Boonen S, et al. Denosumab treatment in postmenopausal women with osteoporosis does not interfere with fracture-healing: results from the FREEDOM trial. J Bone Joint Surg Am. 2012 Dec 5;94(23):2113-9. doi: 10.2106/JBJS.K.00774. PMID: 23097066. Exclusion Code: X9.

11. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost. 2008 Feb;99(2):338-42. PMID: 18278183. Exclusion Code: X3.
12. Agrawal S, Krueger DC, Engelke JA, et al. Between-meal risedronate does not alter bone turnover in nursing home residents. J Am Geriatr Soc. 2006 May;54(5):790-5. doi: 10.1111/j.1532-5415.2006.00696.x. PMID: 16696745. Exclusion Code: X3.
13. Ahmed LA, Schirmer H, Fonnebo V, et al. Validation of the Cummings' risk score; how well does it identify women with high risk of hip fracture: the Tromso Study. Eur J Epidemiol. 2006;21(11):815-22. doi: 10.1007/s10654-006-9072-3. PMID: 17119878. Exclusion Code: X9.
14. Ahmed LA, Shigdel R, Joakimsen RM, et al. Measurement of cortical porosity of the proximal femur improves identification of women with nonvertebral fragility fractures. Osteoporos Int. 2015 Aug;26(8):2137-46. doi: 10.1007/s00198-015-3118-x [doi]. PMID: 25876879. Exclusion Code: X7.
15. Albaba M, Cha SS, Takahashi PY. The Elders Risk Assessment Index, an electronic administrative database-derived frailty index, can identify risk of hip fracture in a cohort of community-dwelling adults. Mayo Clin Proc. 2012 Jul;87(7):652-8. doi: 10.1016/j.mayocp.2012.01.020. PMID: 22766085. Exclusion Code: X14.
16. Albanese CV, De Terlizzi F, Passariello R. Quantitative ultrasound of the phalanges and DXA of the lumbar spine and proximal femur in evaluating the risk of osteoporotic vertebral fracture in postmenopausal women. Radiol Med. 2011 Feb;116(1):92-101. doi: 10.1007/s11547-010-0577-1 [doi]. PMID: 20927655. Exclusion Code: X11.
17. Albertsson DM, Mellstrom D, Petersson C, et al. Validation of a 4-item score predicting hip fracture and mortality risk among elderly women. Ann Fam Med. 2007 Jan-Feb;5(1):48-56. doi: 10.1370/afm.602. PMID: 17261864. Exclusion Code: X14.
18. Allin S, Munce S, Schott AM, et al. Quality of fracture risk assessment in post-fracture care in Ontario, Canada. Osteoporos Int. 2013 Mar;24(3):899-905. doi: 10.1007/s00198-012-2111-x [doi]. PMID: 22930241. Exclusion Code: X3.
19. Alman AC, Johnson LR, Calverley DC, et al. Diagnostic capabilities of fractal dimension and mandibular cortical width to identify men and women with decreased bone mineral density. Osteoporos Int. 2012 May;23(5):1631-6. doi: 10.1007/s00198-011-1678-y [doi]. PMID: 21633828. Exclusion Code: X12.
20. Amstrup AK, Jakobsen NF, Lomholt S, et al. Inverse Correlation at the Hip Between Areal Bone Mineral Density Measured by Dual-Energy X-ray Absorptiometry and Cortical Volumetric Bone Mineral Density Measured by Quantitative Computed Tomography. J Clin Densitom. 2016 Apr-Jun;19(2):226-33. doi: 10.1016/j.jocd.2015.01.002. PMID: 25700661. Exclusion Code: X9.
21. Anastasilakis AD, Polyzos SA, Makras P, et al. Circulating semaphorin-4D and plexin-B1 levels in postmenopausal women with low bone mass: the 3-month effect of zoledronic acid, denosumab or teriparatide treatment. Expert Opin Ther Targets. 2015 Mar;19(3):299-306. doi: 10.1517/14728222.2014.983078 [doi]. PMID: 25395071. Exclusion Code: X9.
22. Anastasilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res. 2009 Oct;41(10):721-9. doi: 10.1055/s-0029-1224109. PMID: 19536731. Exclusion Code: X3.
23. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12. doi: 10.1001/jama.291.14.1701. PMID: 15082697. Exclusion Code: X3.
24. Ando H, Otoda T, Ookami H, et al. Dosing time-dependent effect of raloxifene on plasma plasminogen activator inhibitor-1 concentrations in post-menopausal women with osteoporosis. Clin Exp Pharmacol Physiol. 2013 Mar;40(3):227-32. doi: 10.1111/1440-1681.12055 [doi]. PMID: 23323567. Exclusion Code: X9.

25. Ang CL, Singh G, Goh AS, et al. Densitometry trends in postmenopausal Asian women undergoing bisphosphonate treatment. Singapore Med J. 2011 Sep;52(9):677-80. PMID: 21947146. Exclusion Code: X9.
26. Anpalahan M, Morrison SG, Gibson SJ. Hip fracture risk factors and the discriminability of hip fracture risk vary by age: a case-control study. Geriatr Gerontol Int. 2014 Apr;14(2):413-9. doi: 10.1111/ggi.12117 [doi]. PMID: 23879545. Exclusion Code: X14.
27. Arabi A, Salamoun M, Ballout H, et al. Densitometer type and impact on risk assessment for osteoporosis. J Clin Densitom. 2005 Fall;8(3):261-6. PMID: 16055954. Exclusion Code: X7.
28. Archer DF, Pinkerton JV, Utian WH, et al. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. Menopause. 2009 Nov-Dec;16(6):1109-15. doi: 10.1097/gme.0b013e3181a818db [doi]. PMID: 19543129. Exclusion Code: X7.
29. Asaoka D, Nagahara A, Hojo M, et al. Efficacy of alfacalcidol and alendronate on lumbar bone mineral density in osteoporotic patients using proton pump inhibitors. Biomedical Reports. 2016;5(2):165-70. Exclusion Code: X8.
30. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res. 2010 Feb;25(2):404-14. doi: 10.1359/jbmr.090731 [doi]. PMID: 19594305. Exclusion Code: X9.
31. Aubry-Rozier B, Stoll D, Krieg MA, et al. What was your fracture risk evaluated by FRAX(R) the day before your osteoporotic fracture? Clin Rheumatol. 2013 Feb;32(2):219-23. doi: 10.1007/s10067-012-2106-1 [doi]. PMID: 23114631. Exclusion Code: X9.
32. Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res. 2012 Mar;27(3):687-93. doi: 10.1002/jbmr.1472 [doi]. PMID: 22095631. Exclusion Code: X9.
33. Azagra R, Zwart M, Aguye A, et al. Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool? Maturitas. 2016 Jan;83:65-71. doi: 10.1016/j.maturitas.2015.10.002. PMID: 26546077. Exclusion Code: X8.
34. Bachmann G, Crosby U, Feldman RA, et al. Effects of bazedoxifene in nonflushing postmenopausal women: a randomized phase 2 trial. Menopause. 2011 May;18(5):508-14. doi: 10.1097/gme.0b013e3181fa358b [doi]. PMID: 21289525. Exclusion Code: X9.
35. Badurski JE, Kanis JA, Johansson H, et al. The application of FRAX(R) to determine intervention thresholds in osteoporosis treatment in Poland. Pol Arch Med Wewn. 2011 May;121(5):148-55. PMID: 21610662. Exclusion Code: X9.
36. Bai H, Jing D, Guo A, et al. Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. J Int Med Res. 2013 Jun;41(3):697-704. doi: 10.1177/0300060513480917. PMID: 23669294. Exclusion Code: X5.
37. Bal UA, Atar İ, Öktem M, et al. The effect of raloxifene on left ventricular hypertrophy in postmenopausal women: A prospective, randomized, and controlled study. Anadolu Kardiyoloji Dergisi. 2015;15(6):480-4. Exclusion Code: X9.
38. Bala Y, Zebaze R, Ghasem-Zadeh A, et al. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. J Bone Miner Res. 2014 Jun;29(6):1356-62. doi: 10.1002/jbmr.2167 [doi]. PMID: 24519558. Exclusion Code: X7.
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Appendix D Table 1. KQ 1 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
Barr, 2010[317]	G1: invitation to osteoporosis screening G2: control (no invitation to screen)	RCT parallel	Yes	Probably yes	No
Shepstone, 2017[72]	G1: invitation to osteoporosis screening G2: control (no invitation to screen)	RCT parallel	Yes	Probably yes	No

Abbreviations: DXA=dual energy x-ray absorptiometry; G=group; KQ=key question; NA=not applicable; RCT=randomized controlled trial.

Appendix D Table 2. KQ 1 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
Barr, 2010[317]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Shepstone, 2017[72]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Some concerns	Participants healthier than nonparticipants but also more likely to have a parental history of hip fractures; how ever similar prevalence of parental hip fracture betw een screening and control group.

Abbreviations: KQ=key question; NA=not applicable; NR=not reported.

Appendix D Table 3. KQ 1 Risk of Bias Assessment: Part 3

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Confounding of the Effect of Intervention Unlikely in This Study?	FOR COHORTS: Were Participants Analyzed According to Their Initial Intervention Group Throughout Followup?	FOR COHORT STUDIES: Were Intervention Discontinuations or Switches Unlikely To Be Related to Factors That Are Prognostic for the Outcome?	FOR COHORT AND CASE-CONTROL STUDIES: Did the Authors Use an Appropriate Analysis Method That Adjusted for All the Critically Important Confounding Domains?
Barr, 2010[317]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Shepstone, 2017[72]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort

Abbreviations: KQ=key question; NA=not applicable.

Appendix D Table 4. KQ 1 Risk of Bias Assessment: Part 4

First Author, Year	FOR COHORT STUDIES: Did the Authors Avoid Adjusting for Postintervention Variables?	FOR COHORT STUDIES Did the Authors Use an Appropriate Analysis Method That Adjusted for All the Critically Important Confounding Domains and for Time-Varying Confounding?	Bias Arising from Confounding?	Comments
Barr, 2010[317]	NA-not a cohort	NA-not a cohort	No	RCT design mitigates risk of confounding from known and unknown factors.
Shepstone, 2017[72]	NA-not a cohort	NA-not a cohort	No	RCT design mitigates risk of confounding from known and unknown factors.

Abbreviations: KQ=key question; NA=not applicable; RCT=randomized controlled trial.

Appendix D Table 5. KQ 1 Risk of Bias Assessment: Part 5

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Intervention Status Well Defined?	FOR COHORTS AND CASE CONTROLS: Was Information on Intervention Status Recorded at the Time of Intervention?	FOR COHORTS AND CASE CONTROLS Was Information on Intervention Status Unaffected by Knowledge of the Outcome or Risk of the Outcome?	Bias Arising from Measurement of the Intervention ?	Comments
Barr, 2010[317]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	RCT Design so all items NA.
Shepstone, 2017[72]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	RCT Design so all items NA.

Abbreviations: KQ=key question; NA=not applicable; RCT=randomized controlled trial.

Appendix D Table 6. KQ 1 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Barr, 2010[317]	Overall: [%] unclear. Study reports an over 60% response rate but the analysis relevant for this manuscript is the per protocol analysis, and no Ns are provided. (The "ITT" analysis compares responders in the control arm to randomized in the intervention arm and therefore is not a full representation of the randomized arms and would not qualify).	Yes	No	NA
Shepstone, 2017[72]	Overall by 60 months: 10660/12483=85%. Specific Ns vary by outcome and timing of measurement	No	Yes	NA

Abbreviations: ITT=intent to treat; KQ=key question; N=number; NA=not applicable.

Appendix D Table 7. KQ 1 Risk of Bias Assessment: Part 7

First Author, Year	FOR ALL STUDIES: Were Appropriate Statistical Methods Used To Account for Missing Data?	Bias Arising from Missing Outcome Data?	Comments
Barr, 2010[317]	No	Probably yes	Although this level of attrition would be considered high for trials of treatment, it's not unreasonable given the length of follow up and that this was a trial of invitation to screening.
Shepstone, 2017[72]	Yes	No	NA

Abbreviations: KQ=key question.

Appendix D Table 8. KQ 1 Risk of Bias Assessment: Part 8

First Author, Year	FOR RCTs of TREATMENT (NA for Screening): Were the Patients Unaware of Their Intervention Status of Participants?	FOR ALL RCTs: Were the Trial Personnel and Clinicians Unaware of the Intervention Status of Participants?	FOR ALL STUDIES Was Intervention Fidelity Adequate?	FOR ALL STUDIES: Did the Study Have Enough Cross-Overs or Contamination That Would Raise Concern for Bias?	Bias Arising from Departures from Intended Interventions?
Barr, 2010[317]	No	No	No information	No information	No information
Shepstone, 2017[72]	No	No	No information	Yes	Some concerns; no masking of participants or clinicians, standards for usual care changed over the course of the trial, potentially diluting the effect of the intervention

Abbreviations: KQ=key question; NA=not applicable; RCTs=randomized controlled trials.

Appendix D Table 9. KQ 1 Risk of Bias Assessment: Part 9

First Author, Year	FOR ALL STUDIES: Were Benefit Outcomes (e.g., Fractures) Adequately Described, Pre-Specified, Valid, and Reliable?	FOR ALL STUDIES: Were Similar Techniques Used Among Groups To Ascertain Benefit Outcomes?	FOR ALL STUDIES: Was the Duration of Follow-Up Adequate To Assess Benefit Outcomes?	FOR ALL STUDIES: Were Harm Outcomes Adequately Described, Valid and Reliable?
Barr, 2010[317]	Probably yes	Yes	Yes	No information
Shepstone, 2017[72]	Probably yes	Yes	Yes	Yes

Abbreviations: KQ=key question; NA=not applicable.

Appendix D Table 10. KQ 1 Risk of Bias Assessment: Part 10

First Author, Year	FOR ALL STUDIES: Were Similar Techniques Used among Groups To Ascertain Harm Outcomes?	FOR ALL STUDIES: Was the Duration of Follow-Up Adequate To Assess Harm Outcomes?	Bias Arising from Measurement of Outcomes?
Barr, 2010[317]	No information	No information	Probably no
Shepstone, 2017[72]	Yes	Yes	Probably no. Fractures measured from medical records, so likely to have undercounted asymptomatic vertebral fractures; as a result, the study may be have been underpowered to measure these fractures, but this is a precision issue

Abbreviations: KQ=key question; NA=not applicable.

Appendix D Table 11. KQ 1 Risk of Bias Assessment: Part 11

First Author, Year	FOR RCTS AND COHORTS: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Outcomes Measurements within the Domain, Multiple Analyses, or Different Subgroups?	FOR CASE-CONTROL STUDIES: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Definitions of the Intervention?	Bias Arising from Selection of Reported Results?
Barr, 2010[317]	No	No	No
Shepstone, 2017[72]	No	No	No

Abbreviations: KQ=key question; NA=not applicable; RCTs=randomized controlled trials.

Appendix D Table 12. KQ 1 Risk of Bias Assessment: Part 12

First Author, Year	Rating Overall (if You Rate One of the Domains as Having Bias, the Study Cannot Be High Quality)	Rating Justification	Does Quality Rating of Study Vary by Outcome?	Comments
Barr, 2010[317]	Poor	The ITT analysis is not eligible because it does not fully account for all randomized; the per-protocol analysis does not account for contamination or crossovers over the long follow up period; also N and loss-to-follow up for per-protocol is unclear but could at least as high as 40 percent.	No	Pulled Torgeson to fully understand randomization procedures (Torgerson DJ, Thomas RE, Campbell MK, Reid DM (1997) Randomized trial of osteoporosis screening. Use of hormone replacement therapy and quality-of-life results. Arch Intern Med 157:2121–2125)
Shepstone, 2017[72]	Fair	Some concerns regarding potential contamination because of changes in guidelines over time. As a result, the difference between usual care and the intervention arm may have been reduced.Some concerns regarding potentially selection bias (participants potentially healthier but also more likely to have parents with a history of hip fractures)	No	NA

Abbreviations: ITT=intent to treat; KQ=key question; N=number; NR=not reported.

Appendix D Table 13. KQ 2 Systematic Review Risk of Bias Assessments: Part 1

First Author, Year	Describe Interventions and Comparators (MUST describe usual care and combinations)	Did the Review Adhere to Pre-defined Objectives and Eligibility Criteria?	Were the Eligibility Criteria Appropriate for the Review Question?	Were Eligibility Criteria Unambiguous?
Crandall, 2015 [75]	Not applicable	Yes	Yes	Yes
Marques et al, 2015[76]	Fracture Risk Prediction Models	Yes	Yes	Yes
Nayak et al, 2014[119]	Osteoporosis absolute fracture risk assessment instruments	Probably yes	Yes	Yes
Rubin et al, 2013[121]	Risk assessment tools	Yes	Yes	Yes
Steurer et al, 2011[122]	Development of instruments and validation	Yes	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 14. KQ 2 Systematic Review Risk of Bias Assessments: Part 2

First Author, Year	Were All Restrictions in Eligibility Criteria Based on Study Characteristics Appropriate (e.g., date, sample size, study quality, outcomes measured)?	Were Any Restrictions in Eligibility Criteria Based on Sources of Information Appropriate (e.g., publication status or format, language, availability of data)?	Concerns Regarding Specification of Study Eligibility Criteria	Did the Review Search an Appropriate Range of Databases/Electronic Sources for Published and Unpublished Reports?
Crandall, 2015 [75]	Yes	Yes	Low	Probably no
Marques et al, 2015[76]	Yes	Yes	Low	Yes
Nayak et al, 2014[119]	Yes	Yes	Low	Yes
Rubin et al, 2013[121]	Yes	Yes	Low	Probably no
Steurer et al, 2011[122]	Yes	Yes	Low	Yes

Abbreviations: KQ=key question.

Appendix D Table 15. KQ 2 Systematic Review Risk of Bias Assessments: Part 3

First Author, Year	Were Methods Additional to Database Searching Used To Identify Relevant Reports?	Were the Terms and Structure of the Search Strategy Likely To Retrieve as Many Eligible Studies as Possible?	Were Restrictions Based on Date, Publication Format, or Language Appropriate?	Were Efforts Made To Minimize Error in Selection of Studies?
Crandall, 2015 [75]	Probably no	Yes	Yes	No information
Marques et al, 2015[76]	Yes	Yes	Yes	Yes
Nayak et al, 2014[119]	Yes	Yes	Yes	Yes
Rubin et al, 2013[121]	Yes	Yes	No	Yes
Steurer et al, 2011[122]	Yes	Yes	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 16. KQ 2 Systematic Review Risk of Bias Assessments: Part 4

First Author, Year	Concerns Regarding Methods Used To Identify and/or Select Studies	Were Efforts Made To Minimize Error in Data Collection?	Were Sufficient Study Characteristics Available for Both Review Authors and Readers To Be Able To Interpret the Results?	Were All Relevant Study Results Collected for Use in the Synthesis?
Crandall, 2015 [75]	Unclear or some concerns	No information	Yes	Yes
Marques et al, 2015[76]	Low	Yes	Probably yes	Yes
Nayak et al, 2014[119]	Low	Yes	Yes	Yes
Rubin et al, 2013[121]	Unclear or some concerns	No information	Yes	Yes
Steurer et al, 2011[122]	Low	Yes	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 17. KQ 2 Systematic Review Risk of Bias Assessments: Part 5

First Author, Year	Was Risk of Bias (or Methodological Quality) Formally Assessed Using an Appropriate Tool?	Were Efforts Made To Minimize Error in Risk of Bias Assessment?	Concerns Regarding Methods Used To Collect Data and Appraise Studies	Did the Synthesis Include All Studies That It Should?
Crandall, 2015 [75]	No	No information	Unclear or some concerns	Yes
Marques et al, 2015[76]	Yes	Yes	Low	Yes
Nayak et al, 2014[119]	Probably yes	No information	Low	Yes
Rubin et al, 2013[121]	Yes	Yes	Low	Yes
Steurer et al, 2011[122]	Yes	No information	Low	Yes

Abbreviations: KQ=key question.

Appendix D Table 18. KQ 2 Systematic Review Risk of Bias Assessments: Part 6

First Author, Year	Were All Pre-defined Analyses Reported or Departures Explained?	Was the Synthesis Appropriate Given the Degree of Similarity in the Research Questions, Study Designs and Outcomes across Included Studies?	Was Between-Study Variation (Heterogeneity) Minimal or Addressed in the Synthesis?	Were the Findings Robust (e.g., as Demonstrated through Sensitivity Analyses)?
Crandall, 2015 [75]	Yes	Yes	Probably yes	No information
Marques et al, 2015[76]	Probably yes	Yes	Probably no	Probably yes
Nayak et al, 2014[119]	Probably yes	Yes	Yes	No information
Rubin et al, 2013[121]	Yes	Yes	Yes	Probably yes
Steurer et al, 2011[122]	Yes	Yes	No information	No information

Abbreviations: KQ=key question.

Appendix D Table 19. KQ 2 Systematic Review Risk of Bias Assessments: Part 7

First Author, Year	Were Biases in Primary Studies Minimal or Addressed in the Synthesis?	Concerns Regarding the Synthesis	Did the interpretation of Findings Address All of the Concerns Identified in Domains 1 to 4?	Was the Relevance of Identified Studies to the Review's Research Question Appropriately Considered?	Did the Reviewers Avoid Emphasizing Results on the Basis of Their Statistical Significance?	Risk of Bias in the Review
Crandall, 2015 [75]	No	Unclear or some concerns	Probably no	Yes	Yes	Unclear or some concerns
Marques et al, 2015[76]	Probably yes	Low	Yes	Yes	Yes	Low
Nayak et al, 2014[119]	Yes	Low	Yes	Yes	Probably yes	Low
Rubin et al, 2013[121]	Yes	Low	Yes	Yes	Yes	Low
Steurer et al, 2011[122]	Yes	Unclear or some concerns	No	Yes	Yes	Unclear or some concerns

Abbreviations: KQ=key question.

Appendix D Table 20. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name; Year	Patients	Index Test(s):	Reference Standard and Target Condition
Adler, 2003[77]	Men enrolled in a pulmonary clinic (January-May 2001) and a rheumatology clinic (Nov 2001-March 2002) at a single VA medical center; received questionnaire and DXA scan; patients with previous DXA testing ineligble	Osteoporosis Self-assessment Tool (OST) (risk=[(weight in kg-age in years)*0.2, truncated to integer])	DXA
Bansal, 2015 [56]	All women between the ages of 50 and 64.5 years who underwent DXA during a 6-month period (March 1, 2012–August 31, 2012) and were enrolled in a primary care practice of the Mayo Clinic in Rochester, MN	FRAX	DXA
Ben Sedrine, 2001[78]	all female patients either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an outpatient osteoporosis center located at the University of Lie`ge, Lie`ge, Belgium.	SCORE	DXA
Brenneman, 2003[81]	Post-menopausal women ages 60–79 in the OPRA study	SCORE SOF-based screening tool	DXA
Cadarette, 2001[82]	Post-menopausal women in CaMOS	SCORE ABONE ORAI *weight criterion and NOF also evalated	DXA
Cadarette, 2004[83]	Women ≥45 years recruited prospectively from university setting and retrospectively analyzed form family practices	ORAI OST	DXA
Cass, 2006[84]	Primary care, women	ORAI and SCORE	DXA
Cass, 2013[85]	Primary care, men	MORES	DXA
Cass, 2016[114]	Primary care, men, NHANES III	MORES, FRAX	DXA
Chan, 2006[86]	Community-based elderly women	ORAI, SCORE, ABONE, OSTA	DXA
Cook et al, 2005[87]	UK, DXA scanning clinics, patients referred from general practicioners based on 1+ clinical risk factors for OP	Two QUS systems: CUBA Clinical (BUA, VOS), Sunlight Omnisense (distal radius, proximal phalanx mid finger, mid-shaft tibia)	DXA, LS-4, and total hip
Crandall, 2014[57]	Postemenopausal women enrolled in the WHI Observational or Clinical Trial Studies	OST, SCORE, USPSTF criteria (FRAX MOF risk >=9.3%)	DXA
D'Amelio, 2005[88]	Post menopausal women referred to a university-based bone metabolic unit for DXA.	NOF, OST, ORAI	DXA T Score -2.5 or less
D'Amelio, 2013[89]	Postemenopausal women recruited from general practice	NOF ORAI OST AMMEB	DXA
Geusens, 2002 [90]	Postmenopausal women 45 years and older, US and Netherlands, 81.8% white	OST, ORAI, SCORE, SOFSURF	DXA
Gnudi, 2005[91]	Postmenopausal Italian women requiring a DXA scan	Gnudi et al clinical prediction tool	DXA

Appendix D Table 20. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name; Year	Patients	Index Test(s):	Reference Standard and Target Condition
Gourlay, 2005[79]	Post menopausal women referred for DXA scans at an outpatient osteoporosis center in Belgium, based on suspicion of osteoporosis.	OST, ORAI, SCORE	DXA T Score -2.5 or less
Gourlay, 2008 [92]	US ambulatory white women age 65 years and older	OST, ORAI, SCORE	DXA
Harrison, 2006[93]	Caucasian females, 55-80 years (referred to clinical radiology, intended use of index test (QUS x2) underwent DXA and categorized as non-osteoporosis and osteoporosis. Subsequently underwent QUS and risk assessment using demographics and then combined algorithms-QUS used to predict osteoporosis	QUS x2	DXA
Jimenez-Nunez, 2013[94]	Women from primary and tertiary care, diagnosis, no prior testing	4 risk scores + PIXI of the heel	DXA of the hip and spine
Kung, 2003[95]	Women in Hong Kong recruited from the community	OSTA index and QUI	DXA
Kung, 2005[96]	Community of Asian (Southern Chinese) men; develop index based on clinical factors; compare clinical index with calcaneal QUS in predicting BMD (T< -2.5) by DXA	Clinical index	Calcaneal QUS; target condition -osteoporosis as determined by BMD at the hip and spine by DXA
Leslie, 2013[113]	All women ages 50-64 with medical coverage and valid DXA measurements from the lumbar spine and hip, from Manitoba, Canada	FRAX, OST	DXA
Lynn, 2008[97]	US Caucasian (4658) and Hong Kong Chinese (1914) from the MrOS study with DXA and QUS measurements to compare screening tools (OST, MOST, QUI) to DXA	OST, MOST, QUI	DXA
Machado, 2010[98]	Population-based sample of Portugese men age 50 or over	OST< 1, OSTA< 2	DXA T Score -2.5 or less at any of the three sites (LS, FN, TH) measured
Martinez-Aguila, 2007[99]	Postemenopausal women age 40 to 69 referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture.	ORAI (>=9), OST (<2), OSIRIS(<=1)	DXA T Score -2.5 or less at FN or LS
Mauck, 2005[100]	Population-based sample of postmenopausal women age 45 years and older in Rochester, MN	SCORE >=6 ORAI >=9 NOF >=1	DXA T Score -2.5 or less at FN or LS
McLeod, 2015[101]	Women referred for screening in Canada, no prior testing	QUS and OST	DXA
Morin, 2009[102]	Population-based sample of all women age 40 to 59 and over that received DXA testing in Manitoba, Canada. Note criteria for BMD testing in women younger than 65 include premature ovarian failure, history of steroid use, prior fracture, xray evidence of osteopenia, and other pertinent clinical risk factors.	OST <=1	DXA T Score -2.5 or less at FN or LS or Total Hip
Nguyen, 2004[103]	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia.	DOESCore, FOSTA, SOFSURF, ORAI	DXA T Score < -2.5 (Reference ranges unspecified)

Appendix D Table 20. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name; Year	Patients	Index Test(s):	Reference Standard and Target Condition
Oh, 2013[104]	National, population-based health and nutrition cohort.	OSTA	DXA
Oh, 2016[105]	Population based sample of Korean men age 50 and older	OSTA	DXA
Pang, 2014[106]	Persons age 70 and over recruited from general practice, excluded persons with history of fracture	OST, FRAX w/o BMD MOF and Hip	DXA
Richards, 2014[108]	Male VA patients	OST	DXA
Richy, 2004[80]	Postmenopausal White women	OST	DXA
Shepherd, 2007[110]	Men 50 years or older with DXA scan in NHANES III	MORES	DXA
Shepherd, 2010[115]	men ≥50 included in NHANES	MORES	BMD dxa osteo
Sinnott, 2006[111]	AA men, age 35 and older (outpatient general medicine clinics at veteran hospital; intended use of clinical assessment tools and calcaneous ultrasound compared with the reference measure of BMD by DXA; no description of presentation in article; no prior testing): index text is ultrasound of calcaneous on non-dominant foot, OUTCOME is low bone mass	Ultrasound of calcaneous on non-dominant foot	BMD by DXA at the 1) lumbar spine(L1-L4) and 2)non-dominant hip(femoral neck, trochanter, total hip)
Zimering, 2007[112]	Men age 40 years or older, ambulatory veterans attending general medicine clinics, endocrinology clinics, or osteoporosis clinics	Mscore OST MSCORE (age-weight)	DXA

Abbreviations: AA=African American; ABONE=assessing age, body size, and estrogen use; AMMEB=Age, Years after Menopause, Age at Menarche, Body Mass Index; BMD=bone mineral density; BUA=broadband attenuation; CaMOS=Canadian Multicentre Osteoporosis Study; DOEScore=Dubbo Osteoporosis Epidemiology Score; DXA=dual energy x-ray absorptiometry; DXA T=dual energy x-ray _; FN=femoral neck; FOSTA=Female Osteoporosis Self-assessment Tool for Asia; FRAX=Fracture Risk Assessment tool; LS=lumbar spine; LS-4=lumbar spine 4; MOF=major osteoporotic fracture defined as fractures of the proximal femur, distal radius, proximal humerus, and clinical vertebral fractures; MORE=Multiple Outcomes of Raloxifene Trial; MOST=Male Osteoporosis Screening Tool; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; MSCORE=male, simple calculated osteoporosis risk estimation; NHANES III=National Health And Nutrition Examination Survey III; NOF=National Osteoporosis Foundation; OP=osteoporosis; OPRA=Osteoporosis Population-based Risk Assessment; ORAI=Osteoporosis Risk Assessment Instrument; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SOF=Study of Osteoporotic Fractures; SOFSURF=Study of Osteoporotic Fractures Simple Useful Risk Factors; UK=United Kingdom; US=United States; USPSTF=United States Preventive Services Task Force; VA=Veterans' Administration; VOS=velocity of sound; WHI=Women's Health Initiative.

Appendix D Table 21. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name; Year	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?
Adler, 2003[77]	Data from two cross-sectional studies conducted among patients enrolled in a pulmonary clinic (evaluated from Jan-May 2001) and a rheumatology clinic (evaluated from Nov 2001-Mar 2002) at a single VA medical center.	Unclear	Yes	Yes
Bansal, 2015 [56]	Conducted retrospective record review of women ages 50–64.5 years old to determine clinical factors and FRAX scores of women undergoing a DXA at researcher's institution over a 6-month period.	Yes	Yes	Yes
Ben Sedrine, 2001[78]	Gathered data from patients consulting spontaneously or referred for a BMD measurement between Jan 1996 and Sep 1999 to outpatient osteoporosis center located at University of Liege.	Unclear	Yes	Yes
Brenneman, 2003[81]	Data from first arm of OPRA study where BME testing was aimed at all women. Eligible subjects were contacted by a mailing that invited all women to receive a DXA bone scan free of charge.	Yes	Yes	Unclear
Cadarette, 2001[82]	Menopausal women age 45 years or older with DXA data at the femoral neck were included from 6 sites in the CaMos study. In the CaMos, an age-, sex-, and region-stratefied random sample of the Canadian population was selected using a telephone-based sampling frame.	Yes	Yes	Yes
Cadarette, 2004[83]	Two groups of women were studied. Women 45 years or older presenting for BMD testing between Nov 11, 1999, and May 25, 2000, at an ambulatory care center affiliated with the University of Toronto were recruited prospectively. Women taking bone active medications other than hormone replacement, with a prior fragility fracture, or with major risk factors for secondary osteoporosis were excluded. The records of a second group of women attending two family practice clinics affiliated with the University of Toronto were reviewed retrospectively. Women age 45 years and older with a baseline DXA report since January 1997 were eligible.	Yes	Yes	Yes
Cass, 2006[84]	Postmenopausal women age 45 years or older receiving usual care at a university-based family practice clinic.	Yes	Yes	Yes
Cass, 2013[85]	Cross-sectional study of men who attended primary care outpatient clinics for usual care.	Yes	Yes	Yes
Cass, 2016[114]	Men age 50 years or older from the NHANES III data set.	Yes	Yes	Yes
Chan, 2006[86]	Chinese postmenopausal women age 55 years and older were recruited from the Tanjong Rhu community in the eastern part of Singapore.	Unclear	Yes	Unclear

Appendix D Table 21. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name; Year	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?
Cook et al, 2005[87]	Patients referred by general practitioner to DXA screening clinic	Unclear	Yes	Unclear
Crandall, 2014[57]	Participants from 3 clinical centers (Tucson and Phoenix, Arizona; Pittsburgh, Pennsylvania; and Birmingham, Alabama) that were part of the WHI.	Yes	Yes	Yes
D'Amelio, 2005[88]	Postmenopausal women who came to the Department of Internal Medicine to undergo bone densitometry with DXA from Aug 10, 2003, to Sep 15, 2003.	Unclear	Yes	Yes
D'Amelio, 2013[89]	Postmenopausal women referred from 32 general practitioners. Physicians were asked to send patients according to a randomization list.	Yes	Yes	Yes
Geusens, 2002 [90]	Postmenopausal women 45 years and older from US clinics and general practice in the Netherlands	yes	yes	yes
Gnudi, 2005[91]	White, postmenopausal women living in the district of Bologna, Italy and requiring DXA for BMD measurement at both the spine and hip for clinical reasons or checkups.	Yes	Yes	Yes
Gourlay, 2005[79]	Postmenopausal women age 45 and older either self-referred or were referred by a physician for a bone mineral density scan between january 1996 and September 1999 to an outpatient osteoporosis center at the University of Liege, Liege, Belgium.	Yes	Yes	Yes
Gourlay, 2008 [92]	US ambulatory white women age 65 years and older, from poulatio based listings	yes	yes	yes
Harrison, 2006[93]	White Caucasian females ages 55 to 70 (mean 61, SD 4) years who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans were invited to take part in the study	Unclear	Yes	Unclear
Jimenez-Nunez, 2013[94]	Described as random from 2 sites	Yes	Yes	Yes
Kung, 2003[95]	Women from community, all comers who did not meet exclusion	Unclear	Yes	Yes
Kung, 2005[96]	Men from community, all comers who did not meet exclusion	Yes	Yes	Yes
Leslie, 2013[113]	From a database of all DXA results performed from 1990 to March 2007 in Manitoba, Canada	Yes	Yes	Yes

Appendix D Table 21. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name; Year	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?
Lynn, 2008[97]	US participants were recruited using population-based listings at six clinical settings in Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA. Hong Kong participants were recruited using a combination of private solicitation and public advertising from community centers, housing estates, and the general community. Men who had bilateral hip replacements or who were unable to walk without the assistance of another person were excluded.	Yes	Yes	Unclear
Machado, 2010[98]	Participants were randomly selected from a list of registered voters in Santo António dos Olivais, Coimbra, Portugal. People were invited to participate by mail explaining the nature and purposes of the study.	Yes	Yes	Yes
Martinez-Aguila, 2007[99]	Questionnaire mailed to all postmenopausal patients referred by gynecologists to the rheumatology department of the Hospital Universitari de Bellvitge.	No	Yes	Unclear
Mauck, 2005[100]	Secondary data analysis of an existing population-based cohort of postmenopausal women in Rochester, MN who were participating in an ongoing, prospective study designed to assess osteoporosis prevalence, risk factors, and outcomes. Women were recruited from an age-stratified random sample of Rochester women using the medical records linkage system of the Rochester Epidemiology Project.	Yes	Yes	Yes
McLeod, 2015[101]	Patients referred for screening to one facility	Yes	Yes	Yes
Morin, 2009[102]	Designed retrospective historical cohort study of women ages 40 to 59 years who underwent clinical BMD testing in the province for evaluation of fracture risk using a comprehensive health care databases of the Province of Manitoba in Canada.	Yes	Yes	Unclear
Nguyen, 2004[103]	All men and women age 60 or above living in Dubbo, Australia were invited to participate in the study.	Yes	Yes	Yes
Oh, 2013[104]	Study data is based on data acquired in the KNHANES. The KNHANES is a nationwide survey to assess the health and nutritional status of a non-institutionalized representative sample of the Korean population. A stratified, multi-stage, clustered probability sampling design was used to select participants from residential districts.	Yes	Yes	Yes

Appendix D Table 21. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name; Year	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?
Oh, 2016[105]	Study data is based on data acquired in the KNHANES. The KNHANES is a nationwide survey to assess the health and nutritional status of a non-institutionalized representative sample of the Korean population. A stratified, multi-stage, clustered probability sampling design was used to select participants from residential districts.	Yes	Yes	Yes
Pang, 2014[106]	The study invited the participation of GPs from outer metropolitan areas with poor access to BMD. GPs involved identified individuals age 70 and older from their practice databases. Individuals were invited to have a BMD evaluation at no personal cost.	Yes	Yes	Yes
Park, 2003[107]	From a menopause clinic, not referred from elsewhere	Unclear	Yes	Yes
Richards, 2014[108]	Attending primary care clinics at 4 participating VA Medical Centers	Unclear	Yes	Yes
Richy, 2004[80]	Patients seen at an out-patient osteoporosis centre	Unclear	Yes	Yes
Shepherd, 2007[110]	Analysis of men age 50 years and older included in the NHANES III data set who had a valid DXA test.	Unclear	Yes	Unclear
Shepherd, 2010[115]	Men age 50 years and older who had been included in any of the NHANES 1999 to 2000, 2001 to 2002, and 2003 to 2004 datasets and who had a valid whole-body DXA scan.	Yes	Yes	Yes
Sinnott, 2006[111]	Subjects were recruited from outpatient general medicine clinics at the Jesse Brown VA Medical Center over an 11-month period in 2004	Unclear	Yes	Yes
Zimering, 2007[112]	Men age 40 years or older were screened by 7 investigators from a population of ambulatory, community-dwelling veterans who attended general medical clinics (70%), endocrinology clinics (20%), or osteoporosis clinics (10%) at the Department of Veterans Affairs Medical Center in Lyons, New Jersey between September 1998 and September 2000.	Unclear	Yes	Yes

Abbreviations: AL=Alabama; CA=California; DXA=dual energy x-ray absorptiometry; GP=general practitioner; KNHANES=Korea National Health and Nutrition Examination Survey; MN=Minnesota; NHANES III=National Health and Nutrition Examination Survey III; OPRA=Osteoporosis Population-based Risk Assessment; PA=Pennsylvania; SD=standard deviation; US=United States; VA=Veterans' Administration; WHI=Women's Health Initiative.

Appendix D Table 22. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name; Year	Could the Selection of Patients Have Introduced Bias?	Patient Selection Comments	Describe the Index Test and How It Was Conducted and Interpreted	Were the Index Test Results Interpreted without Knowledge of the Results of the Reference Standard?
Adler, 2003[77]	Unclear	Risk of spectrum bias used this ref for patient selection methods - appears random, majority of sample (107 of 181): Adler, Osteoporosis in Pulmonary Clinic Patientsa : Does Point-of-Care Screening Predict Central Dual-Energy X-ray Absorptiometry? Chest	Yes	Unclear
Bansal, 2015[56]	Unclear	Women of this age group likely had some recognized risk of osteoporosis or fracture risk (a majority [69.7%] had a previous DXA), so potential for spectrum bias	FRAX, MOF risk >=9.3%	Unclear
Ben Sedrine, 2001[78]	Unclear	Risk of spectrum bias.	Yes	Yes
Brenneman, 2003[81]	Low	Patients recruited by mailing to random sample	Yes	Unclear
Cadarette, 2001[82]	Low	Age-, sex-, and region-stratified random sample of the Canadian population selected using telephone-based sampling frame	Yes	Unclear
Cadarette, 2004[83]	Low	NA	Yes	Unclear
Cass, 2006[84]	Low	NR	Yes	Yes
Cass, 2013[85]	Low	NR	Yes	Yes
Cass, 2016[114]	Low	NHANES III is based on a probability sample of 40,000 civilian noninstitutionalized individuals	Yes	Yes
Chan, 2006[86]	Unclear	No information on participant inclusion/exclusion criteria.	Yes	Unclear
Cook et al, 2005[87]	Unclear	Sample has potential for bias toward low BMD due to recruitment from DXA clinic (all patients referred by doctor for clinical risk factors)	Two QUS tests - CUBA clinical and Sunlight Omnisense measurements. Performed on non-dominant side with same ultrsaound gel. System quality verification tests each day.	Unclear
Crandall, 2014[57]	Low	NA	Yes	Unclear
D'Amelio, 2005[88]	Unclear	Potential for spectrum bias, given the study population was referred specifically for DXA testing, in some cases for suspected secondary osteoporosis.	Yes	Unclear
D'Amelio, 2013[89]	Low	NA	Yes	Unclear

Appendix D Table 22. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name; Year	Could the Selection of Patients Have Introduced Bias?	Patient Selection Comments	Describe the Index Test and How It Was Conducted and Interpreted	Were the Index Test Results Interpreted without Knowledge of the Results of the Reference Standard?
Geusens, 2002 [90]	Low	NR	OST: age and weight ORAI: age, weight, estrogen use SCORE: race, rheumatoid arthritis, history of non-traumatic fracture, HRT usage, age and weight SOFSURF: age, weight, current smoker, history of postmenopausal fracture	Unclear
Gnudi, 2005[91]	Low	Patient refered to densitometry unit, possible spectrum bias	Yes	Yes
Gourlay, 2005[79]	Unclear	Potential for spectrum bias, given the study population was referred specifically for DXA testing.	Yes	Yes
Gourlay, 2008 [92]	Low	NR	OST: age and weight ORAI: age, weight, estrogen use SCORE: race, rheumatoid arthritis, history of non-traumatic fracture, HRT usage, age and weight	Low
Harrison, 2006[93]	Low	No details on setting or how participants were selected	QUS x2	Unclear
Jimenez-Nunez, 2013[94]	Low	Approach to randomization using "cards" is more casual than best practice	4 risk scores + PIXI of the heel, algorithms were developed	Yes
Kung, 2003[95]	Low	Interesting that the study claims to be early postmenopausal but the age mean is 62 which makes it seem unlikely that this is actually the case	Index characteristics through interview and qui of right heel by technician	Unclear
Kung, 2005[96]	Low	Unclear who chose to participate relative to larger group, excluded abnormal TSH group	Index developed by authors based on characteristics	Unclear
Leslie, 2013[113]	Low	NR	OST, FRAX without BMD	Unclear
Lynn, 2008[97]	Low	Only exclusions listed were hip replacement and inability to walk without a cane	OST, MOST, QUI	Unclear
Machado, 2010[98]	Low	NR	Yes	Unclear
Martinez-Aguila, 2007[99]	Unclear	Patients were all referred for DXA, so potential for spectrum bias.	Yes	Unclear
Mauck, 2005[100]	Low	NR	Yes	Unclear

Appendix D Table 22. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name; Year	Could the Selection of Patients Have Introduced Bias?	Patient Selection Comments	Describe the Index Test and How It Was Conducted and Interpreted	Were the Index Test Results Interpreted without Knowledge of the Results of the Reference Standard?
McLeod, 2015[101]	Low	NA	QUS of BUA and SOS of left calcaneus & personal data based on questionnaire	Yes
Morin, 2009[102]	Unclear	Population is younger women 40-59 that received a DXA, however, in this province younger women are only eligible to have coverage for DXA testing if they have clinical risks for secondary osteoporosis, history of prior fracture, or xray evidence of osteop	Yes	Unclear
Nguyen, 2004[103]	Low	NA	Yes	Unclear
Oh, 2013[104]	Low	NA	Yes	Unclear
Oh, 2016[105]	Low	NR	Yes	Unclear
Pang, 2014[106]	Low	NA	Yes	Unclear
Park, 2003[107]	Low	NR	OSTA: age and weight.	Unclear
Richards, 2014[108]	Low	NR	OST: age and weight.	Unclear
Richy, 2004[80]	Low	NR	SCORE: race, rheumatoid arthritis, history of non-traumatic fracture, HRT usage, age and weight ORAI: age, weight, estrogen use OSIRIS: age, weight, HRT use, history of low trauma fracture OST: age and weight	Unclear
Shepherd, 2007[110]	Low	NHANES uses a complex, multistage, probability sampling design to select participants representative of the civilian, non-institutionalized population of the coterminous United States, excluding Indian reservations. (i.e. not random or consecutive sampling)	Yes	Unclear
Shepherd, 2010[115]	Low	NR	Yes	Unclear
Sinnott, 2006[111]	Low	Selection of participants may be a convenience sample but unclear. Men were recruited from general medicine clinics so selection bias likely low	Ultrasound of calcaneous on non-dominant foot	Unclear

Appendix D Table 22. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name; Year	Could the Selection of Patients Have Introduced Bias?	Patient Selection Comments	Describe the Index Test and How It Was Conducted and Interpreted	Were the Index Test Results Interpreted without Knowledge of the Results of the Reference Standard?
Zimering, 2007[112]	Unclear	Convenience sample 30% came from specialty clinics (endo or OP) for total cohort, but unknown for valdiation cohort Excluded those unable to assess risk factors or DXA, though did not exclude based on known medical comorbidities or bone active medications (glucocorticoids). Reported only 14% on glucocorticoids, and 4% with RA	Yes	Unclear

Abbreviations: BMD=bone mineral density; BUA=broadband attenuation; DXA=dual energy x-ray absorptiometry; HRT=hormone replacement therapy; MOST=Male Osteoporosis Screening Tool; NA=not applicable; NHANES=National Health And Nutrition Examination Survey; NR=not reported; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OSTA=Osteoporosis Self-assessment Tool for Asians; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; RA=radiographic absorptiometry; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SOS=speed of sound; TSH=thyroid stimulating hormone.

Appendix D Table 23. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name; Year	If a Threshold Was Used, Was It Pre-specified?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Index Test Comments	Describe the Reference Standard and How It Was Conducted and Interpreted
Adler, 2003[77]	Yes	Low	Used three cutoffs for OST - two based on published literature, one cutoff based on what they thought was appropriate	HANES reference database for hip Hologic reference source for spine Age, gender, race of reference group not reported
Bansal, 2015[56]	Yes	Low	NA	DXA, T-score < -2.5 but no other details provided
Ben Sedrine, 2001[78]	Yes	Low	Authors did report on outcomes of clinical prediction tools using a priori cutoffs. But also did calibrate tool for this population using AUC curve.	Hologic QDR reference values specifically established for the population of Liege, Belgium (local reference values)
Brenneman, 2003[81]	Yes	Low	SCORE cutoff was recalibrated using study data to achieve sensitivity of approximately 90%. Developer cut off >=6 Study cutoff >=8	NHANES III, do not specify age or gender of reference group
Cadarette, 2001[82]	Yes	Low	Used cutoffs based on those of the developers of the study	Canadian young adult normal values at the femoral neck. (Authors note that the Canadian young adult normal reference at the femoral neck (mean [SD], 0.857 [0.125] g/cm3) is similar to that reported by NHANES III for non-Hispanic white Americans (mean [SD], 0.858 [0.120] g/cm3).
Cadarette, 2004[83]	Yes	Low	Unclear timing of DXA, reference test, in relationship to index test in prospective and retrospective parts of the study sample	Unclear
Cass, 2006[84]	Yes	Low	NR	NHANES III non-Hispanic White women age 20-29 years old.
Cass, 2013[85]	Yes	Low	NR	NHANES III non-Hispanic White women age 20-29 years old.
Cass, 2016[114]	Yes	Low	Threshold was determined in a split sample, using a development cohort, reported in Shepherd et al, 2007.[110] This analysis focuses on the validation cohort only	NHANES III non-Hispanic White women age 20-29 years old

Appendix D Table 23. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name; Year	If a Threshold Was Used, Was It Pre-specified?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Index Test Comments	Describe the Reference Standard and How It Was Conducted and Interpreted
Chan, 2006[86]	Yes	Low	Study only reports outcomes for Femoral Neck at the prespecified thresholds, the Lumbar Spine outcomes are reported using empirically derived thresholds.	Unclear
Cook et al, 2005[87]	Yes	Unclear	Threshold question - yes and no used a 90% sensitivity threshold, but also created a cut off level based on the highest combined value of Sn and Sp.	T-scores were computed using the databases supplied with the systems
Crandall, 2014[57]	Unclear	Unclear	The study mentions the existing thresholds used for the instruments from the literature, but outcomes are not reported by these thresholds.	NHANES III normative reference database (presumably young non-hispanic white females 20-29, though this is not specifically reported)
D'Amelio, 2005[88]	Yes	Low	NR	Unclear
D'Amelio, 2013[89]	Yes	Low	The thresholds mentioned in study do not correspond entirely to thresholds used by other studies.	Unclear
Geusens, 2002 [90]	yes	low	NR	FN: non-hispanic female white women age 20-29 (NHANES) LS: unclear
Gnudi, 2005[91]	Yes	Low	Do not report on blinded index test assessment. Had three apriori cutoffs from development cohort to achieve 97%, 98% and 99% sensitivity	Reference values were those reported by Norland for the European female population
Gourlay, 2005[79]	No	Unclear	Did not use pre-specified cutoffs for ORAI, OST, or SCORE. Instead, picked cut-off to achieve Sn 90% for each age group under and over 65 years. (last para p.922	T score reference range was NHANES III non-Hispanic white women age 20-29 years at the femoral neck
Gourlay, 2008 [92]	yes	low	NR	FN: non-hispanic female white women age 20-29 (NHANES) LS: manufacturers norms for women age 30 years
Harrison, 2006[93]	Yes	Low	NR	Hologic reference data for the T and z scores calculated using Hologic reference dataa for the lumbar spine and NHANES reference data for the proximal femur

Appendix D Table 23. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name; Year	If a Threshold Was Used, Was It Pre-specified?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Index Test Comments	Describe the Reference Standard and How It Was Conducted and Interpreted
Jimenez-Nunez, 2013[94]	Yes	Low	NR	Manufacturer's reference for the Spanish population
Kung, 2003[95]	Yes	Low	Index based on characteristics can be biased based on analysis decisions	Peak young Chinese mean values used for calculating T-scores: L1–L4 BMD
Kung, 2005[96]	Yes	Low	The authors are developing their own index test and so by definition are experimenting withtheir data	Unclear
Leslie, 2013[113]	Yes	Low	NR	Femoral T-scores calculated based on NHANES III white female reference; lumbar spine used T-scores used manufacturer's USA white female reference values
Lynn, 2008[97]	Yes	Low	NR	US: NHANES Hong Kong: local Chinese reference ranges
Machado, 2010[98]	Yes	Low	NR	NHANES III young normal references values (sex unspecified) for FN; manufacturer's database for male Caucasian references values for LS (age unspecified)
Martinez-Aguila, 2007[99]	Yes	Low	NR	T -Scores from reference range from a study conducted in a Spanish population of healthy subjects of same sex with peak bone mass
Mauck, 2005[100]	Yes	Low	NR	T scores based on references ranges for young healthy women age 20-29 years in the local community area
McLeod, 2015[101]	Yes	Low	NR	NHANES III
Morin, 2009[102]	Yes	Low	Sn and Sp reported for multiple thresholds, the threshold of <=1 is what has been used in other studies, so data was only extracted for this threshold.	Reports T Scores for LS used manufacturers US white female reference ranges, based on revised NHANES III, but these are only applicable to FN, and the study states this reference range was used for LS.
Nguyen, 2004[103]	Yes	Low	Validation cohort only.	Used BMD values of young Australian women at either the femoral neck or lumbar spine as reference to determine T score
Oh, 2013[104]	No	Unclear	The authors do not report findings for the predefined threshold of OSTA< instead they report findings for a different threshold that they selected to maximize discriminative ability.	Sexspecific norms for young Japanese women
Oh, 2016[105]	Unclear	Unclear	Unclear whether OSTA threshold used was prespecified.	Sex specific norms for young Japanese men

Appendix D Table 23. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name; Year	If a Threshold Was Used, Was It Pre-specified?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Index Test Comments	Describe the Reference Standard and How It Was Conducted and Interpreted
Pang, 2014[106]	No	Unclear	Thresholds were not prespecified, rather they were chosen to maximize discriminative ability.	Manufacturer's sex specific normative databse and an ethnic database.
Park, 2003[107]	Yes	Low	NR	Reference range for young Korean women
Richards, 2014[108]	Yes	Low	NR	NHANES III
Richy, 2004[80]	Yes	Low	NR	Reference values specifically established for the population of Liege.
Shepherd, 2007[110]	Yes	Low	Do not report on blinded index test assessment. Threshold is determined in development cohort in this study. Applied to validation cohort.	T scores derived from race/ethnicity and sex-specific bone mineral density for Hispanic, non-Hispanic white, and non-Hispanic black men ages 20-29.
Shepherd, 2010[115]	Yes	Low	NR	White men age 20-29; whole body DXA Hologic QDR-4500A
Sinnott, 2006[111]	Unclear	Low	NR	T-scores were calculated using the manufacturer's reference values, namely a young Caucasian male database for the hip and a Caucasian female database for the spine
Zimering, 2007[112]	Yes	Low	Do not report on blinded index test assessment. Threshold is determined in development cohort in this study. Applied to validation cohort.	T score <= -2.5 compared to NHANES III young male, ethnicity/race- specific reference data

Abbreviations: AUC=area under the curve; BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; GE=General Electric; NR=not reported; ORAI=Osteoporosis Risk Assessment Instrument; OST=osteoporosis self-assessment tool; OSTA=Osteoporosis Self-assessment Tool for Asians; QUI=ultrasound index; QUS=quantitative ultrasound; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; Sn=sensitivity; Sp=specificity.

Appendix D Table 24. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name; Year	Is the Reference Standard Likely To Correctly Classify the Target Condition?	Were the Reference Standard Results Interpreted without Knowledge of the Results of the Index Test?	Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?	Reference Standard Comments
Adler, 2003[77]	Yes	Unclear	Low	NR
Bansal, 2015[56]	Yes	Unclear	Low	NR
Ben Sedrine, 2001[78]	Yes	Yes	Low	From discussion: "All of our DXA tests come from the same densitometers and from the same clinical unit.
Brenneman, 2003[81]	Yes	Unclear	Low	NR
Cadarette, 2001[82]	Yes	Unclear	Low	NR
Cadarette, 2004[83]	Yes	Unclear	Low	Unclear timing of DXA, reference test, in relationship to index test in prospective and retrospective parts of the study sample
Cass, 2006[84]	Yes	Yes	Low	Specific reference range for T scores not reported, but used manufacturer's ranges, so likely NHANES.
Cass, 2013[85]	Yes	Yes	Low	NR
Cass, 2016[114]	Yes	Yes	Low	NR
Chan, 2006[86]	Unclear	Unclear	Unclear	No information on the specific reference ranges used to determine T-Score.
Cook et al, 2005[87]	Yes	Unclear	Unclear	NR
Crandall, 2014[57]	Yes	Unclear	Low	NR
D'Amelio, 2005[88]	Yes	Unclear	Low	No information about masking of test results, but given objective calculations that go into both the index and reference test, low chance of bias.
D'Amelio, 2013[89]	Unclear	Unclear	Unclear	Reference range for T score NR.
Geusens, 2002 [90]	Yes	Unclear	Low	NR
Gnudi, 2005[91]	Yes	Yes	Low	Do not report on blinded reference test assessment.
Gourlay, 2005[79]	Yes	Yes	Low	NR
Gourlay, 2008 [92]	Yes	Unclear	Low	NR
Harrison, 2006[93]	Yes	Unclear	Low	NR
Jimenez-Nunez, 2013[94]	Yes	Yes	Low	NR
Kung, 2003[95]	Yes	Unclear	Low	NR
Kung, 2005[96]	Yes	Yes	Low	NR
Leslie, 2013[113]	Yes	Unclear	Low	NR

Appendix D Table 24. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name; Year	Is the Reference Standard Likely To Correctly Classify the Target Condition?	Were the Reference Standard Results Interpreted without Knowledge of the Results of the Index Test?	Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?	Reference Standard Comments
Lynn, 2008[97]	Yes	Unclear	Low	All obtained from MrOS (sequence of data collection not described)
Machado, 2010[98]	Yes	Unclear	Low	NR
Martinez-Aguila, 2007[99]	Yes	Unclear	Low	Did not use NHANES reference standards; but may be appropriate since conducted in a Spanish population.
Mauck, 2005[100]	Yes	Unclear	Low	Used a local reference range for T score values.
McLeod, 2015[101]	Yes	Yes	Low	NR
Morin, 2009[102]	Yes	Yes	Low	NR
Nguyen, 2004[103]	Yes	Unclear	Low	Local reference range for young Australian women at the FN or LS was used.
Oh, 2013[104]	Yes	Unclear	Low	NR
Oh, 2016[105]	Yes	Unclear	Low	NR
Pang, 2014[106]	Yes	Unclear	Low	NR
Park, 2003[107]	Yes	Unclear	Unclear	NR
Richards, 2014[108]	Yes	Yes	Unclear	NR
Richy, 2004[80]	Yes	Unclear	Unclear	NR
Shepherd, 2007[110]	Yes	Yes	Low	Index test was developed after DXA done, so presumably reference test interpretation blinded.
Shepherd, 2010[115]	Yes	Unclear	Low	NR
Sinnott, 2006[111]	Yes	Unclear	Low	Threshold values not explicity provided.
Zimering, 2007[112]	Yes	Unclear	Low	Do not report on blinded reference test assessment.

Abbreviations: BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; FN=femoral neck; LS=lumbar spine; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; NHANES III=National Health And Nutrition Examination Survey; NR=not reported.

Appendix D Table 25. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 6

First Author's Last Name; Year	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions between Index Test(s) and Reference Standard	Was There an Appropriate Interval between Index Test(s) and Reference Standard?	Did All Patients Receive a Reference Standard?	Did Patients Receive the Same Reference Standard?	Were All Patients Included in the Analysis?
Adler, 2003[77]	Excluded patients who had previously had a DXA scan (i.e. the reference test)	1 month	Yes	Unclear	Yes	Yes
Bansal, 2015[56]	None	FRAX input collected at time of DXA or from review of medical records.	Yes	Yes	Yes	Yes
Ben Sedrine, 2001[78]	Data on those with missing data for index and DXA test were not reported	Not reported: gathered retrospective medical data on BMD measurement and risk factors between January 1996 and 1999.	Unclear	Yes	Yes	Unclear
Brenneman, 2003[81]	1986 recruited 428 consented 416 had complete data	Occurred concurrently	Yes	Yes	Yes	Yes
Cadarette, 2001[82]	69 participants missing data to calculate clinical decision rules	Not specifically reported. All baseline data collected 2/2016-9/2017, presumably includes questionnaire and DXA testing.	Unclear	Yes	Yes	No
Cadarette, 2004[83]	Of retrospective sample, 66 did not have data on estrogen use. Assumed to be negative. Only patients with DXA included.	Unclear	Unclear	Yes	Yes	No
Cass, 2006[84]	Yes	Yes	Yes	Yes	Yes	No
Cass, 2013[85]	Yes	Yes	Yes	Yes	Yes	No
Cass, 2016[114]	Details NR	NR	Unclear	Yes	Yes	Yes
Chan, 2006[86]	No	Yes	Yes	Yes	Yes	Unclear
Cook et al, 2005[87]	None	None	Yes	Yes	Yes	Yes
Crandall, 2014[57]	No	Yes	Yes	Yes	Yes	Yes
D'Amelio, 2005[88]	NR	Clinical risk factors collected at the time of DXA scan	Yes	Yes	Yes	Yes
D'Amelio, 2013[89]	Yes	Yes	Yes	Yes	Yes	No
Geusens, 2002 [90]	NA	unclear	unclear	yes	yes	yes
Gnudi, 2005[91]	NR	NR	Unclear	Yes	Yes	Unclear
Gourlay, 2005[79]	NR	NR	Unclear	Yes	Yes	Unclear

Appendix D Table 25. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 6

First Author's Last Name; Year	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions between Index Test(s) and Reference Standard	Was There an Appropriate Interval between Index Test(s) and Reference Standard?	Did All Patients Receive a Reference Standard?	Did Patients Receive the Same Reference Standard?	Were All Patients Included in the Analysis?
Gourlay, 2008 [92]	NA	unclear	unclear	yes	yes	yes
Harrison, 2006[93]	NR	NR	Unclear	Yes	Yes	Unclear
Jimenez-Nunez, 2013[94]	Nursing home, homebound, prior diagnosis of osteo, on osteo drugs, serious acute or chronic disease, hip replacement, steroids	Same day	Unclear	Yes	Yes	Unclear
Kung, 2003[95]	History or evidence of metabolic bone disease, menopause before 40, history of cancer, evidence of sig renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride or calcitonin	NR	Unclear	Yes	Yes	Yes
Kung, 2005[96]	History or evidence of metabolic bone disease, hightory of cancer, evidence of sig renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride or calcitonin, abnormal biochemisty including renal and liver function, serum calcium, phosphate, total alkaline phosphatase, and TSH	NR	Unclear	Yes	Yes	Yes
Leslie, 2013[113]	NR	NR	Unclear	Yes	Yes	Yes
Lynn, 2008[97]	NR	NR	Unclear	Yes	Yes	Na
Machado, 2010[98]	NR	NR	Unclear	Yes	Yes	Yes
Martinez-Aguila, 2007[99]	Yes	NR	Unclear	Yes	Yes	No
Mauck, 2005[100]	NR	Yes	Yes	Yes	Yes	Yes
McLeod, 2015[101]	Previous diagnosis, progressive terminal illness	Within 3 weeks	Yes	Yes	Yes	Yes
Morin, 2009[102]	NR	Unclear	Unclear	Yes	Yes	Yes

Appendix D Table 25. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 6

First Author's Last Name; Year	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions between Index Test(s) and Reference Standard	Was There an Appropriate Interval between Index Test(s) and Reference Standard?	Did All Patients Receive a Reference Standard?	Did Patients Receive the Same Reference Standard?	Were All Patients Included in the Analysis?
Nguyen, 2004[103]	NR	Not explicitly, but given study design presume it was concurrent.	Yes	Yes	Yes	Yes
Oh, 2013[104]	Yes	Yes	Yes	Yes	Yes	Yes
Oh, 2016[105]	Yes	Yes	Yes	Yes	Yes	Yes
Pang, 2014[106]	Yes	Yes	Yes	Yes	Yes	Yes
Park, 2003[107]	NA	Unclear	Unclear	Yes	Yes	Yes
Richards, 2014[108]	NA	Unclear	Unclear	No	Yes	No
Richy, 2004[80]	NA	Unclear	Unclear	Yes	Yes	Yes
Shepherd, 2007[110]	From Looker et al Bone mineral measurements were performed on 3176 older men in NHANES III, but 86, or 3%, were rejected for technical reasons after review, leaving 3090 with acceptable data	NR	Unclear	Yes	Yes	Yes
Shepherd, 2010[115]	Yes	Yes	Yes	Yes	Yes	Yes
Sinnott, 2006[111]	NR	NR	Unclear	Yes	Yes	Yes
Zimering, 2007[112]	NR	Not reported, presumably concurrent testing	Unclear	Yes	Yes	No

Abbreviations: BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; NHANES III=National Health And Nutritionexamination Survey III; NR=not reported; TSH=thyroid stimulating hormone.

Appendix D Table 26. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 7

First Author's Last Name; Year	Could the Patient Flow Have Introduced Bias?	Patient Flow Comments	Overall Judgement	Overall Comments
Adler, 2003[77]	Low	From Adler, Osteoporosis in Pulmonary Clinic Patientsa : Does Point-of-Care Screening Predict Central Dual-Energy X-ray Absorptiometry? Chest Volume 123, Issue 6, June 2003, Pages 2012–2018 98 or 107 patients received DXA scan from pulmonary cohort; unknown	Low	Unclear for domain of patient selection. Also unclear how many excluded for no DXA, but from pulmonary cohort appears small. Would give it a FAIR for ROB
Bansal, 2015[56]	Low	None	Unclear	Potential for spectrum bias because younger women with DXA likely have had some unspecified risk factors. Some risk of bias introduced by retrospective design as women age 50-64 would typically not have DXA ordered in the absence of increased risks for osteoporosis.
Ben Sedrine, 2001[78]	Unclear	No report of timing between index and reference test	Low	Risk of spectrum bias. No mention of who was excluded or if any dropped out; unclear if results looked at independently blind; Unclear for domain of flow and timing.
Brenneman, 2003[81]	Low	416 includes those with complete information not sure how many were dropped due to incomplete data; sounds like data collected all at the same time	Low	416 includes those with complete information not sure how many were dropped due to incomplete data; sounds like data collected all at the same time; not sure if blinded interpretation
Cadarette, 2001[82]	Low	Multisite study with different DXA machines in each site. T scores were calculated from cross-calibrated Hologic BMD equivalent. Baseline period < 2 years.	Low	Unclear it assessments were blind; unclear on timing of assessments; excluded those who had osteoporosis and taking bone sparing medications, those with secondary osteoporosis, those with missing data
Cadarette, 2004[83]	Low	Study authors collected clinical risk factors taken at the same time as the DXA scan for the retrospective sample of patients For prospective study, presumably concurrent.	Low	Unclear on assessment timing; unclear on blinding; looks like those with missing data were excluded
Cass, 2006[84]	Low	23 enrolled patients did not undergo DXA scan so were not included. 173 eligible patients declined to participate.	Low	NR
Cass, 2013[85]	Low	40 patients did not undergo DXA so were dropped from the analysis.	Low	NR
Cass, 2016[114]	Low	NR	Low	NR

Appendix D Table 26. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 7

First Author's Last Name; Year	Could the Patient Flow Have Introduced Bias?	Patient Flow Comments	Overall Judgement	Overall Comments
Chan, 2006[86]	Unclear	The Number eligible is not reported, the number of dropouts is not reported, only the final N analyzed is reported.	unclear	Some concerns in multiple domains of risk of bias lead to an overal rating of uncler.
Cook et al, 2005[87]	Low	NR	Unclear	Patient selection has the potential to skew the sample tow ard low BMD
Crandall, 2014[57]	Low	Main analysis w as restricted to a subgroup of non HRT users by design (, supplemental analyses include HRT users and all w omen [including those w ith preventive use of HRT])	Low	NR
D'Amelio, 2005[88]	Low	NR	Low	NR
D'Amelio, 2013[89]	Low	Some patients initially enrolled w ere excluded because it w as determined they did not meet study criteria.	Low	NR
Geusens, 2002 [90]	unclear	Unclear because of lack of clarity around timing of the tests	unclear	No details on how the reference standard data w ere collected or the time interval betw een it and the index test
Gnudi, 2005[91]	Low	While authors don't report on timing betw een reference and index test, validation cohort w as recruited over 6 months (<2 years)	Low	NR
Gourlay, 2005[79]	Unclear	NR	Unclear	NR
Gourlay, 2008 [92]	unclear	Unclear because of lack of clarity around timing of the tests	unclear	No details on how the reference standard data w ere collected or the time interval betw een it and the index test
Harrison, 2006[93]	Unclear	Participants underw ent DXA and w ere categorized as non -osteo or osteo prior to QUS or risk indices	Low	Low -to-high given that osteoporosis status determined first
Jimenez-Nunez, 2013[94]	Low	random sample done w ith some sort of cards	Low	NR
Kung, 2003[95]	Low	NR	Low	NR
Kung, 2005[96]	Low	It is not clear w hat the time frame betw een clinical assessment of risk factors and QUS; how ever should be little impact; I put that all participants received the same reference standard (referring to the validated group here)	Low	NR
Leslie, 2013[113]	Low	NR	Low	NR
Lynn, 2008[97]	Low	NR	Low	Data w as collected prospectively from MrOS study and then analyzed as part of this study focus.

Appendix D Table 26. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 7

First Author's Last Name; Year	Could the Patient Flow Have Introduced Bias?	Patient Flow Comments	Overall Judgement	Overall Comments
Machado, 2010[98]	Low	Interval between clinical risks and BMD inferred to be < 2 years.	Low	NR
Martinez-Aguila, 2007[99]	Unclear	30 eligible patients were excluded for missing data. Clinical risk factors assessed retrospectively by asking participants to answer them based on the date of their BMD testing.	Unclear	NR
Mauck, 2005[100]	Low	NR	Low	NR
McLeod, 2015[101]	Low	Effort made to contact patient, enroll and conduct OST and QUS within 3 weeks of DXA scan to complete study assessments prior to provider receiving DXA results and talking with patient.	Low	NR
Morin, 2009[102]	Unclear	Unclear for timing between DXA and index test	Unclear	NR
Nguyen, 2004[103]	Low	NR	Low	NR
Oh, 2013[104]	Low	Some patients meeting prelim criteria based on age were not eligible for a variety of reasons.	Low	Low ROB for the test thresholds used by study authors.
Oh, 2016[105]	Low	Excluded some men for probably valid reasons	Low	NR
Pang, 2014[106]	Low	Some patients meeting prelim age criteria not eligible to be included.	Low	Low ROB for the test thresholds used by study authors.
Park, 2003[107]	Unclear	Unclear because of lack of clarity around timing of the tests	Unclear	No details on how the reference standard data were collected or the time interval between it and the index tes
Richards, 2014[108]	Unclear	Unclear because of lack of clarity around timing of the tests. 2 patients were excluded from the analysis because no bmd tests were done but not the primary cause of the unclear rating	Unclear	No details on how the reference standard data were collected or the time interval between it and the index tes
Richy, 2004[80]	Unclear	Unclear because of lack of clarity around timing of the tests	Unclear	No details on how the reference standard data were collected or the time interval between it and the index tes
Shepherd, 2007[110]	Low	NR	Low	NR
Shepherd, 2010[115]	Low	Excluded men without DXA available, though not specifically reported NHANES enrolls subjects prospectively so clinical risks and DXA likely collected concurrently.	Low	NR

Appendix D Table 26. Risk of Bias for Assessing Accuracy of Risk Prediction Instruments for Identifying Osteoporosis: Part 7

First Author's Last Name; Year	Could the Patient Flow Have Introduced Bias?	Patient Flow Comments	Overall Judgement	Overall Comments
Sinnott, 2006[111]	Low	The flow was not specifically described, but appears sequence was clinical assessment followed by ultrasound and then DXA.	Low	Primarily due to: 1) no information on the type of sampling. Assuming conveneience sampling; 2) not clear about the sequence of testing, but low risk of bias.
Zimering, 2007[112]	Unclear	No report of timing between index and reference test or on missing data in the validation cohort; presumably concurrent testing	Unclear	NR

Abbreviations: BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; HRT=hormone replacement therapy; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; NHANES=National Health And Nutritionexamination Survey; NR=not reported; OST=osteoporosis self-assessment tool; QUS=quantitative ultrasound; ROB=risk of bias.

Appendix D Table 27. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 1

First Author, Year	Patients (Setting, Intended Use of Index Test, Presentation, Prior Testing)	Index Test(s)	Reference Standard and Target Condition	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?	Could the Selection of Patients Have Introduced Bias?	Comments
Boonen et al, 2005[116]	Commmunty dwelling postmenopausal women,	QUS	t-score below 2.5 using dxa	Community dwelling postmenopausal women who had been referred for bone densitometry at 1 facility in Belgium	Yes	Yes	Yes	Low	NR
Cook et al, 2005[87]	UK, DXA scanning clinics, patients referred from general practicioners based on 1+ clinical risk factors for OP	Two QUS systems: CUBA Clinical (BUA, VOS), Sunlight Omnisense (distal radius, proximal phalanx mid finger, mid-shaft tibia)	DXA, LS-4, and total hip	Patients referred by general practitioner to DXA screening clinic	Unclear	Yes	Unclear	Unclear	Sample has potential for bias toward low BMD due to recruitment from DXA clinic (all patients referred by MD for clinical risk factors)
Harrison et al, 2006[93]	Caucasian females, 55-80 years (referred to clinical radiology, intended use of index test (QUS x2) underwent DXA and categorized as non-osteoporosis and osteoporosis. Subsequently underwent QUS and risk assessment using demographics and then combined algorithms-QUS used to predict osteoporosis	QUS x2	DXA	White Caucasian females ages 55 to 70 years (mean 61, SD 4) who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans were invited to take part in the study	Unclear	Yes	Unclear	Low	No details on setting or how participants were selected

Appendix D Table 27. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 1

First Author, Year	Patients (Setting, Intended Use of Index Test, Presentation, Prior Testing)	Index Test(s)	Reference Standard and Target Condition	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?	Could the Selection of Patients Have Introduced Bias?	Comments
Jimenez-Nunez et al, 2013[94]	Women from primary and tertiary care, diagnosis, no prior testing	4 risk scores + PIXI of the heel	DXA of the hip and spine	Described as random from 2 sites	Yes	Yes	Yes	Low	NR
Kung et al, 2003[95]	Women in Hong Kong recruited from the community	OSTA index and QUI	DXA	Women from community, all comers who did not meet exclusion	Unclear	Yes	Yes	Low	Although noted to be early post-menopausal, mean age is 62
Kung et al, 2005[96]	Community of Asian (Southern Chinese) men; develop index based on clinical factors; compare clinical index with calcaneal QUS in predicting BMD (T<-2.5 by DXA	Clinical index	Calcaneal QUS; target condition is osteoporosis, determined by BMD at the hip and spine by DXA	Men from community, all comers who did not meet exclusion	Yes	Yes	Yes	Low	Unclear who chose to participate relative to larger group, excluded abnormal TSH group

Appendix D Table 27. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 1

First Author, Year	Patients (Setting, Intended Use of Index Test, Presentation, Prior Testing)	Index Test(s)	Reference Standard and Target Condition	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?	Could the Selection of Patients Have Introduced Bias?	Comments
Lynn et al, 2008[97]	US Caucasian (4658) and Hong Kong Chinese (1914) from the MrOS study with DXA and QUS measurements to compare screening tools (OST, MOST, QUI) to DXA	OST, MOST, QUI	DXA	US participants were recruited using population-based listings at 6 clinical settings in Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; San Diego, CA. Hong Kong participants were recruited using combination of private solicitation and public ads from community centers, housing estates, and the general community. Men who had bilateral hip replacements or were unable to walk without the assistance of another person were excluded.	Yes	Yes	Unclear	Low	NR
McLeod et al, 2015[101]	Women referred for screening in Canada, no prior testing	QUS and OST	DXA	Patients referred for screening to one facility	Yes	Yes	Yes	Low	NA

Appendix D Table 27. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 1

First Author, Year	Patients (Setting, Intended Use of Index Test, Presentation, Prior Testing)	Index Test(s)	Reference Standard and Target Condition	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?	Could the Selection of Patients Have Introduced Bias?	Comments
Minnock et al, 2008[117]	Causian women underwent clinical risk factor questionnaire, QUS and DXA in order to determine whether a combined clinical assessment tool + QUS would be predictive of osteoporosis (low bone mass) by DXA	Combined clinical risk facors+ QUS	DXA	Women were referred to DXA scanning clinic at Great Western Hospital, Swindon, UK. Referral was performed by the patients GPs, or hospital based clinics	Unclear	Yes	Unclear	Unclear	Insufficient information
Richy et al, 2004[118]	Two cohorts of postmenopasual women, age 45 and older; purpose was to study #1 -develop an clinical algorithm tool+ QUS (n=407 women)with bone mass as the outcome measure, as derived from DXA, and then in study #2 used a second cohort (202 women) to validate the algorithm by comparing it to QUS alone and to the OST; community screening clinic; no prior testing	Clinical algorithm; QUS	DXA for low bone mass; osteoporosis	Women who attended public screening for Osteoporosis	Yes	Yes	Yes	Low	NR

Appendix D Table 27. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 1

First Author, Year	Patients (Setting, Intended Use of Index Test, Presentation, Prior Testing)	Index Test(s)	Reference Standard and Target Condition	Describe Methods of Patient Selection	Was a Consecutive or Random Sample of Patients Enrolled?	Was a Case-Control Design Avoided?	Did the Study Avoid Inappropriate Exclusions?	Could the Selection of Patients Have Introduced Bias?	Comments
Sinnott et al, 2006[111]	AA men, age 35 and older (outpatient general medicine clinics at veteran hospital; intended use of clinical assessment tools and calcaneous ultrasound compared with the reference measure of BMD by DXA; no description of presentation in article; no prior testing): index text is ultrasound of calcaneous on non-dominant foot, outcome is low bone mass	ultrasound of calcaneous on non-dominant foot	BMD by DXA at the 1) lumbar spine (L1-L4) and 2) non-dominant hip(femoral neck, trochanter, total hip)	Subjects were recruited from outpatient general medicine clinics at the Jesse Brown VA Medical Center over an 11-month period in 2004	Unclear	Yes	Yes	Low	Selection of participants may be a convenience sample but unclear. Men were recruited from general medicine clinics so selection bias likely low

Abbreviations: AL=Alabama; BMD=bone mineral density; BUA=broadband attenuation; CA=California; DXA=dual energy x-ray absorptiometry; GPs=general practitioners; KQ=key question; LS-4=lumbar spine 4; MD=medical doctor; MN=Minnesota; MOST=Male Osteoporosis Screening Tool; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; NA=not applicable; OP=osteoporosis; OR=Oregon; OST=osteoporosis self-assessment tool; OSTA=Osteoporosis Self-assessment Tool for Asians; PA=Pennsylvania; QUI=ultrasound index; QUS=quantitative ultrasound; SD=standard deviation; TSH=thyroid-stimulating hormone; UK=United Kingdom; US=United States; VA=Veterans' Administration; VOS=velocity of sound.

Appendix D Table 28. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 2

First Author, Year	Describe the Index Test and How It Was Conducted and Interpreted	Were the Index Test Results Interpreted without Knowledge of the Results of the Reference Standard?	If a Threshold Was Used, Was It Pre-Specified?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Comments
Boonen et al, 2005[116]	QUS, DXR, RA	Yes	Yes	Low	NR
Cook et al, 2005[87]	Two QUS tests - CUBA clinical and Sunlight Omnisense measurements. Performed on non-dominant side with same ultrsaound gel. System quality verification tests each day.	Unclear	Yes	Unclear	Threshold question - yes and no used a 90% sensitivity threshold, but also created a cut off level based on the highest combined value of Sn and Sp. ROB assessment - depends on if QUS studies read independently of DXA imaging.
Harrison et al, 2006[93]	QUS x2	Unclear	Yes	Unclear	Osteoporosis status determined before index tests conducted, but unclear if results available
Jimenez-Nunez et al, 2013[94]	4 risk scores + PIXI of the heel, algorithms were developed	Yes	Yes	Low	NR
Kung et al, 2003[95]	Index characteristics through interview and QUI of right heel by technician	Unclear	Yes	Low	Index based on characteristics can be biased based on analysis decisions
Kung et al, 2005[96]	Index developed by authors based on characteristics	Unclear	Yes	Low	NR
Lynn et al, 2008[97]	OST, MOST, QUI	Unclear	Yes	Low	NR
McLeod et al, 2015[101]	QUS of BUA and SOS of left calcaneus & personal data based on questionnaire	Yes	Yes	Low	NR
Minnock et al, 2008[117]	Combined clinical risk facors+ QUS	Unclear	Yes	Low	NR
Richy et al, 2004[118]	Clinical algorithm; QUS	Unclear	Yes	Low	NR
Sinnott et al, 2006[111]	Ultrasound of calcaneous on non-dominant foot	Unclear	Unclear	Low	NR

Abbreviations: BUA=broadband attenuation; DXR=digital x-ray radiogrammetry; MOST=Male Osteoporosis Screening Tool; NR=not reported; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; RA=radiographic absorptiometry; Sn=sensitivity; SOS=speed of sound; Sp=specificity.

Appendix D Table 29. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 3

First Author, Year	Describe the Reference Standard and How It Was Conducted and Interpreted	Is the Reference Standard Likely To Correctly Classify the Target Condition?	Were the Reference Standard Results Interpreted without Knowledge of the Results of the Index Test?	Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?	Comments
Boonen et al, 2005[116]	DXA, BMD of the lumbar spiine and proximal femur	Yes	Unclear	Low	NR
Cook et al, 2005[87]	DXA. BMD of the lumbar spine and total hip	Yes	Unclear	Unclear	NR
Harrison et al, 2006[93]	DXA, BMD of the femoral neck and total hip	Yes	Unclear	Low	NR
Jimenez-Nunez et al, 2013[94]	DXA, BMD of the hip and spine	Yes	Yes	Low	NR
Kung et al, 2003[95]	DXA: BMD of the lumbar spine, femoral neck	Yes	Unclear	Low	NR
Kung et al, 2005[96]	DXA: BMD of the lumbar spine, femoral neck	Yes	Yes	Low	NR
Lynn et al, 2008[97]	DXA, lumbar spine and proximal femur	Yes	Unclear	Low	All obtained from MrOS (sequence of data collection not described)
McLeod et al, 2015[101]	DXA: BMD of the lumbar spine, left and right femoral neck	Yes	Yes	Low	NR
Minnock et al, 2008[117]	DXA, BMD of the lumbar spine, femoral neck, and total hip	Yes	Unclear	Low	NR
Richy et al, 2004[118]	DXA, BMD of the femoral neck	Yes	Yes	Low	NR
Sinnott et al, 2006[111]	DXA; BMD of the hip, spine	Yes	Unclear	Low	NR

Abbreviations: BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; KQ=key question; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; NR=not reported; QUS=quantitative ultrasound.

Appendix D Table 30. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 4

First Author, Year	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions between Index Test(s) and Reference Standard	Was There an Appropriate Interval between Index Test(s) and Reference Standard?	Did All Patients Receive a Reference Standard?	Did Patients Receive the Same Reference Standard?	Were All Patients Included in the Analysis?
Boonen et al, 2005[116]	On treatment for osteo, peripheral oedema	Same day	Yes	Yes	Yes	Yes
Cook et al, 2005[87]	None	None	Yes	Yes	Yes	Yes
Harrison et al, 2006[93]	NR	NR	Unclear	Yes	Yes	Unclear
Jimenez-Nunez et al, 2013[94]	Nursing home, homebound, prior diagnosis of osteo, on osteo drugs, serious acute or chronic disease, hip replacement, steroids	Same day	Unclear	Yes	Yes	Unclear
Kung et al, 2003[95]	History or evidence of metabolic bone disease, menopause before 40, history of cancer, evidence of sig renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride or calcitonin	NR	Unclear	Yes	Yes	Yes
Kung et al, 2005[96]	History or evidence of metabolic bone disease, hightory of cancer, evidence of sig renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride or calcitonin, abnormal biochemisty including renal and liver function, serum calcium, phosphate, total alkaline phosphatase, and TSH	NR	Unclear	Yes	Yes	Yes
Lynn et al, 2008[97]	NR	NR	Unclear	Yes	Yes	NA
McLeod et al, 2015[101]	Previous diagnosis, progressive terminal illness	Within 3 weeks	Yes	Yes	Yes	Yes
Minnock et al, 2008[117]	NR	NR	Unclear	Yes	Yes	No
Richy et al, 2004[118]	NR	NR	Unclear	Yes	Yes	Yes
Sinnott et al, 2006[111]	NR	NR	Unclear	Yes	Yes	Yes

Abbreviations: NA=not applicable; NR=not reported; TSH=thyroid-stimulating hormone.

Appendix D Table 31. Risk of Bias Assessment for KQ 2a Imaging Studies Predicting Bone Density Status: Part 5

First Author, Year	Could the Patient Flow Have Introduced Bias?	Comments	Overall Judgement	Overall Comments
Boonen et al, 2005[116]	Low	NR	Low	Not a community-based sample. Women referred for bone densitometry.
Cook et al, 2005[87]	Low	NR	Unclear	Patient selection has the potential to skew the sample tow ard low BMD
Harrison et al, 2006[93]	Unclear	Participants underw ent DXA and w ere categorized as non -osteo or osteo prior to QUS or risk indices	Unclear	Osteoporosis status determined first
Jimenez-Nunez et al, 2013[94]	Low	Random sample done w ith some sort of cards	Low	NR
Kung et al, 2003[95]	Low	NR	Low	NR
Kung et al, 2005[96]	Low	It is not clear w hat the time frame betw een clinical assessment of risk factors and QUS; how ever should be little impact; I put that all participants received the same reference standard (referring to the validated group here)	Low	NR
Lynn et al, 2008[97]	Low	NR	Low	NR
McLeod et al, 2015[101]	Low	Effort made to contact patient, enroll and conduct OST and QUS w ithin 3 w eeks of DXA scan to complete study assessments prior to provider receiving DXA results and talking w ith patient.	Low	NR
Minnock et al, 2008[117]	Low	NR	Unclear	Initial sample is 274 but number in analysis is 235 because of missing data, impact of missing data unclear
Richy et al, 2004[118]	Low	NR	Low	NR
Sinnott et al, 2006[111]	Low	The flow w as not specifically described, but appears sequence w as clinical assessment follow ed by ultrasound and then DXA.	Low	NR

Abbreviations: BMD=body mineral density; DXA=dual energy x-ray absorptiometry; KQ=key question; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; NR=not reported; OST=osteoporosis self-assessment tool; QUS=quantitative ultrasound.

Appendix D Table 32. KQ 2a Prediction Studies Risk of Bias: Part 1

First Author, Year	Describe Screening or Treatment Interventions and Comparators	Prediction Model Development as well as Testing of Predictive Performance in Other Individuals (External Validation), Both in the Same Publication	Testing the Predictive Performance of a Previously Developed Prediction Model in Other Individuals (External Validation)	For Validity Were Appropriate Data Sources Used ?
Ahmed, 2014[129]	1. Garvan FRC with BMD, adjusted for age, prior fracture, prior fall 2. Garvan FRC, adjusted for body weight, age, prior fracture, prior fall.	No	Yes- Val only	Yes
Azagra, 2011[181]	FRAX (Spain)	No	No	Probably no
Bauer, 2007[163]	Quantitative US	No	No	Yes
Berry, 2013[195]	Assess contribution of repeat BMD in 4 years to fx risk : 1. BMD at basline and Fx risk 2. BMD percent change and Fx risk 3. BMD at baseline and BMD Percent change and Fx risk	No	Yes- Val only	Yes
Chan, 2012[168]	1. FNBMD (adjusted for age, falls, prior fracture) 2. QUS (BUA) plus FNBMD (adjusted for age, falls, prior fracture)	No	Yes- Val only	Yes
Chan, 2013[192]	1. FNplus BMD (adjusted for age, falls, prior fracture) 2. QUS (BUA) plus FNBMD (adjusted for age, falls, prior fracture)	No	Yes- Val only	Yes
Crandall, 2014[58]	Comparison of three screening strategies for women age 50-64: 1. USPSTF Strategy (FRAX 3.0 without BMD, with follow up BMD testing for fx risk >= 9.3%)- 10 yr horizon 2. OST-horizon unknown, this was developed to identify osteoporosis, not fracture 3. SCORE-horizon unknown, this was developed to identify osteoporosis, not fracture	No	Yes- Val only	Yes
Hans, 2011[165]	TBS alone, DXA alone, TBS plus DXA	No	No	Probably yes
Hillier, 2007[194]	Imaging screening: DXA, initial BMD, repeat BMD, change in BMD, initial BMD plus change in BMD	No	No	Yes
Hippisley-Cox, 2012[130]	Qfracture updated with additional clinical predictors and outcomes	Yes- Dev and Val	Yes- Val only	Yes
Iki, 2014[164]	DXA - spine areal BMD, trabecular bone score	No	No	Yes
Iki, 2015 [132]	FRAX and TBS	no	Yes- Val only	yes
Kalveston, 2016 [133]	FRAX and BMD	Yes- Val only	Yes- Val only	Yes

Appendix D Table 32. KQ 2a Prediction Studies Risk of Bias: Part 1

First Author, Year	Describe Screening or Treatment Interventions and Comparators	Prediction Model Development as well as Testing of Predictive Performance in Other Individuals (External Validation), Both in the Same Publication	Testing the Predictive Performance of a Previously Developed Prediction Model in Other Individuals (External Validation)	For Validity Were Appropriate Data Sources Used ?
Kanis, 2007[32]	FRAX	Yes- Dev and Val	No	Yes
Kwok, 2012[167]	Imaging screening: QUS (BUA, SOS, QUI measures), DXA (tHIP, fnHIP, spine BMD)	No	No	Yes
Leslie, 2010[131]	CAROC	No	Yes	Yes
Leslie, 2012[127]	FRAX	No	Yes- Dev and Val	Yes
Leslie, 2012[123]	FRAX with and without DXA	No	Yes	Yes
Leslie, 2013[166]	Trabecular bone score	No	No	Yes
Lo, 2011[159]	FRC	No	Yes- Val only	Probably yes
Lundin, 2015 [179]	FRAX and BMD	no	Yes- Val only	yes
Melton, 2005[342]	NOF model including femoral neck BMD and clinical risk factors (personal fx history, FHx, low BWT, smoking status)	No	Yes- Val only	Yes
Miller, 2002[180]	Heel SXR, Heel QUS, forearm DXA, finger DXA; NORA study	No	No	Yes
Morin, 2009[102]	body weight, BMI, OST (OST was developed to predict osteoporosis)	No	Yes	Yes
Nguyen, 2004[144]	QUS. DOES	No	No	Yes
Rubin, 2013[128]	FRAX (no BMD), OST, ORAI, OSIRIS, SCORE (all but FRAX were developed to predict osteoporosis not fracture), Age alone	No	Yes- Val only	Yes
Stewart, 2006[162]	DXA	No	Yes- Val only	Yes
van Geel, 2014[124]	FRAX, Garvan FRC	No	Yes- Val only	Yes

Abbreviations: BMD=bone mineral density; BMI=body mass index; BUA=broadband attenuation; BWT=body weight; CAROC=Canadian Association of Radiologists and Osteoporosis Canada; DOES=Dubbo Osteoporosis Epidemiology Study; DXA=dual energy x-ray absorptiometry; FNBMD=femoral neck bone mineral density; fnHIP=femoral neck of hip; FNplus=femoral neck plus; FRAX=Fracture Risk Assessment tool; FRC=Fracture Risk Calculator; Fx=fracture; NOF=National Osteoporosis Foundation; NORA=National Osteoporosis Risk Assessment; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SOS=speed of sound; SXR=single x-ray absorptiometry; TBS=trabecular bone score; tHIP=total hip; US=United States; USPSTF=United States Preventive Services Task Force.

Appendix D Table 33. KQ 2a Prediction Studies Risk of Bias: Part 2

First Author, Year	For Validity Were All Inclusions and Exclusions of Participants Appropriate?	For Validity Were Participants Enrolled at a Similar State of Health, or Were Predictors Considered To Account for Any Dissimilarities?	Risk of Bias Introduced by Selection of Participants	Justification of Bias Rating	Comments
Ahmed, 2014[129]	Yes	Yes	Low	NR	NR
Azagra, 2011[181]	Yes	Yes	Unclear	Cohort was assembled from participants referred for screening by primary or specialty care physicians. Thus, the cohort does not represent an entirely unselected population.	NR
Bauer, 2007[163]	Yes	Yes	Low	NR	NR
Berry, 2013[195]	Yes	Yes	Low	NR	NR
Chan, 2012[168]	Yes	Yes	Low	NR	NR
Chan, 2013[192]	No	Yes	High	High concern for spectrum bias in the subgroup analysis, since participants in the analysis were limited to those with BMD < -2.5	NR
Crandall, 2014[58]	Yes	Yes	Low	NR	NR
Hans, 2011[165]	Probably yes	Probably yes	Low	NR	NR
Hillier, 2007[194]	Probably yes	Yes	Low	NR	NR
Hippisley-Cox, 2012[130]	Probably yes	Probably yes	Low	NR	NR
Iki, 2014[164]	Yes	Yes	Low	NR	NR
Iki, 2015 [132]	yes	yes	low	Population-based cohort	None
Kalvesten, 2016 [133]	yes	yes	low	Population-based recruitment into study.	None
Kanis, 2007[32]	No information	Probably yes	Low	NR	Inclusion/exclusion criteria for the 11 independent validation cohorts is not included.
Kwok, 2012[167]	Yes	Yes	Low	NR	NR
Leslie, 2010[131]	No information	Probably no	Low	Database covers population in Manitoba age 50 with a first bone desnity measurement, and all citizens of Manitoba have university access to publicly funded medical care including BMD.	NR

Appendix D Table 33. KQ 2a Prediction Studies Risk of Bias: Part 2

First Author, Year	For Validity Were All Inclusions and Exclusions of Participants Appropriate?	For Validity Were Participants Enrolled at a Similar State of Health, or Were Predictors Considered To Account for Any Dissimilarities?	Risk of Bias Introduced by Selection of Participants	Justification of Bias Rating	Comments
Leslie, 2012[127]	No information	Probably no	Low	Database covers population in Manitoba age 50 with a first bone desnity measurement, and all citizens of Manitoba have university access to publicly funded medical care including BMD.	NR
Leslie, 2012[123]	No information	Probably no	Low	Database covers population in Manitoba age 50 with a first bone desnity measurement, and all citizens of Manitoba have university access to publicly funded medical care including BMD.	NR
Leslie, 2013[166]	No information	Probably no	Low	Database covers all women in Manitoba age 50 with a first bone desnity measurement, and all citizens of Manitoba have university access to publicly funded medical care including BMD.	NR
Lo, 2011[159]	Probably no	Probably yes	Unclear	Possible spectrum bias due to use of population of women referred for DXA testing. Other exclusions may also have introduced some selection bias. Impact of these cannot be determined. Only about 94,000 of an eligible population of 500,000 were analyzed.	Study limited to women age 50 to 85 who were referred to have bone density scanning. Women without continuous membership both prior and following DXA scans, and those for whom DXA results were not electronically accessible and those with missing race/eth
Lundin, 2015 [179]	yes	yes	low	Population based recruitment strategy.	None
Melton, 2005[342]	No information	No information	Unclear	NR	NR
Miller, 2002[180]	Yes	No information	Unclear	It is unclear whether sites selected people with similar underlying characteristics.	NR

Appendix D Table 33. KQ 2a Prediction Studies Risk of Bias: Part 2

First Author, Year	For Validity Were All Inclusions and Exclusions of Participants Appropriate?	For Validity Were Participants Enrolled at a Similar State of Health, or Were Predictors Considered To Account for Any Dissimilarities?	Risk of Bias Introduced by Selection of Participants	Justification of Bias Rating	Comments
Morin, 2009[102]	No information	Probably no	Low	Database covers all women in Manitoba 40 to 59 with a first bone desnity measurement, and all citizens of Manitoba have university access to publicly funded medical care including BMD.	NR
Nguyen, 2004[144]	No information	No information	Unclear	unclear whether patients selected from database similar underlying characteristics	NR
Rubin, 2013[128]	Yes	Yes	Low	NR	NR
Stewart, 2006[162]	Yes	No information	Low	NR	NR
van Geel, 2014[124]	Probably yes	Yes	Low	NR	NR

Abbreviations: BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; KQ=key question; NR=not reported.

Appendix D Table 34. KQ 2a Prediction Studies Risk of Bias: Part 3

First Author, Year	For Validity Were Predictors Defined and Assessed in a Similar Way for All Participants?	For Validity Were Predictors Defined and Assessed in a Similar Way to Predictors in the Development Model?	Risk of Bias Introduced by Predictors or Their Assessment	Justification of Bias Rating	Comments
Ahmed, 2014[129]	yes	yes	Low	NR	NR
Azagra, 2011[181]	Yes	Yes	Low	NR	NR
Bauer, 2007[163]	Yes	Yes	YesLow	NR	NR
Berry, 2013[195]	Yes	Yes	Low	NR	NR
Chan, 2012[168]	Yes	Yes	Low	NR	NR
Chan, 2013[192]	Yes	Yes	Low	NR	NR
Crandall, 2014[58]	Yes	Yes for FRAX and OST, probably no for SCORE	Low	Authors show that use of different age cut off for prior history of fracture would likely have little impact.	NR
Hans, 2011[165]	NA-NOT VAL	NA-NOT VAL	Low	NR	NR
Hillier, 2007[194]	NA-NOT VAL	NA-NOT VAL	Low	NR	NR
Hippisley-Cox, 2012[130]	Yes	Yes	Low	NR	NR
Iki, 2014[164]	Yes	NA-NOT VAL	Low	NR	NR
Iki, 2015 [132]	yes	yes	low	In person interviews	None
Kalvesten, 2016 [133]	yes	yes	low	Questionnaire-based assessment, all relevant predictors assessed.	None
Kanis, 2007[32]	Probably yes	Probably yes	Low	NR	NR
Kwok, 2012[167]	NA-NOT VAL	NA-NOT VAL	Low	Imaging prediction of fracture - not clinical prediction tool	NR
Leslie, 2010[131]	Yes	No	Unclear	The final risk category was modified to reflect the presence of additional risk factors: any prior osteoporotic fracture (from 1987 to the date of BMD testing) and/or recent systemic corticosteroid use (in the year before BMD testing).	NR
Leslie, 2012[127]	Yes	No	Unclear	Parental hip fracture information missing for FRAX probability estimates prior to 2005, adjusted using age- and sex-specific adjustment factors derived from 2005 to 2008 parental hip fracture responses	NR
Leslie, 2012[123]	Yes	No	Unclear	Parental hip fracture information missing for FRAX probability estimates prior to 2005, adjusted using age- and sex-specific adjustment factors derived from 2005 to 2008 parental hip fracture responses	NR

Appendix D Table 34. KQ 2a Prediction Studies Risk of Bias: Part 3

First Author, Year	For Validity Were Predictors Defined and Assessed in a Similar Way for All Participants?	For Validity Were Predictors Defined and Assessed in a Similar Way to Predictors in the Development Model?	Risk of Bias Introduced by Predictors or Their Assessment	Justification of Bias Rating	Comments
Leslie, 2013[166]	Yes	NA	Low	TBS assessed the same way for all	NR
Lo, 2011[159]	Yes	Probably yes	Low	NR	NR
Lundin, 2015 [179]	Yes, for DXA No, for FRAX	Yes, for DXA No information, for FRAX	low for DXA unclear for FRAX	The study does not describe how inputs to FRAX were obtained	NR
Melton, 2005[342]	Yes	Probably yes	Low	NR	NR
Miller, 2002[180]	Yes	NA	Low	Peripheral bone densitometry done in simiarl ways for all	NR
Morin, 2009[102]	Yes	No information	Unclear	Unclear whether data for OST (age, weight) was collected before fracture for all participants	NR
Nguyen, 2004[144]	Yes	NA	NALow	QUS done in similar ways for all	NR
Rubin, 2013[128]	Yes	No information	Low	NR	NR
Stewart, 2006[162]	Yes	Yes	Low	NR	NR
van Geel, 2014[124]	Probably yes	Probably yes	Low	NR	NR

Abbreviations: BMD=bone mineral density; BMI=body mass index; BUA=broadband attenuation; BWT=body weight; CAROC=Canadian Association of Radiologists and Osteoporosis Canada; DOES=Dubbo Osteoporosis Epidemiology Study; DXA=dual energy x-ray absorptiometry; FHx=fracture history; FNBMD=femoral neck BMD; fnHIP=femoral neck of hip; FNplus=femoral neck plus; FRAX=Fracture Risk Assessment tool; FRC=Fracture Risk Calculator; Fx=fracture; KQ=key question; NOF=National Osteoporosis Foundation; NORA=National Osteoporosis Risk Assessment; NR=not reported; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SOS=speed of sound; SXR=single x-ray absorptiometry; TBS=trabecular bone score; tHIP=total hip; US=United States; USPSTF=United States Preventive Services Task Force; VAL=validity.

Appendix D Table 35. KQ 2a Prediction Studies Risk of Bias: Part 4

First Author, Year	For Validity Was a Pre-Specified Outcome Definition Used?	For Validity Was the Outcome Defined and Determined in a Similar Way for All Participants?	For Validity Was the Outcome Defined and Determined in a Similar Way to the Outcome in the Development Model?	For Validity Was the Outcome Determined without Knowledge of Predictor Information?
Ahmed, 2014[129]	Yes	Yes	Yes	No information
Azagra, 2011[181]	Yes	Yes	Yes	Yes
Bauer, 2007[163]	Yes	Yes	Yes	No information
Berry, 2013[195]	Yes	Yes	Yes	No information
Chan, 2012[168]	Yes	Yes	Probably yes	No information
Chan, 2013[192]	Yes	Yes	Probably yes	No information
Crandall, 2014[58]	Yes	Yes	No for OST and SCORE, Yes for FRAX	No information
Hans, 2011[165]	Yes	Yes	NA-NOT VAL	Yes
Hillier, 2007[194]	Yes	Yes	NA-NOT VAL	Yes
Hippisley-Cox, 2012[130]	Yes	Yes	Yes	Yes
Iki, 2014[164]	Yes	Yes	NA-NOT VAL	Yes
Iki, 2015 [132]	yes	yes	yes	no information
Kalvesten, 2016 [133]	yes	yes	yes	no information
Kanis, 2007[32]	No information	No	Probably yes	No information
Kwok, 2012[167]	Yes	Yes	NA-NOT VAL	Yes
Leslie, 2010[131]	Yes	Yes	No information	Probably yes
Leslie, 2012[127]	Yes	Yes	No information	Probably yes
Leslie, 2012[123]	Yes	Yes	No information	Probably yes
Leslie, 2013[166]	Yes	Yes	Yes	Yes
Lo, 2011[159]	Yes	Yes	Probably yes	No information
Lundin, 2015 [179]	yes	yes	yes	no information
Melton, 2005[342]	Yes	Yes	Probably no	Yes
Miller, 2002[180]	Yes	Yes	Yes	Yes
Morin, 2009[102]	Yes	Yes	No information	No information
Nguyen, 2004[144]	Yes	Yes	Yes	Yes
Rubin, 2013[128]	Yes	Yes	No information	Yes
Stewart, 2006[162]	Yes	Yes	Yes	No information
van Geel, 2014[124]	Yes	Yes	Probably yes	Yes

Abbreviations: FRAX=Fracture Risk Assessment tool; KQ=key question; OST=osteoporosis self-assessment tool; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; VAL=validity.

Appendix D Table 36. KQ 2a Prediction Studies Risk of Bias: Part 5

First Author, Year	Risk of Bias Introduced by the Outcome or Its Determination	Justification of Bias Rating	Comments
Ahmed, 2014[129]	Low	NR	NR
Azagra, 2011[181]	Low	NR	NR
Bauer, 2007[163]	Low	NR	NR
Berry, 2013[195]	Low	NR	NR
Chan, 2012[168]	Low	NR	NR
Chan, 2013[192]	Low	NR	NR
Crandall, 2014[58]	Unclear	Both OST and SCORE were initially developed and validated for prediction of low BMD. In this study they are being used to predict fracture. It's unclear what impact this will have.	NR
Hans, 2011[165]	Low	NR	NR
Hillier, 2007[194]	Low	NR	NR
Hippisley-Cox, 2012[130]	Low	NR	NR
Iki, 2014[164]	Low	NR	NR
Iki, 2015 [132]	low	fractures were confirmed	None
Kalvesten, 2016 [133]	low	Confirmation of all self-reported fractures. Outcomes censored at 10 years.	NR
Kanis, 2007[32]	Unclear	Fracture ascertainment was by self-report in some cohorts and by medical record or radiology report confirmation in other cohorts.	NR
Kwok, 2012[167]	Low	Did not exclude traumatic fractures; would just have to take fragility fracture #s	NR
Leslie, 2010[131]	Low	NR	NR
Leslie, 2012[127]	Low	NR	NR
Leslie, 2012[123]	Low	NR	NR
Leslie, 2013[166]	Low	NR	NR
Lo, 2011[159]	Low	NR	NR
Lundin, 2015 [179]	low	Identification of fractures from population based claims/diagnosis data.	None
Melton, 2005[342]	High	13.3% fractures were due to severe trauma, another 18.3% unclear cause	NR
Miller, 2002[180]	High	self-reported factures	NR
Morin, 2009[102]	Unclear	unclear whether OST variables collected for all women before fracture outcome, OST developed and validated for prediction of low BMD	NR
Nguyen, 2004[144]	Low	NR	NR
Rubin, 2013[128]	Unclear for all but FRAX (low)	OST, SCORE, ORAI, OSIRIS developed and validated for prediction of low BMD, not fracture risk.	NR
Stewart, 2006[162]	Low	NR	NR
van Geel, 2014[124]	Low	NR	NR

Abbreviations: BMD=bone mineral density; KQ=key question; NR=not reported; OST=osteoporosis self-assessment tool; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool.

Appendix D Table 37. KQ 2a Prediction Studies Risk of Bias: Part 6

First Author, Year	Describe Missing Data on Predictors and Outcomes as well as Methods Used for Missing Data (What Was the Missing Data, How Was It Managed? Focus on Diff between N Eligible and N Analyzed, Other Data Issues)	For Validity Were There a Reasonable Number of Outcome Events? (Bring Up for Discussion if Low)	For Validity Was the Time Interval Between Predictor Assessment and Outcome Determination Appropriate?	For Validity Were All Enrolled Participants Included in the Analysis?
Ahmed, 2014[129]	Subjects with missing data were excluded.	Yes	Yes for 5 years, No for 10 years	Yes
Azagra, 2011[181]	Not clear how missing data handled.	Yes	Yes	No
Bauer, 2007[163]	No missing data.	Yes	Yes	Yes
Berry, 2013[195]	No data on parental history of hip fracture, set to "no".	Yes	Yes	Yes
Chan, 2012[168]	No missing data described	Yes	Yes	Probably no
Chan, 2013[192]	No missing data described	Yes	Yes	Probably no
Crandall, 2014[58]	Missing data set to "not present". Most common predictor missing was parental hip fx history.	Yes	Yes	Yes
Hans, 2011[165]	N eligble NR (over 34,000, see comments) N included 29407	Yes	Probably yes	Probably yes
Hillier, 2007[194]	9704 enrolled in SOF, 8141 women had follow up (93%), 4124 had repeat BMD measurement, excluded patients with incident hip or non-spine fractures between BMD measurement (72, 513 respectively)	Yes	Yes	Probably no
Hippisley-Cox, 2012[130]	Did not report amount of missing data (particularly for BMI, smoking Status, alcohol intake), though report mulitple imputation was used. Qresearch database > 13,000,000 patients but only 4,726,046 used for development and validation cohorts. Only inclusi	Yes	Probably yes	No
Iki, 2014[164]	789 eligible 665 analyzed 112 lost to follow up 4 unassessable VFA 8 developed disease affecting bone metabolism	Yes	Yes	Probably yes
Iki, 2015 [132]	No information about the men excluded from the analysis.	probably no	probably no	probably yes
Kalvesten, 2016 [133]	Only subjects with complete data were included in analysis.	yes	yes	probably no
Kanis, 2007[32]	Sensitivity analyses used to assess impact of missing predictor information.	Probably yes	Yes	No information

Appendix D Table 37. KQ 2a Prediction Studies Risk of Bias: Part 6

First Author, Year	Describe Missing Data on Predictors and Outcomes as well as Methods Used for Missing Data (What Was the Missing Data, How Was It Managed? Focus on Diff between N Eligible and N Analyzed, Other Data Issues)	For Validity Were There a Reasonable Number of Outcome Events? (Bring Up for Discussion if Low)	For Validity Was the Time Interval Between Predictor Assessment and Outcome Determination Appropriate?	For Validity Were All Enrolled Participants Included in the Analysis?
Kwok, 2012[167]	N (eligible)=2000, N (analyzed)=1921, those missing QUS or DXA readings excluded, invalid QUS readings excluded	Probably yes	Probably yes	No
Leslie, 2010[131]	Unclear	Yes	Yes	Yes
Leslie, 2012[127]	Unclear	Yes	Yes	Yes
Leslie, 2012[123]	Unclear	Yes	Yes	Yes
Leslie, 2013[166]	NR	Yes	Yes	Probably yes
Lo, 2011[159]	Women with missing data on race/ethnicity and BMD were excluded from analysis.	Yes	Yes	Yes
Lundin, 2015[179]	Missing data for 5 participants	yes	yes	yes
Melton, 2005[342]	1,479 approached, 1,315 eligible, 655 consented, only 393 included in analysis - unclear why	Probably yes	Yes	No
Miller, 2002[180]	NR	Yes	No	Unclear
Morin, 2009[102]	NR	Yes	Yes	Unclear
Nguyen, 2004[144]	NR	Yes	Unclear	Unclear
Rubin, 2013[128]	Eligible: 5000 Analysis: 3614 Exclusion: 334 missing questionnaire data, 246 diagnosed with/treated for OP, reported "near complete follow-up" in registry	Probably yes	Probably no	Yes
Stewart, 2006[162]	Nonresponse analysis done.	Yes	Yes	Yes
van Geel, 2014[124]	Random sample: 1686, analysis sample: 506 Missing: no coop with MD (272), no coop with patient (448), untraceable/deceased (207), age <60 (110)	Probably yes	Probably no	Yes

Abbreviations: BMD=bone mineral density; BMI=body mass index; DXA=dual energy x-ray absorptiometry; KQ=key question; MD=medical doctor; N=number; NR=not reported; OP=osteoporosis; QUS=quantitative ultrasound; SOF=study of osteoporotic fractures; VFA=vertebral fracture assessment.

Appendix D Table 38. KQ 2a Prediction Studies Risk of Bias: Part 7

First Author, Year	For Validity Were Participants with Missing Data Handled Appropriately?	Risk of Bias Introduced by Sample Size or Participant Flow	Justification of Bias Rating	Comments
Ahmed, 2014[129]	Yes	Low for 5 yr outcomes; unclear for 10 yr outcomes	Inadequate duration of follow-up for 10 year risk predictions.	NR
Azagra, 2011[181]	No information	Unclear	Unclear eligible N	NR
Bauer, 2007[163]	Yes	Low	NR	No mention of missing data
Berry, 2013[195]	Yes	Low	NR	NR
Chan, 2012[168]	Yes	Unclear	Some members of the cohort began before the use of QUS was introduced, so they would not be eligible. It's still not clear why of the 3678 eligible in the cohort, < 1,000 comprised the analytic sample	NR
Chan, 2013[192]	Yes	Unclear	NR	NR
Crandall, 2014[58]	Yes	Low	NR	NR
Hans, 2011[165]	Probably yes	Low	NR	No mention of missing data Only says matching of personal identifier information with the administrative data repository in over 34,000 DXA patients was achieved in over 99%
Hillier, 2007[194]	Yes	Low	NR	NR
Hippisley-Cox, 2012[130]	Probably yes	Unclear	Unclear exclusion criteria	Over 13 million in database, only 4.7 million used
Iki, 2014[164]	Probably yes	Low	NR	NR
Iki, 2015 [132]	probably yes	Unclear	Follow-up was only 4.5 yrs, but using a 10 year risk prediction. 93% of those enrolled were included in the analysis.	NR
Kalvesten, 2016 [133]	probably yes	unclear	The entire study cohort was about 9000, but not all had complete data for calculation of FRAX and DXA measurement. Thus, analysis restricted to those with complete data, those included were younger and a little healthier and had lower prevalence of prior fracture; though BMD measures were similar.	NR
Kanis, 2007[32]	Probably yes	Low	NR	NR
Kwok, 2012[167]	Probably yes	Low	2.5% excluded for missing data (small)	NR
Leslie, 2010[131]	No information	Unclear	NR	NR
Leslie, 2012[127]	No information	Unclear	NR	NR
Leslie, 2012[123]	No information	Unclear	NR	NR
Leslie, 2013[166]	Probably yes	Low	99% accuracy and completeness	NR
Lo, 2011[159]	Probably yes	Low	NR	NR
Lundin, 2015 [179]	yes	low	No concerns	NR

Appendix D Table 38. KQ 2a Prediction Studies Risk of Bias: Part 7

First Author, Year	For Validity Were Participants with Missing Data Handled Appropriately?	Risk of Bias Introduced by Sample Size or Participant Flow	Justification of Bias Rating	Comments
Melton, 2005[342]	No information	High	Only about 50% of eligible patietns consented, and of those only 2/3 included for analysis	NR
Miller, 2002[180]	No information	Unclear	Unclear whether follow up window is sufficient	NR
Morin, 2009[102]	No information	Unclear	Unclear what proportion of cohort did not have information on predictors	NR
Nguyen, 2004[144]	No information	Unclear	The average time between imaging and fractures is unclear	NR
Rubin, 2013[128]	No information	Unclear	Only 3 year follow-up while FRAX predicts 10 year fracture for women over 40 years old	NR
Stewart, 2006[162]	Probably yes	Low	NR	NR
van Geel, 2014[124]	Probably yes	Unclear	FRAX and Garvan predict 10 year risk - follow-up only for 5 years. Likely underestimates risk. 124 of 630 patients lost to follow-up	NR

Abbreviations: DXA=dual energy x-ray absorptiometry; FRAX=Fracture Risk Assessment tool; KQ=key question; N=number; NR=not reported; QUS=quantitative ultrasound.

Appendix D Table 39. KQ 2a Prediction Studies Risk of Bias: Part 8

First Author, Year	For Validity Were Non-Binary Predictors Handled Appropriately?	For Validity Were Any Complexities in the Data Accounted for Appropriately?	For Validity Was the Model Recalibrated or Was It Likely That Recalibration Was Not Needed?	Risk of Bias Introduced by the Analysis
Ahmed, 2014[129]	Probably yes	No information	Probably no	Unclear for AUC High for NRIs at both 5 and 10 yrs.
Azagra, 2011[181]	Yes	Probably yes	Yes	Low
Bauer, 2007[163]	Yes	No information	No information	Low
Berry, 2013[195]	Yes	No information	Probably yes	Low
Chan, 2012[168]	Probably yes	No information	Yes	Varies by outcome
Chan, 2013[192]	Probably yes	No information	Yes	Varies by outcome
Crandall, 2014[58]	Yes	No information	No information	Unclear
Hans, 2011[165]	Yes	Probably yes	Probably yes	Low
Hillier, 2007[194]	Probably yes	Yes	Yes	Low
Hippisley-Cox, 2012[130]	Probably yes	Yes	Yes	Low
Iki, 2014[164]	Yes	Probably yes	Yes	Low
Iki, 2015 [132]	Yes	no information	yes	low
Kalvesten, 2016 [133]	yes	no information	yes	low
Kanis, 2007[32]	Yes	Probably yes	Probably yes	Low
Kwok, 2012[167]	Yes	Yes	NA-NOT VAL	Low
Leslie, 2010[131]	Yes	No information	No	Low
Leslie, 2012[127]	Yes	No information	No	Low
Leslie, 2012[123]	Yes	No information	No	Low
Leslie, 2013[166]	Yes	No information	No	Low
Lo, 2011[159]	Yes	No information	Probably yes	Low
Lundin, 2015 [179]	yes	no	yes	low
Melton, 2005[342]	Yes	Probably yes	Yes	Low
Miller, 2002[180]	Yes	No information	No	Low
Morin, 2009[102]	Yes	No information	No	Low
Nguyen, 2004[144]	Yes	No information	No	Low
Rubin, 2013[128]	Yes	Yes	Yes	Low
Stewart, 2006[162]	NA	Probably no	Na	Low
van Geel, 2014[124]	Yes	Probably yes	Yes	Low

Abbreviations: AUC=area under the curve; KQ=key question; NA=not applicable; NRI=net reclassification improvement; VAL=validity.

Appendix D Table 40. KQ 2a Prediction Studies Risk of Bias: Part 9

First Author, Year	Justification of Bias Rating	Comments	Overall Judgement of Risk of Bias	Justification of Bias Rating
Ahmed, 2014[129]	Except for perhaps hip fx in women at 5 yrs, calibration plots suggest underestimation of risk at lower risk levels, and overestimation of risk at higher risk levels.	The NRI thresholds used were based on quintiles of the sample distribution of fracture risks. Thresholds used for NRI should be based on sensible and accepted thresholds to define risk groups.	Unclear for AUCs, High for NRIs	NRI risk thresholds not based on sensible/acceptable categories to define risk, they were based on sample distribution. Inadequate follow up for 10 year risk prediction.
Azagra, 2011[181]	NR	NR	Unclear	Some concerns about selection bias due to source of study population and attrition of subjects over period of follow up.
Bauer, 2007[163]	NR	NR	Low	NR
Berry, 2013[195]	NR	NR	Low	NR
Chan, 2012[168]	Low for AUC, High for NRI	The NRI thresholds used were based on tertiles of the sample distribution. Thresholds used for NRI should be based on sensible and accepted thresholds to define risk groups.	Varies by outcome	Unclear for AUC, High For NRI
Chan, 2013[192]	Low for AUC, High for NRI	The NRI thresholds used were based on tertiles of the sample distribution. Thresholds used for NRI should be based on sensible and accepted thresholds to define risk groups.	High	Spectrum bias introducted by subgroup analysis.
Crandall, 2014[58]	NR	NR	Unclear	OST and SCORE were not developed and validated to predict fractures; they were developed and validated to predict low BMD/osteoporosis.
Hans, 2011[165]	NR	If multiple DXA scans, just took first one	Low	NR
Hillier, 2007[194]	Removed patients with incident fractures.	NR	Low	NR
Hippisley-Cox, 2012[130]	NR	NR	Unclear	Unclear because of partipant flow
Iki, 2014[164]	NR	NR	Low	NR
Iki, 2015 [132]	Evidence of good calibration	None	unclear	Length of follow-up only 4.5 years for a 10-year prediction.
Kalvesten, 2016 [133]	NR	None	low	No serious risks of bias. Eligible Outcomes include the discrimination of DXA for predicting fracture, and FRAX (without DXA BMD) for predicting fracture. The diagnostic performance of FRAX for predicting osteoporosis is not eligible because there was 2.1 years between FRAX assessment and DXA measurement. For same reason FRAX w/BMD not eligible as well.

Appendix D Table 40. KQ 2a Prediction Studies Risk of Bias: Part 9

First Author, Year	Justification of Bias Rating	Comments	Overall Judgement of Risk of Bias	Justification of Bias Rating
Kanis, 2007[32]	NR	NR	Low	NR
Kwok, 2012[167]	NR	NR	Low	Did not exclude traumatic fractures in definition of "all fractures" but we can just take the data for fragility fractures)
Leslie, 2010[131]	NR	NR	Unclear	Effect of adjustment to final risk category unclear
Leslie, 2012[127]	Model demonstrates the effect of using various non-femoral neck BMD measures	NR	Unclear	Effect of adjustments of absence of data on parental hip fractures unclear
Leslie, 2012[123]	Model demonstrates the effect of not using BMD	NR	Unclear	Effect of adjustments of absence of data on parental hip fractures unclear
Leslie, 2013[166]	NR	NR	Low	NR
Lo, 2011[159]	NR	NR	Unclear	Selection bias and spectrum bias due to how cohort was assembled.
Lundin, 2015 [179]	Most of the items are NA.	None	low	No serious risks of bias
Melton, 2005[342]	for patients with multiple fractures, only included the first fracture, but unclear if different types of fractures in same person or same types of fracture	NR	High	Due to sampling, definition of outcome
Miller, 2002[180]	NR	NR	High	Self-reported fracture outcomes
Morin, 2009[102]	NR	NR	Unclear	Unclear whether data for OST (age, weight) was collected before fracture for all participants, unclear what proportion of cohort did not have information on predictors. OST was not developed and validated to predict fractures.
Nguyen, 2004[144]	NR	NR	Unclear	Proportion and management of missing data unclear
Rubin, 2013[128]	NR	NR	Unclear	For short follow-up duration to predict 10 year risk. All but FRAX were not developed and validated to predict fractures.
Stewart, 2006[162]	NR	NR	Low	NR
van Geel, 2014[124]	NR	NR	Unclear	Follow-up period shorter than instrument

Abbreviations: AUC=area under the curve; BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; NR=not reported; NRI=net reclassification improvement; OST=osteoporosis self-assessment tool; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; Yrs=years.

Appendix D Table 41. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 1

First Author, Year	Describe Interventions and Comparators (MUST Describe Usual Care and Combinations)	Did the Review Adhere to Pre-defined Objectives and Eligibility Criteria?	Were the Eligibility Criteria Appropriate for the Review Question?	Were Eligibility Criteria Unambiguous?
Crandall et al, 2012[221]	Treatments to prevent fractures vs. Placebo	Yes	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 42. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 2

First Author, Year	Were All Restrictions in Eligibility Criteria Based on Study Characteristics Appropriate?	Were Any Restrictions in Eligibility Criteria Based on Sources of Information Appropriate?	Concerns Regarding Specification of Study Eligibility Criteria	Did the Review Search an Appropriate Range of Databases/Electronic Sources for Published and Unpublished Reports?
Crandall et al, 2012[221]	Yes	Yes	Low	Yes

Abbreviations: KQ=key question.

Appendix D Table 43. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 3

First Author, Year	Were Methods Additional to Database Searching Used To Identify Relevant Reports?	Were the Terms and Structure of the Search Strategy Likely To Retrieve as Many Eligible Studies as Possible?	Were Restrictions Based on Date, Publication Format, or Language Appropriate?	Were Efforts Made To Minimize Error in Selection of Studies?
Crandall et al, 2012[221]	Yes	Yes	Probably yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 44. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 4

First Author, Year	Concerns Regarding Methods Used To Identify and/or Select Studies	Were Efforts Made To Minimize Error in Data Collection?	Were Sufficient Study Characteristics Available for Both Review Authors and Readers To Be Able To Interpret The Results?	Were All Relevant Study Results Collected for Use in the Synthesis?
Crandall et al, 2012[221]	Low	No information	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 45. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 5

First Author, Year	Was Risk of Bias (or Methodological Quality) Formally Assessed Using an Appropriate Tool?	Were Efforts Made To Minimize Error in Risk of Bias Assessment?	Concerns Regarding Methods Used To Collect Data and Appraise Studies	Did the Synthesis Include All Studies That It Should?
Crandall et al, 2012[221]	Yes	No information	Low	Yes

Abbreviations: KQ=key question.

Appendix D Table 46. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 6

First Author, Year	Were All Pre-defined Analyses Reported or Departures Explained?	Was the Synthesis Appropriate Given the Degree of Similarity in the Research Questions, Study Designs and Outcomes across Included Studies?	Was Between-Study Variation (Heterogeneity) Minimal or Addressed in the Synthesis?	Were the Findings Robust?
Crandall et al, 2012[221]	Yes	Yes	Yes	Yes

Abbreviations: KQ=key question.

Appendix D Table 47. KQ 4 and KQ5 Systematic Review Risk of Bias Assessments: Part 7

First Author, Year	Were Biases in Primary Studies Minimal or Addressed in the Synthesis?	Concerns Regarding the Synthesis	Did the Interpretation of Findings Address All of the Concerns Identified in Domains 1 to 4?	Was the Relevance of Identified Studies to the Review's Research Question Appropriately Considered?	Did the Reviewers Avoid Emphasizing Results on the Basis of Their Statistical Significance?	Risk of Bias in the Review
Crandall et al, 2012[221]	Yes	Unclear or some concerns	Yes	Yes	Yes	Low

Abbreviations: KQ=key question.

Appendix D Table 48. KQ 4 and 5 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
Abrahamsen, 2010[273]	G1: Alendronate G2: Untreated	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Adachi, 2009[250]	G1: alendronate 10 mg daily (generic preparation) G2: Placebo	RCT parallel	Yes	Yes	Probably yes
Barrett-Connor, 2002[311]	G1: Raloxifene (60mg/day) G2: Raloxifene (120mg/day) G2: Placebo	Post-hoc or subgroup analysis of RCT	Yes	Yes	No
Barrett-Connor, 2004[310]	G1: Raloxifene (60mg/day or 120mg/day) G2: Placebo	RCT parallel	Yes	Yes	No
Bone, 2000[216]	G1: Alendonate 10 mg /day G2: conjugage equine estrogen 0.625 mg /day) G3: Alendronate + CEE G4: placebo	RCT parallel	Yes	No information	No
Bone, 2008[237]	G1: Denosumab G2: Placebo	RCT parallel	Probably yes	Probably yes	No
Boonen, 2012[218]	G1: intravenous infusion of zoledronic acid (5 mg) for 12 months G2: Placebo	RCT parallel	Yes	yes	No
Cartsos, 2008 [297]	Intervention: Bisphosphonate use Comparator: no bisphosphonate use	Case-control (how they described)	NA-not an RCT	NA-not an RCT	NA-not an RCT
Chapurlat, 2013[284]	G1: ibandronate G2: placebo	RCT parallel	Probably yes	Yes	No
Cryer, 2005[252]	G1: alendronate 70 mg weekly G2: placebo	RCT parallel	Yes	Yes	No
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	G1: alendronate 5mg per day for 2 years, then 10 mg per day for 3 years G2: placebo	RCT parallel	Yes	Yes	No
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	G1: Denosumab G2: Placebo	RCT parallel	Probably yes	Probably yes	No
Eisman, 2004[255]	G1:alendronate 70 mg weekly G2: placebo	RCT parallel	Yes	Yes	No
Fogelman, 2000[226]	G1: Risedronate 5 mg/d X 24 months G2: Placebo	RCT parallel	No information	No information	No
Greenspan, 2002[254]	G1: alendronate 70 mg weekly G2: placebo	RCT parallel	No information	No information	No

Appendix D Table 48. KQ 4 and 5 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
Greenspan, 2003[249]	G1: Alendonate 10 mg /day G2: conjugated equine estrogen 0.625 mg /day with or without medroxyprogesterone 2.5mg daily based on uterus presence G3: Alendronate + CEE G4: placebo	RCT parallel	Yes	Yes	No
Grey, 2010[274]	G1: Zolendronate 5 mg IV x 1 dose G2: Placebo	RCT parallel	Yes	Yes	Probably yes
Hosking, 2003[202]	G1: Risedronate 5 mg/d X 3 months G2: Alendronate 70 mg/once weekly X 3 months G3: Placebo	RCT parallel	Yes	Yes	No
Hosking, 2003[202]	G1: alendronate 70 mg weekly G2: Risendronate 5 mg daily G3: Placebo	RCT parallel	Yes	Yes	No
Johnell, 2002[246]	RLX 60, placebo	RCT parallel	Yes	Yes	Probably no
Keech, 2005[312]	G1: Raloxifene 60 mg / day G2 : Placebo	Post-hoc or subgroup analysis of RCT	Yes	Yes	No
Kung, 2000[343]	G1: alendronate 10 mg daily G2: placebo	RCT parallel	No information	No information	No
Lasco, 2011[241]	G1: Teriparatide + calcium + vitamin D G2: Calcium + vitamin D	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Lewiecki, 2007[236]	G1: Denosumab (included varying dosages over 3 and 6 months) G2: Alenbronate G3: Placebo	RCT parallel	Probably yes	Probably yes	No
McCloskey, 2012[245]	G1: 60 mg Denosumab SC q 6 mos for 36 mos G2: Placebo	RCT parallel	No information	No information	No
McClung, 2004[285]	G1: 0.5mg ibandronate daily G2: 1.0mg ibandronate daily G3: 2.5mg ibandronate daily G4:placebo	RCT parallel	No information	No information	No
McClung, 2006[306]	G1: Lasofoxifene 0.25 mg/day G2: Lasofoxifene 1.0 mg/day G3: Raloxifene 60 mg/day G4: Placebo	RCT parallel	No information	No information	No

Appendix D Table 48. KQ 4 and 5 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
McClung, 2006[209]	G1: Denosumab 6 mg Q3mo G2: Denosumab 14 mg Q3mo G3: Denosumab 30 mg Q3mo G4: Denosumab 14 mg Q6mo G5: Denosumab 60 mg Q6mo G6: Denosumab 100 mg Q6mo G7: Denosumab 210 mg Q6mo G8: Alendronate 70 mg weekly G9: placebo	RCT parallel	No information	No information	No
McClung, 2009[275]	G1: Zoledronic acid 5 mg IV q 12 mos for 2 doses G2: Zoledronic acic 5mg IV once and placebo at 12 mos G3: Placebo at baseline and 12 mos	RCT parallel	Yes	Yes	No
Meunier, 1999[307]	raloxifene, 60 mg, 150 mg or placebo	RCT parallel	No information	Probably yes	No
Miller, 2008[308]	G1: Bazedoxifene 10 mg G2: Bazedoxifene 20 mg G3: Bazedoxifene 40 mg G4: Raloxifene 60 mg G5: Placebo	RCT parallel	yes	yes	No
Morii, 2003[309]	raloxifene, 2 dosage amounts vs placebo	RCT parallel	No information	No information	Probably no
Murphy, 2001[272]	G1: MK-677 25 mg daily G2: alendronate 10 mg daily G3: MK-677 and alendronate G4: placebo **pull out G2 and G4 data only for KQ5	RCT parallel	Yes	Yes	No
Nakamura, 2012[239]	G1: Denosumab 14 mg G2: Denosumab 60 mg G3: Denosumab 100 mg G4: Placebo	RCT parallel	No information	No information	No
Orwoll, 2003[240]	G1: 20 µg teriparatide: 151 G2:40 µg teriparatide: 139 G3: placebo: 147	RCT parallel	Yes	Yes	No
Pazianas, 2008 [298]	Intervention: oral bisphosphate use Comparator: No bisphosphate use	case-control (how they described)	NA-not an RCT	NA-not an RCT	NA-not an RCT

Appendix D Table 48. KQ 4 and 5 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
Ravn, 1996[286]	G1: 0.25mg ibandronate daily G2: 0.5mg ibandronate daily G3: 1.0mg ibandronate daily G4: 2.5mg ibandronate daily G5: 5.0 mg ibandronate daily G6: placebo	RCT parallel	No information	No information	No
Reginster, 2005[287]	G1: 50mg ibandronate monthly 1 month, followed by 50 mg monthly 2 months for half the sample and 100 mg monthly for 2 months for the other half G2: 100mg ibandronate monthly for 3 months G3: 150mg ibandronate monthly for 3 months G4: placebo for 3 months	RCT parallel	No information	No information	Yes
Rhee, 2012[344]	G1: Bisphosphonate use G2: non bisphosphonate use	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Riis, 2001[288]	G1: 2.5mg ibandronate daily continuous therapy G2: 20mg ibandronate intermittent cyclical therapy G3: Placebo	RCT parallel	No information	No information	No
Samelson, 2014[345]	G1: 60 mg Denosumab SC q 6 mos for 36 mos G2: Placebo	Post-hoc or subgroup analysis of RCT	No information	No information	Probably no
Shiraki, 2003[283]	G1: Risedronate 5 mg/d X 36 weeks G2: Placebo	RCT cluster	No information	No information	No
Simon, 2013[346]	G1: 60 mg Denosumab SC q 6 mos for 36 mos G2: Placebo	RCT parallel	No information	No information	No
Sontag, 2010[242]	G1: Raloxifene in women without baseline prevalent vertebral fracture G2: Placebo in women without baseline prevalent vertebral fracture	Post-hoc or subgroup analysis of RCT	Yes	Yes	No
Sorensen, 2008[247]	G1: bisphosphonate therapy* G2: placebo *Study examined all busphosphonates used in Danish prescription database, predominently alendronate, etidronate. Only 5 control patients used risendronate. No patients used zolendronic acid.	Case-control	NA-not an RCT	NA-not an RCT	NA-not an RCT
Tanko, 2003[289]	G1: 5mg ibandronate weekly G2: 10mg ibandronate weekly G3: 20mg ibandronate weekly G4: placebo	RCT parallel	No information	No information	No

Appendix D Table 48. KQ 4 and 5 Risk of Bias Assessment: Part 1

First Author, Year	Describe Interventions and Comparators	Study Design	FOR RCTs: Was Method of Randomization Adequate?	FOR RCTs: Was Allocation Concealment Adequate?	For RCTs: Were There Baseline Imbalances That Suggest a Problem with Randomization?
Thiebaud, 1997[290]	G1: 2.5mg ibandronate IV every 3 months G2: .5mg ibandronate IV every 3 months G3: 1mg ibandronate IV every 3 months G4: 2mg ibandronate IV every 3 months G5: placebo	RCT parallel	No information	No information	No
Tucci, 1996[253]	G1: Alendronate 5mg daily G2: Alendronate 10 mg daily G3: Alendronate 20 daily for 2 years then 5 mg daily for 1 year G4: placebo	RCT parallel	Yes	Yes	No
Van Staa, 1997[347]	G1: Cyclinical Etidronate (1 or more cyclical etidronate prescriptions) G2: Nonosteoporosis control (as recorded in their medical records and no bisphosphonate use)	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2010[348]	Gastric & esophagus events	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2011[349]	Stroke	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2012[350]	Cardiac and atherosclerosis	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2011[351]	Femoral shaft and subtrochanteric fractures	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2012[352]	Jaw disease	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT

Abbreviations: CEE=conjugated equine estrogen; G=group; KQ=key question; mg=milligram; mg/d=milligram per day; mo=month; NA=not applicable; RCT=randomized controlled trials.

Appendix D Table 49. KQ 4 and 5 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-Up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
Abrahamsen, 2010[273]	Probably no	Yes	Yes	NA-not a case-control	Probably no	Women treated with alendronate by definition have increased risk of fracture, prompting their treatment with the drug.
Adachi, 2009[250]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably yes	Alendronate group had greater proportion of patients with history of UGI disease, active UGI disease, esophogeal disease, no statistical comparison is given, but the differences are large enough to warrant some concern for risk of bias as it does not appear that these differences were corrected for in the analysis.
Barrett-Connor, 2002[311]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Barrett-Connor, 2004[310]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	Not enough information on randomization process.
Bone, 2000[216]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Bone, 2008[237]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	No information on allocation concealment
Boonen, 2012[218]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Cartsos, 2008[297]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	Yes	data comes from medical claims data; possible errors in coding; does not include uninsured; sample not representative of total population
Chapurlat, 2013[284]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Cryer, 2005[252]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR

Appendix D Table 49. KQ 4 and 5 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-Up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	No information on allocation concealment
Eisman, 2004[255]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Fogelman, 2000[226]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Greenspan, 2002[254]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	The article does not include information on randomization or concealment
Greenspan, 2003[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Grey, 2010[274]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably yes	The authors did not clearly adjust for baseline fracture.
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Johnell, 2002[246]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Keech, 2005[312]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Kung, 2000[343]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	The article does not include information on randomization or concealment
Lasco, 2011[241]	no	yes	NA	NA-not a case-control	yes	One arm has osteoporosis and other has osteopenia; the differences between arms could have served as a prognostic factor and contribute to confounding.
Lewiecki, 2007[236]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	No information on allocation concealment.

Appendix D Table 49. KQ 4 and 5 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-Up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
McCloskey, 2012[245]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No information	NR
McClung, 2004[285]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	no information provided on method of randomization or concealment
McClung, 2006[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	Not enough information on randomization process
McClung, 2006[209]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
McClung, 2009[275]	No	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Meunier, 1999[307]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Miller, 2008[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Morii, 2003[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	Some missing info
Murphy, 2001[272]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Nakamura, 2012[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	No information provided on method of randomization or concealment
Orwoll, 2003[240]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Pazianas, 2008 [298]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	Yes	data comes from medical claims data; possible errors in coding; does not include uninsured; sample not representative of total population
Ravn, 1996[286]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	No information provided on method of randomization or concealment
Reginster, 2005[287]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	Absence of specific BMD criteria led to the inclusion of some participants were not osteoporotic

Appendix D Table 49. KQ 4 and 5 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-Up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
Rhee, 2012[344]	Yes	No	No information	NA-not a case-control	Probably yes	Although the authors attempt to create an new user cohort by excluded anyone with a prescription for 16 months prior to the observation of the outcome, it's unclear whether and how many participants might have been exposed to osteoporosis drugs before that period and stopped taking medications.
Riis, 2001[288]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	no information provided on method of randomization or concealment
Samelson, 2014[345]	Yes	Yes	No information	NA-not a case-control	Probably no	NR
Shiraki, 2003[283]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Simon, 2013[346]	Yes	Yes	Probably yes	NA-not a case-control	Probably no	No detail on method of randomization and allocation concealment.
Sontag, 2010[242]	yes	yes	NA	NA-not a case-control	Probably no	NR
Sorensen, 2008[247]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Yes	No	NR
Tanko, 2003[289]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	no information provided on method of randomization or concealment
Thiebaud, 1997[290]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	no information provided on method of randomization or concealment Slight differences length of menopause
Tucci, 1996[253]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Van Staa, 1997[347]	Yes	Yes	Yes	NA-not a case-control	Probably no	NR
Vestergaard, 2010[348]	Yes	Yes	irrelevant, claim there is no missing data	NA-not a case-control	No	NR

Appendix D Table 49. KQ 4 and 5 Risk of Bias Assessment: Part 2

First Author, Year	FOR COHORTs: Was Selection into the Study Unrelated to Intervention or Unrelated to Outcome?	FOR COHORTs: Do Start of Follow-Up and Start of Intervention Coincide for Most Subjects?	FOR COHORTs: Were Adjustment Techniques Used That Are Likely To Correct for the Presence of Selection Biases?	FOR CASE-CONTROLS: Were the Controls Sampled from the Population That Gave Rise to the Cases, or Using Another Method That Avoids Selection Bias?	Bias Arising from Randomization or Selection?	Comments
Vestergaard, 2011[349]	Yes	Yes	irrelevant, claim there is no missing data	Yes	No	NR
Vestergaard, 2012[350]	Yes	Yes	irrelevant, claim there is no missing data	NA-not a case-control	No	NR
Vestergaard, 2011[351]	Yes	Yes	irrelevant, claim there is no missing data	NA-not a case-control	No	NR
Vestergaard, 2012[352]	Yes	Yes	irrelevant, claim there is no missing data	NA-not a case-control	No	NR

Abbreviations: NA=not applicable; NR=not reported.

Appendix D Table 50. KQ 4 and 5 Risk of Bias Assessment: Part 3

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Confounding of the Effect of Intervention Unlikely in This Study?	FOR COHORTS: Were Participants Analyzed According to Their Initial Intervention Group throughout Followup?	FOR COHORT STUDIES: Were Intervention Discontinuations or Switches Unlikely To Be Related to Factors That Are Prognostic for the Outcome?	FOR COHORT AND CASE-CONTROL STUDIES: Did the Authors Use an Appropriate Analysis Method That Adjusted for all the Critically Important Confounding Domains?
Abrahamsen, 2010[273]	Probably no	Yes	No information	Probably yes
Adachi, 2009[250]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Barrett-Connor, 2002[311]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Barrett-Connor, 2004[310]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Bone, 2000[216]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Bone, 2008[237]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Boonen, 2012[218]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cartsos, 2008 [297]	Probably no	NA-not a cohort	NA-not a cohort	No information
Chapurlat, 2013[284]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cryer, 2005[252]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Eisman, 2004[255]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Fogelman, 2000[226]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Greenspan, 2002[254]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Greenspan, 2003[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Grey, 2010[274]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Johnell, 2002[246]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Keech, 2005[312]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Kung, 2000[343]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Lasco, 2011[241]	No	Yes	No information	No information
Lewiecki, 2007[236]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
McCloskey, 2012[245]	Probably yes	Yes	Yes	Probably yes
McClung, 2004[285]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
McClung, 2006[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
McClung, 2006[209]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
McClung, 2009[275]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Meunier, 1999[307]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Miller, 2008[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort

Appendix D Table 50. KQ 4 and 5 Risk of Bias Assessment: Part 3

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Confounding of the Effect of Intervention Unlikely in This Study?	FOR COHORTS: Were Participants Analyzed According to Their Initial Intervention Group throughout Followup?	FOR COHORT STUDIES: Were Intervention Discontinuations or Switches Unlikely To Be Related to Factors That Are Prognostic for the Outcome?	FOR COHORT AND CASE-CONTROL STUDIES: Did the Authors Use an Appropriate Analysis Method That Adjusted for all the Critically Important Confounding Domains?
Morii, 2003[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Murphy, 2001[272]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Nakamura, 2012[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Orw oll, 2003[240]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Pazianas, 2008 [298]	Probably no	NA-not a cohort	NA-not a cohort	Yes
Ravn, 1996[286]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Reginster, 2005[287]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Rhee, 2012[344]	Yes	Yes	Unclear, all sw itches dropped from analysis	NA
Riis, 2001[288]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Samelson, 2014[345]	Probably yes	Yes	Yes	Probably yes
Shiraki, 2003[283]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Simon, 2013[346]	Probably yes	Yes	Yes	Probably yes
Sontag, 2010[242]	Yes	NA	Yes	No
Sorensen, 2008[247]	No	NA-not a cohort	NA-not a cohort	Yes
Tanko, 2003[289]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Thiebaud, 1997[290]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Tucci, 1996[253]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Van Staa, 1997[347]	Yes	NA	NA	NA
Vestergaard, 2010[348]	No	No information	No information	No
Vestergaard, 2011[349]	No	No information	No information	No
Vestergaard, 2012[350]	No	No information	No information	No
Vestergaard, 2011[351]	No information	No information	No	Yes
Vestergaard, 2012[352]	No	No information	No information	No

Abbreviations: KQ=key question; NA=not applicable.

Appendix D Table 51. KQ 4 and 5 Risk of Bias Assessment: Part 4

First Author, Year	FOR COHORT STUDIES: Did the Authors Avoid Adjusting for Postintervention Variables?	FOR COHORT STUDIES Did the Authors Use an Appropriate Analysis Method That Adjusted for All the Critically Important Confounding Domains and for Time-Varying Confounding?	Bias Arising from Confounding?	Comments
Abrahamsen, 2010[273]	yes	Probably yes	Probably yes	NR
Adachi, 2009[250]	NA-not a cohort	NA-not a cohort	No	NR
Barrett-Connor, 2002[311]	NA-not a cohort	NA-not a cohort	NA	NR
Barrett-Connor, 2004[310]	NA-not a cohort	NA-not a cohort	NA	NR
Bone, 2000[216]	NA-not a cohort	NA-not a cohort	No	NR
Bone, 2008[237]	NA-not a cohort	NA-not a cohort	no	NR
Boonen, 2012[218]	NA-not a cohort	NA-not a cohort	No	NR
Cartsos, 2008 [297]	NA-not a cohort	NA-not a cohort	Probably yes	Possible patients could have been taking other treatments that were not documented; no mention of how confounding was handled or if considered
Chapurlat, 2013[284]	NA-not a cohort	NA-not a cohort	N/A	NR
Cryer, 2005[252]	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	NA-not a cohort	NA-not a cohort	no	NR
Eisman, 2004[255]	NA-not a cohort	NA-not a cohort	No	NR
Fogelman, 2000[226]	NA-not a cohort	NA-not a cohort	No information	NR
Greenspan, 2002[254]	NA-not a cohort	NA-not a cohort	No	NR
Greenspan, 2003[249]	NA-not a cohort	NA-not a cohort	No	NR
Grey, 2010[274]	NA-not a cohort	NA-not a cohort	No	NR
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	No information	NR
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	No	NR
Johnell, 2002[246]	NA-not a cohort	NA-not a cohort	Probably no	NR
Keech, 2005[312]	NA-not a cohort	NA-not a cohort	NA	NR
Kung, 2000[343]	NA-not a cohort	NA-not a cohort	No	NR
Lasco, 2011[241]	No information	No information	Yes	One arm has osteoporosis and other has osteopenia; the differences between arms could have served as a prognostic factor and contribute to confounding
Lewiecki, 2007[236]	NA-not a cohort	NA-not a cohort	No	NR
McCloskey, 2012[245]	Probably yes	NA	No information	The analysis was prespecified according to the methods and does not appear to be a subgroup. The are looking at efficacy across the range of baseline FRAX risk.

Appendix D Table 51. KQ 4 and 5 Risk of Bias Assessment: Part 4

First Author, Year	FOR COHORT STUDIES: Did the Authors Avoid Adjusting for Postintervention Variables?	FOR COHORT STUDIES Did the Authors Use an Appropriate Analysis Method That Adjusted for All the Critically Important Confounding Domains and for Time-Varying Confounding?	Bias Arising from Confounding?	Comments
McClung, 2004[285]	NA-not a cohort	NA-not a cohort	NA	NA, Not a cohort or case control
McClung, 2006[306]	NA-not a cohort	NA-not a cohort	No	Not a cohort or case control
McClung, 2006[209]	NA-not a cohort	NA-not a cohort	No	NR
McClung, 2009[275]	NA-not a cohort	NA-not a cohort	No	RCT design mitigates risk of confounding from known and unknown factors.
Meunier, 1999[307]	NA-not a cohort	NA-not a cohort	Probably no	NR
Miller, 2008[308]	NA-not a cohort	NA-not a cohort	No	NR
Morii, 2003[309]	NA-not a cohort	NA-not a cohort	Probably no	NR
Murphy, 2001[272]	NA-not a cohort	NA-not a cohort	No	NR
Nakamura, 2012[239]	NA-not a cohort	NA-not a cohort	NA	NR
Orwoll, 2003[240]	NA-not a cohort	NA-not a cohort	No	Not a cohort study
Pazianas, 2008 [298]	NA-not a cohort	NA-not a cohort	Probably no	possible patients could have been taking other treatments that were not documented
Ravn, 1996[286]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Reginster, 2005[287]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Rhee, 2012[344]	No	No	Yes	They also dropped all patients with switches, which potentially selectively drops patients with reactions to initial drug therapy
Riis, 2001[288]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Samelson, 2014[345]	Yes	NA, if item 10 is yes/probably yes	Probably no	Treatment assignment is random; CV risks were balanced between groups.
Shiraki, 2003[283]	NA-not a cohort	NA-not a cohort	No information	NR
Simon, 2013[346]	Probably yes	NA	Probably no	NR
Sontag, 2010[242]	No	NA	Yes	During a 1-year extension phase, women were permitted to take other bone-active agents, except for oral estrogen or estrogen–progestin therapy. 16.4% and 12.3% of women in the placebo and raloxifene 60 mg/day groups, respectively, used other bone-active agent
Sorensen, 2008[247]	NA-not a cohort	NA-not a cohort	No	NR
Tanko, 2003[289]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Thiebaud, 1997[290]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR

Appendix D Table 51. KQ 4 and 5 Risk of Bias Assessment: Part 4

First Author, Year	FOR COHORT STUDIES: Did the Authors Avoid Adjusting for Postintervention Variables?	FOR COHORT STUDIES Did the Authors Use an Appropriate Analysis Method That Adjusted for All the Critically Important Confounding Domains and for Time-Varying Confounding?	Bias Arising from Confounding?	Comments
Tucci, 1996[253]	NA-not a cohort	NA-not a cohort	No	NR
Van Staa, 1997[347]	NA	NA	No	NR
Vestergaard, 2010[348]	Yes	Probably no	Probably yes	Given the results it's likely that there were other underlying variables that they didn't fully account for. For example, are all NSAIDS in the drugs registry? What about OTC NSAIDS? Given that a third of their sample had fractures, likely they had pain t
Vestergaard, 2011[349]	Yes	Probably no	Probably yes	NR
Vestergaard, 2012[350]	Yes	Probably no	Probably yes	Given the results it's likely that there were other underlying variables that they didn't fully account for. For example, did they fully control for all other causes of MI such as smoking and hypertension.
Vestergaard, 2011[351]	Probably no	Probably yes	No	NR
Vestergaard, 2012[352]	Yes	Probably no	Probably yes	NR

Abbreviations: FRAX=Fracture Risk Assessment tool; KQ=key question; MI=myocardial infarction; NA=not applicable; NR=not reported; NSAIDS=nonsteroidal anti-inflammatory drugs; OTC=over the counter.

Appendix D Table 52. KQ 4 and 5 Risk of Bias Assessment: Part 5

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Intervention Status Well Defined?	FOR COHORTS AND CASE CONTROLS: Was Information on Intervention Status Recorded at the Time of Intervention?	FOR COHORTS AND CASE CONTROLS Was Information on Intervention Status Unaffected by Knowledge of the Outcome or Risk of the Outcome?	Bias Arising from Measurement of the Intervention?	Comments
Abrahamsen, 2010[273]	Yes	Yes	Yes	Probably no	NR
Adachi, 2009[250]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Barrett-Connor, 2002[311]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Barrett-Connor, 2004[310]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Bone, 2000[216]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Bone, 2008[237]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Boonen, 2012[218]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort	NR
Cartsos, 2008 [297]	No	No	Probably yes	yes	intervention based on dispensing information from claims data, information on dose not available
Chapurlat, 2013[284]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Cryer, 2005[252]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Eisman, 2004[255]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Fogelman, 2000[226]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No information	NR
Greenspan, 2002[254]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Greenspan, 2003[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Grey, 2010[274]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No information	NR
Hosking, 2003[202]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Johnell, 2002[246]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Keech, 2005[312]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Kung, 2000[343]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Lasco, 2011[241]	Yes	Yes	No information	Probably no	NR
Lewiecki, 2007[236]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
McCloskey, 2012[245]	Yes	Yes	Yes	No	It was prespecified.
McClung, 2004[285]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
McClung, 2006[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	not a cohort or case control
McClung, 2006[209]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR

Appendix D Table 52. KQ 4 and 5 Risk of Bias Assessment: Part 5

First Author, Year	FOR COHORTS AND CASE CONTROLS: Is Intervention Status Well Defined?	FOR COHORTS AND CASE CONTROLS: Was Information on Intervention Status Recorded at the Time of Intervention?	FOR COHORTS AND CASE CONTROLS Was Information on Intervention Status Unaffected by Knowledge of the Outcome or Risk of the Outcome?	Bias Arising from Measurement of the Intervention?	Comments
McClung, 2009[275]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	RCT Design so all items NA.
Meunier, 1999[307]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Miller, 2008[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	no	NR
Morii, 2003[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Murphy, 2001[272]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Nakamura, 2012[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Orw oll, 2003[240]	NA-not a cohort	NA-not a cohort	NA-not a cohort	no	NR
Pazianas, 2008 [298]	No	No	Probably yes	yes	intervention based on dispensing information from claims data, information on dose etc. not available
Ravn, 1996[286]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Reginster, 2005[287]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Rhee, 2012[344]	Yes	Yes	Yes	No	NR
Riis, 2001[288]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Samelson, 2014[345]	Probably yes	Yes	Yes	Probably no	NR
Shiraki, 2003[283]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No information	NR
Simon, 2013[346]	Yes	Yes	Yes	Probably no	NR
Sontag, 2010[242]	Yes	Yes	Yes	Probably no	NR
Sorensen, 2008[247]	Yes	Yes	Yes	No	NR
Tanko, 2003[289]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Thiebaud, 1997[290]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Tucci, 1996[253]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Van Staa, 1997[347]	No	Yes	Yes	Yes	intervention status defined as patients w ho had received a prescription
Vestergaard, 2010[348]	No	No information	Yes	Probably yes	NR
Vestergaard, 2011[349]	No	No information	Yes	Probably yes	NR
Vestergaard, 2012[350]	No	No information	Yes	Probably yes	NR
Vestergaard, 2011[351]	Yes	Probably yes	None	No	NA, no attrition
Vestergaard, 2012[352]	No	No information	Yes	Probably yes	NR

Abbreviations: NA=not applicable; NR=not reported; RCT=randomized controlled trials.

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Abrahamsen, 2010[273]	Overall: NR G1: 3.1% G2: 3.0% Vary by outcome: Probably no	No	Yes	NA-not a case-control
Adachi, 2009[250]	Overall:16.2 [%] G1: 18.6 [%] G2: 11.6% [%] Vary by Outcome? No	No	Yes	NA-not a case-control
Barrett-Connor, 2002[311]	Overall:26% G1: 26% G2: 25% G3: 26% Vary by Outcome? No	Yes	No	NA
Barrett-Connor, 2004[310]	Overall: 26% G1: 26.2 G2: 25.2 G3: 26.4 Vary by Outcome? no	No	Yes	NA
Bone, 2000[216]	Overall: 24.7 [%] G1: 24/92 = 26% G4: 16/50 = 32% Other reasons for attrition: withdrew conset, lost to follow-up, protocol violations, no signficant varation between groups	Yes	Yes	NA-not a case-control
Bone, 2008[237]	Overall attrition: 3/332=0.09% G1: 2/166 (1.2%) G2: 1/166 (0.06%)	No	Yes	NA-not a cohort
Boonen, 2012[218]	Overall: 11% G1: 10% G2: 12% Vary by Outcome? No	No	Yes	na-not a case control
Cartsos, 2008[297]	NA- no attrition	NA- no attrition	NA- no attrition	NA- no attrition

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Chapurlat, 2013[284]	Overall:0.67 G1: 0 G2: 1.3 Vary by Outcome? No Follow-up Overall: Unclear G1: Unclear G2: Unclear	No	Yes	NA- no attrition
Cryer, 2005[252]	Overall:13.7 [%] G1: 13.8 [%] G2: 13.5[%] G3: [%] No	No	Probably yes	NA-not a case-control
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Patients missing follow-up xray Overall: 379 / 6459 (5.9%) G1: 198 / 3195 (6.2%) G2: 181 /3183 (5.7)	No	Yes	NA-not a case-control
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Attrition varies by outcome, lowest for fractures: 475/7868 (6.03%) G1: 231/3933 (5.87%) G2: 244/3935 (6.20%)	No	Yes	NA-not a cohort
Eisman, 2004[255]	Overall: 6.2 [%] G1: 8.0 [%] G2: 4.5 [%] Vary by Outcome? No	No	Probably yes	NA-not a case-control
Fogelman, 2000[226]	G1: 40/179 = 22% G2: 37/180 = 21%	Yes	Yes	NA-not a case control
Greenspan, 2002[254]	Overall: 6.9% G1: 6.3% G2: 7.5% Vary by Outcome? No	No	Yes	NA-not a case-control
Greenspan, 2003[249]	Overall: 10[%] G1: 8.6% G2: 9.7 % G3: 9.6 % G4: 10.8% Vary by Outcome? No	No	Yes	NA-not a case-control

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Grey, 2010[274]	Overall: 2 [%] G1: 4 [%] G2: 0 [%] Vary by Outcome? No Information	No	Yes	NA-not a case-control
Hosking, 2003[202]	Attrition was only reported at 3 months. G1: 19.8% G2: 21.5% G2: 17.6%	No	No	NA-not a case control
Hosking, 2003[202]	Overall: 25[%] G1: 21.5 [%] G2: 19.8 [%] G3: 17.6 [%] Vary by Outcome? Yes Clincal AE leading to discontinuation: Overall: 17 [%] G1: 14.1 [%] G2: 14.0 [%] G3: 11.1 [%] **of note these are attrition % at 3 months. The study went on for 12 months, b	Yes	Yes	No
Johnell, 2002[246]	Overall: 17%; differences by group NR	No	Yes	NA- no attrition
Keech, 2005[312]	Overall: NR G1: 29% G2: 33% Vary by Outcome? No	Yes	No	NA
Kung, 2000[343]	Overall:80 [%] G1: 80[%] G2: 80 [%] G3: [%] Vary by Outcome? No	Yes	Yes	NA-not a case-control
Lasco, 2011[241]	Overall:0	NA- no attrition	NA- no attrition	NA
Lewiecki, 2007[236]	Overall attrition: 5/365=1.00% G1: 0/46 (0%) G2: 5/319 (1.57%)	No	Yes	NA-not a cohort

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
McCloskey, 2012[245]	Overall:82% G1: NR G2: NR Vary by Outcome? Probably No	No	No information	NA-not a case-control
McClung, 2004[285]	Overall: 16% G1: 15% G2: 13% G3: 18% G4: 17% no	No	Yes	NA-not a case-control
McClung, 2006[306]	Overall:36% G1: 37% G2: 30% G3: 29% G4: 31% Vary by Outcome? No	Yes	No information	NA-not a case-control
McClung, 2006[209]	Overall:10 [%] Not reported by group overal. For below only reported by drug (not dosing group) Vary by Outcome? Yes Withdraw al of consent G1-G7: 8 [%] G8: 2 [%] G9: 7 [%] Adverse effects G1-G7: 2 [%] G8: 0 [%] G9: 2 [%]	No	Yes	NA-not a case-control
McClung, 2009[275]	Overall:90% (Calculated) G1: 91.4% G2: 85.1% G3: 93.1% Vary by Outcome? No	No	no	NA-not a case-control
Meunier, 1999[307]	Overall: 20 of 129 at 24 months (19%), of these, 14 in year 1; differences by group NR	No	Yes	NA- no attrition

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Miller, 2008[308]	Overall:[%] 29.7 percent (N=470) discontinued treatment, another 2.9 % (46) failed to return. Additionally the flow chart shows patients who did not complete because of "subject request" and "other."	Yes	Yes	NA-not a case-control
Morii, 2003[309]	Overall: 13%; differences by group NR	No	Yes	NA- no attrition
Murphy, 2001[272]	Overall:15% at 6 mo, 30% at 12 months, 41% at 18 months No data by group G1: [%] G2: [%] G3: [%] Vary by Outcome? No Information	No for 6 months, Yes for 12 and 18 months.	Probably yes	NA-not a case-control
Nakamura, 2012[239]	Overall:8.0 G1: (5/53)9.4 G2: (4/54) 7.4 G3: (5/50)10 G4: (3/55) 5.5 Vary by Outcome? Probably No	No	No information	NA
Orwoll, 2003[240]	Overall:77[17.6%] G1:17 [12%] G2:28 [19%] G3:36 [26%] No Information by outcome	Yes	No	NA- no attrition
Pazianas, 2008 [298]	NA- no attrition	NA- no attrition	NA- no attrition	NA- no attrition
Ravn, 1996[286]	Overall: 39/180, 22% G1: 4/30,13% G2: 8/30, 27% G3: 4/30, 13% G4: 6/30, 20% G5: 12/30, 40% G6: 5/30, 17% no	Yes	Yes	NA-not a case-control

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Reginster, 2005[287]	Overall: 3% G1: 0 G2: 0 G3: 0 G4: 3% G5: 8% no	No	Yes	NA-not a case-control
Rhee, 2012[344]	No attrition because data are from registry	NA- no attrition	NA- no attrition	NA- no attrition
Riis, 2001[288]	Overall: 14% G1: 15% G2: 15% G3: 11% no	No	Yes	NA-not a case-control
Samelson, 2014[345]	Overall:82% for the main FREEDOM trial, but this analysis was a subgroup analysis of patients at increased CV risk and with adequate imaging studies. Only 1045 of 2363 patients eligible had evaluation data at baseline and follow up. G1: NR G2: NR Vary by	Yes	No information	NA-not a case-control
Shiraki, 2003[283]	G1: 9/56=16% G2: 9/54=17%	No	No information	NA-not a case control
Simon, 2013[346]	Overall:82% (This is for the overall FREEDOM study; 83% in DXA substudy, 86% in QCT substudy, attrition by treatment group NR) Vary by Outcome? Probably No	No	No information	NA-not a case-control
Sontag, 2010[242]	This article reports only ITT results, but based on original trial, Overall:26% G1: 26% G2: 25% G3: 26% Vary by Outcome? no	Yes	No	NA
Sorensen, 2008[247]	NA-not an RCT	NA-not an RCT	NA-not an RCT	Yes

Appendix D Table 53. KQ 4 and 5 Risk of Bias Assessment: Part 6

First Author, Year	FOR RCTS and COHORTS: What Was the Overall Attrition? What Was the Attrition by Group? Did Attrition Vary for Different Outcomes?	FOR RCTS and COHORTS: Did the Study Have High Attrition Raising Concern for Bias?	FOR RCTS and COHORTS: Are the Proportion of Participants and Reasons for Missing Data Similar across Interventions?	FOR CASE-CONTROLS: Are the Proportion of Participants and Reasons for Missing Data Similar across Cases and Controls?
Tanko, 2003[289]	Overall: 14% G1: NR G2: NR G3: NR G4: NR G5: NR no	No	Yes	NA-not a case-control
Thiebaud, 1997[290]	Overall: 10% G1: 12.5% (3/24) G2: 3.7% (1/27) G3: 11.5% (3/26) G4: 8.7% (2/23) G5: 7.7% (2/26) Vary by Outcome? No	No	Yes	NA-not a case-control
Tucci, 1996[253]	Overall:29/478 = 6.0% (from Ns in Table IV) G1: 9.2% G2: 6.4% G3: 8.5% G4: 3.1%	No	No information	NA-not a case-control
Van Staa, 1997[347]	No attrition	NA- no attrition	NA	NA
Vestergaard, 2010[348]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2011[349]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2012[350]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2011[351]	NA, no attrition	NA, no attrition	No	NA-not an RCT
Vestergaard, 2012[352]	None	No	NA, no attrition	NA, no attrition

Abbreviations: AE=adverse event; DXA=dual energy x-ray absorptiometry; FREEDOM=Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; G=group; KQ=key question; NA=not applicable; NR=not reported; QCT=quantitative computed tomography; RCT=randomized controlled trials.

Appendix D Table 54. KQ 4 and 5 Risk of Bias Assessment: Part 7

First Author, Year	FOR ALL STUDIES: Were Appropriate Statistical Methods Used To Account for Missing Data?	Bias Arising from Missing Outcome Data?	Comments
Abrahamsen, 2010[273]	Yes	No	NR
Adachi, 2009[250]	No information	Probably no	Authors do not specifically say they perform an intention to treat analysis.
Barrett-Connor, 2002[311]	Yes	Probably yes	NR
Barrett-Connor, 2004[310]	Yes	No	NR
Bone, 2000[216]	Yes	Probably yes	There was >20% attrition, and over 30% attrition in one of the arms.
Bone, 2008[237]	Yes	No	NR
Boonen, 2012[218]	Yes	No	NR
Cartsos, 2008 [297]	NA- no attrition	No information	No mention of how missing data was handled
Chapurlat, 2013[284]	Yes	Probably no	NR
Cryer, 2005[252]	Yes	Probably no	There is a small difference in reasons for discontinuation. More patients in placebo dropped out due to any clinical AE, however this difference is judged to be small.
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Yes	No	Missing data = missing xray at follow-up FIT1 (Black, 1996) Overall: 81 / 2027 = 4.0% G1: 41 / 981 = 4.2% G2: 40 / 965 = 4.1% FIT2 (Cummings, 1998 (8400)) Overall: 298/4432 (6.7%) G1: 157 / 2214 (7.1%) G2: 141 / 2218 (6.4%) Combining FIT1 and FIT2
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Yes	no	NR
Eisman, 2004[255]	Yes	Probably no	More withdrawals for clinical AE in alendronate group vs placebo, but no testing. Results show no difference in discontinuation for UGI AEs
Fogelman, 2000[226]	Yes	probably no	NR
Greenspan, 2002[254]	Yes	No	NR
Greenspan, 2003[249]	Yes	No	ITT analysis
Grey, 2010[274]	Yes	No	NR
Hosking, 2003[202]	Unclear	Probably yes	Unclear what attrition was at 12 months.
Hosking, 2003[202]	Yes	No information	NR
Johnell, 2002[246]	Yes	Probably no	NR
Keech, 2005[312]	Yes	Probably yes	NR
Kung, 2000[343]	Yes	Probably yes	NR
Lasco, 2011[241]	NA- no attrition	Probably no	NR
Lewiecki, 2007[236]	No information	no	NR

Appendix D Table 54. KQ 4 and 5 Risk of Bias Assessment: Part 7

First Author, Year	FOR ALL STUDIES: Were Appropriate Statistical Methods Used To Account for Missing Data?	Bias Arising from Missing Outcome Data?	Comments
McCloskey, 2012[245]	Probably yes	Probably no	NR
McClung, 2004[285]	Yes	No	NR
McClung, 2006[306]	Yes	Probably yes	17, not a case control; overall attrition a little high
McClung, 2006[209]	Yes	No	NR
McClung, 2009[275]	Probably no	unclear	Risk of bias for harms data because it is limited to ITT analysis.
Meunier, 1999[307]	Yes	No	NR
Miller, 2008[308]	Yes	probably no	NR
Morii, 2003[309]	Yes	Probably no	NR
Murphy, 2001[272]	Probably yes	Probably yes	Per protocol analysis probably okay for harms outcomes. Table 6 suggests similar AE profile, but reasons for discontinuation not provided by group.
Nakamura, 2012[239]	Yes	Probably no	NR
Orwoll, 2003[240]	Yes	Probably yes	Differential attrition between arms
Pazianas, 2008 [298]	NA- no attrition	No information	No mention of how missing data was handled
Ravn, 1996[286]	No information	Probably no	high overall and differential attrition; however, safety appears to have been collected and reported on a larger subset of the population
Reginster, 2005[287]	Yes	No	NR
Rhee, 2012[344]	NA- no attrition	no	NR
Riis, 2001[288]	Yes	No	NR
Samelson, 2014[345]	No	Probably yes	NR
Shiraki, 2003[283]	Yes	Probably no	NR
Simon, 2013[346]	Yes	Probably no	NR
Sontag, 2010[242]	Yes	Probably yes	NR
Sorensen, 2008[247]	Yes	No	*Authors report Danish registry information is complete.
Tanko, 2003[289]	Yes	Probably no	Unable to calculate group attrition
Thiebaud, 1997[290]	Yes	Probably no	Used ITT but one patient who dropped out before treatment because of inability to administer the drug was not included. Missing values were not replaced.
Tucci, 1996[253]	Yes	Probably no	Study was extended for a third year, 14 subjects did not consent to blinded treatment for a third year, 5 declined third year altogether.
Van Staa, 1997[347]	NA	No information	The study did not provide any information on attrition or missing data.
Vestergaard, 2010[348]	NA, no attrition	No	NR
Vestergaard, 2011[349]	NA, no attrition	No	NR
Vestergaard, 2012[350]	NA, no attrition	No	NR
Vestergaard, 2011[351]	NA-not an RCT	No information	NR
Vestergaard, 2012[352]	NA, no attrition	No	NR

Abbreviations: AE=adverse event; FIT=fracture intervention trial; ITT=intent to treat; KQ=key question; NA=not applicable; NR=not reported; UGI=upper gastrointestinal.

Appendix D Table 55. KQ 4 and 5 Risk of Bias Assessment: Part 8

First Author, Year	FOR RCTs OF TREATMENT: Were the Patients Unaware of the Intervention Status of Participants?	FOR ALL RCTs: Were the Trial Personnel and Clinicians Unaware of the Intervention Status of Participants?	FOR ALL STUDIES: Was Intervention Fidelity Adequate?	FOR ALL STUDIES: Did the Study Have Enough Cross-Overs or Contamination That Would Raise Concern for Bias?	Bias Arising from Departures From Intended Interventions?	Departures from Interventions Comments
Abrahamsen, 2010[273]	NA-not an RCT	NA-not an RCT	Probably yes	No information	Probably no	NR
Adachi, 2009[250]	Yes	Yes	No information	No information	Probably no	No data on adherence
Barrett-Connor, 2002[311]	Yes	Yes	Probably yes	Probably no	Probably no	In year 4 could take additional medications.
Barrett-Connor, 2004[310]	Yes	Yes	Yes	No	No	stated in larger study that 92% of women took more than 80% of study medication
Bone, 2000[216]	Yes	Yes	No information	No information	No	The authors did not report crossover, but were thorough about patient accounting
Bone, 2008[237]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
Boonen, 2012[218]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
Cartsos, 2008 [297]	NA-not an RCT	NA-not an RCT	No information	No information	No information	Fidelity, not sure if participants took medication correctly; no information on cross-overs but not clear if other treatments were allowed
Chapurlat, 2013[284]	Yes	Yes	Yes	No	No	NR
Cryer, 2005[252]	Yes	Yes	Yes	No	No	
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Yes	Yes	Yes	No	No	NR
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
Eisman, 2004[255]	NR	Yes	Yes	No	No	mean compliance 95% and 96% for alendronate and placebo groups

Appendix D Table 55. KQ 4 and 5 Risk of Bias Assessment: Part 8

First Author, Year	FOR RCTs OF TREATMENT: Were the Patients Unaware of the Intervention Status of Participants?	FOR ALL RCTs: Were the Trial Personnel and Clinicians Unaware of the Intervention Status of Participants?	FOR ALL STUDIES: Was Intervention Fidelity Adequate?	FOR ALL STUDIES: Did the Study Have Enough Cross-Overs or Contamination That Would Raise Concern for Bias?	Bias Arising from Departures From Intended Interventions?	Departures from Interventions Comments
Fogelman, 2000[226]	Yes	Yes	No information	Probably no	Probably no	NR
Greenspan, 2002[254]	Yes	Yes	Probably yes	Probably no	Probably no	NR
Greenspan, 2003[249]	Yes	Yes	Yes	No	No	NR
Grey, 2010[274]	Yes	Yes	Yes	No	No	NR
Hosking, 2003[202]	Yes	Yes	Yes	No	No	NR
Hosking, 2003[202]	Yes	Yes	Yes	No information	No	>75% adherence to medications
Johnell, 2002[246]	Yes	Yes	Yes	No	Probably no	NR
Keech, 2005[312]	Yes	Yes	Yes	No	No	NR
Kung, 2000[343]	Yes	Yes	No information	No information	Probably no	NR
Lasco, 2011[241]	NA-not an RCT	NA-not an RCT	Probably yes	Probably no	Probably no	NR
Lewiecki, 2007[236]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
McCloskey, 2012[245]	Yes	Yes	Yes	No information	No	NR
McClung, 2004[285]	Yes	Yes	Yes	No	No	compliance in mid to high 80s
McClung, 2006[306]	Yes	Yes	No information	No information	probably yes	adherence unknown
McClung, 2006[209]	Yes	Yes	Yes	No	No	Of note-double blinding for denosumab but NOT alendronate (open label); all answers are for denosumab. For alendronate (no, no, yes, no information, probably yes)
McClung, 2009[275]	yes	yes	Probably yes	Probably no	Probably no	NR
Meunier, 1999[307]	Yes	Yes	Probably yes	No	No	NR
Miller, 2008[308]	Yes	probably yes	No information	No information	Probably no	NR
Morii, 2003[309]	Yes	No information	Probably yes	No	No	NR
Murphy, 2001[272]	Yes	Yes	Yes	No	No	Only 4 patients failed to take >75% of assigned drug

Appendix D Table 55. KQ 4 and 5 Risk of Bias Assessment: Part 8

First Author, Year	FOR RCTs OF TREATMENT: Were the Patients Unaware of the Intervention Status of Participants?	FOR ALL RCTs: Were the Trial Personnel and Clinicians Unaware of the Intervention Status of Participants?	FOR ALL STUDIES: Was Intervention Fidelity Adequate?	FOR ALL STUDIES: Did the Study Have Enough Cross-Overs or Contamination That Would Raise Concern for Bias?	Bias Arising from Departures From Intended Interventions?	Departures from Interventions Comments
Nakamura, 2012[239]	Probably yes	Probably yes	Yes	No	No	NR
Orwoll, 2003[240]	Yes	Yes	Yes	Probably no	Probably no	Patient-administered injections of placebo or drug
Pazianas, 2008[298]	NA-not an RCT	NA-not an RCT	No information	No information	No information	Fidelity, not sure if participants took medication correctly; no information on cross-overs but not clear if other treatments were allowed
Ravn, 1996[286]	Yes	No	No information	No	Probably no	Data safety review committee (DSRC) was not blinded to treatment, and they monitored adverse events during each step. Information on compliance was not provided
Reginster, 2005[287]	NA-not an RCT	NA-not an RCT	Probably no	No	Probably yes	No way to determine if participants took dose
Rhee, 2012[344]	Yes	Yes	Yes	No	No	NR
Riis, 2001[288]	Probably yes	Probably yes	Yes	No	Probably no	NR
Samelson, 2014[345]	Yes	Yes	Probably yes	No information	Probably no	NR
Shiraki, 2003[283]	Yes	Yes	No information	Probably no	Probably no	NR
Simon, 2013[346]	Yes	Yes	Probably yes	No information	No	NR
Sontag, 2010[242]	Probably yes	Probably yes	No	Probably no	Probably no	Study reported as double-blind but no other details provided. Placebo arm received active treatment after 1 year but results are not reported separately for before and after receipt of active treatment
Sorensen, 2008[247]	NA-not an RCT	NA-not an RCT	Probably yes	No information	Probably no	NR

Appendix D Table 55. KQ 4 and 5 Risk of Bias Assessment: Part 8

First Author, Year	FOR RCTs OF TREATMENT: Were the Patients Unaware of the Intervention Status of Participants?	FOR ALL RCTs: Were the Trial Personnel and Clinicians Unaware of the Intervention Status of Participants?	FOR ALL STUDIES: Was Intervention Fidelity Adequate?	FOR ALL STUDIES: Did the Study Have Enough Cross-Overs or Contamination That Would Raise Concern for Bias?	Bias Arising from Departures From Intended Interventions?	Departures from Interventions Comments
Tanko, 2003[289]	Yes	Yes	No information	No	Probably no	Large proportion of patients in each study group took ≥75% of study medication: 89% placebo, 88.8% (5 mg), 90.1% (10 mg) and 88.7% (20 mg) patients.
Thiebaud, 1997[290]	Yes	No	No information	No	Probably no	Information on compliance was not provided Investigator was not blind for all arms
Tucci, 1996[253]	Yes	Yes	Yes	No	No	Investigators only evaluated blinded results (excluded patients who declined blinding for third year)
Van Staa, 1997[347]	NA-not an RCT	NA-not an RCT	No information	No	No information	Did not evaluate adherence
Vestergaard, 2010[348]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2011[349]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2012[350]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2011[351]	No information	NA-no benefits outcomes	NA-no benefits outcomes	NA-no benefits outcomes	Probably no	NR
Vestergaard, 2012[352]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR

Abbreviations: KQ=key question; NA=not applicable; RCT=randomized controlled trials.

Appendix D Table 56. KQ 4 and 5 Risk of Bias Assessment: Part 9

First Author, Year	FOR ALL STUDIES: Were Benefit Outcomes Adequately Described, Pre-specified, Valid, and Reliable?	FOR ALL STUDIES: Were Similar Techniques Used among Groups To Ascertain Harm Outcomes?	FOR ALL STUDIES: Was the Duration of Follow-Up Adequate To Assess Harm Outcomes?	Bias Arising from Measurement of Outcomes?	Comments
Abrahamsen, 2010[273]	NA-no benefits outcomes	Probably yes	Probably yes	Probably yes	Not able to identify atypia.
Adachi, 2009[250]	NA-no benefits outcomes	Yes	Yes	Probably no	There was not specific information about how often patient's assessed for harms, though did describe adequate blinding of patients.
Barrett-Connor, 2002[311]	NA-no benefits outcomes	Yes	Yes	No	NR
Barrett-Connor, 2004[310]	Yes	Yes	Yes	No	NR
Bone, 2000[216]	Probably Yes	Probably yes	Yes	Probably yes	Report that patients were seen at 3, 6, 12, 18, 24 months, but don't specifically describe clinical assessment (i.e. patient assessed for harms at this time)
Bone, 2008[237]	Yes	Yes	Probably yes	Probably no	NR
Boonen, 2012[218]	Yes	Yes	Yes	No	NR
Cartsos, 2008 [297]	NA-no benefits outcomes	Probably yes	Probably yes	Probably yes	Not clear how outcomes were measured due to only a code being provided
Chapurlat, 2013[284]	Yes	Probably yes	Yes	No	NR
Cryer, 2005[252]	Yes	Yes	Yes	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Yes	Yes	Yes	No	NR
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Yes	Yes	Probably yes	Probably no	NR
Eisman, 2004[255]	Yes	Yes	Yes	No	NR
Fogelman, 2000[226]	Probably Yes	Yes	Yes	Probably no	NR
Greenspan, 2002[254]	NA-no benefits outcomes	Yes	Yes	No	NR

Appendix D Table 56. KQ 4 and 5 Risk of Bias Assessment: Part 9

First Author, Year	FOR ALL STUDIES: Were Benefit Outcomes Adequately Described, Pre-specified, Valid, and Reliable?	FOR ALL STUDIES: Were Similar Techniques Used among Groups To Ascertain Harm Outcomes?	FOR ALL STUDIES: Was the Duration of Follow-Up Adequate To Assess Harm Outcomes?	Bias Arising from Measurement of Outcomes?	Comments
Greenspan, 2003[249]	Yes	Yes	Yes	No	NR
Grey, 2010[274]	Probably yes	Probably yes	Yes	Probably no	Looked at parent article to identify clinical assessment of harms - no information. The antiresorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women.
Hosking, 2003[202]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Johnell, 2002[246]	NA-no benefits outcomes	Yes	Probably yes	Probably no	12 month study
Keech, 2005[312]	NA-no benefits outcomes	Yes	Yes	No	NR
Kung, 2000[343]	NA-no benefits outcomes	Yes	Yes	Probably yes	No information on how harms ascertained
Lasco, 2011[241]	NA-no benefits outcomes	No information	No information	Probably no	NR
Lewiecki, 2007[236]	Yes	Yes	Probably yes	Probably no	NR
McCloskey, 2012[245]	Yes	NA-no harms outcomes	NA-no harms outcomes	No	NR
McClung, 2004[285]	NA-no benefits outcomes	Yes	Yes	No	NR
McClung, 2006[306]	NA-no benefits outcomes	Yes	Yes	No	NR
McClung, 2006[209]	Yes	Yes	Yes	No	NR
McClung, 2009[275]	NA-no benefits outcomes	yes	yes	Probably no	NR
Meunier, 1999[307]	NA-no benefits outcomes	Yes	Yes	Probably no	Follow up was 2 years
Miller, 2008[308]	NA-no benefits outcomes	Yes	Yes	Probably no	NR
Morii, 2003[309]	NA-no benefits outcomes	Yes	Yes	Probably no	NR
Murphy, 2001[272]	Yes	Yes	Yes	No	NR
Nakamura, 2012[239]	Yes	Yes	Probably yes	No	NR
Orwoll, 2003[240]	Yes	Yes	Probably no	Probably no	NR
Pazianas, 2008[298]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Ravn, 1996[286]	NA-no benefits outcomes	Yes	Yes	No	NR

Appendix D Table 56. KQ 4 and 5 Risk of Bias Assessment: Part 9

First Author, Year	FOR ALL STUDIES: Were Benefit Outcomes Adequately Described, Pre-specified, Valid, and Reliable?	FOR ALL STUDIES: Were Similar Techniques Used among Groups To Ascertain Harm Outcomes?	FOR ALL STUDIES: Was the Duration of Follow-Up Adequate To Assess Harm Outcomes?	Bias Arising from Measurement of Outcomes?	Comments
Reginster, 2005[287]	NA-no benefits outcomes	Yes	Yes	No	NR
Rhee, 2012[344]	NA-no benefits outcomes	Yes	Yes	No	NR
Riis, 2001[288]	NA-no benefits outcomes	Yes	Yes	No	NR
Samelson, 2014[345]	NA-no benefits outcomes	Yes	Yes	Probably yes	Post hoc analysis and the approach to reporting cardiovascular events in this analysis is different from reporting in the main FREEDOM trial where cardiovascular events were adjudicated by a panel.
Shiraki, 2003[283]	NA-no benefits outcomes	Yes	Yes	Probably yes	NR
Simon, 2013[346]	Probably Yes	NA-no harms outcomes	NA-no harms outcomes	Probably no	NR
Sontag, 2010[242]	Yes	Yes	Yes	Probably no	NR
Sorensen, 2008[247]	NA-no benefits outcomes	Yes	Probably yes	Probably no	Case control - harms only identified in the case group
Tanko, 2003[289]	NA-no benefits outcomes	Yes	Yes	No	NR
Thiebaud, 1997[290]	NA-no benefits outcomes	Yes	Yes	No	NR
Tucci, 1996[253]	Yes	Yes	Yes	No	Of note, there are some data on reduction of vertebral fractures, but investigators have planned another arm with future reporting. This study not powered for fracture reduction.
Van Staa, 1997[347]	NA-no benefits outcomes	Yes	Yes	No	NR
Vestergaard, 2010[348]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Vestergaard, 2011[349]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Vestergaard, 2012[350]	NA-no benefits outcomes	yes	Probably yes	Probably yes	NR
Vestergaard, 2011[351]	Probably Yes	Probably no	Yes	Probably yes	NR
Vestergaard, 2012[352]	NA-no benefits outcomes	yes	Probably yes	Probably yes	NR

Abbreviations: FREEDOM=Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; KQ=key question; NA=not applicable; NR=not reported.

Appendix D Table 57. KQ 4 and 5 Risk of Bias Assessment: Part 10

First Author, Year	FOR RCTS AND COHORTS: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Outcomes Measurements within the Domain, Multiple Analyses, or Different Subgroups?	FOR CASE-CONTROL STUDIES: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Definitions of the Intervention?	Bias Arising from Selection of Reported Results?	Comments
Abrahamsen, 2010[273]	Probably yes	NA-not a case-control	Probably no	NR
Adachi, 2009[250]	Yes	NA-not a case-control	No	NR
Barrett-Connor, 2002[311]	No	NA-not a case-control	No	NR
Barrett-Connor, 2004[310]	No	NA-not a case-control	No	NR
Bone, 2000[216]	Yes	NA-not a case-control	No	NR
Bone, 2008[237]	Probably no	NA-not a case-control	Probably no	NR
Boonen, 2012[218]	Yes	NA-not a case-control	Probably no	NR
Cartsos, 2008 [297]	NA-not an RCT	Probably yes	Probably no	None
Chapurlat, 2013[284]	No	NA-not a case-control	No	NR
Cryer, 2005[252]	Yes	NA-not a case-control	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Yes	NA-not a case-control	No	NR
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Probably no	NA-not a case-control	Probably no	NR
Eisman, 2004[255]	Yes	NA-not a case-control	No	NR
Fogelman, 2000[226]	Yes	NA-not a case-control	No	NR
Greenspan, 2002[254]	Yes	NA-not a case-control	No	NR
Greenspan, 2003[249]	Yes	NA-not a case-control	No	NR
Grey, 2010[274]	Yes	NA-not a case-control	No	NR
Hosking, 2003[202]	Yes	NA-not a case-control	No	NR
Hosking, 2003[202]	Yes	NA-not a case-control	No	NR
Johnell, 2002[246]	Probably yes	NA-not a case-control	Probably no	NR
Keech, 2005[312]	No	NA-not a case-control	No	NR
Kung, 2000[343]	Yes	NA-not a case-control	No	NR
Lasco, 2011[241]	Probably no	NA-not a case-control	Probably no	NR
Lewiecki, 2007[236]	Probably no	NA-not a case-control	Probably no	NR
McCloskey, 2012[245]	No	NA-not a case-control	Probably no	NR
McClung, 2004[285]	No	No	No	NR
McClung, 2006[306]	No	NA-not a case-control	No	NR

Appendix D Table 57. KQ 4 and 5 Risk of Bias Assessment: Part 10

First Author, Year	FOR RCTS AND COHORTS: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Outcomes Measurements within the Domain, Multiple Analyses, or Different Subgroups?	FOR CASE-CONTROL STUDIES: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Definitions of the Intervention?	Bias Arising from Selection of Reported Results?	Comments
McClung, 2006[209]	Yes	NA-not a case-control	No	Study was powered for primary outcome of urinary markers, not harms. Report nominal p values for harms
McClung, 2009[275]	probably yes	NA-not a case-control	Probably no	NR
Meunier, 1999[307]	Yes	NA-not a case-control	Probably no	NR
Miller, 2008[308]	Probably no	NA-not a case-control	Probably no	NR
Morii, 2003[309]	Yes	NA-not a case-control	Probably no	NR
Murphy, 2001[272]	Yes	NA-not a case-control	No	NR
Nakamura, 2012[239]	No	NA-not a case-control	No	NR
Orwoll, 2003[240]	Probably yes	NA-not a case-control	Probably no	NR
Pazianas, 2008 [298]	NA-not an RCT	Probably yes	Probably no	NR
Ravn, 1996[286]	No	No	No	NR
Reginster, 2005[287]	No	No	No	NR
Rhee, 2012[344]	No	NA-not a case-control	No	NR
Riis, 2001[288]	No	No	No	NR
Samelson, 2014[345]	Probably yes	NA-not a case-control	No	It is not clear how the cardiovascular adverse events reported in this study relate to the harms provided in the main FREEDOM trial. This appears to be a post-hoc analysis.
Shiraki, 2003[283]	Yes	NA-not a case-control	No	NR
Simon, 2013[346]	Probably yes	NA-not a case-control	Probably no	NR
Sontag, 2010[242]	Probably no	NA-not a case-control	Probably no	NR
Sorensen, 2008[247]	NA-not an RCT	Yes	No	NR
Tanko, 2003[289]	No	No	No	NR
Thiebaud, 1997[290]	No	No	No	NR
Tucci, 1996[253]	Yes	NA-not a case-control	No	Stepwise Tukey trend test to adjust for multiple comparisons
Van Staa, 1997[347]	Yes	NA-not a case-control	No	Intervention status defined as patients who had received a prescription; adherence not measured; attrition and how missing data was handled was not reported

Appendix D Table 57. KQ 4 and 5 Risk of Bias Assessment: Part 10

First Author, Year	FOR RCTS AND COHORTS: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Outcomes Measurements within the Domain, Multiple Analyses, or Different Subgroups?	FOR CASE-CONTROL STUDIES: Is the Reported Effect Estimate Unlikely To Be Selected, on the Basis of the Results, from Multiple Definitions of the Intervention?	Bias Arising from Selection of Reported Results?	Comments
Vestergaard, 2010[348]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2011[349]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2012[350]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2011[351]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2012[352]	Probably no	NA-not a case-control	Probably no	NR

Abbreviations: FREEDOM=Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; KQ=key question; NA=not applicable; NR=not reported; RCT=randomized controlled trials.

Appendix D Table 58. KQ 4 and 5 Risk of Bias Assessment: Part 11

First Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Abrahamsen, 2010[273]	Poor	Risk of bias from residual confounding and measurement of outcomes	No
Adachi, 2009[250]	Fair	Baseline differences between groups raise some concerns for risk of bias.	No
Barrett-Connor, 2002[311]	Fair	About 25% lost to follow-up. Also year 4 data allows additional therapy for osteoporosis which was different per group though small number (<7%) - this study included year 4 partcipants but didn't report concomittant medicationss. Additionally, there was differential loss to follow-up due to excessive bone loss in the placebo group (3% vs 1%).	No
Barrett-Connor, 2004[310]	Fair	About 25% lost to follow-up. Also year 4 data allows additional therapy for osteoporosis which was different per group though small number (<7%) - this study included year 4 partcipants but didn't report concomittant meds. (No sensitivity analysis looking at 3 years of data where no additional meds.) Additionally, there was differential loss to follow-up due to excessive bone loss in the placebo group (3% vs 1%).	No
Bone, 2000[216]	Poor	High attrition and no information about how harms were specified or assessed.	No
Bone, 2008[237]	Fair	Some uncertainties in reporting of randomization, allocation concealment, blinding	no
Boonen, 2012[218]	Good	NR	No
Cartsos, 2008 [297]	Poor	not clear how outcomes were measured. fidelity, not sure if participants took medication correctly; no information on cross-overs but not clear if other treatments were allowed No mention of how missing data was handled sample not representative of total population intervention based on dispensing information from claims data, information on dose not available	No
Chapurlat, 2013[284]	Fair	Considering IVR with minimization scheme to be just adequate and unclear way drop outs handled.	No
Cryer, 2005[252]	Good	fair for differential attrition, no information on contamination	No
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[251]	Good	NR	No
Cummings, 2009[238]; Watts, 2012[314]; McClung, 2012[243]; Boonen, 2011[244]	Fair	Some uncertainties in reporting of randomization, allocation concealment, blinding	no
Eisman, 2004[255]	Good	NR	No
Fogelman, 2000[226]	Fair	NR	No
Greenspan, 2002[254]	Fair	missing info on randomization. Also no washout period for patients previously on bisphosphonates.	No
Greenspan, 2003[249]	Good	NR	No
Grey, 2010[274]	Fair	Differences in baseline fracture rates, minimal specification of harm outcomes.	No
Hosking, 2003[202]	Fair	NR	No
Hosking, 2003[202]	Fair	Fair or Poor depending on how rate Attirtion module	No

Appendix D Table 58. KQ 4 and 5 Risk of Bias Assessment: Part 11

First Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Johnell, 2002[246]	Good	NR	No
Keech, 2005[312]	Fair	About 25% lost to follow-up. Also year 4 data allows additional therapy for osteoporosis which was different per group though small number (<7%) - this study included year 4 partcipants but didn't report concomittant medications. (No sensitivity analysis looking at 3 years of data where no additional meds.) Additionally, there was differential loss to follow-up due to excessive bone loss in the placebo group (3% vs 1%).	No
Kung, 2000[343]	Poor	No information on randomization methods, fidelity, contamination, 20% attrition with not enough info to judge differential attrition, and poorly specified harms outcomes (very specirfic patient self-reported adverse experiences, with no indication as to seriousness of AE, whether the AE resulted in discontinuation, and further, the data offered is number of events, not number of women, making it difficult to know whether the risk is higher in one group, compared to the other.	No
Lasco, 2011[241]	Poor	Potential for confounding	No
Lewiecki, 2007[236]	Fair	Some uncertainties in reporting of randomization, allocation concealment, blinding	No
McCloskey, 2012[245]	Fair	No detail on randomization and allocation concealment prevents this from being rated as Good. No fatal flaws	No
McClung, 2004[285]	Fair	No information provided on method of randomization or concealment	No
McClung, 2006[306]	Fair	Overall attrition high, not a lot of information provided on randomization process; Fidelity issue: no information on if participants actually took their assigned doses	No
McClung, 2006[209]	Good	Good for denosumab. For alendronate Poor for lack of blinding.	No
McClung, 2009[275]	Fair	Higher risk of bias for harms than benefits (ITT analysis understates harms)	No
Meunier, 1999[307]	Good	Documentation on randomization missing, outcomes mostly self report	no
Miller, 2008[308]	Fair	Not possible to say how missing cases were accounted for in the analysis. Study has a potential to underestimate harms by using N randomized in the denominator and N retained in the numerator.	No
Morii, 2003[309]	Fair	NR	No
Murphy, 2001[272]	Poor	Very poor attrition at 12 and 18 months, and unable to assess differential attrition, missing information on randomization	No
Nakamura, 2012[239]	Fair	The article was lacking information on method of randomization and concealment; lack of information on those who discontiuned study	No
Orwoll, 2003[240]	fair	Differential attrition; higher in treatment arm; used ITT to adjust for analysis	No
Pazianas, 2008 [298]	Poor	fidelity, not sure if participants took medication correctly; no information on cross-overs but not clear if other treatments were allowed No mention of how missing data was handled sample not representative of total population intervention based on dispensing information from claims data, information on dose etc. not available	No

Appendix D Table 58. KQ 4 and 5 Risk of Bias Assessment: Part 11

First Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Ravn, 1996[286]	Fair	High attrition, however, safety appears to have been collected and reported on a larger subset of the population. No information provided on method of randomization or concealment.	No
Reginster, 2005[287]	Fair	No information provided on method of randomization or concealment Information on compliance was not provided	No
Rhee, 2012[344]	Poor	Potential bias arising from creation of an new user cohort and from restriction to those without switches	No
Riis, 2001[288]	Fair	No information provided on method of randomization or concealment	No
Samelson, 2014[345]	Poor	No detail on randomization and allocation concealment prevents the main trial from being rated as Good. Attrition/missing data and outcome measurement in this specific sub-study make this analysis high risk of bias, thus Poor Quality.	No
Shiraki, 2003[283]	Fair	NR	No
Simon, 2013[346]	Fair	In the end, the only outcome that is of interest are wrist fractures in subgroups based on baseline risk.	No
Sontag, 2010[242]	Poor	The open label portion of the trial allowed patient choice, and as result, outcomes could be result of confounding because of prognostic variables	No
Sorensen, 2008[247]	Good	NR	No
Tanko, 2003[289]	Fair	No information provided on method of randomization or concealment not able to calculate group attrition	No
Thiebaud, 1997[290]	Fair	No information provided on method of randomization or concealment Slight differences length of menopause Information on compliance was not provided Investigator was not blind for all arms	No
Tucci, 1996[253]	Fair	Randomization methods, fidelity, contamination missing info.	No
Van Staa, 1997[347]	Poor	NR	No
Vestergaard, 2010[348]	Poor	Concerns include lack of adjustment for all potential confounders, particularly OTC NSAID use and smoking. Additionally, the study does not control for adherence.	no
Vestergaard, 2011[349]	Poor	Concerns include lack of adjustment for all potential confounders. For example, smoking, hypertension, diabetes could explain the stroke, and it's possible that these underlying conditions are highly associated with both the osteoporosis medications and the outcome.	No
Vestergaard, 2012[350]	Poor	Concerns include lack of adjustment for all potential confounders. For example, smoking and hypertension could explain the stroke, and it's possible that these underlying conditions are highly associated with both the osteoporosis medications and the outcome.	No
Vestergaard, 2011[351]	Poor	Concerns include lack of adjustment for all potential confounders, particularly underlying disease that might also be related to the choice of medication for steoporosis and the outcome. Additionally the outcome did not distinguish between typical and typical fractures.	No

Appendix D Table 58. KQ 4 and 5 Risk of Bias Assessment: Part 11

First Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Vestergaard, 2012[352]	Poor	Concerns include lack of adjustment for all potential confounders, particularly underlying causes of inflammatory jaw disease (e.g., autoimmune disorders) that might also be related to risk factors for osteoporosis. Additionally the outcome includes many varied conditions with different etiologies that might be unrelated to osteoporosis.	No

Abbreviations: AE=adverse event; ITT=intent to treat; IVR=interactive voice response; KQ=key question; NR=not reported; NSAIDS=nonsteroidal anti-inflammatory drugs; OTC=over the counter.

Appendix E Table 1. Overview of 2010 Included Studies and Inclusion/Exclusion Status in Current Report

First Author, Year	Status in Current Report	Reasons for Exclusion
Adler, 2003[77]	Include	NA
Alexandersen, 2005[353]	Exclude	BMD screening after identification of fractures
Anderson, 2003 [354]	Exclude	Not osteoporotic women, WHI
Anderson, 2004[355]	Exclude	Wrong population
Ascott-Evans, 2003[204]	Include	NA
Barrett-Connor, 2006[233]	Exclude	Wrong population
Bauer, 1997 [356]	Exclude	No AUCs
Bauer, 2007[163]	Include	NA
Ben Sedrine, 2001[78]	Include	NA
Black, 2001[145]	Exclude	Wrong or no outcome
Black, 2007[219]	Exclude	Wrong population
Brenneman, 2003[81]	Include	NA
Cadarette, 2001[82]	Include	NA
Cadarette, 2004[83]	Include	NA
Cadarette, 2008[357]	Exclude	Not a relevant comparison
Cass, 2006[84]	Include	NA
Cauley, 2003[313]	Exclude	Not osteoporotic women, WHI
Chesnut, 1995[203]	Include	NA
Chesnut, 2000[359]	Exclude	Wrong intervention
Chesnut, 2004[360]	Exclude	Wrong population
Chlebowski, 2003[361]	Exclude	Not osteoporotic women, WHI
Colon-Emeric, 2002[143]	Exclude	Wrong or no outcome
Cook, 2005[87]	Include	NA
Crabtree, 2002[362]	Exclude	Wrong or no intervention
Cranney, 2002[363]	Exclude	Calcitonin was not an Included intervention
Cryer, 2002[364]	Exclude	Wrong study design
Cummings, 1998[200]	Include	NA
Cummings, 2006[365]	Exclude	Wrong or no outcome
Curb, 2006[366]	Exclude	not osteoporotic women, WHI
Cushman, 2004 [367]	Exclude	not osteoporotic women, WHI
D'Amelio, 2005[88]	Include	NA
Dargent-Molina, 2003[368]	Exclude	not in externally validated cohort
Delmas, 2002[232]	Include	NA
Diez-Perez, 2007[369]	Exclude	not in externally validated cohort
Donaldson, 2009[339]	Include	NA
Dursun, 2001[207]	Exclude	Wrong or no comparator
Ensrud, 2009[178]	Include	NA
Ettinger, 1999[231]	Include	NA
Frediani, 2006[370]	Exclude	BMD screening after identification of fractures
Gennari, 1985[371]	Exclude	calcitonin was not an Included intervention
Girman, 2002[146]	Exclude	Wrong clinical setting
Gluer, 2003[372]	Exclude	Not original research
Gnudi, 2005[91]	Include	NA
Goh, 2007[269]	Exclude	Wrong study design
Gonnelli, 2005[373]	Exclude	Not a key question reviewed in the current report (DXA in men)
Gourlay, 2005[79]	Include	NA
Grbic, 2008[281]	Exclude	Wrong population
Greenfield, 2007[374]	Exclude	Greenfield, 2007 is an Exclude for wrong population Note, the authors of Nelson, 2010 have a discrepancy in the author names in References versus their tables.
Greenspan, 2005[375]	Exclude	Superseded by the current meta-analysis in this update.
Greenspan, 2007[36]	Include	NA
Hans, 1996[376]	Exclude	No AUCs
Hans, 2008[377]	Exclude	Not in externally validated cohort
Harris, 2008[378]	Exclude	Superseded by the current meta-analysis in this update.

Appendix E Table 1. Overview of 2010 Included Studies and Inclusion/Exclusion Status in Current Report

First Author, Year	Status in Current Report	Reasons for Exclusion
Harrison, 2006[93]	Include	NA
Heckbert, 2008[256]	Exclude	Wrong population
Herd, 1997[228]	Include	NA
Hillier, 2007[194]	Include	NA
Hippisley-Cox, 2009[150]	Include	NA
Hizmetli, 1998[379]	Exclude	Calcitonin was not an Included intervention
Hooper, 2005[227]	Exclude	Wrong population
Hosking, 1998[215]	Exclude	Wrong population
Hsia, 2006 [380]	Exclude	Not osteoporotic women, WHI
Kanis, 2007[32]	Include	NA
Karam, 2007[293]	Exclude	Superseded by the current meta-analysis in this update.
Kaufman, 2005[381]	Exclude	Wrong or no intervention
Khaw, 2004 [382]	Exclude	No AUCs
Kurland, 2000[383]	Exclude	Wrong population
LaCroix, 2005[384]	Exclude	Wrong or no comparator
Lenart, 2008[263]	Exclude	Wrong or no comparator
Liberman, 1995[199]	Include	NA
Lynn, 2008[97]	Include	NA
MacLean, 2008[270]	Exclude	Superseded by new evidence
Manson, 2003[385]	Exclude	Not osteoporotic women, WHI
Martinez-Aguila, 2007[99]	Include	NA
Masoni, 2005[386]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Mauck, 2005[100]	Include	NA
McClung, 2004[285]	Include	NA
Meunier, 1997[229]	Include	NA
Minnock, 2008[117]	Include	NA
Mortensen, 1998[224]	Include	NA
Mulleman, 2002[387]	Exclude	Not a key question reviewed in the current report (DXA in men)
Nayak, 2006[120]	Exclude	Superseded by the current meta-analysis in this update.
Neer, 2001[388]	Exclude	Wrong population
Nelson, 2009[73]	Include	NA
Nelson, 2009[74]	Include	NA
Nguyen, 2004 [103]	Include	NA
Odvina, 2005[264]	Exclude	Wrong or no comparator
Office of Drug Safety, 2004[257]	Exclude	Wrong population
Orwoll, 2003[240]	Include	NA
Overgaard, 1992[389]	Exclude	Wrong intervention
Pols, 1999[201]	Include	NA
Pouilles, 1997[230]	Exclude	Wrong population
Reid, 2002[217]	Include	NA
Richards, 2008[390]	Exclude	Not in externally validated cohort
Richy, 2004[80]	Include	NA
Rico, 1995[391]	Exclude	calcitonin was not an Included intervention
Robbins, 2007[151]	Exclude	Not osteoporotic women, WHI
Rossouw, 2002[392]	Exclude	Not osteoporotic women, WHI
Rossouw, 2007[393]	Exclude	Not osteoporotic women, WHI
Rud, 2005[109]	Include	NA
Rud, 2007[394]	Exclude	Study does not look at fracture outcomes
Russell, 2001[395]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Salaffi, 2005[396]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Sandhu, 2010[142]	Include	NA

Appendix E Table 1. Overview of 2010 Included Studies and Inclusion/Exclusion Status in Current Report

First Author, Year	Status in Current Report	Reasons for Exclusion
Sawka, 2005[397]	Exclude	Superseded by the current meta-analysis in this update.
Schuit, 2004[23]	Exclude	Wrong or no outcome
Sedrine, 2002[158]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Shepherd, 2007[110]	Include	NA
Shiraki, 2003[283]	Include	NA
Sinnott, 2006[111]	Include	NA
Sorensen, 2008[247]	Include	NA
Stefanick, 2006 [398]	Exclude	Not osteoporotic women, WHI
Stewart, 2006[162]	Include	NA
Tracz, 2006[399]	Exclude	Wrong or no intervention-- testosterone
Valimaki, 2007[225]	Include	NA
Van der Klift, 2002[400]	Exclude	Not a key question reviewed in the current report (DXA in men)
Van Staa, 1997[347]	Include	NA
Varenna, 2005[358]	Exclude	No AUCs
Vestergaard, 2007[401]	Exclude	Wrong or no comparator
Wallace, 2003[402]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Wassertheil-Smoller, 2003 [403]	Exclude	Not osteoporotic women, WHI
Wei, 2004[141]	Exclude	Bone measurement happens after outcome
Wells, 2008[404]	Exclude	Wrong population
Wells, 2008[405]	Exclude	Wrong population
Wells, 2008[406]	Exclude	Wrong or no intervention

Abbreviations: AUC=area under the curve; BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; MA=meta-analysis; NA=not applicable; WHI=Women's Health Initiative.

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Cadarette, 2001[82] Low	ABONE, NOF, ORAI, SCORE	ABONE	CaMOS - Canadian study of women from the general population recruited from 1996-1997, 97% white Canada	ABONE: Age, body size, no estrogen use or no estrogen use for at least 6 months
Chan, 2006[86] unclear	ABONE, ORAI, OSTA, SCORE	ABONE	Free-living ambulant Chinese postmenopausal women, 55 years and older (Tanjong Rhu community in Singapore) Singapore	ABONE: Age, body size, no estrogen use or no estrogen use for at least 6 months
D'Amelio, 2005[88] Low	NOF, OST, ORAI, AMMEB	AMMEB	Postmenopausal Caucasian Italian women referred to university bone metabolic unit for DXA within the Departmen of Internal Medicine. 13% were noted to have secondary osteoporosis.	AMMEB: age, BMI, age at menarche, and postmenopausal period
D'Amelio, 2013[89] Low	AMMEB, NOF, ORAI, OSTA	AMMEB	Menopausal women from general practices in Italy. Race not reported.	AMMEB: age, BMI, age at menarche, and postmenopausal period
Nguyen, 2004[103] Low	DOESCore, ORAI, OSTA, SOFSURF	DOESCore	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia. (98.6% white) Australia	DOESCore: age, body weight, previous fracture
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	FRAX: Hip	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)
Pang, 2014[106] Low	FRAX	FRAX: Hip without BMD (>3%)	Men and women age 70 and older who presented to a participating GP, excluded persons with prior h/o fracture Australia	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)

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First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	FRAX: MOF	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)
Pang, 2014[106] Low	FRAX	FRAX: MOF FRAX without BMD (>6.5%)	Men and women age 70 and older who presented to a participating GP, excluded persons with prior h/o fracture Australia	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)
Leslie, 2013[113] Low	FRAX, OST	FRAX: MOF without BMD	Population-based sample of all women ages 50-64 yr with medical coverage and valid DXA measurements from the lumbar spine and spine in Manitoba from 1990-March 2007 Canada	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)
Bansal, 2015[56] Fair	FRAX	FRAX: MOF without BMD (>=9.3%)	All women between the ages of 50 and 64.5 years who underwent DXA during a 6-month period (March 1, 2012–August 31, 2012) and were enrolled in a primary care practice of the Mayo Clinic in Rochester, Minnesota United States	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)
Cass, 2016[114] Low	FRAX, MORES (reported previously in Shepherd, 2007[110]	FRAX: MOF without BMD (>=9.3%)	Men age 50 and older in the NHANES III (1988-1994) with a valid DXA scan United States	FRAX without BMD (age, sex, race/ethnicity, body mass index (BMI), paternal history of hip fracture, personal history of a low-impact fracture, smoking, alcohol consumption, use of glucocorticoids, history of rheumatoid arthritis, and history of secondary causes of osteoporosis)

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Crandall, 2014[57] Low	USPSTF (FRAX), OST, SCORE	FRAX: MOF without BMD (>=9.3%)	50-64 years of age, postmenopausal, and free from serious medical conditions (WHI) and not using menopausal hormone therapy (in main analysis) United States	USPTSF - FRAX 10 yr risk of MOF without the BMD of >=9.3%
Gnudi, 2005[91] Low	Gnudi et al clinical prediction tool	Gnudi et al clinical prediction tool	Postmenopausal Italian women requiring a DXA scan Italy	Age at menarche, weight, years since menopause previous fracture, weight, fracture in subject's mother, arm help to get up from sitting
Cass, 2013[85] Low	ORAI, SCORE, MORES	MORES	Men who attended unviersity-based primary care clinics for usual care; over 60 years of age United States	MORES: Age, weight, COPD
Shepherd, 2007[110]; Cass, 2016[114] Low	MORES	MORES	Men 50 years or older with DXA scan in NHANES III, conducted between 1988 and 1994 United States	MORES: Age, weight, COPD
Shepherd, 2010[115] Low	MORES	MORES	Men 50 years or older with DXA scan any of the NHANES 1999 to 2000, 2001 to 2002, and 2003 to 2004 datasets United States	MORES: Age, weight, COPD
Lynn, 2008[97] Low	MOST, OST	MOST	Community-dwelling, ambulatory men, age 65 years or older United States and Hong Kong	MOST: weight, QUI
Zimering, 2007[112] Unclear	Reduced MSCORE, MSCORE, OST	MSCORE	Men age 40 years or older, ambulatory veterans attending general medicine clinics, endocrinology clinics, or osteoporosis clinics United States	MSCORE: age, weight, gastrectomy, emphysema, prior fracture
Cadarette, 2001[82] Low	ABONE, NOF, ORAI, SCORE	NOF	CaMOS - Canadian study of women from the general population recruited from 1996-1997, 97% white Canada	NOF: weight, age, previous fracture, smoking, family history of fracture
D'Amelio, 2005[88] Low	NOF, OST, ORAI, AMMEB	NOF	Postmenopausal Caucasian italian women referred to university bone metabolic unit for DXA within the Departmen of Internal Medicine. 13% were noted to have secondary osteoporosis. Italy	NOF: weight, age, previous fracture, smoking, family history of fracture
D'Amelio, 2013[89] Low	AMMEB, NOF, ORAI, OSTA	NOF	Menopausal women from general practices in Italy. Race not reported.	NOF: weight, age, previous fracture, smoking, family history of fracture

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Mauck, 2005[100] Low	NOF, ORAI, SCORE	NOF	Population-based sample of postmenopausal women age 45 years and older in Rochester, MN United States	NOF >=1
Cadarette, 2001[82] Low	ABONE, NOF, ORAI, SCORE	ORAI	CaMOS - Canadian study of women from the general population recruited from 1996-1997, 97% white Canada	ORAI: age, weight, current estrogen use
Cadarette, 2004[83] Low	ORAI, OST	ORAI	Caucasian Women >=45 years recruited prospectively from university setting and retrospectively analyzed form family practices in Canada Canada	ORAI: age, weight, current estrogen use
Cass, 2006[84] Low	ORAI, SCORE, MORES	ORAI	Postmenopausal women, 45 years of age and older (receiving usaual care at university-based family practice clinic in the US). Diverse practice, 29% White, 43% Black, 28% Hispanic United States	ORAI: age, weight, current estrogen use
Chan, 2006[86] unclear	ABONE, ORAI, OSTA, SCORE	ORAI	Free-living ambulant Chinese postmenopausal women, 55 years and older (Tanjong Rhu community in Singapore) Singapore	ORAI: age, weight, current estrogen use
Cook et al, 2005[87] unclear	ORAI, OSIRIS, OST, SCORE, SOFSURF	ORAI	Post-menopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of one or more clinical risk factor for osteoporosis in the UK. Race not reported. United Kingdom	ORAI: age, weight, current estrogen use
D'Amelio, 2005[88] Low	NOF, OST, ORAI, AMMEB	ORAI	Postmenopausal Caucasian Italian women referred to university bone metabolic unit for DXA within the Departmen of Internal Medicine. 13% were noted to have secondary osteoporosis. Italy	ORAI: age, weight, current estrogen use
D'Amelio, 2013[89] Low	AMMEB, NOF, ORAI, OSTA	ORAI	Menopausal women from general practices in Italy. Race not reported.	ORAI: age, weight, current estrogen use
Geusens, 2002[90] Unclear	OST, ORAI, SOFSURF, SCORE	ORAI	Community-dwelling women 45 years and older recruited from 1994-1995, 82% white United States	ORAI: age, weight, current estrogen use

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Gourlay, 2005[79] unclear	ORAI, OST, SCORE	ORAI	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	ORAI: age, weight, current estrogen use
Gourlay, 2008[92] Unclear	OST, ORAI, SCORE	ORAI	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age 65 and older. United States	ORAI: age, weight, current estrogen use
Harrison et al, 2006[93] Low	ORAI, OSIRIS, OST, SCORE	ORAI	White Caucasian females age 55 to 70 (mean 61, SD 4) years who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on ra	ORAI: age, weight, current estrogen use
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	ORAI	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	ORAI: age, weight, current estrogen use
Martinez-Aguila, 2007[99] Unclear	ORAI, OSIRIS, OST	ORAI	Postemenopausal women age 40 to 69 referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture. Race not reported. Spain	ORAI: age, weight, current estrogen use
Mauck, 2005[100] Low	NOF, ORAI, SCORE	ORAI	Population-based sample of postmenopausal women age 45 years and older in Rochester, MN, 99% white United States	ORAI: age, weight, current estrogen use
Nguyen, 2004[103] Low	DOESCore, ORAI, OSTA, SOFSURF	ORAI	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia. (98.6% white) Australia	ORAI: age, weight, current estrogen use

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Richy, 2004[80] Unclear	ORAI, OSIRIS, OST, SCORE	ORAI	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	ORAI: age, weight, current estrogen use
Rud, 2005[109] Low	SCORE, ORAI, OST	ORAI	White women from the general population recruited for the Danish Osteoporosis Prevention Study (DOPS) Denmark	ORAI: age, weight, current estrogen use
Cook et al, 2005[87] unclear	ORAI, OSIRIS, OST, SCORE, SOFSURF	OSIRIS	Post-menopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of one or more clinical risk factor for osteoporosis United Kingdom	OSIRIS: age, weight, HRT use, history of low trauma fracture
Harrison et al, 2006[93] Low	ORAI, OSIRIS, OST, SCORE	OSIRIS	White Caucasian females ages 55 to 70 (mean 61, SD 4) years who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on ra	OSIRIS: age, weight, HRT use, history of low trauma fracture
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	OSIRIS	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	OSIRIS: age, weight, HRT use, history of low trauma fracture
Martinez-Aguila, 2007[99] Unclear	ORAI, OSIRIS, OST	OSIRIS	Postemenopausal women age 40 to 69 referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture. Race not reported. Spain	OSIRIS: age, weight, HRT use, history of low trauma fracture
Richy, 2004[80] Unclear	ORAI, OSIRIS, OST, SCORE	OSIRIS	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	OSIRIS: age, weight, HRT use, history of low trauma fracture

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Adler, 2003[77] Low	OST	OST	Men enrolled in a pulmonary clinic (January-May 2001) and a rheumatology clinic (Nov 2001-March 2002) at a single VA medical center; received questionnaire and DXA scan; patients with previous DXA testing ineligible United States	OST: age, weight
Cadarette, 2004[83] Low	ORAI, OST	OST	Caucasian Women >=45 years recruited prospectively from university setting and retrospectively analyzed form family practices in Canada Canada	OST: age, weight
Cook et al, 2005[87] unclear	ORAI, OSIRIS, OST, SCORE, SOFSURF	OST	Post-menopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of one or more clinical risk factor for osteoporosis United Kingdom	OST: age, weight
Crandall, 2014[57] Low	USPSTF (FRAX), OST, SCORE	OST	50-64 years of age, postmenopausal, and free from serious medical conditions (WHI) and not using menopausal hormone therapy (in main analysis) United States	OST: age, weight
D'Amelio, 2005[88] Low	NOF, OST, ORAI, AMMEB	OST	Postmenopausal Caucasian Italian women referred to university bone metabolic unit for DXA within the Departmen of Internal Medicine. 13% were noted to have secondary osteoporosis.	OST: age, weight
D'Amelio, 2013[89] Low	AMMEB, NOF, ORAI, OSTA	OST	Menopausal women from general practices in Italy. Race not reported.	OST: age, weight
Geusens, 2002[90] Unclear	OST, ORAI, SOFSURF, SCORE	OST	Community-dwelling women 45 years and older recruited from 1994-1995, 82% white United States	OST: age, weight
Gourlay, 2005[79] unclear	ORAI, OST, SCORE	OST	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	OST: age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Gourlay, 2008[92] Unclear	OST, ORAI, SCORE	OST	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age 65 and older. United States	OST: age, weight
Harrison et al, 2006[93] Low	ORAI, OSIRIS, OST, SCORE	OST	White Caucasian females ages 55 to 70 (mean 61, SD 4) years who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on ra	OST: age, weight
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	OST	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	OST: age, weight
Leslie, 2013[113] Low	FRAX, OST	OST	Population-based sample of all women ages 50-64 years with medical coverage and valid DXA measurements from the lumbar spine and spine in Manitoba from 1990-March 2007 Canada	OST: age, weight
Lynn, 2008[97] Low	MOST, OST	OST	Community-dwelling, ambulatory men, age 65 years or older United States and Hong Kong	OST: age, weight
Machado, 2010[98] Low	OST, OSTA	OST	Population-based sample of Portuguese men age 50 or over randomly selected from the 19,000 registered voters between 1998-1999 Portugal	OST: age, weight
Martinez-Aguila, 2007[99] Unclear	ORAI, OSIRIS, OST	OST	Postemenopausal women age 40 to 69 referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture. Race not reported. Spain	OST: age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
McLeod, 2015[101] Low	OST	OST	Women referred for screening in the Regina General Hospital, Saskatchewan, Canada, between 2010 and 2011 with no prior testing Canada	OST: age, weight
Morin, 2009[102] Unclear	OST	OST	Population-based sample of all women age 40 to 59 and over that received DXA testing in Manitoba, Canada. Note criteria for BMD testing in women younger than 65 include premature ovarian failure, h/o steroid use, prior fracture, xray evidence of osteopen	OST: age, weight
Pang, 2014[106] Low	OST	OST	Men and women age 70 and older who presented to a participating GP, excluded persons with prior h/o fracture Australia	OST: age, weight
Richards, 2014[108] Unclear	OST	OST	Male VA patients, older than 50 year attending primary care clinics at 4 participating VA Medical Centers United States	OST: age, weight
Richy, 2004[80] Unclear	ORAI, OSIRIS, OST, SCORE	OST	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	OST: age, weight
Rud, 2005[109] Low	SCORE, ORAI, OST	OST	White women from the general population recruited for the Danish Osteoporosis Prevention Study (DOPS) Denmark	OST: age, weight
Sinnott, 2006[111] Low	OST	OST	African American men, age 35 and older from outpatient general medicine VA clinics in 2004 United States	OST: age, weight
Zimering, 2007[112] Unclear	Reduced MSCORE, MSCORE, OST	OST	Men age 40 years or older, ambulatory veterans attending general medicine clinics, endocrinology clinics, or osteoporosis clinics United States	OST: age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Chan, 2006[86] unclear	ABONE, ORAI, OSTA, SCORE	OSTA	Free-living ambulant Chinese postmenopausal women, 55 years and older (Tanjong Rhu community in Singapore) Singapore	OSTA: age, weight
Kung, 2003[95] Low	OSTA	OSTA	Women in Hong Kong recruited from the community, postmenopausal Hong Kong	OSTA: age, weight
Kung, 2005[96] Low	OSTA	OSTA	Community of Asian (Southern Chinese) men; develop index based on clinical factors; compare clinical index with calcaneal QUS in predicting BMD (T< -2.5) by Dexa Hong Kong	OSTA: age, weight
Machado, 2010[98] Low	OST, OSTA	OSTA	Population-based sample of Portuguese men age 50 or over randomly selected from the 19,000 registered voters between 1998-1999 Portugal	OSTA: age, weight
Nguyen, 2004[103] Low	DOESCore, ORAI, OSTA, SOFSURF	OSTA	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia. (98.6% white) Australia	OSTA: age, weight
Oh, 2013[104] Low	OSTA	OSTA	Postmenopausal women, 50 years and older, KHAHNES data set Republic of Korea	OSTA: age, weight
Oh, 2016[105] Low	OSTA	OSTA	Population-based sample of Korean men (KNHANES) age 50 and older. Republic of Korea	OSTA: age, weight
Park, 2003[107] Unclear	OSTA	OSTA	Postmenopausal women at a menopause clinic in Korea not currently using hormone replacement therapy (HRT) Republic of Korea	OSTA: age, weight
Zimering, 2007[112] Unclear	Reduced MSCORE, MSCORE, OST	Reduced MSCORE (age and weight-variable specific scores)	Men age 40 years or older, ambulatory veterans attending general medicine clinics, endocrinology clinics, or osteoporosis clinics United States	Reduced MSCORE: Age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Ben Sedrine, 2001[78] Low	SCORE	SCORE	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Brenneman, 2003[81] Low	SCORE, SOF	SCORE	Post-menopausal women in the Osteoporosis Population-based Risk Assessment (OPRA) study, Group Health participants United States	SCORE: race, rheumatoid arthritis, low trauma fracture, never received HRT, age, weight
Cadarette, 2001[82] Low	ABONE, NOF, ORAI, SCORE	SCORE	CaMOS - Canadian study of women from the general population recruited from 1996-1997, 97% white Canada	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Cass, 2006[84] Low	ORAI, SCORE, MORES	SCORE	Postmenopausal women, 45 years of age and older (receiving usaual care at university-based family practice clinic in the US). Diverse practice, 29% White, 43% Black, 28% Hispanic. United States	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Chan, 2006[86] unclear	ABONE, ORAI, OSTA, SCORE	SCORE	Free-living ambulant Chinese postmenopausal women, 55 years and older (Tanjong Rhu community in Singapore) Singapore	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Cook et al, 2005[87] Unclear	ORAI, OSIRIS, OST, SCORE, SOFSURF	SCORE	Post-menopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of one or more clinical risk factor for osteoporosis United Kingdom	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Crandall, 2014[57] Low	USPSTF (FRAX), OST, SCORE	SCORE	50-64 years of age, postmenopausal, and free from serious medical conditions (WHI) and not using menopausal hormone therapy (in main analysis) United States	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Gourlay, 2005[79] unclear	ORAI, OST, SCORE	SCORE	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Gourlay, 2008[92] Unclear	OST, ORAI, SCORE	SCORE	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age 65 and older. United States	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Harrison et al, 2006[93] Low	ORAI, OSIRIS, OST, SCORE	SCORE	White Caucasian females ages 55 to 70 (mean 61, SD 4) years who were referred to Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on ra	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Jimenez-Nunez, 2013[94] Low	ORAI, OSIRIS, OST, SCORE	SCORE	Caucasian women, were at least 50 years old, had a menopausal status for at least 12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialy clinics in Spain Spain	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Mauck, 2005[100] Low	NOF, ORAI, SCORE	SCORE	Population-based sample of postmenopausal women age 45 years and older in Rochester, MN, 99% white United States	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Richy, 2004[80] Unclear	ORAI, OSIRIS, OST, SCORE	SCORE	Caucasian women either consulting spontaneously or referred for a BMD measurement between January 1996 and September 1999 to an osteoporosis outpatient center in Liege, Belgium Belgium	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight
Rud, 2005[109] Low	SCORE, ORAI, OST	SCORE	White women from the general population recruited for the Danish Osteoporosis Prevention Study (DOPS) Denmark	SCORE: race, rheumatoid arthritis, low trauma fracture after age 45, never received HRT, age, weight

Appendix F Table 1. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 1

First Author's Last Name, Year Risk of Bias	Describe Screening or Treatment Interventions and Comparators	Name of Tool	Cohort or Study Population Name and Descriptor	Risk Prediction Variables
Brenneman, 2003[81] Low	SCORE, SOF	SOF	Post-menopausal women in the Osteoporosis Population-based Risk Assessment (OPRA) study, Group Health participants United States	First-degree relative with hip fracture, current weight less than at age 25, diagnosed with dementia, using corticosteroids, using seizure medication, using benzodiazepines, had a fracture age 50, not taking HRT, on feet <4 h/day, heart rate >80 beats/min, was >5′7″ at age 25, 80+ years old (add 1 point each). African American, walk for exercise, can rise from chair without arms (subtract 1 point each)
Cook et al, 2005[87] unclear	ORAI, OSIRIS, OST, SCORE, SOFSURF	SOFSURF	Post-menopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of one or more clinical risk factor for osteoporosis. United Kingdom	SOFSURF: age, weight, smoking, fracture history
Geusens, 2002[90] Unclear	OST, ORAI, SOFSURF, SCORE	SOFSURF	Community-dwelling women 45 years and older recruited from 1994-1995, 82% white United States	SOFSURF: age, weight, smoking, fracture history
Nguyen, 2004[103] Low	DOESCore, ORAI, OSTA, SOFSURF	SOFSURF	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia. (98.6% white) Australia	SOFSURF: age, weight, smoking, fracture history

Abbreviations: ABONE=assessing age, body size, and estrogen use; AMMEB=Age, Years after Menopause, Age at Menarche, Body Mass Index; BMD=bone mineral density; CaMOS=Canadian Multicentre Osteoporosis Study; COPD=chronic obstructive pulmonary disease; DOEScore=Dubbo Osteoporosis Epidemiology Score; DXA=dual energy x-ray absorptiometry; FRAX=Fracture Risk Assessment tool; GP=general practitioner; h/o=history of; HRT=hormone replacement therapy; kg=kilogram; KNHANES=Korean National Health and Nutrition Examination Survey; MORE=Multiple Outcomes of Raloxifene Trial; MOST=Male Osteoporosis Screening Tool; MSCORE=male, simple calculated osteoporosis risk estimation; NA=not applicable; NR=not reported; NOF=National Osteoporosis Foundation; OPRA=Osteoporosis Population-based Risk Assessment; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; RA=rheumatoid arthritis; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SD=standard deviation; SOF=Study of Osteoporotic Fractures; SOFSURF=Study of Osteoporotic Fractures Simple Useful Risk Factors; US=United States; USPSTF=United States Preventative Services Task Force; WHI=Women's Health Initiative.

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Cadarette, 2001[82] Low	ABONE	2434	2365	Femoral neck: 240 (105)	66.4 (SD 8.8)	2365 (100)	Femoral neck
Chan, 2006[86] unclear	ABONE	135	135	Femoral Neck: 33 (24) Spine: 37 (27)	68.4 (SD 5.5)	135 (100)	Primary was femoral neck; spine was also analysed
D'Amelio, 2005[88] Low	AMMEB	553 (estimated based on 95% paticipation rate)	525	249 (47.4%) (Site not specified by implied to be the lowest of either FN or LS)	Only provided by bone density status: Normal BMD: 57.3 (6.6) Osteopenic BMD: 60.2 (7.8) Osteoporotic BMD: 62.2 (6.7)	525 (100)	Lumbar spine and femoral neck
D'Amelio, 2013[89] Low	AMMEB	NR	995	335 (33.7)unclear what BMD site this is based on	65 (8)	995 (100)	Lumbar spine and femoral neck
Nguyen, 2004[103] Low	DOESCore	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) FN 30.0% (95% CI, 25.8 to 34.6) LS 26.1% (22.1% to 30.6%)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Jimenez-Nunez, 2013[94] Low	FRAX: Hip	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Pang, 2014[106] Low	FRAX: Hip without BMD (>3%)	626	626	Lumbar Spine: 32 (5.2) Femoral Neck:47 (8.7) Total hip: 34 (5.4) Lowest any site: 77 (12.3)	78.2 (SD 5.8)	282 (45.1)	Lumbar spine, femoral neck, and total hip
Jimenez-Nunez, 2013[94] Low	FRAX: MOF	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Pang, 2014[106] Low	FRAX: MOF FRAX without BMD (>6.5%)	626	626	Lumbar Spine: 32 (5.2) Femoral Neck:47 (8.7) Total hip: 34 (5.4) Lowest any site: 77 (12.3)	78.2 (SD 5.8)	282 (45.1)	Lumbar spine, femoral neck, and total hip
Leslie, 2013[113] Low	FRAX: MOF without BMD	18315	18315	18.8% based on lowest T-score measurement from among those available for the lumbar spine and hip	57 (4)	18315 (100)	Proximal femur (femoral neck, total hip, trochanter) and lumbar spine

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First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Bansal, 2015[56] Fair	FRAX: MOF without BMD (>=9.3%)	464	464	25.8 % based on femoral neck and/or lumbar spine	57.4 (NR)	464 (100)	Femoral neck, lumbar spine
Cass, 2016[114] Low	FRAX: MOF without BMD (>=9.3%)	1498	1498	4.5% based on total hip and/or femoral neck	64.2 (9.7)	0 (0)	Total hip and femoral neck
Crandall, 2014[57] Low	FRAX: MOF without BMD (>=9.3%)	2857	2857	174 (5)	57.7 (based on entire sample of 5167)	2857 (100)	Femoral neck, total hip and lumbar spine (outcomes reported based on FN BMD)
Gnudi, 2005[91] Low	Gnudi et al clinical prediction tool	478	478	37.2% based on FN or LS	64.3 (7.6)	478 (100)	Lumbar spine and femoral neck
Cass, 2013[85] Low	MORES	386	346	15 (4.3)	70.2 (SD 6.9)	0 (0)	Femoral neck and total hip
Shepherd, 2007[110]; Cass, 2016[114] Low	MORES	1498	1498	4.4% based on total hip	64.2 (9.7)	0 (0)	Total hip
Shepherd, 2010[115] Low	MORES	2984	2944	10.3% (95% CI, 9.0 to 11.7) based on BMD at any site; 4.3% (95% CI, 3.5 to 5.4) based on BMD at lumbar spine only.	63 (SD NR)	0 (0)	Lumbar spine, and other sites not specifically reported.
Lynn, 2008[97] Low	MOST	US: 4658 Hong Kong: 1914	US: 4658 Hong Kong: 1914	US femoral neck: 5%, lumbar spine: 3% Total spine: 10% Hong Kong femoral neck: 5%, lumbar spine: 2% Total spine: 5%	All age 65 or more	0 (0)	Femoral neck, lumbar spine, or total hip
Zimering, 2007[112] Unclear	MSCORE	197	197	11% based on femoral neck	68.2 (10.2)	0 (0)	Femoral neck
Cadarette, 2001[82] Low	NOF	2434	2365	239 (10%) based on femoral neck	66.4 (SD 8.8)	2365 (100)	Femoral neck

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
D'Amelio, 2005[88] Low	NOF	553 (estimated based on 95% paticipation rate)	525	249 (47.4%) (Site not specified by implied to be the lowest of either FN or LS)	Only provided by bone density status: Normal BMD: 57.3 (6.6) Osteopenic BMD: 60.2 (7.8) Osteoporotic BMD: 62.2 (6.7)	525 (100)	Lumbar spine and femoral neck
D'Amelio, 2013[89] Low	NOF	NR	995	335 (33.7), unclear what BMD site this is based on	65 (8)	995 (100)	Lumbar spine and femoral neck
Mauck, 2005[100] Low	NOF	NR	202	Overall: 69 (34%) (Based on FN T score, would have been 7% if based on LS T Score) age 45-64: 11 (5%) age 65+ : 58 (29%)	Mean 69.2 (SD 11.9) N (%) age 45-64: 79 (39%) >=65: 123 (61%)	202 (100)	Lumbar spine and femoral neck
Cadarette, 2001[82] Low	ORAI	2434	2365	241 (10%) based on femoral neck	66.4 (SD 8.8)	2365 (100)	Femoral neck
Cadarette, 2004[83] Low	ORAI	NR	644	106 (16.5%) based on lowest value of femoral neck or lumbar spine 10.5% based on femoral neck 11.2% based on lumbar spine	62.4 (11.2)	190 (100)	Femoral neck, lumbar spine
Cass, 2006[84] Low	ORAI	399 eligible, 226 enrolled (the remainder declined enrollment)	203	Hip Only: 1.0% Spine Only: 7.9% Both: 2.0%	60.2 (SD 9.6)	226 (100)	Total hip and total lumbar spine; lowest T Score from either was used.
Chan, 2006[86] unclear	ORAI	135	135	Femoral Neck: 33 (24) Spine: 37 (27)	68.4 (SD 5.5)	135 (100)	Primary was femoral neck; spine was also analysed
Cook et al, 2005[87] unclear	ORAI	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine, proximal femur

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
D'Amelio, 2005[88] Low	ORAI	553 (estimated based on 95% paticipation rate)	525	249 (47.4%) (Site not specified by implied to be the lowest of either FN or LS)	Only provided by bone density status: Normal BMD: 57.3 (6.6) Osteopenic BMD: 60.2 (7.8) Osteoporotic BMD: 62.2 (6.7)	525 (100)	Lumbar spine and femoral neck
D'Amelio, 2013[89] Low	ORAI	NR	995	335 (33.7)unclear what BMD site this is based on	65 (8)	995 (100)	Lumbar spine and femoral neck
Geusens, 2002[90] Unclear	ORAI	NR	1102	US Clinic sample (Based on FN site): 14% US trial sample (site not specified, presumably FN): 21% Netherlands population sample (site not specified, presumably FN): 19%	US clinic sample: 61.3 (SD 9.6) NR for other samples	1102 (100)	Lumbar spine and femoral neck
Gourlay, 2005[79] unclear	ORAI	4035	4035	9.5% based on femoral neck[79]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Gourlay, 2008[92] Unclear	ORAI	7779	7679	20.5% (based on FN site)	2714 (34.9%) >=75y 5065 (65.1%) age 67-74	7679 (100)	Lumbar spine and femoral neck
Harrison et al, 2006[93] Low	ORAI	207	207	70 (33.8) at any site	61 (4)	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[94] Low	ORAI	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Martinez-Aguila, 2007[99] Unclear	ORAI	694	665	117 (17.6%) based on lowest BMD at spine or femoral neck 16.7% based on LS 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
Mauck, 2005[100] Low	ORAI	NR	202	Overall: 69 (34%) (Based on FN T score, would have been 7% if based on LS T Score) age 45-64: 11 (5%) age 65+ : 58 (29%)	Mean 69.2 (SD 11.9) N (%) age 45-64: 79 (39%) >=65: 123 (61%)	202 (100)	Lumbar spine and femoral neck

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Nguyen, 2004[103] Low	ORAI	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) FN 30.0% (95% CI, 25.8 to 34.6) LS 26.1% (22.1% to 30.6%)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Richy, 2004[80] Unclear	ORAI	4035	4035	18.5% based on femoral neck[78] 9.5% based on total hip[78] 24.3% based on spine[78] 32% based on any site[80]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Rud, 2005[109] Low	ORAI	2016	2009	92 (4.6%) based on lowest T score in the femoral neck, total hip, and lumbar spine	50.5 (48.4-52.6)	2009 (100)	Femoral neck, total hip, lumbar spine
Cook et al, 2005[87] unclear	OSIRIS	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine, proximal femur
Harrison et al, 2006[93] Low	OSIRIS	207	207	70 (33.8) at any site	61 (4)	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[94] Low	OSIRIS	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Martinez-Aguila, 2007[99] Unclear	OSIRIS	694	665	117 (17.6%) based on lowest BMD at spine or femoral neck 16.7% based on LS 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
Richy, 2004[80] Unclear	OSIRIS	4035	4035	18.5% based on femoral neck[78] 9.5% based on total hip[78] 24.3% based on spine[78] 32% based on any site[80]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Adler, 2003[77] Low	OST	NR	181	15.6% based on lowest T score of spine, total hip, or femoral neck	64.3 (12.3)	0 (0)	Spine, femoral neck, total hip
Cadarette, 2004[83] Low	OST	NR	644	106 (16.5%) based on lowest value of femoral neck or lumbar spine 10.5% based on femoral neck 11.2% based on lumbar spine	62.4 (11.2)	190 (100)	Femoral neck, lumbar spine
Cook et al, 2005[87] unclear	OST	208	208	45 (21.6) any site	59.7 (29-87)	208 (100)	Lumbar spine, proximal femur

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Crandall, 2014[57] Low	OST	2857	2857	NR (5)	57.7 (based on entire sample of 5167)	2857 (100)	Femoral neck, total hip and lumbar spine (outcomes reported based on FN BMD)
D'Amelio, 2005[88] Low	OST	553 (estimated based on 95% paticipation rate)	525	249 (47.4%) (Site not specified by implied to be the lowest of either FN or LS)	Only provided by bone density status: Normal BMD: 57.3 (6.6) Osteopenic BMD: 60.2 (7.8) Osteoporotic BMD: 62.2 (6.7)	525 (100)	Lumbar spine and femoral neck
D'Amelio, 2013[89] Low	OST	NR	995	335 (33.7)unclear what BMD site this is based on	65 (8)	995 (100)	Lumbar spine and femoral neck
Geusens, 2002[90] Unclear	OST	NR	1102	US Clinic sample (Based on FN site): 14% US trial sample (site not specified, presumably FN): 21% Netherlands population sample (site not specified, presumably FN): 19%	US clinic sample: 61.3 (SD 9.6) NR for other samples	1102 (100)	Lumbar spine and femoral neck
Gourlay, 2005[79] unclear	OST	4035	4035	9.5% based on femoral neck[79]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Gourlay, 2008[92] Unclear	OST	7779	7617	20.5% (based on FN site)	2714 (34.9%) >=75y 5065 (65.1%) age 67-74	7617 (100)	Lumbar spine and femoral neck
Harrison et al, 2006[93] Low	OST	207	207	70 (33.8) at any site	61 (4)	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[94] Low	OST	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Leslie, 2013[113] Low	OST	18315	18315	18.8% based on lowest T-score measurement from among those available for the lumbar spine and hip	57 (4)	18315 (100)	Proximal femur (femoral neck, total hip, trochanter) and lumbar spine

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Lynn, 2008[97] Low	OST	US: 4658 Hong Kong: 1914	US: 4658 Hong Kong: 1914	US femoral neck: 5%, lumbar spine: 3% Total spine: 10% Hong Kong femoral neck: 5%, lumbar spine: 2% Total spine: 5%	All age 65 or more	0 (0)	Femoral neck, lumbar spine, or total hip
Machado, 2010[98] Low	OST	202	202	35 (16.8%) based on lowest T score at any site 30 (14.9%) based on LS 10 (5%) based on FN 2 (1%) based on total hip	63.8(8.2) 75.7% were less than 70 years	0 (0)	Femoral neck, total hip, and lumbar spine, but the lowest value at any site was used to determine osteoporosis.
Martinez-Aguila, 2007[99] Unclear	OST	694	665	117 (17.6%) based on lowest BMD at spine or femoral neck 16.7% based on LS 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
McLeod, 2015[101] Low	OST	174	174	18 (10.3%)	59 (6.7)	174 (100)	Femoral neck, lumbar spine
Morin, 2009[102] Unclear	OST	8254	8254	1,226 (14.9%) at any site	52.7 (4.9)	8254 (100)	Femoral neck, total hip, and proximal femur, lumbar spine
Pang, 2014[106] Low	OST	626	626	Lumbar Spine: 32 (5.2) Femoral Neck:47 (8.7) Total hip: 34 (5.4) Lowest any site: 77 (12.3)	78.2 (SD 5.8)	282 (45.1)	Lumbar spine, femoral neck, and total hip
Richards, 2014[108] Unclear	OST	520	518	92 (17.8%)	66 (NR)	0 (0)	Femoral neck and total hip
Richy, 2004[80] Unclear	OST	4035	4035	18.5% based on femoral neck[78] 9.5% based on total hip[78] 24.3% based on spine[78] 32% based on any site[80]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Rud, 2005[109] Low	OST	2016	2009	92 (4.6%) based on lowest T score in the femoral neck, total hip, and lumbar spine	50.5 (48.4-52.6)	2009 (100)	Femoral neck, total hip, lumbar spine
Sinnott, 2006[111] Low	OST	128	128	7% (any site)	63.8 (14.8)	0 (0)	Lumbar spine (L1–L4) and the non-dominant hip (femoral neck, trochanter, total hip)
Zimering, 2007[112] Unclear	OST	197	197	11% based on femoral neck	68.2 (10.2)	0 (0)	Femoral neck

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Chan, 2006[86] unclear	OSTA	135	135	Femoral Neck: 33 (24) Spine: 37 (27)	68.4 (SD 5.5)	135 (100)	Primary was femoral neck; spine was also analysed
Kung, 2003[95] Low	OSTA	722	722	femoral neck: 21.5%, lumbar spine: 30.6% either region: 37.7%	62 (8)	722 (100)	Femoral neck, lumbar spine, or either
Kung, 2005[96] Low	OSTA	356	356	femoral neck: 11.2%, lumbar spine: 10.1% either region: 15.8%	64 (range 50-90)	0 (0)	Femoral neck, lumbar spine, or either
Machado, 2010[98] Low	OSTA	202	202	34 (16.8%) based on lowest T score at any site 30 (14.9%) based on LS 10 (5%) based on FN 2 (1%) based on total hip	63.8(8.2) 75.7% were less than 70 years	0 (0)	Femoral neck, total hip, and lumbar spine, but the lowest value at any site was used to determine osteoporosis.
Nguyen, 2004[103] Low	OSTA	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) FN 30.0% (95% CI, 25.8 to 34.6) LS 26.1% (22.1% to 30.6%)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Oh, 2013[104] Low	OSTA	1046	1046	Based on T score at LS: 252 (24.1) Based on T score at FN: 155 (14.8) Based on lowest T score at any site: 310 (29.6)	62.3 (SD 8.2)	1046 (100)	Total femur, femoral neck, and L1-L4 spine
Oh, 2016[105] Low	OSTA	1353	1110	Based on -2.5 at Femoral neck: 35 (3.2%) Based on -2.5 at Lspine: 73 (6.6%) Based on lowest at any site: 91 (8.2%)	63.5 (8.3)	0 (0)	Total femur, femoral neck, L1-L4 spine
Park, 2003[107] Unclear	OSTA	1101	1101	119 (11%)	59.1 (7.7)	1101 (100)	Femoral neck
Zimering, 2007[112] Unclear	Reduced MSCORE (age and weight-variable specific scores)	197	197	11% based on femoral neck	68.2 (10.2)	0 (0)	Femoral neck

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Ben Sedrine, 2001[78] Low	SCORE	4035	4035	18.5% based on femoral neck[78] 9.5% based on total hip[78] 24.3% based on spine[78] 32% based on any site[80]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Brenneman, 2003[81] Low	SCORE	428	416	126 (30.3%) based on lowest T score of hip or lumbar spine	69.3 (5.5)	416 (100)	Hip, lumbar spine
Cadarette, 2001[82] Low	SCORE	2434	2365	239 (10%) based on femoral neck	66.4 (SD 8.8)	2365 (100)	Femoral neck
Cass, 2006[84] Low	SCORE	399 eligible, 226 enrolled (the remainder declined enrollment)	203	Hip Only: 1.0% Spine Only: 7.9% Both: 2.0%	60.2 (SD 9.6)	226 (100)	Total hip and total lumbar spine; lowest T Score from either was used.
Chan, 2006[86] unclear	SCORE	135	135	Femoral Neck: 33 (24) Spine: 37 (27)	68.4 (SD 5.5)	135 (100)	Primary was femoral neck; spine was also analysed
Cook et al, 2005[87] Unclear	SCORE	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine, proximal femur
Crandall, 2014[57] Low	SCORE	2857	2857	NR (5)	57.7 (based on entire sample of 5167)	2857 (100)	Femoral neck, total hip and lumbar spine (outcomes reported based on FN BMD)
Gourlay, 2005[79] unclear	SCORE	4035	4035	9.5% based on femoral neck[79]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Gourlay, 2008[92] Unclear	SCORE	7779	7235	20.5% (based on FN site)	2714 (34.9%) >=75y 5065 (65.1%) age 67-74	7235 (100)	Lumbar spine and femoral neck
Harrison et al, 2006[93] Low	SCORE	207	207	70 (33.8) at any site	61 (4)	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[94] Low	SCORE	505	505	20% any site	61 (7)	505 (100)	Total femur, femoral neck, and lumbar spine
Mauck, 2005[100] Low	SCORE	NR	202	Overall: 69 (34%) (Based on FN T score, would have been 7% if based on LS T Score) age 45-64: 11 (5%) age 65+ : 58 (29%)	Mean 69.2 (SD 11.9) N (%) age 45-64: 79 (39%) >=65: 123 (61%)	202 (100)	Lumbar spine and femoral neck

Appendix F Table 2. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 2

First Author's Last Name, Year Risk of Bias	Name of Tool	N Eligible	N for Analysis	N (%) with Osteoporosis Report for Each Site	Age	N (Percent) Female	Location of BMD
Richy, 2004[80] Unclear	SCORE	4035	4035	18.5% based on femoral neck[78] 9.5% based on total hip[78] 24.3% based on spine[78] 32% based on any site[80]	61.5 (8.8)	4035 (100)	Femoral neck, total hip, lumbar spine[78]
Rud, 2005[109] Low	SCORE	2016	2009	92 (4.6%) based on lowest T score in the femoral neck, total hip, and lumbar spine	50.5 (48.4-52.6)	2009 (100)	Femoral neck, total hip, lumbar spine
Brenneman, 2003[81] Low	SOF	428	416	126 (30.3%) based on lowest T score of hip or lumbar spine	69.3 (5.5)	416 (100)	Hip, lumbar spine
Cook et al, 2005[87] unclear	SOFSURF	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine, proximal femur
Geusens, 2002[90] Unclear	SOFSURF	NR	1102	US Clinic sample (Based on FN site): 14%	US clinic sample: 61.3 (SD 9.6) NR for other samples	1102 (100)	Lumbar spine and femoral neck
Nguyen, 2004[103] Low	SOFSURF	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) FN 30.0% (95% CI, 25.8 to 34.6) LS 26.1% (22.1% to 30.6%)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck

Abbreviations: BMD=body mass index; FN=femoral neck; L1-L4=lumbar 1 to lumbar 4; LS=lumbar spine; N=number; NR=not reported; SD=standard deviation; US=United States.

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Cadarette, 2001[82] Low	ABONE	Canadian young adult normal values at the femoral neck. (Authors note that the Canadian young adult normal reference at the femoral neck (mean [SD], 0.857 [0.125] g/cm3) is similar to that reported by NHANES III for non-Hispanic white Americans (mean [SD], 0.858 [0.120] g/cm3).	Hologic QDR 4500 Hologic QDR 2000 Hologic QDR 1000 Lunar DPX	BMD at femoral neck used to determine T score	No	NA
Chan, 2006[86] unclear	ABONE	NR	DXA (Hologic QDR 4500A), NR	BMD at femoral neck used to determine T score	Unclear	NA
D'Amelio, 2005[88] Low	AMMEB	NR	Hologic QDR 4500	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
D'Amelio, 2013[89] Low	AMMEB	NR	DXA (Hologic QDR 4500), NR	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score.	Unclear	NA
Nguyen, 2004[103] Low	DOESCore	Reference ranges for calculation of T scores not described. Under "Measurements": used BMD values of young Australian women at either the femoral neck or lumbar spine as reference to determine T score	LUNAR DPX-L densitometer	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
Jimenez-Nunez, 2013[94] Low	FRAX: Hip	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (software ENCORE 2006)	Lowest score at femoral neck or lumbar spine	No	NA
Pang, 2014[106] Low	FRAX: Hip without BMD (>3%)	Manufacturer's sex specific normative databse and an ethnic database.	Lunar Prodigy limited fan-beam machine, NR	NR	Unclear	NA
Jimenez-Nunez, 2013[94] Low	FRAX: MOF	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (software ENCORE 2006)	Lowest score at femoral neck or lumbar spine	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Pang, 2014[106] Low	FRAX: MOF FRAX without BMD (>6.5%)	Manufacturer's sex specific normative databse and an ethnic database.	Lunar Prodigy limited fan-beam machine, NR	NR	Unclear	NA
Leslie, 2013[113] Low	FRAX: MOF without BMD	Femoral T-scores calculated based on NHANES III white female reference; lumbar spine used T-scores used manufacturer's USA white female reference values	NR	Lowest score at lumbar spine and hip	No	NA
Bansal, 2015[56] Fair	FRAX: MOF without BMD (>=9.3%)	NR	NR	NR	No	NA
Cass, 2016[114] Low	FRAX: MOF without BMD (>=9.3%)	NHANES III non-Hispanic White women age 20-29 years old	NR	NR	No	NA
Crandall, 2014[57] Low	FRAX: MOF without BMD (>=9.3%)	NHANES III normative reference database (presumably young non-hispanic white females 20-29, though this is not specifically reported)	DXA (Hologic QDR 4500A), NR	Femoral neck	Unclear	NA
Gnudi, 2005[91] Low	Gnudi et al clinical prediction tool	"Reference values were those reported by Norland for the European female population." Age not given	Norland XR 36	NR	No	NA
Cass, 2013[85] Low	MORES	NHANES III non-Hispanic White women age 20-29 years old.	DXA (Hologic QDR 4500A), NR (Standardized conversion formulas furnished by GE Health Care)	"positive" test is a T score of -2.5 at the femoral neck OR total hip	Unclear	NA
Shepherd, 2007[110]; Cass, 2016[114] Low	MORES	T scores derived from race/ethnicity and sex-specific bone mineral density for Hispanic, non-Hispanic white, and non-Hispanic black men ages 20-29.	Hologic QDR	NR	No	NA
Shepherd, 2010[115] Low	MORES	White men age 20-29; whole body DXA Hologic QDR-4500A	NR	NR	No	no
Lynn, 2008[97] Low	MOST	US: NHANES Hong Kong: local Chinese reference ranges	Hologic QDR 4500W bone densitometers	Results presented for femoral neck, lumbar spine, total hip, or any site	No	NA
Zimering, 2007[112] Unclear	MSCORE	T score <= -2.5 compared to NHANES III young male, ethnicity/race- specific reference data	Hologic QDR 4500 SL	NR	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Cadarette, 2001[82] Low	NOF	Canadian young adult normal values at the femoral neck. (Authors note that the Canadian young adult normal reference at the femoral neck (mean [SD], 0.857 [0.125] g/cm3) is similar to that reported by NHANES III for non-Hispanic white Americans (mean [SD], 0.858 [0.120] g/cm3).	Hologic QDR 4500 Hologic QDR 2000 Hologic QDR 1000 Lunar DPX	BMD at femoral neck used to determine T score	No	NA
D'Amelio, 2005[88] Low	NOF	NR	Hologic QDR 4500	NR	No	NA
D'Amelio, 2013[89] Low	NOF	NR	DXA (Hologic QDR 4500), NR	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score.	Unclear	NA
Mauck, 2005[100] Low	NOF	T scores based on references ranges for young healthy women age 20-29 years in the local community area	QDR2000 instrument; Hologic, Waltham, Mass	NR	Yes	Age
Cadarette, 2001[82] Low	ORAI	Canadian young adult normal values at the femoral neck. (Authors note that the Canadian young adult normal reference at the femoral neck (mean [SD], 0.857 [0.125] g/cm3) is similar to that reported by NHANES III for non-Hispanic white Americans (mean [SD], 0.858 [0.120] g/cm3).	Hologic QDR 4500 Hologic QDR 2000 Hologic QDR 1000 Lunar DPX	BMD at femoral neck used to determine T score	No	NA
Cadarette, 2004[83] Low	ORAI	NR	Hologic Lunar Norland Unknown	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
Cass, 2006[84] Low	ORAI	NHANES III non-Hispanic White women age 20-29 years old.	DXA (Hologic QDR 4500A), NR	"positive" test is a T score of -2.5 at the femoral neck OR total hip	Unclear	NA
Chan, 2006[86] unclear	ORAI	NR	DXA (Hologic QDR 4500A), NR	BMD at femoral neck used to determine T score	Unclear	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Cook et al, 2005[87] unclear	ORAI	T-scores were computed using the databases supplied with the systems	Hologic QDR-4500C	Lowest value of lumbar spine or total hip used to classify as osteoporosis	No	NA
D'Amelio, 2005[88] Low	ORAI	NR	Hologic QDR 4500	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
D'Amelio, 2013[89] Low	ORAI	NR	DXA (Hologic QDR 4500), NR	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score.	Unclear	NA
Geusens, 2002[90] Unclear	ORAI	FN: non-hispanic female white women age 20-29 (NHANES) LS: unclear	The brand of DXA manufacturer varied among centers, and included Norland, Hologic, and Lunar machines	NR	No	NA
Gourlay, 2005[79] unclear	ORAI	T score reference range was NHANES III non-Hispanic white women age 20-29 years at the femoral neck	Hologic QDR 1000, 2000 and 4500 densitometers	BMD at femoral neck used to determine T score	No	NA
Gourlay, 2008[92] Unclear	ORAI	FN: non-hispanic female white women age 20-29 (NHANES) LS: manufacturers norms for women age 30 years	Hologic	NR	No	NA
Harrison et al, 2006[93] Low	ORAI	Hologic reference data for the T and z scores calculated using Hologic reference dataa for the lumbar spine and NHANES reference data for the proximal femur	GE Lunar Prodigy (GE Lunar Corporation, Madison, WI, USA) or the Hologic Discovery (Hologic Inc., Bedford, Massachusetts, USA).	Value of -2.5 or below at the total hip, femoral neck or lumbar spine	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Jimenez-Nunez, 2013[94] Low	ORAI	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (software ENCORE 2006)	Lowest score at femoral neck or lumbar spine	No	NA
Martinez-Aguila, 2007[99] Unclear	ORAI	T -Scores from reference range from a study conducted in a Spanish population of healthy subjects of same sex with peak bone mass	Hologic QDR	Lowest site at femoral neck or lumbar spine	No	NA
Mauck, 2005[100] Low	ORAI	T scores based on references ranges for young healthy women age 20-29 years in the local community area	QDR2000 instrument; Hologic, Waltham, Mass	BMD at femoral neck used to determine T score	Yes	Age
Nguyen, 2004[103] Low	ORAI	Reference ranges for calculation of T scores not described. Under "Measurements": used BMD values of young Australian women at either the femoral neck or lumbar spine as reference to determine T score	LUNAR DPX-L densitometer	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
Richy, 2004[80] Unclear	ORAI	Reference values specifically established for the population of Liege.	Hologic QDR2000	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score. Individual T score by site also reported	No	NA
Rud, 2005[109] Low	ORAI	T scores for the femoral neck and total hip calculated using NHANES III reference values Hologic references values were used for the lumbar spine. Authors do not specify if age matched reference group was used or young white women.	Hologic QDR 1000/W and QDR 2000	NR	No	NA
Cook et al, 2005[87] unclear	OSIRIS	T-scores were computed using the databases supplied with the systems	Hologic QDR-4500C	Lowest value of lumbar spine or total hip used to classify as osteoporosis	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Harrison et al, 2006[93] Low	OSIRIS	Hologic reference data for the T and z scores calculated using Hologic reference dataa for the lumbar spine and NHANES reference data for the proximal femur	GE Lunar Prodigy (GE Lunar Corporation, Madison, WI, USA) or the Hologic Discovery (Hologic Inc., Bedford, Massachusetts, USA).	Value of -2.5 or below at the total hip, femoral neck or lumbar spine	No	NA
Jimenez-Nunez, 2013[94] Low	OSIRIS	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (softw are ENCORE 2006)	Low est score at femoral neck or lumbar spine	No	NA
Martinez-Aguila, 2007[99] Unclear	OSIRIS	T Scores from reference range from a study conducted in a Spanish population of healthy subjects of same sex w ith peak bone mass	Hologic QDR	Low est site at femoral neck or lumbar spine	No	NA
Richy, 2004[80] Unclear	OSIRIS	Reference values specifically established for the population of Liege.	Hologic QDR2000	Low est BMD at total hip, femoral neck, or lumbar spine used to determine T score. Individual T score by site also reported	No	NA
Adler, 2003[77] Low	OST	NHANES reference database for hip Hologic reference source for spine Age, gender, race of reference group not reported	Hologic QDR 4500	NR	No	NA
Cadarette, 2004[83] Low	OST	NR	Hologic Lunar Norland Unknow n	Low est BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
Cook et al, 2005[87] unclear	OST	T-scores w ere computed using the databases supplied w ith the systems	Hologic QDR-4500C	Low est value of lumbar spine or total hip used to classify as osteoporosis	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Crandall, 2014[57] Low	OST	NHANES III normative reference database (presumably young non-hispanic white females 20-29, though this is not specifically reported)	DXA (Hologic QDR 4500A), NR	Femoral neck	Unclear	NA
D'Amelio, 2005[88] Low	OST	NR	Hologic QDR 4500	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
D'Amelio, 2013[89] Low	OST	NR	DXA (Hologic QDR 4500), NR	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score.	Unclear	NA
Geusens, 2002[90] Unclear	OST	FN: non-hispanic female white women age 20-29 (NHANES) LS: unclear	The brand of DXA manufacturer varied among centers, and included Norland, Hologic, and Lunar machines	NR	No	NA
Gourlay, 2005[79] unclear	OST	T score reference range was NHANES III non-Hispanic white women age 20-29 years at the femoral neck	Hologic QDR 1000, 2000 and 4500 densitometers	BMD at femoral neck used to determine T score	No	NA
Gourlay, 2008[92] Unclear	OST	FN: non-hispanic female white women age 20-29 (NHANES) LS: manufacturers norms for women age 30 years	Hologic	NR	No	NA
Harrison et al, 2006[93] Low	OST	Hologic reference data for the T and z scores calculated using Hologic reference dataa for the lumbar spine and NHANES reference data for the proximal femur	GE Lunar Prodigy (GE Lunar Corporation, Madison, WI, USA) or the Hologic Discovery (Hologic Inc., Bedford, Massachusetts, USA).	Value of -2.5 or below at the total hip, femoral neck or lumbar spine	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Jimenez-Nunez, 2013[94] Low	OST	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (software ENCORE 2006)	Lowest score at femoral neck or lumbar spine	No	NA
Leslie, 2013[113] Low	OST	Femoral T-scores calculated based on NHANES III white female reference; lumbar spine used T-scores used manufacturer's USA white female reference values	NR	Lowest score at lumbar spine and hip	No	NA
Lynn, 2008[97] Low	OST	US: NHANES Hong Kong: local Chinese reference ranges	Hologic QDR 4500W bone densitometers	Results presented for femoral neck, lumbar spine, total hip, or any site	No	NA
Machado, 2010[98] Low	OST	NHANES III young normal references values (sex unspecified) for FN; manufacturer's database for male caucasian references values for LS (age unspecified)	Hologic QDR 4500/c bone densitometer	NR	No	NA
Martinez-Aguila, 2007[99] Unclear	OST	T Scores from reference range from a study conducted in a Spanish population of healthy subjects of same sex with peak bone mass	Hologic QDR	Lowest site at femoral neck or lumbar spine	No	NA
McLeod, 2015[101] Low	OST	NHANES III	GE Lunar Prodigy densitometer	Results presented for femoral neck and lumbar spine	No	NA
Morin, 2009[102] Unclear	OST	Reports T Scores for LS used manufacturers US white female reference ranges, based on revised NHANES III, but these are only applicable to FN, and the study states this reference range was used for LS.	Lunar Prodigy; GE Lunar, Madison, WI, USA).	NR	No	NA
Pang, 2014[106] Low	OST	Manufacturer's sex specific normative databse and an ethnic database.	Lunar Prodigy limited fan-beam machine, NR	NR	Unclear	NA

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First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Richards, 2014[108] Unclear	OST	NHANES III	DXA on either the Hologic (Hologic Inc., Bedford, MA) or the Lunar (GE Healthcare, Madison, WI) scanner, specific to each participating center. To adjust for systematic differences in BMD by DXA, values were standardized to the Hologic BMD using published	NR	No	NA
Richy, 2004[80] Unclear	OST	Reference values specifically established for the population of Liege.	Hologic QDR2000	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score. Individual T score by site also reported	No	NA
Rud, 2005[109] Low	OST	T scores for the femoral neck and total hip calculated using NHANES III reference values Hologic references values were used for the lumbar spine. Authors do not specify if age matched reference group was used or young white women.	Hologic QDR 1000/W and QDR 2000	NR	No	NA
Sinnott, 2006[111] Low	OST	T-scores were calculated using the manufacturer's reference values, namely a young Caucasian male database for the hip and a Caucasian female database for the spine	GE lunar machine (General Electric, Madison, Wis.)	Results presented for total hip, femoral neck or trochanter	No	NA
Zimering, 2007[112] Unclear	OST	T score <= -2.5 compared to NHANES III young male, ethnicity/race- specific reference data	Hologic QDR 4500 SL	NR	No	NA

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First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Chan, 2006[86] unclear	OSTA	NR	DXA (Hologic QDR 4500A), NR	BMD at femoral neck used to determine T score	Unclear	NA
Kung, 2003[95] Low	OSTA	Peak young Chinese mean values used for calculating T-scores: L1–L4 BMD 1.02±0.11 g/cm2, femoral neck 0.77±0.09 g/cm2, total hip BMD 0.86±0.10 g/cm2,	Sahara ultrasound bone densitometer (Hologic)	Results presented for femoral neck, or femoral neck or lumbar spine	No	NA
Kung, 2005[96] Low	OSTA	NR	QDR 2000 Plus, Hologic	Results presented for femoral neck, lumbar spine, or femoral neck or lumbar spine	No	NA
Machado, 2010[98] Low	OSTA	NHANES III young normal references values (sex unspecified) for FN; manufacturer's database for male caucasian references values for LS (age unspecified)	Hologic QDR 4500/c bone densitometer	NR	No	NA
Nguyen, 2004[103] Low	OSTA	Reference ranges for calculation of T scores not described. Under "Measurements": used BMD values of young Australian women at either the femoral neck or lumbar spine as reference to determine T score	LUNAR DPX-L densitometer	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA
Oh, 2013[104] Low	OSTA	Sex-specific normal values for young Japanese women.	QDR Discovery fan beam densitometer (Hologic), Hologic Discovery software (version 13.1)	NR	Unclear	NA
Oh, 2016[105] Low	OSTA	Gender specific norms for young Japanese men.	Hologic	Defined Osteo as BMd of -2.5 or -2.0 (did both) at the femoral neck or lumbar spine.	No	n/a
Park, 2003[107] Unclear	OSTA	Reference range for young Korean women	GE Lunar Model DPQ-IQ,	NR	No	NA

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First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Zimering, 2007[112] Unclear	Reduced MSCORE (age and weight-variable specific scores)	T score <= -2.5 compared to NHANES III young male, ethnicity/race- specific reference data	Hologic QDR 4500 SL	NR	No	NA
Ben Sedrine, 2001[78] Low	SCORE	Hologic QDR reference values specifically established for the population of Liege, Belgium (local reference values)	Hologic	NR	No	NA
Brenneman, 2003[81] Low	SCORE	NHANES III do not specify age or gender of reference group	Hologic QDR 2000	NR	No	NA
Cadarette, 2001[82] Low	SCORE	Canadian young adult normal values at the femoral neck. (Authors note that the Canadian young adult normal reference at the femoral neck (mean [SD], 0.857 [0.125] g/cm3) is similar to that reported by NHANES III for non-Hispanic white Americans (mean [SD], 0.858 [0.120] g/cm3).	Hologic QDR 4500 Hologic QDR 2000 Hologic QDR 1000 Lunar DPX	BMD at femoral neck used to determine T score	No	NA
Cass, 2006[84] Low	SCORE	NHANES III non-Hispanic White women age 20-29 years old.	DXA (Hologic QDR 4500A), NR	"positive" test is a T score of -2.5 at the femoral neck OR total hip	Unclear	NA
Chan, 2006[86] unclear	SCORE	NR	DXA (Hologic QDR 4500A), NR	BMD at femoral neck used to determine T score	Unclear	NA
Cook et al, 2005[87] Unclear	SCORE	T-scores were computed using the databases supplied with the systems	Hologic QDR-4500C	Lowest value of lumbar spine or total hip used to classify as osteoporosis	No	NA
Crandall, 2014[57] Low	SCORE	NHANES III normative reference database (presumably young non-hispanic white females 20-29, though this is not specifically reported)	DXA (Hologic QDR 4500A), NR	Femoral neck	Unclear	NA
Gourlay, 2005[79] unclear	SCORE	T score reference range was NHANES III non-Hispanic white women age 20-29 years at the femoral neck	Hologic QDR 1000, 2000 and 4500 densitometers	BMD at femoral neck used to determine T score	No	NA

Appendix F Table 3. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 3

First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Gourlay, 2008[92] Unclear	SCORE	FN: non-hispanic female white women age 20-29 (NHANES) LS: manufacturers norms for women age 30 years	Hologic	NR	No	NA
Harrison et al, 2006[93] Low	SCORE	Hologic reference data for the T and z scores calculated using Hologic reference dataa for the lumbar spine and NHANES reference data for the proximal femur	GE Lunar Prodigy (GE Lunar Corporation, Madison, WI, USA) or the Hologic Discovery (Hologic Inc., Bedford, Massachusetts, USA).	Value of -2.5 or below at the total hip, femoral neck or lumbar spine	No	NA
Jimenez-Nunez, 2013[94] Low	SCORE	Manufacturer's reference for the Spanish population	GE Lunar Prodigy Advance DEXA densitometer (software ENCORE 2006)	Lowest score at femoral neck or lumbar spine	No	NA
Mauck, 2005[100] Low	SCORE	T scores based on references ranges for young healthy women age 20-29 years in the local community area	QDR2000 instrument; Hologic, Waltham, Mass	BMD at femoral neck used to determine T score	Yes	Age
Richy, 2004[80] Unclear	SCORE	Reference values specifically established for the population of Liege.	Hologic QDR2000	Lowest BMD at total hip, femoral neck, or lumbar spine used to determine T score. Individual T score by site also reported	No	NA
Rud, 2005[109] Low	SCORE	T scores for the femoral neck and total hip calculated using NHANES III reference values Hologic references values were used for the lumbar spine. Authors do not specify if age matched reference group was used or young white women.	Hologic QDR 1000/W and QDR 2000	NR	No	NA
Brenneman, 2003[81] Low	SOF	NHANES III do not specify age or gender of reference group	Hologic QDR 2000	NR	No	NA

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First Author's Last Name, Year Risk of Bias	Name of Tool	T-Score References Ranges	Machine and Software Version if Reported	Other Comments on BMD Test	Did Analysis Include Additional Adjustments?	If Yes, List Adjustment Variables
Cook et al, 2005[87] unclear	SOFSURF	T-scores were computed using the databases supplied with the systems	Hologic QDR-4500C	Lowest value of lumbar spine or total hip used to classify as osteoporosis	No	NA
Geusens, 2002[90] Unclear	SOFSURF	FN: non-hispanic female white women age 20-29 (NHANES) LS: unclear	The brand of DXA manufacturer varied among centers, and included Norland, Hologic, and Lunar machines	NR	No	NA
Nguyen, 2004[103] Low	SOFSURF	Reference ranges for calculation of T scores not described. Under "Measurements": used BMD values of young Australian women at either the femoral neck or lumbar spine as reference to determine T score	LUNAR DPX-L densitometer	Lowest BMD at femoral neck, or lumbar spine used to determine T score.	No	NA

Abbreviations: BMD=body mass index; cm=centimeter; DEXA or DXA=dual energy X-ray absorptiometry; FN=femoral neck; G=gram; LS=lumbar spine; NA=not applicable; NHANES=National Health And Nutrition Examination Survey; NR=not reported; SD=standard deviation; WI=Wisconsin.

Appendix F Table 4. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Cadarette, 2001[82] Low	ABONE	NR Likely < 2 years	AUROC with respect to DXA outcome of T score=< -2.5 at femoral neck ABONE: 0.72 (0.02)	ABONE >=2: 83.3 (78.5-88.0)	ABONE >=2: 47.7 (45.6-49.8)
Chan, 2006[86] unclear	ABONE	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	ABONE>=3: 0.70 (0.63-0.78)	ABONE >=3: 81.8% (NR)	ABONE >=3: 55.9% (NR)
D'Amelio, 2005[88] Low	AMMEB	NR	AMMEB>=10: 0.71 (NR)	NR	NR
D'Amelio, 2013[89] Low	AMMEB	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	AMMEB>=10: 0.63 (NR)	NR	NR
Nguyen, 2004[103] Low	DOESCore	Concurrent	DOEScore for T score<-2.5: 0.75 (SE 0.03)	DOEScore >10 : 82% (NR)	DOEScore >10: 52% (NR)
Jimenez-Nunez, 2013[94] Low	FRAX: Hip	None	FRAX Hip: 0.82 (NR)	Threshold NR for sensitivity	Threshold NR for specificity
Pang, 2014[106] Low	FRAX: Hip without BMD (>3%)	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	Based on lowest BMD at any site (FN, Total Hip, LS) FRAX: 0.70 (0.64-0.75)	Based on lowest BMD at any site, FRAX Score >3% 92.2	Based on lowest BMD at any site, FRAX Score >3% 37.1
Jimenez-Nunez, 2013[94] Low	FRAX: MOF	None	FRAX MOF: 0.82 (NR)	Threshold NR for sensitivity	Threshold NR for specificity
Pang, 2014[106] Low	FRAX: MOF FRAX without BMD (>6.5%)	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	Based on lowest BMD at any site FRAX: 0.68 (0.63-0.74)	Based on lowest BMD at any site, FRAX Score >6.5% 89.6	Based on lowest BMD at any site, FRAX Score >6.5% 35.0
Leslie, 2013[113] Low	FRAX: MOF without BMD	NR	FRAX AUROC for T score<=-2.5: 0.67 (0.66-0.68)	NR	NR
Bansal, 2015[56] Fair	FRAX: MOF without BMD (>=9.3%)	NR	FRAX MOF risk >=9.3%: 0.58 (NR)	FRAX MOF risk ≥9.3%: 37 FRAX MOF risk ≥5.5%: 80.4	FRAX MOF risk ≥9.3%: 74 FRAX MOF risk ≥5.5%: 26.8

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Cass, 2016[114] Low	FRAX: MOF without BMD (>=9.3%)	NR	FRAX AUROC with respect to DXA outcome of T score=<-2.5 at total hip: 0.79 (0.74-0.84)	FRAX MOF risk >=9.3%: 0.39 (0.27-0.51)	FRAX MOF risk >=9.3%: 0.89 (0.87-0.91)
Crandall, 2014[57] Low	FRAX: MOF without BMD (>=9.3%)	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	FRAX MOF risk >=9.3%: 0.60 (0.56-0.63)	FRAX MOF risk >=9.3%: 33.3 (26.3-40.4)	FRAX MOF risk >=9.3%: 86.4 (85.1-87.7)
Gnudi, 2005[91] Low	Gnudi et al clinical prediction tool	NR	Compared to T score <=-2.5 either FN or LS Gnudi et al clinical prediction tool: 0.744 (SE 0.023)	Cutoffs based on predicted probablity to have low BMD (PPL-BMD) (1) PPL-BMD = 0.090 (2) PPL-BMD = 0.132 (3) PPL-BMD = 0.156 Gnudi et al clinical prediction tool: (1) 97.2% (2) 95.5% (3) 91.6%	Cutoffs based on predicted probablity to have low BMD (PPL-BMD) (1) PPL-BMD = 0.090 (2) PPL-BMD = 0.132 (3) PPL-BMD = 0.156 Gnudi et al clinical prediction tool: (1) 16.9% (2) 27.7% (3) 31.0%
Cass, 2013[85] Low	MORES	Concurrent	MORES>=6: 0.82 (0.71-0.92)	MORES>=6: 0.80 (0.52-0.96)	MORES>=6: 0.70 (0.64-0.74)
Shepherd, 2007[110]; Cass, 2016[114] Low	MORES	NR	AUROC for MORES with respect to DXA outcome of T score=< -2.5 at total hip 0.842: 0.842 (0.811-0.873) (reported as 0.87 in Cass, 2016[114])	MORES >= 6: 0.95 (0.81-0.99)	MORES >= 6: 0.61 (0.57-0.64)
Shepherd, 2010[115] Low	MORES	NR	MORES>=6 at any site: 0.73 (NR) MORES>=6 at lumbar spine: 0.66 (NR)	MORES >=6 at any site: 0.66 (95% CI, 0.58 to 0.72) MORES>=6 at lumbar spine: 0.58 (95% CI, 0.46 to 0.69)	MORES >=6 at any site: 0.68 (95% CI, 0.65 to 0.70) MORES>=6 at lumbar spine: 0.65 (95% CI, 0.63 to 0.68)

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Lynn, 2008[97] Low	MOST	NR	MOST US Lumbar spine (SE): 0.782 (0.019) Total hip: 0.889 (0.016) Femoral neck: 0.808 (0.014) Any site: 0.799 (0.012) Hong Kong Lumbar spine (SE): 0.814 (0.016) Total hip: 0.892 (0.016) Femoral neck: 0.876 (0.018) Any site: 0.831 (0.014)	NR	NR
Zimering, 2007[112] Unclear	MSCORE	NR	MSCORE: 0.84 (0.74-0.95)	MSCORE >9: 88	MSCORE>9: 57
Cadarette, 2001[82] Low	NOF	NR Likely < 2 years	AUROC with respect to DXA outcome of T score=<-2.5 at femoral neck NOF: 0.70 (0.02)	NOF Cutoff Score >=1 risk factor: 96.2 (93.8-98.6)	NOF Cutoff Score >=1 risk factor: 17.8 (16.2-19.4)
D'Amelio, 2005[88] Low	NOF	NR	NOF>=1 : 0.60 (NR)	NR	NR
D'Amelio, 2013[89] Low	NOF	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	NOF>=1: 0.60 (NR)	NR	NR
Mauck, 2005[100] Low	NOF	Concurrent	Unadjusted analysis for NOF Overall: 0.70 (0.63-0.77) Age 45-64: 0.69 (0.51-0.70) Age >=65: 0.60 (0.51-0.70)	NOF>=1 risk factor Overall: 100% (95% CI, 95% to 100%) Age 45-64: 100% (95% CI, 72 to 100%) Age 65+: 100% (95% CI, 94% to 100%)	NOF>=1 risk factor NOF Overall: 10% (95% CI, 5% to 16%) Age 45-64: 19% (95% CI, 11% to 31%) Age 65+: 0% (95% CI, 0% to 6%)
Cadarette, 2001[82] Low	ORAI	NR Likely < 2 years	AUROC with respect to DXA outcome of T score=<-2.5 at femoral neck ORAI: 0.79 (0.01)	ORAI>=9: 97.5 (95.5-99.5)	ORAI>=9: 27.8 (25.9-29.7)
Cadarette, 2004[83] Low	ORAI	Unknown	AUROC with respect to DXA outcome of T score=<-2.5 by lowest value at femoral neck or lumbar spine ORAI: 0.802 (SE 0.02)	ORAI>8: 92.5 (85.6-96.7)	ORAI>8: 38.7 (34.5-42.9)

Appendix F Table 4. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Cass, 2006[84] Low	ORAI	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	ORAI>=9: 0.74 (0.63-0.84)	ORAI>=9: 0.68 (0.49-0.88)	ORAI>=9: 0.66 (0.59-0.73)
Chan, 2006[86] unclear	ORAI	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	AUC for ORAI value >=9: NR ORAI value >=20: 0.76 (0.68-0.84)	ORAI value >=9: 100% (NR)	ORAI value >=9: 9.8% (NR)
Cook et al, 2005[87] unclear	ORAI	None	ORAI: 0.664 (95% CI, 0.739 to 0.595)	ORAI<14: 0.43	ORAI<14: 0.86
D'Amelio, 2005[88] Low	ORAI	NR	ORAI>8: 0.32 (NR)	NR	NR
D'Amelio, 2013[89] Low	ORAI	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	ORAI >8: 0.68 (NR)	NR	NR
Geusens, 2002[90] Unclear	ORAI	NR	NR	ORAI >8: 90%(95% CI, 85% to 95%)	ORAI >8: 52% (95% CI, 49% to 55%)
Gourlay, 2005[79] unclear	ORAI	NR	Reported by age groups: Age 45-64 ORAI 0.75 (95% CI, 0.71 to 0.79) Age 65+ ORAI 0.75 (95% CI, 0.71 to 0.78)	Reported by age groups: Age 45-64 ORAI (Higher Risk >=8) Age 65+ ORAI (Higher Risk >=13) 89.2 (95% CI, 84.6 to 92.8)	Reported by age groups: Age 45-65 ORAI (Higher Risk >=8) 46.2 (95% CI, 44.2 to 48.2) Age 65+ ORAI (Higher Risk >=13) 44.7 (95% CI, 42.0 to 47.5)
Gourlay, 2008[92] Unclear	ORAI	NR	ORAI >=9 for lowest site (FN or LS): 0.70 (95% CI, 0.69 to 0.71)	NR for T score<=-2.5	NR for T score<=-2.5
Harrison et al, 2006[93] Low	ORAI	NR	ORAI: 0.67 (NR)	NR	NR

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Jimenez-Nunez, 2013[94] Low	ORAI	None	ORAI: 0.684 (NR)	ORAI>=9: 78	ORAI>=9: 52
Martinez-Aguila, 2007[99] Unclear	ORAI	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	ORAI>=9 for T-score < –2.5: 0.62 (95% CI 0.56 to 0.67)	ORAI>=9: 64.1 (95% CI 54.7 to 72.7)	ORAI>=9: 58.9 (95% CI 54.7 to 63.1)
Mauck, 2005[100] Low	ORAI	Concurrent	Unadjusted analyses for ORAI Overall: 0.84 (0.78-0.89) Age 45-64: 0.82 (0.71-0.94) Age >=65: 0.79 (0.71-0.87)	ORAI >=9 Overall: 99% (95% CI, 92% to 100%) Age 45-64: 91% (95% CI, 59% to 100%) Age 65+: 100% (95 % CI, 94% to 100%)	ORAI >=9 Overall: 36% (95% CI, 28% to 44%) Age 45-64: 69% (95% CI, 57% to 80%) Age 65+: 0% (95 % CI, 0% to 6%)
Nguyen, 2004[103] Low	ORAI	Concurrent	NR	ORAI >15: 61% (NR)	ORAI >15: 68% (NR)
Richy, 2004[80] Unclear	ORAI	NR	ORAI Total hip: 74.1 (NR) Femoral neck: 70.6 (NR) Lumbar spine: 64.4 (NR) Any site: 67 (NR)	ORAI>=8 Total hip: 90 Femoral neck: 82 Lumbar spine: 76 Any site: 76	ORAI<8 Total hip: 43 Femoral neck: 45 Lumbar spine: 45 Any site: 48
Rud, 2005[109] Low	ORAI	NR	AUROC for ORAI with respect to DXA outcome of T score=<-2.5 for any of three sites: femoral neck, total hip, lumbar spine: 0.64 (0.58–0.70)	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 ORAI 1) cutoff>8: 50 (44–56) (<-2.0) 2) cutoff>2: 81 (76–8	ORAI 1) cutoff>8: 75 (73–77)(<-2.0) 2) cutoff>2: 39 (37–41)(<-2.0) 3) cutoff>2: 37 (35–39)(<-2.5)
Cook et al, 2005[87] unclear	OSIRIS	None	OSIRIS: 0.747 (95% CI, 0.805 to 0.702)	OSIRIS<0: 70	OSIRIS<0: 73
Harrison et al, 2006[93] Low	OSIRIS	NR	OSIRIS: 0.70 (NR)	NR	NR

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Jimenez-Nunez, 2013[94] Low	OSIRIS	None	OSIRIS: 0.711 (NR)	OSIRIS<=-3: 81	OSIRIS<=-3: 54
Martinez-Aguila, 2007[99] Unclear	OSIRIS	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	OSIRIS<=1 for T-score < –2.5: 0.63 (95% CI, 0.57 to 0.69)	OSIRIS<=1: 58.1 (95% CI, 48.6 to 67.2)	OSIRIS<=1: 67.9 (95% CI, 63.8 to 71.8)
Richy, 2004[80] Unclear	OSIRIS	NR	OSIRIS Total hip: 81.7 (NR) Femoral neck: 77.2 (NR) Lumbar spine: 69 (NR) Any site: 73 (NR)	OSIRIS<1 Total hip: 84 Femoral neck: 75 Lumbar spine: 63 Any site: 64	OSIRIS>=1 Total hip: 63 Femoral neck: 66 Lumbar spine: 65 Any site: 69
Adler, 2003[77] Low	OST	1 month	AUROC with respect to DXA outcome of T score=<-2.5 for any of three sites femoral neck, total hip, lumbar spine OST<2 Lumbar spine 0.845 (0.731-0.960) Femoral Neck 0.814 (0.717-0.910) Total Hip 0.866 (0.768-0.963) Any site 0.836 (0.747-0.924)	Cutoff used by study authors (OST<3) 93% Cutoff used for older men (ref 10), (OST<2) 82% Cutoff used for white women (ref 6), (OST<1) 75% All compared to DXA outcome of any T score (LS, FN, TH) < -2.5	Cutoff used by study authors (OST<3) 66% Cutoff used for older men (ref 10), (OST<2) 74% Cutoff used for white women (ref 6), (OST<1) 80% All compared to DXA outcome of any T score (LS, FN, TH) =< -2.5
Cadarette, 2004[83] Low	OST	Unknown	AUROC with respect to DXA outcome of T score=<-2.5 by lowest value at femoral neck or lumbar spine OST: 0.733 (SE 0.02)	OST<2: 95.3 (89.3-98.5)	OST<2: 39.6 (35.4-43.9)
Cook et al, 2005[87] unclear	OST	None	OST: 0.716 (95% CI, 0.775 to 0.669)	OST<=-1: 52	OST<=-1: 82
Crandall, 2014[57] Low	OST	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	OST<2: 0.75 (0.72-0.78)	OST<2: 79.3 (73.2-85.4)	OST<2: 70.1 (68.4-71.8)
D'Amelio, 2005[88] Low	OST	NR	OST<2: 0.33 (CI NR)	NR	NR

Appendix F Table 4. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
D'Amelio, 2013[89] Low	OST	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	OST<2: 0.32 (NR)	NR	NR
Geusens, 2002[90] Unclear	OST	NR	NR	OST <2: 88% (95% CI, 83% to 93%)	OST <2: 52% (95% CI, 49% to 55%)
Gourlay, 2005[79] Unclear/	OST	NR	Reported by age groups: Age 45-64 OST 0.77 (95% CI, 0.73 to 0.81) Age 65+ OST 0.76 (0.73 to 0.79)	Reported by age groups: Age 45-64 OST (Higher Risk <=1) 89.2 (95%CI, 82.8 to 93.8) 88.5 (95% CI, 82.0 to 93.3) Age 65+ OST (Higher Risk <=-1) 84.6 (95%CI, 79.5 to 89.0)	Reported by age groups: Age 45-64 OST (Higher Risk <=1) 45.0 (95%CI, 43.0 to 47.0) Age 65+ OST (Higher Risk <=-1) 47.5 (95%CI, 44.7 to 50.3)
Gourlay, 2008[92] Unclear	OST	NR	OST <=-1 0.76 (95% CI, 0.74 to 0.77) for FN site 0.72 (95 %CI, 0.71 to 0.73) for lowest site (FN or LS)	OST <=-1: 85% (95% CI, 83% to 87%)	OST <=-1: 48% (inferred from 1-Specificity)
Harrison et al, 2006[93] Low	OST	NR	OST: 0.69 (NR)	NR	NR
Jimenez-Nunez, 2013[94] Low	OST	None	OST: 0.71 (NR)	OST<=-1: 83	OST<=-1: 52
Leslie, 2013[113] Low	OST	NR	OST AUROC for T score<=-2.5: 0.72 (0.71-0.73)	NR	NR
Lynn, 2008[97] Low	OST	NR	OST US Lumbar spine (SE): 0.662 (0.022) Total hip: 0.823 (0.020) Femoral neck: 0.740 (0.016) Any site: 0.714 (0.014) Hong Kong Lumbar spine (SE): 0.717 (0.018) Total hip: 0.855 (0.018) Femoral neck: 0.849 (0.019) Any site: 0.759 (0.016)	OST <2 87.6%	OST <2 36.1%

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Machado, 2010[98] Low	OST	NR	OST <2: 0.63 (95% CI, 0.52 to 0.73)	OST <2: 61.8% (NR)	OST < 2: 63.7% (NR)
Martinez-Aguila, 2007[99] Unclear	OST	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	OST <=1 for T-score < –2.5: 0.64 (95% CI 0.59 to 0.69)	OST <2: 69.2 (95% CI 60.0 to 77.4)	OST <2: 58.8 (95% CI 54.5 to 62.9)
McLeod, 2015[101] Low	OST	3 weeks	OST Femoral neck: 0.807 (95% CI, 0.692 to 0.985) Lumbar spine: 0.706 (95% CI, 0.559 to 0.852)	OST cutoff of <2, for diagnosing using femoral neck sites: 87.5 OST cutoff of <2, for diagnosing using lumbar spine sites: 78.6	OST cutoff of <2, for diagnosing using femoral neck sites: 62.7 OST cutoff of <2, for diagnosing using lumbar spine sites: 63.7
Morin, 2009[102] Unclear	OST	NR	OST Using lowest T score from femoral neck 0.77 (95% CI, 0.75 to 0.79) Using T score from any site: 0.71 (95% CI, 0.69 to 0.72)	OST<=1: Using lowest T score from any site: 46.8% (95% CI, 45.7 to 47.9) Using FN T Score: 60.2% (95% CI, 59.2% to 61.3%)	OST<=1: Using lowest T score from any site: 81.1% (95% CI, 80.3% to 82.0%) Using FN T score: 78.8 (95% CI, 77.9% to 79.6%)
Pang, 2014[106] Low	OST	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	Based on lowest BMD at any site OST threshold of 0 (not clear if this means <=0 or <0) 0.76 (0.71-0.82)	Based on lowest BMD at any site (OST Threshold = 0: not clear if this means <=0 or <0) 90.9	Based on lowest BMD at any site (OST Threshold = 0: not clear if this means <=0 or <0) 39.9
Richards, 2014[108] Unclear	OST	NR	OST: 0.67 (NR)	OST≤-6: 82.6% OST <=0: 40.2%	OST>-6: 33.6% OST <=0: 85.4%
Richy, 2004[80] Unclear	OST	NR	OST <2 Total hip: 81.3 (NR) Femoral neck: 76.8 (NR) Lumbar spine: 68.6 (NR) Any site: 72.6 (NR)	OST<2 Total hip: 97 Femoral neck: 92 Lumbar spine: 85 Any site: 86	OST<2 Total hip: 34 Femoral neck: 37 Lumbar spine: 37 Any site: 40

Appendix F Table 4. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Rud, 2005[109] Low	OST	NR	AUROC for OST with respect to DXA outcome of T score=<-2.5 for any of three sites: femoral neck, total hip, lumbar spine: 0.68 (0.63–0.74)	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 OST 1) cutoff <2: 92 (64–100) (<-2.5) 2) cutoff<5: 92 (89–9	OST 1) cutoff <2: 71 (69–73)(<-2.5) 2) cutoff<5: 24 (22–26)(<-2.0) 3) cutoff<5: 23 (21–25)(<-2.5)
Sinnott, 2006[111] Low	OST	NR	OST: 0.89 (0.75–1.03)	OST<4: 89 OST<2: 89%	OST<4: 54 OST<2: 71%
Zimering, 2007[112] Unclear	OST	NR	OST: 0.81 (0.70-0.92)	OST<2 (cutoff established in elderly male population): 75 OST <3 (cutoff established in male veteran popualation): 75	OST<2 (cutoff established in elderly male population): 68 OST<3 (cutoff established in male veteran popualation): 59
Chan, 2006[86] unclear	OSTA	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	OSTA<=-2: 0.82 (0.75-0.90)	OSTA<= -1: 97%	OSTA<= -1: 43.1%
Kung, 2003[95] Low	OSTA	NR	OSTA femoral neck: 0.80 (95% CI 0.78–0.84) femoral neck or lumbar spine: 0.75 (95% CI 0.72–0.79)	OSTA<=-1 Femoral neck: 88% Femoral neck or lumbar spine: 79%	OSTA<=-1 Femoral neck: 54% Femoral neck or lumbar spine: 60%
Kung, 2005[96] Low	OSTA	NR	OSTA femoral neck: 0.85 (95% CI 0.80–0.89) lumbar spine: 0.79 (95% CI 0.74–0.83) femoral neck or lumbar spine: 0.78 (95% CI 0.73–0.82)	OSTA<=-1 Femoral neck: 83% Lumbar spine: 72% Femoral neck or lumbar spine: 71%	OSTA<=-1 Femoral neck: 67% Lumbar spine: 65% Femoral neck or lumbar spine: 68%
Machado, 2010[98] Low	OSTA	NR	OSTA <2: 0.62 (95% CI, 0.51 to 0.72)	OSTA <2: 55.9% (NR)	OSTA <2: 67.9% (NR)
Nguyen, 2004[103] Low	OSTA	Concurrent	NR	OSTA <-1: 41% (NR) FN	OSTA <-1: 24% (NR) FN

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Oh, 2013[104] Low	OSTA	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	OSTA <=-1 for T score<=-2.5 at femoral neck or lumbar spine NR OSTA <=0 for T score<=-2.5 at femoral neck or lumbar spine 0.617 (SE 0.11)	OSTA=<-1 for T score<=-2.5 at femoral neck or lumbar spine 76.1 (71.0-80.8) OSTA= <0 for T score<=-2.5 at femoral neck or lumbar spine 94.2 (91.0-96.5)	OSTA=<-1 for T score<=-2.5 at femoral neck or lumbar spine 67.1 (63.6-70.5)
Oh, 2016[105] Low	OSTA	NR	OSTA<=1: 0.627 (SE 0.016) OSTA<= 0: 0.665 (SE 0.021)	OSTA<=1: 92.3 (95% CI, 84.8 to 96.9) OSTA<=0: 84.6 (95% CI, 75.5 to 91.3)	OSTA<=1: 33.2 (95% CI, 30.3 to 36.2) OSTA<=0: 48.4 (95% CI, 45.3 to 51.5)
Park, 2003[107] Unclear	OSTA	NR	OSTA: 0.873 (NR)	OSTA≤-1: 87%	OSTA>=<-1: 67%
Zimering, 2007[112] Unclear	Reduced MSCORE (age and weight-variable specific scores)	NR	Reduced MSCORE: 0.81 (0.69-0.92)	Reduced MSCORE>9: 85	Reduced MSCORE>9: 58
Ben Sedrine, 2001[78] Low	SCORE	NR	SCORE AUC (SE) with respect to DXA Tscore < -2.5 at each of the following sites: Femoral neck 0.75 (0.010) Total hip 0.78 (0.012) Lumbar spine 0.66 (0.010) Any site 0.71 (0.009) Hip (total or neck) or spine 0.74 (0.012) All sites 0.78 (0.015)	SCORE >=6, T<-2.5 Total hip 98.2 Femoral neck 96.9 Lumbar spine 93.5 Any site 93.9 Hip (total or neck) or spine 98.1 All sites 98.0 study cutoff >=8, T<-2.5 Total hip 93.7 Femoral neck 88.4 Lumbar spine 81.0 Any site 82.4 Hip (total or neck) or spine	SCORE>=6, T<-2.5 Total hip 19.7 Femoral neck 21.4 Lumbar spine 21.7 Any site 23.7 Hip (total or neck) or spine 20.1 All sites 19.0 study cutoff >=8, T<-2.5 Total hip 37.3 Femoral neck 39.5 Lumbar spine 39.3 Any site 42.4 Hip (total or neck) or spine
Brenneman, 2003[81] Low	SCORE	Concurrent	AUROC with respect to DXA outcome of T score=<-2.5 for total hip or lumbar spine SCORE: 0.73 (SE 0.03)	SCORE>=7: 93.7 (88.3, 99.1)	SCORE>=7: 23.8 (9.6, 38.0)

Appendix F Table 4. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 4

First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Cadarette, 2001[82] Low	SCORE	NR Likely < 2 years	AUROC with respect to DXA outcome of T score=<-2.5 at femoral neck SCORE: 0.80 (0.01)	SCORE>=6: 99.6 (98.8-100)	SCORE>=6: 17.9 (16.2-19.5)
Cass, 2006[84] Low	SCORE	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	SCORE>=6: 0.67 (0.54-0.79)	SCORE>=6: 0.54 (0.34-0.75)	SCORE>=6: 0.72 (0.65-0.78)
Chan, 2006[86] unclear	SCORE	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	SCORE: 0.80 (0.72-0.87)	SCORE>=6: 100%	SCORE>=6: 30.4%
Cook et al, 2005[87] Unclear	SCORE	None	SCORE: 0.720, (95% CI, 0.674 to 0.779)	SCORE<12: 0.5	SCORE<12: 0.83
Crandall, 2014[57] Low	SCORE	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	SCORE >7: 0.72 (0.69-0.76)	SCORE >7: 74.1 (67.6-80.7)	SCORE >7: 70.8 (69.1-72.5)
Gourlay, 2005[79] unclear	SCORE	NR	Reported by age groups: Age 45-64 SCORE 0.76 (95% CI, 0.72 to 0.80) Age 65+ SCORE 0.75 (95% CI 0.71 to 0.78)	Reported by age groups: Age 45-65 SCORE (Higher Risk >=7) 88.5 (95% CI, 82.0 to 93.3) Age 65+ SCORE (Higher Risk >=11) 88.8 (95% CI, 84.1 to 92.5)	Reported by age groups: Age 45-66 SCORE (Higher Risk >=7) 39.8 (95% CI, 37.8 to 41.7) Age 65+ SCORE (Higher Risk >=11) 42.3 (95% CI, 39.6 to 45.1)
Gourlay, 2008[92] Unclear	SCORE	NR	SCORE >=6 0.71 (95% CI, 0.70 to 0.72) for lowest site (FN or LS)	NR for T score<=-2.5	NR for T score<=-2.5
Harrison et al, 2006[93] Low	SCORE	NR	SCORE: 0.67 (NR)	NR	NR
Jimenez-Nunez, 2013[94] Low	SCORE	None	SCORE: 0.672 (NR)	SCORE>=6: 68	SCORE>=6: 60

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First Author's Last Name, Year Risk of Bias	Tool	Period of Time between Risk Prediction Measurement and BMD Measurement (Specify Unit of Time)	AUC (95% CI)	Sensitivity	Specificity (95% CI)
Mauck, 2005[100] Low	SCORE	Concurrent	Unadjusted analyses SCORE Overall: 0.87 (0.81-0.92) Age 45-64: 0.85 (0.72-0.99) Age >=65: 0.80 (0.72-0.88)	SCORE>=6 Overall: 100% (95% CI, 95% to 100%) Age 45-64 : 100% (95% CI, 72% to 100%) Age 65+: 100% (95% CI, 94% to 100%)	SCORE>=6 Overall: 25% (95% CI, 18% to 33%) Age 45-64 :41% (95% CI, 29% to 54%) Age 65+: 8% (95% CI, 3% to 17%)
Richy, 2004[80] Unclear	SCORE	NR	SCORE Total hip: 78.5 (NR) Femoral neck: 74.9 (NR) Lumbar spine: 66.6 (NR) Any site: 70.8 (NR)	SCORE >=7 Total hip: 94 Femoral neck: 88 Lumbar spine: 81 Any site: 86	SCORE<7 Total hip: 37 Femoral neck: 40 Lumbar spine: 39 Any site: 40
Rud, 2005[109] Low	SCORE	NR	AUROC for SCORE with respect to DXA outcome of T score=<-2.5 for any of three sites: femoral neck, total hip, lumbar spine: 0.68 (0.63–0.73)	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 SCORE 1) n/a (wrong DXA threshold) 2) cutoff>3: 90 (86–93)	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 SCORE 1) n/a (wrong DXA threshold) 2) cutoff>3: 28 (25–29)(
Brenneman, 2003[81] Low	SOF	Concurrent	AUROC with respect to DXA outcome of T score=<-2.5 for total hip or lumbar spine SOF: 0.54 (SE 0.03)	SOF>= 5: 32.6 (26.6, 38.6)	SOF>= 5: 76.0 (63.5, 88.6)
Cook et al, 2005[87] unclear	SOFSURF	None	SOFSURF: 0.717 (95% CI, 0.777 to 0.670)	SOFSURF<1 0.72	SOFSURF<1 0.67
Geusens, 2002[90] Unclear	SOFSURF	NR	NR	SOFSURF >=-1: 92% (95% CI, 88% to 96%)	SOFSURF >=-1: 37% (95% CI, 34% to 40%)
Nguyen, 2004[103] Low	SOFSURF	Concurrent	NR	SOFSURF >1.7 : 78% (NR)	SOFSURF >10 : 36% (NR)

Abbreviations: AA=African American; ABONE=assessing age, body size, and estrogen use; AMMEB=Age, Years after Menopause, Age at Menarche, Body Mass Index; BMD=bone mineral density; CaMOS=Canadian Multicentre Osteoporosis Study; COPD=chronic obstructive pulmonary disease; DOEScore=Dubbo Osteoporosis Epidemiology Score; DXA=dual energy x-ray absorptiometry; FRAX=Fracture Risk Assessment tool; GP=general practitioner; h/o=history of;

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HRT=hormone replacement therapy; kg=kilogram; KNHANES=Korean National Health and Nutrition Examination Survey; MORE=Multiple Outcomes of Raloxifene Trial; MOST=Male Osteoporosis Screening Tool; MSCORE=male, simple calculated osteoporosis risk estimation; NA=not applicable; NR=not reported; NOF=National Osteoporosis Foundation; OPRA=Osteoporosis Population-based Risk Assessment; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; QUI=ultrasound index; QUS=quantitative ultrasound; RA=rheumatoid arthritis; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; SD=standard deviation; SOF=Study of Osteoporotic Fractures; SOFSURF=Study of Osteoporotic Fractures Simple Useful Risk Factors; TH=total hip; US=United States; USPSTF=United States Preventative Services Task Force; WHI=Women's Health Initiative.

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Cadarette, 2001[82] Low	ABONE	NR	NR	NR	Cutoffs as designated by original developers
Chan, 2006[86] unclear	ABONE	NR	NR	NR	Data also presented for lumbar spine
D'Amelio, 2005[88] Low	AMMEB	NR	NR	NR	None
D'Amelio, 2013[89] Low	AMMEB	NR	NR	NR	None
Nguyen, 2004[103] Low	DOESCore	NR	DOEScore >10: 55% (NR)	LR+ are also reported.	None
Jimenez-Nunez, 2013[94] Low	FRAX: Hip	NR	NR	NR	Does not specify thresholds for specificity and sensitivity
Pang, 2014[106] Low	FRAX: Hip without BMD (>3%)	Based on lowest BMD at any site, FRAX Score >3% 97.1	Based on lowest BMD at any site, FRAX Score >3% 17.1	Also reports based on BMD at each individual site, and lowest of the two hip sites.	None
Jimenez-Nunez, 2013[94] Low	FRAX: MOF	NR	NR	NR	Does not specify thresholds for specificity and sensitivity
Pang, 2014[106] Low	FRAX: MOF FRAX without BMD (>6.5%)	Based on lowest BMD at any site, FRAX Score >6.5% 96.2	Based on lowest BMD at any site, FRAX Score >6.5% 16.8	Also reports based on BMD at each individual site, and lowest of the two hip sites.	None
Leslie, 2013[113] Low	FRAX: MOF without BMD	NR	NR	NR	None
Bansal, 2015[56] Fair	FRAX: MOF without BMD (>=9.3%)	NR	NR	NR	None
Cass, 2016[114] Low	FRAX: MOF without BMD (>=9.3%)	FRAX MOF risk >=9.3%: 0.97 (0.96-0.98)	FRAX MOF risk >=9.3%: 0.14 (0.09-0.20)	NR	None
Crandall, 2014[57] Low	FRAX: MOF without BMD (>=9.3%)	NR	FRAX MOF risk >=9.3%: 13.7 (10.4-17.0)	NR	None

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First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Gnudi, 2005[91] Low	Gnudi et al clinical prediction tool	Cutoffs based on predicted probablity to have low BMD (PPL-BMD) (1) PPL-BMD = 0.090 (2) PPL-BMD = 0.132 (3) PPL-BMD = 0.156 Gnudi et al clinical prediction tool: (1) 90.9% (2) 91.2% (3) 86.1%	Cutoffs based on predicted probablity to have low BMD (PPL-BMD) (1) PPL-BMD = 0.090 (2) PPL-BMD = 0.132 (3) PPL-BMD = 0.156 Gnudi et al clinical prediction tool: (1) 40.9% (2) 43.9% (3) 44.1%	NR	None
Cass, 2013[85] Low	MORES	MORES>=6: 0.99 (0.96-1.00)	MORES>=6: 0.11 (0.06-0.18)	NR	Data reported on includes information for validation study. Article also reports information for development study.
Shepherd, 2007[110]; Cass, 2016[114] Low	MORES	MORES>=6: 0.10 (0.08-0.13)[114]	MORES>=6: 1.00 (0.99-1.00)[114]	Simulation study yielded number needed to screen to prevent 1 additional hip fracture in 10,000 men 50 years of older Universal DXA: 595; universal MORES for referral to DXA: 279	Abstracted data for validation cohort only.
Shepherd, 2010[115] Low	MORES	NR	NR	NR	Outcomes by race/ethnicity also provided
Lynn, 2008[97] Low	MOST	NR	NR	NR	None
Zimering, 2007[112] Unclear	MSCORE	MSCORE>9: 98	MSCORE>9: 16	NR	The study also reports data for a African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort, so it was not pure external validation cohort
Cadarette, 2001[82] Low	NOF	NR	NR	NR	Cutoffs as designated by original developers

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First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
D'Amelio, 2005[88] Low	NOF	NR	NR	NR	None
D'Amelio, 2013[89] Low	NOF	NR	NR	NR	None
Mauck, 2005[100] Low	NOF	NOF>=1 risk factor NOF Overall: 100% (95% CI, 75% to 100%) Age 45-64: 100% (95% CI, 75% to 100%) Age 65+: NA	NOF>=1 risk factor Overall: 37% (95% CI, 30% to 44%) Age 45-64: 17% (95% CI, 9% to 28%) Age 65+: 48% (95% CI, 38% to 57%)	+LR and -LR are also presented	Age-adjusted analysis: AUC NOF 0.65 (0.58-0.71) Sn NOF: 100% (95% CI, 55% to 100%) Sp NOF: 10% (4% to 29%) NPV NOF: 100% (95% CI, 30% to 100%) PPV NOF: 27% (95% CI, 17% to 41%)
Cadarette, 2001[82] Low	ORAI	NR	NR	NR	Cutoffs as designated by original developers
Cadarette, 2004[83] Low	ORAI	NR	NR	NR	Study also looked at weight criterion and OST-chart tool that was developed just for this study (not validated)
Cass, 2006[84] Low	ORAI	ORAI>=9: 0.94 (0.90-0.98)	ORAI >=9: 0.20 (0.11-0.29)	NR	Includes subgroup analysis for non-hispanic White, Hispanic, and African American groups
Chan, 2006[86] unclear	ORAI	NR	NR	NR	Data also presented for lumbar spine
Cook et al, 2005[87] unclear	ORAI	ORAI<14: 0.84	ORAI<14 0.48	NR	None
D'Amelio, 2005[88] Low	ORAI	NR	NR	NR	None
D'Amelio, 2013[89] Low	ORAI	NR	NR	NR	None
Geusens, 2002[90] Unclear	ORAI	NR	NR	NR	The study reported on 4 cohorts in all apart from the US-based clinic sample (1 population-based cohort and 1 clinic-based sample in Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the US). The study did not rep

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Gourlay, 2005[79] unclear	ORAI	NR	NR	LR ratios are also reported, but I didn't pull them because there are like 18 of them; if we decide to synthesize this outcome, we can go back and pull them.	Other results reported in Ben Sedrine et al, 2001[78] and Richy et al, 2004[80] Data in this study reports findings by age group.
Gourlay, 2008[92] Unclear	ORAI	NR	NR	NR	None
Harrison et al, 2006[93] Low	ORAI	NR	NR	NR	None
Jimenez-Nunez, 2013[94] Low	ORAI	NR	NR	NR	None
Martinez-Aguila, 2007[99] Unclear	ORAI	ORAI>=9: 25.0 (95% CI 20.2 to 30.3)	ORAI>=9: 88.5 (95% CI 84.8 to 91.6)	NR	None
Mauck, 2005[100] Low	ORAI	ORAI >=9 Overall: 44% (95% CI, 36% to 53%) Age 45-64: 32% (95% CI, 17% to 51%) Age 65+: 48% (95 % CI, 38% to 57%)	ORAI >=9 Overall: 98% (95% CI, 89% to 100%) Age 45-64: 98% (95% CI, 89% to 100%) Age 65+: NA	+LR and -LR are also presented	Age-adjusted analysis: AUC ORAI 0.79 (0.74-0.83) Sn ORAI: 98% (95% CI, 51% to 100%) Sp ORAI: 40% (30% CI to 56%) NPV ORAI: 77% (95% CI, 46% to 100%) PPV ORAI: 29% (95% CI, 18% to 59%)
Nguyen, 2004[103] Low	ORAI	NR	ORAI >15: 57% (NR)	LR+ are also reported.	None
Richy, 2004[80] Unclear	ORAI	ORAI<8 Total hip: 98 Femoral neck: 92 Lumbar spine: 85 Any site: 80	ORAI>=8 Total hip: 14 Femoral neck: 26 Lumbar spine: 31 Any site: 41	NR	Other results reported in Ben Sedrine et al, 2001[78] and Gourlay et al, 2005[78]

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Rud, 2005[109] Low	ORAI	ORAI 1) cutoff>8: 91 (90–93)(<-2.0) 2) cutoff>2: 17 (15–19)(<-2.0) 3) cutoff>2: 6 (5–7)(<-2.5)	ORAI 1) cutoff>8: 23 (19–26)(<-2.0) 2) cutoff>2: 93 (91–95)(<-2.0) 3) cutoff>2: 98 (96–99)(<-2.5)	When the authors evaluated the performance of these clinical prediction tools as the developers described with cutoffs and using FN DXA of -2.5 as reference, did not perform well in this population of women that was generally younger (by >10 years) and us	None
Cook et al, 2005[87] unclear	OSIRIS	OSIRIS<0: 89	OSIRIS<0: 42	NR	None
Harrison et al, 2006[93] Low	OSIRIS	NR	NR	NR	None
Jimenez-Nunez, 2013[94] Low	OSIRIS	NR	NR	NR	None
Martinez-Aguila, 2007[99] Unclear	OSIRIS	OSIRIS<=1: 88.4 (95% CI, 84.9 to 91.3)	OSIRIS<=1: 27.9 (95% CI 22.3 to 33.9)	NR	None
Richy, 2004[80] Unclear	OSIRIS	OSIRIS>=1 Total hip: 97 Femoral neck: 92 Lumbar spine: 84 Any site: 80	OSIRIS<1 Total hip: 19 Femoral neck: 34 Lumbar spine: 37 Any site: 50	NR	Other results reported in Ben Sedrine et al, 2001[78] and Gourlay et al, 2005[78]

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Adler, 2003[77] Low	OST	Cutoff used by study authors (OST<3) 98% Cutoff used for older men (ref 10), (OST<2) 97% Cutoff used for white women (ref 6), (OST<1) 95% All compared to DXA outcome of any T score (LS, FN, TH)=< -2.5	Cutoff used by study authors (OST<3) 33% Cutoff used for older men (ref 10), (OST<2) 38% Cutoff used for white women (ref 6), (OST<1) 41% All compared to DXA outcome of any T score (LS, FN, TH)=< -2.5	none	Subgroup analyses for race, age deciles, cortocosteroid treatment. AUCs (no CI): White: 0.848 Black: 0.800 50-59: 0.938 60-69: 0.894 70-79: 0.696 >=80: 0.993 Current CS treatment: 0.786 No current CS: 0.803
Cadarette, 2004[83] Low	OST	NR	NR	NR	Study also looked at weight criterion and OST-chart tool that was developed just for this study (not validated)
Cook et al, 2005[87] unclear	OST	OST<=-1: 56	OST<=-1: 44	NR	None
Crandall, 2014[57] Low	OST	NR	OST<2: 14.7 (12.4-16.9)	NR	None
D'Amelio, 2005[88] Low	OST	NR	NR	NR	None
D'Amelio, 2013[89] Low	OST	NR	NR	NR	None
Geusens, 2002[90] Unclear	OST	NR	NR	NR	The study reported on 4 cohorts in all apart from the US-based clinic sample (1 population-based cohort and 1 clinic-based sample in Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the US). The study did not rep
Gourlay, 2005[79] unclear	OST	NR	NR	LR ratios are also reported, but I didn't pull them because there are like 18 of them; if we decide to synthesize this outcome, we can go back and pull them.	Other results reported in Ben Sedrine et al, 2001[78] and Richy et al, 2004[80] Data in this study reports findings by age group.

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Gourlay, 2008[92] Unclear	OST	NR	NR	LR- 0.31 LR+ 1.64	None
Harrison et al, 2006[93] Low	OST	NR	NR	NR	None
Jimenez-Nunez, 2013[94] Low	OST	NR	NR	NR	None
Leslie, 2013[113] Low	OST	NR	NR	NR	None
Lynn, 2008[97] Low	OST	OST <2 97.4%	OST <2 9.7%	NR	None
Machado, 2010[98] Low	OST	OST <2: 89.2%	OST <2: 25.6% (NR)	NR	Calculation for OST: 0.2×(body weight in kilograms−age in years), truncate to yield an integer
Martinez-Aguila, 2007[99] Unclear	OST	OST <2: 89.9 (95% CI 86.3 to 92.9)	OST <2: 26.4 (95% CI 21.5 to 31.7)	NR	None
McLeod, 2015[101] Low	OST	NR	NR	NR	Score of <2 considered to optimal to achieve close to 90% sensitivity
Morin, 2009[102] Unclear	OST	NR	NR	NR	None
Pang, 2014[106] Low	OST	Based on lowest BMD at any site(OST Threshold = 0: not clear if this means <=0 or <0) 96.9	Based on lowest BMD at any site (OST Threshold = 0: not clear if this means <=0 or <0) 17.5	Also reports based on BMD at each individual site, and lowest of the two hip sites.	None
Richards, 2014[108] Unclear	OST	NR	NR	NR	This study also reported sensivity and specificity of FRAX without BMD to predict osteoporosis, but did not report the threshold value, so it is not clear how to interpret it. Also reports results by race and age. Findings suggest that "an OST index of ≤5
Richy, 2004[80] Unclear	OST	OST<2 Total hip: 99 Femoral neck: 95 Lumbar spine: 89 Any site: 86	OST<2 Total hip: 13 Femoral neck: 25 Lumbar spine: 31 Any site: 41	NR	Other results reported in Ben Sedrine et al, 2001[78] and Gourlay et al, 2005[78]

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Rud, 2005[109] Low	OST	OST 1) cutoff <2: 100 (99–100) (<-2.5) 2) cutoff<5: 96 (93–97)(<-2.0) 3) cutoff<5: 99 (97–100)(<-2.5)	OST 1) cutoff <2: 2 (1–3)(<-2.5) 2) cutoff<5: 15 (14–17)(<-2.0) 3) cutoff<5: 6.0 (4–7)(<-2.5)	When the authors evaluated the performance of these clinical prediction tools as the developers described with cutoffs and using FN DXA of -2.5 as reference, did not perform well in this population of women that was generally younger (by >10 years) and us	None
Sinnott, 2006[111] Low	OST	OST<4: 98 OST<2: 99	OST<4: 13 OST<2: 19	NR	Score of 4 considered optimal for African-American men
Zimering, 2007[112] Unclear	OST	OST<2 (cutoff established in elderly male population): 96 OST<3 (cutoff established in male veteran popualation): 95	OST<2 (cutoff established in elderly male population): 22 OST<3 (cutoff established in male veteran popualation): 17	NR	The study also reports data for a African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort, so it was not pure external validation cohort
Chan, 2006[86] unclear	OSTA	NR	NR	NR	Data also presented for lumbar spine
Kung, 2003[95] Low	OSTA	NR	NR	NR	None
Kung, 2005[96] Low	OSTA	NR	NR	NR	None
Machado, 2010[98] Low	OSTA	OSTA < 2: 88.4% (NR)	OSTA < 2: 26.0% (NR)	NR	Calculation for OSTA: 0.2×body weight in kilograms (truncate to yield an integer)−0.2×age in years (truncate to yield an integer)
Nguyen, 2004[103] Low	OSTA	NR	OSTA <-1: 28% (NR) FN	LR+ are also reported.	None

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Oh, 2013[104] Low	OSTA	OSTA=<-1 for T score<=-2.5 at femoral neck or lumbar spine 87.0 (83.9-89.6) OSTA =<0 for T score<=-2.5 at femoral neck or lumbar spine 92.3 (88.1-95.4)	OSTA=<-1 for T score<=-2.5 at femoral neck or lumbar spine 49.4 (44.8-54.0) OSTA =<0 for T score<=-2.5 at femoral neck or lumbar spine 35.9 (32.6-39.3)	OST=<-1 or T score<=-2.5 at femoral neck or lumbar spine Positive Likelihood Ratio 2.32 (2.05, 2.61) Negative Likelihood Ratio 0.36 (0.29, 0.44) OSTA=<0 for T score<=-2.5 at femoral neck or lumbar spine Positive Likelihood Ratio 1.33 (1.26, 1.40) Negative	None
Oh, 2016[105] Low	OSTA	OSTA<=1: 98.0 (95.9 to 99.2) OSTA<=0: 97.2 (95.4 to 98.5)	OSTA<=1: 11.0 (8.9 to 13.4) OSTA<= 0: 12.8 (10.2 to 15.7)	NR	None
Park, 2003[107] Unclear	OSTA	OSTA≤-1: 98%	OSTA>-1=<: 24%	NR	None
Zimering, 2007[112] Unclear	Reduced MSCORE (age and weight-variable specific scores)	Reduced MSCORE>9: 97	Reduced MSCORE>9: 18	NR	The study also reports data for a African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort, so it was not pure external validation cohort

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Ben Sedrine, 2001[78] Low	SCORE	SCORE>=6, T<-2.5 Total hip 99.0 Femoral neck 96.8 Lumbar spine 91.2 Any site 89.1 Hip (total or neck) or spine 98.8 All sites 99.3 study cutoff >=8, T<-2.5 Total hip 98.3 Femoral neck 93.7 Lumbar spine 86.5 Any site 83.4 Hip (total or neck) or spine	SCORE>=6, T<-2.5 Total hip 11.3 Femoral neck 21.9 Lumbar spine 27.7 Any site 37.0 Hip (total or neck) or spine 14.0 All sites 7.3 study cutoff >=8, T<-2.5 Total hip 13.5 Femoral neck 25.0 Lumbar spine 30.0 Any site 40.6 Hip (total or neck) or spine 1	NR	Other results reported in Gourlay et al, 2005[79] and Richy et al, 2004[80] SCORE>6, T<-2.5 Sn- Women >=65 Total hip 100 Femoral neck 99.8 Lumbar spine 98.7 Any site 98.9 Hip (total or neck) or spine 100.0 All sites 100.0 Sp- Women >=65 Total
Brenneman, 2003[81] Low	SCORE	NR	NR	NR	SCORE cutoff recalibrated from >=6 to >=7 to account for the age group of this sample
Cadarette, 2001[82] Low	SCORE	NR	NR	NR	Cutoffs as designated by original developers
Cass, 2006[84] Low	SCORE	SCORE>=6: 0.93 (0.89-0.97)	SCORE>=6: 0.19 (0.09-0.29)	NR	Includes subgroup analysis for non-hispanic White, Hispanic, and African American groups
Chan, 2006[86] unclear	SCORE	NR	NR	NR	Data also presented for lumbar spine
Cook et al, 2005[87] Unclear	SCORE	SCORE<12: 0.85	SCORE<12: 0.46	NR	None
Crandall, 2014[57] Low	SCORE	NR	SCORE >7: 14.1 (11.9-16.4)	NR	None
Gourlay, 2005[79] unclear	SCORE	NR	NR	LR ratios are also reported, but I didn't pull them because there are like 18 of them; if we decide to synthesize this outcome, we can go back and pull them.	Other results reported in Ben Sedrine et al, 2001[78] and Richy et al, 2004[80] Data reports previous findings from other studies by age group.
Gourlay, 2008[92] Unclear	SCORE	NR	NR	NR	None
Harrison et al, 2006[93] Low	SCORE	NR	NR	NR	None

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Jimenez-Nunez, 2013[94] Low	SCORE	NR	NR	NR	None
Mauck, 2005[100] Low	SCORE	SCORE>=6 Overall: 100% (95% CI, 89% to 100%) Age 45-64 :100% (95% CI, 88% to 100%) Age 65+: 100% (95% CI, 48% to 100%)	SCORE>=6 Overall: 41% (95% CI, 34% to 39%) Age 45-64 :22% (95% CI, 11% to 35%) Age 65+: 50% (95% CI, 40% to 59%)	+LR and -LR are also presented	Age-adjusted analysis: AUC SCORE 0.85 (0.80-0.89) Sn SCORE: 100% (95% CI, 55% to 100%) Sp SCORE: 29% (95% CI, 18% to 48%) NPV SCORE: 100% ((5% CI, 51% to 100%) PPV SCORE: 27% (95% CI, 17% to 48%)
Richy, 2004[80] Unclear	SCORE	SCORE<7 Total hip: 98 Femoral neck: 94 Lumbar spine: 87 Any site: 86	SCORE >=7 Total hip: 14 Femoral neck: 25 Lumbar spine: 30 Any site: 41	NR	Other results reported in Ben Sedrine et al, 2001[78] and Gourlay et al, 2005[78]
Rud, 2005[109] Low	SCORE	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 SCORE 1) n/a (wrong DXA threshold) 2) cutoff>3: 95 (92–97)(	1) a priori cut off based on developers cutoffs and DXA outcome of T score FN=< -2.5 2) cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome lowest T score of FN, TH, LS=< -2.5 SCORE 1) n/a (wrong DXA threshold) 2) cutoff>3: 16 (14–18)(	When the authors evaluated the performance of these clinical prediction tools as the developers described with cutoffs and using FN DXA of -2.5 as reference, did not perform well in this population of women that was generally younger (by >10 years) and us	None
Brenneman, 2003[81] Low	SOF	NR	NR	NR	None
Cook et al, 2005[87] unclear	SOFSURF	SOFSURF<1 0.89	SOFSURF<1 0.42	NR	None

Appendix F Table 5. Characteristics and Results of Studies of Risk Prediction Instruments for Identifying Osteoporosis: Part 5

First Author's Last Name, Year Risk of Bias	Name of Tool	NPV	PPV	Other Outcomes	Comments (Subgroup Analysis, Other Notes)
Geusens, 2002[90] Unclear	SOFSURF	NR	NR	NR	The study reported on 4 cohorts in all apart from the US-based clinic sample (1 population-based cohort and 1 clinic-based sample in Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the US). The study did not rep
Nguyen, 2004[103] Low	SOFSURF	NR	SOFSURF >10 : 47% (NR)	LR+ are also reported.	None

Abbreviations: AUC=area under the curve; BMD=bone mineral density; CI=confidence interval; DOEScore=Dubbo Osteoporosis Epidemiology Score; DXA=dual energy x-ray absorptiometry; FN=femoral neck; FRAX=Fracture Risk Assessment tool; LR=likelihood ratio; LS=lumbar spine; MOF=major osteoporotic fracture defined as fractures of the proximal femur, distal radius, proximal humerus, and clinical; NA=not applicable; NOF=National Osteoporosis Foundation; NPV=negative predictive value; NR=not reported; ORAI=Osteoporosis Risk Assessment Instrument; OSIRIS=Osteoporosis Index of Risk; OST=osteoporosis self-assessment tool; OSTA=Osteoporosis Self-assessment Tool for Asians; PPL=predicted probability of low; PPV=positive predictive value; ROC=receiver operating characteristics; SCORE=Simple Calculated Osteoporosis Risk Estimation Tool; Sn=sensitivity; SOFSURF=Study of Osteoporotic Fractures Simple Useful Risk Factors; Sp=specificity; TH=total hip.

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
Boonen et al, 2005[116] Low	Women Baseline mean age: 61 (50-75) Belgium N=221	41/221 (18.5%) had T<-2.5; proportion with baseline fractures NR	Included if community-dwelling postmenopausal women who had been consecutively referred to the Leuven University Center for Metabolic Bone Diseases for bone densitometry. Excluded if receiving therapy for osteoporosis, including hormone therapy, SERMs or bisphosphonates; having peripheral edema (to avoid interference with ultrasound transmission)	DXR standardized protocol and analyzed with the X-Posure System version 2 software, RA performed with a self-contained single energy X-ray system QUS - calcaneal ultrasound attenuation was measured using the Sahara equipment (Hologic)	Areal bone density was measured using the DXA QDR 4500a fan beam system; national reference data were used to derive T-scores at the lumbar spine (vertebrae L2–L4) and the total hip region	QUS -calcaneous against hip or spine T score <-2.5	0.72 (SE: 0.04)
						DXR (non-dominant hand) against hip or spine T score <-2.5	0.84 (SE: 0.03)
						RA BMD of the 2nd, 3rd, and 4th digits of the non-dominant hand against hip or spine T score <-2.5	0.80 (SE: 0.03)
Kung et al, 2003[95] Low	Women Baseline mean age: 62 (43-81) Hong Kong N=767	FN BMD (g/cm^2): 0.61±0.10; 18.7% had a history of fragility fractures	Included if community-based study of southern Chinese women Community-based study of southern Chinese men in Hong Kong ≤6 months postmenopausal. Excluded from analysis if they had a history or evidence of metabolic bone disease (other than postmenopausal bone loss, hyper- or hypo-parathyroidism, Paget's disease, osteomalacia, renal osteodystrophy, or osteogenesis imperfecta), menopause before the age of 40 years, presence of cancer(s) with known metastasis to bone, evidence of significant renal impairment, at least one ovary removed, both hips previously fractured or replaced, and prior use of any bisphosphonates, fluoride, or calcitonin; abnormal biochemistry	QUS, using Sahara ultrasound bone densitometer (Hologic, Waltham, Mass.) to measure the attenuation slope (broadband ultrasound attenuation, BUA) and the SOS of the right heel, and the QUI (an algorithm that combines the information from measurements of BUA and SOS)	DXA (QDR 2000 plus, Hologic) on the lumbar spine (L1–L4) and left femur (femoral neck, trochanter, Ward's triangle and total hip)	QUI based on femoral neck BMD t-score ≤ -2.5	0.78 (0.74-0.81)

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
Kung et al, 2005[96] Low	Men Baseline mean age: 62 (43-81) Hong Kong N=356	FN BMD (g/cm^2): 0.68±0.12; 15.6% had a history of fragility fractures	Included if community-based study of southern Chinese men in Hong Kong age ≥50 from 1999–2003. Excluded from analysis if they had a history or evidence of metabolic bone disease (hyper- or hypo-parathyroidism, Paget's disease, osteomalacia, renal osteodystrophy, or osteogenesis imperfecta), history of cancer in the preceding 5 years, evidence of significant renal impairment, both hips previously fractured or replaced, and prior use of any bisphosphonates, fluoride, or calcitonin; abnormal biochemistry, including renal and liver function test, serum calcium, phosphate, total alkaline phosphatase, and TSH.	Quantitative bone ultrasound (QUS), using Sahara ultrasound bone densitometer (Hologic, Waltham, Mass.) to measure the attenuation slope (broadband ultrasound attenuation, BUA) and the SOS of the right heel, and the QUI (an algorithm that combines the information from measurements of BUA and SOS)	DXA (QDR 2000 plus, Hologic) on the lumbar spine (L1–L4) and left femur (femoral neck, trochanter, Ward's triangle and total hip)	QUI based on femoral neck BMD t-score ≤ -2.5	0.79 (0.75-0.83)

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
Jimenez-Nunez et al, 2013[94]	Women Mean age: 61 (SD: 8) Spain N=505	T-score: –1.01 (SD: 1.05); no nontraumatic fractures	Included Caucasian woman, at least 50, menopausal for at least 12 months, from tertiary care referred for routine bone density screening by DXA (recruited consecutively) at the Rheumatology Department of Carlos Haya University Hospital. Excluded if nursing home residents or homebound or had any of the following: previous diagnosis of osteoporosis or a history of >12 months with any potential antiosteoporotic drug (bisphosphonate, parathormone, estrogen, strontium ranelate, calcitonin, selective estrogen receptor modulator), serious acute or chronic disease, steroid treatment in the last 6 months, or bilateral hip replacements.	PIXI on nondominant heel, using GE Lunar PIXI densitometer (software 50699)	GE Lunar Prodigy Advance DXA densitometer (software ENCORE 2006, PA + 300274; General Electric, Chalfont St. Giles, UK); T scores and Z scores calculated using the manufacturer's reference for the Spanish population	PIXI vs. T-score ≤ -2.5	0.803 (variance NR)
McLeod et al, 2015[101] Low	Women Mean age: 59.0 (50-80) Canada N=174	57.4% had osteoporosis or osteopenia; 22.4 with fracture after age 40	Included if referred by health care provider for DXA screening to the Regina General Hospital, Saskatchewan, Canada, July 2010- September 2011	Left calcaneal QUS	BMD using DXA (GE Lunar Prodigy densitometer (Madison, WI)	QUS SI based on femoral neck DXA T-score ≤ -2.5	0.892 (0.042; 0.809-0.975)
						QUS T-score based on femoral neck DXA T-score ≤ -2.5	0.898 (0.041; 0.817-0.978)
						QUS SI based on lumbar spine DXA T-score ≤ -2.5	0.696 (0.076; 0.517-0.846)

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
McLeod et al, 2015[101] (continued)						QUS T-score based on lumbar spine DXA T-score ≤ -2.5	0.698 (0.077; 0.548-0.848)
Cook et al, 2005[87] unclear	Women Baseline mean age: 59.7 (29-87) United Kingdom N=208	Osteoporotic at LS or hip: 21.6% (n=45) Osteopenic: 47.6% (n=99) Normal BMD: 30.8% (n=64); fractures NR	Included if postmenopausal women 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	QUS using Sunlight Omnisense ultrasound, measured at the distal radium proximal phalanx of the middle finger, and the mid-shaft tibia (all nondominant) QUS using CUBA Clinical ultrasound measured by BUA and VOS at the calcaneus (all nondominant)	BMD as measured by DXA at the lumbar spine or total hip; no population-specific reference used, T scores computed with databases supplied with systems.	Sunlight distal radius based on DXA T-score ≤ -2.5	0.676 (0.731-0.628)
						Sunlight proximal phalanx based on DXA T-score ≤ -2.5	0.678 (0.737-0.629)
						Sunlight Mid-shaft tibia based on DXA T-score ≤ -2.5	0.582 (0.645-0.521)
						Sunlight combined based on DXA T-score ≤ -2.5	0.698 (0.751-0.654)
						BUA calcaneus based on DXA T-score ≤ -2.5	0.766 (0.805-0.743)
						VOS calcaneus based on DXA T-score ≤ -2.5	0.723 (0.781-0.676)

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Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
Harrison et al, 2006[93] Low	Women Mean age: 61 (SD 4) United Kingdom N=207	Mean MBD: hip FN TH LS (L1 L4) Non-osteoporotic patients: 0.463 (SD -0.46) Osteoporotic patients: 0.369 (SD -1.64)	Included if White women ages 55–70 referred for BMD, 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); exclusion NR	Peripheral DXA scanner, PIXI Peripheral QUS scanner: McCue CubaClinical (McCue plc, Winchester, Hampshire, UK) Peripheral QUS Scanner: GE Lunar Achilles (GE Lunar Corporation, Madison, WI)	Central DXA of the hip FN and TH and LS (L1_L4 on the GE Lunar Prodigy (GE Lunar Corporation, Madison, WI) or the Hologic Discovery (Hologic Inc., Bedford, MA); T and Z scores from the 2 DXA scanners merged, then was transformed into Hologic BMD values before calculation of T and Z scores using Hologic reference data for the lumbar spine and NHANES reference data for the proximal femur	Achilles based on T score ≤ -2.5 of total hip, femoral neck or lumbar spine	0.77 (variance NR)
						CubaClinical based on T score ≤ -2.5 of total hip, femoral neck or lumbar spine	0.75 (variance NR)
						PIXI based on T score ≤ -2.5 of total hip, femoral neck or lumbar spine	0.67 (variance NR)
Lynn et al, 2008[97] Low	Men Mean age NR United States and Hong Kong N=6572 (4,658 U.S. Caucasian men and 1914 Hong Kong Chinese men)	NR	The osteoporotic fractures in men study (MrOS): included if community-dwelling older men (age >65 years) in the U.S. Similar for Hong Kong. Excluded if bilateral hip replacements or unable to walk without assistance	Sahara clinical bone sonometer (Hologic Inc.) of the right calcaneus	BMD was measured for the lumbar spine (L1–L4 in anteroposterior projection) and proximal femur using fan beam DXA with Hologic QDR 4500W bone densitometers (Hologic Inc.). T score defined by using ethnic-specific male normative databases for Causasian and Chinese populations	QUI, based on T score ≤ -2.5 at any site (lumbar spine, femoral neck, total hip) for Causasian men	0.738 (SE 0.014)
						QUI, based on T score ≤-2.5 at any site (lumbar spine, femoral neck, total hip) for Chinese men	0.731 (SE 0.018)
						QUI, based on T score ≤-2.0 at any site (lumbar spine, femoral neck, total hip) for Causasian men	0.696 (SE 0.010)

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
						QUI, based on T score ≤-2.0 at any site (lumbar spine, femoral neck, total hip) for Chinese men	0.720 (SE 0.013)
Minnock et al, 2008[117] Unclear	Women Baseline mean age: 59.7 (29-87) United Kingdom N=235	23.8% had BMD T score of <-2.5 at any site; 32.3% had a history of nontraumatic fracture	Included if postmenopausal Caucasian women recruited through DXA clinics at Great Western Hospital, Swindon, UK. Excluded if disease known to cause secondary osteoporosis	QUS using Sunlight Omnisense ultrasound, measured at the distal radium proximal phalanx of the middle finger, and the mid-shaft tibia using SOS QUS using CUBA Clinical ultrasound measured by BUA and VOS at the	BMD as measured by DXA at the lumbar spine; BMD values determined for the lumbar spine, femoral neck, and total hip and the corresponding T-score calculated based on the NHANES database	Sunlight SOS distal radius based on DXA T-score ≤-2.5	0.72 (0.63-0.80)
						Sunlight proximal phalanx SOS based on DXA T-score ≤-2.5	0.68 (0.60-0.77)
						Sunlight mid-shaft tibia SOS based on DXA T-score ≤-2.5	0.59 (0.47-0.71)
						BUA calcaneus based on DXA T-score ≤-2.5	0.79 (0.72-0.85)
						VOS calcaneus based on DXA T-score ≤-2.5	0.75 (0.67-0.83)
Richy et al, 2004[118] Low	Women Mean age: 63.4 (SD: 6.6) Belgium N=202	Mean BMD (g/cm^2): 0.73 (SD: 0.15); prior fractures NR	Included if healthy postmenopausal women age 45 and older. Excluded if history of osteoporosis, Paget disease, RA, use of bone active drugs other than HRT	QUS (DBMSonic 1200, IGEA, Italy), reporting speed of sound of the nondominant hand, and UBPI using graphic traces of the receiving probe; manufacturer's reference values used to calculate T scores.	Femoral neck DXA (Hologic QDR 4500, Hologic Inc., USA)	QUS based on DXA T score ≤ -2.5	0.69 (variance NR)
						QUS based on DXA T score -1 to -2.49	0.64 (variance NR)
						QUS UBPI based on DXA T score ≤ -2.5	0.71 (variance NR)
						QUS UBPI based on DXA T score -1 to -2.49	0.68 (variance NR)

Appendix F Table 6. Characteristics and Results of Imaging Studies Identifying Bone Density Status: Part 1

Study, Year Risk of Bias	Participant Characteristics Sex Age Mean (Range) Country Sample Size	BMD Status of Sample; Baseline Fracture Rate	Inclusion and Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI, or SE)
Sinnott et al, 2006[111] Low	Men Mean age: 63.8 (SD: 14.8) Chicago, United States N=128	FN BMD (g/cm^2): 1.02 (SD: 0.18); 40% had prior traumatic fractures	Included if African American men 35 and older, recruited from general medicine clinics at the Jesse Brown VA Medical Center. 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)	Ultrasound measurement of the calcaneus, of the nondominant heel, was obtained using an Achilles Plus System (Lunar, Madison, Wis.); results include SOS, BUA and a clinical index named the SI which is a linear combination of SOS and BUA	GE lunar machine (General Electric, Madison, WS) at the lumbar spine (L1–L4) and the non-dominant hip (femoral neck, trochanter, total hip); DXA hip scores used in majority of analysis	Heel T-Score against DXA cutoff T-score of <-2.5	0.93 (0.87–0.99

Abbreviations: AUC=area under the curve; BMD=bone mineral density; BUA=broadband attenuation; CI=confidence interval; DXA=dual energy x-ray absorptiometry; DXR=digital x-ray radiogrammetry; FN=femoral neck; GE=General Electric; HRT=hormone replacement therapy; LS=lumbar spine; MrOS=evaluation of osteoporosis screening tools for the osteoporotic fractures in men; N=number; NHANES=National Health and Nutrition Examination; NR=not reported; QUI=ultrasound index; QUS=quantitative ultrasound; RA=radiographic absorptiometry; SD=standard deviation; SE=standard error; SERMS=Selective estrogen receptor modulators; SI=stiffness index; SOS=speed of sound; TH=total hip; UBPI=ultrasonometric bone profile; UK=United Kingdom; USA=United States of America; VA=Veterans' Administration; VOS=velocity of sound.

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Cheung et al, 2012[176a] Hong Kong Osteoporosis Study	Women Baseline Mean: 62.1 (SD 8.5) (40+) Hong Kong (N=2,266)	Postmenopausal community sample. Excluded if already prescribed treatment for osteoporosis	Lumbar BMD Mean: 0.807 (0.148) Fracture rate: 12.8%	Mean: 4.5 (2.8) years	Major osteoporotic fracture (wrist, clinical spine, hip or humerus) Hip fracture	DXA femoral neck DXA femoral neck	0.711 (0.66-0.763) 0.855 (0.791-0.919)	None
Bolland et al, 2011[171a]	Women Baseline mean age: 74.2 (>55) New Zealand (N=1422)	Post-menopause, no major medical conditions, normal lumbar spine BMD for their age (Z-score>–2), not taking treatment for osteoporosis, excluded those with no BMD measurement at baseline	Femoral neck: Mean: -1.3 Osteoporotic Fracture rate: 15%-20% Fracture rate: 4%	Mean: 8.8 years (0.2 to 11.4)	Hip fractures All fractures	DXA femoral neck DXA femoral neck	0.64 (0.57-0.72) 0.59 (0.56-0.62)	None
Friis-Holmberg et al, 2014[174a] Danish Health Examination Survey cohort	Women and Men Baseline age: 40-90 Denmark (N=12,758)	None	Phalangeal BMD: Women: 0.32 (0.04) Men: 0.36 (0.04) Previous fracture: Women: 5.9% Men: 2.5%)	Mean: 4.3 years (0.3-4.9)	Women Major osteoporotic Hip Men Major osteoporotic Hip	DXA BMD phalanges DXA BMD phalanges DXA BMD phalanges DXA BMD phalanges	0.713 (0.686-0.739) 0.834 (0.777-0.890) 0.638 (0.576-0.701) 0.640 (0.511-0.770)	None

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Kalvesten et al, 2016 [133] Study of Osteoporotic Fracture Low	Women Baseline mean age: 71 (65-80+) United States (N = 5278	Caucasian, community dwelling Excluded if no information on parental history of hip fracture.	Femoral neck BMD: 0.647 (0.111); lumbar spine BMD: 0.854 (0.169); DXR-BMD: 0.485 (0.059) Previous fracture since age 50: 34%	10 years	Major osteoporotic Hip	DXA BMD Femoral neck DXR BMD Metacarpal DXA BMD Femoral neck DXR BMD Metacarpal	0.68 (0.66-0.70) 0.65 (0.63-0.67) 0.75 (0.72-0.77) 0.69 (0.66-0.72)	Age
Leslie et al, 2010[148a] Mantiba Bone Density Program	Women and Men Baseline mean age: Women: 65.7; Men 68.2 (50+) Canada Total: N = 39,603 (Women N=36,730; Men N=2,873)	Medical coverage from Manitoba Health and a valid femoral BMD measurement	Minimum t-score ≤ -2.5 Women: 30.9% Men: 19.3% Fracture rate: 14.9%	10 years	Hip Osteoporotic: Hip, clinical vertebral, forearm, or humerus	DXA BMD femoral neck DXA BMD femoral neck	0.801 (0.783-0.819) 0.679 (0.668-0.690)	None
Lundin et al, 2015 [179] Primary Health Care and Osteoporosis Study (PRIMOS) Low	Women Age: (69-81) Sweden N = 388)	Living in the area of Bagarmossen, Sweden; born between 1920-1930, able to come to the health center	NR	Mean: 9.9	Hip	DXL BMD Heel DXA Femoral neck	0.61 0.66	None

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Stewart et al, 2006[162] Aberdeen Prospective Osteoporosis Screening Study Low	Women Total baseline mean age:48.6 (44-56) QUS subgroup Baseline mean: 47.8 (44-51) Scotland, UK Total: (N=3883) QUS subgroup: (N=775)	Post-menopause, may have received any tx for osteoporosis, fracture self-report must be confirmed by x-ray or clinician	Spine BMD Total: Mean: 1.052 (0.161) QUS subgroup: Mean: 1.066 (0.127) Fracture rate: 10.8% of 1239 who provided self-report	Up to10 years	Osteoporotic only: Hip, vertebral, wrist, and humeral	DXA lumbar spine total sample	0.66 (0.64-0.68)	Age, height, weight, menopausal status, neck BMD (QUS only)
						DXA femoral neck total sample	0.64 (0.63-0.66)	
						DXA lumbar spine QUS subgroup	0.66 (0.62-0.69)	
						DXA femoral neck QUS subgroup	0.70 (0.66-0.73)	
						QUS BUA heel	0.72 (0.69-0.75)	
Sund et al, 2014[170a] Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE)	Women Baseline mean age: 59.1 (47-56) Finland (N = 2,755)	Post-menopause, clinical risk factors, excluded women with hip fractures before 1994	Femoral neck T-score mean: -1. Fracture rate: 20%	Up to 10 years	Hip	DXA femoral neck	73.9 (64.4-83.4)	None
Tamaki et al, 2011[177a] Japanese Population-based Osteoporosis (JPOS) Cohort Study	Women Baseline mean age: 56.7 (9.6) (40-74) Japan (N = 815)	Exclude if no femoral neck BMD, taking osteoporosis drugs or hormore replacement therapy	Femoral neck BMD: .706 (0.111) Fracture rate: 8%	10 years	Major osteoporotic fracture (clinical fracture of the hip, vertebra, distal forearm, or proximal humerus	DXA femoral neck	0.64 (0.57-0.72)	None
					Hip fracture	DXA femoral neck	0.82 (0.67-0.98)	
Tanaka et al, 2011[169a]	Women	Postmenopausal outpatients at a medical	Lumbar BMD	10 years; Median	Long bone and vertebral fracture	DXA lumbar spine	0.598(0.551-0.646)	None

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Nagano Cohort Study	Baseline Mean: 63.3 (SD 10.8) Japan (N=765)	institute receiving treatment for osteopororis and secondary osteoporosis	Mean: 1.010 (0.191) Fracture rate: 11.6%	follow-up 5.1 years	Vertebral fracture	DXA lumbar spine	0.613(0.560-0.666)	
Tanaka et al, 2010[154a] Miyama and Taiji cohorts	Women Baseline mean: 59.5 (11.3) Japan (n=400)	Community cohorts	T score: -1.61 (1.84) Fracture rate: 25%	10 years	Osteoporotic fracture	DXA femoral neck	0.651 (0.575-0.728)	None
Tebé Cordomi et al[175a] Central Initiative System - transport information reporting system (CETIR cohort)	Women Baseline mean age:56.8 (40-90) Spain (N=1231)	Had received a bone density scan, in the age group of interest	T-score mean: -1.4 (1.1) Fracture rate: 15%	Mean: 10.95 years	Major osteoporotic only: forearm, clinical spine, hip, or proximal humerus	Normal BMD DXA femoral neck	0.54 (0.45-0.62)	BMD status
						Osteopenia DXA femoral neck	0.57 (0.52-0.63)	
						Osteoposis DXA femoral neck	0.63 (0.54-0.72)	
Tremollieres et al, 2010[173a] Menopause et Os (MENOS) Study	Women Baseline age: >45 France (N=556)	Post-menopausal. Excluded: past/current treatment for osteoporosis for >3 months, HRT use at baseline	Vertebral BMD Prevalent fracture group: 0.96 (0.126) Nonfracture group: 1.03 (0.148) Fracture rate: 6.6% of 2196	Mean: 13.4 years	Minimal or no trauma only: spine, vertebral, hip, distal forearm, and humeral	Hip BMD	0.66 (0.60-0.73)	None
Sornay-Rendu et al, 2010[172a] Os des Femmes de Lyon (OFELY) cohort	Women Baseline Mean Age: 58.8 (SD 10.3) France (N=867; of these, post-menopausal [N=680])	Post and premenopausal, age 40 years and over	Femoral Neck BMD: Mean: 0.717 (0.12) Fracture rate: 10.3%	10 years	Low trauma nonvertebral and clinical vertebral fracture	DXA femoral neck	0.74 (0.71-0.77)	None

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Iki et al, 2014[164] Japanese Population-Based Osteoporosis (JPOS) Baseline Study Low	Women Follow up mean age: 64.1 Baseline: (53-61) Japan (N=665)	Excluded: history or present condition affecting bone metabolism including glucocorticoid admin, amenorrhea, oligomenorrhea, bilateral oophorectomy, parathyroid gland disease, hyperthyroidism, rheumatoid arthritis, gastrectomy resulting from gastric cancer, myasthenia gravis, or ossification of the posterior longitudinal ligament	Spine BMD: Mean: 0.802 (0.142) History of fragility fracture: 16.5%	Median: 10 years Mean: 8.3 years	Vertebral fracture diagnosed morphometrically when vertebra reduction in any of its anterior, central, and posterior heights by ≥ 20% in follow-up image vs baseline height; and satisfied McCloskey–Kanis criteria or grade 2 or 3 fracture criteria in Genant's method on follow-up image.	DXA aBMD thoracolumbar vertebra	0.673 (0.614-0.732)	NA
						DXA TBS thoracolumbar vertebra	0.682 (0.621-0.743)	
						DXA aBMD & TBS thoracolumbar vertebra	0.700 (0.614-0.732)	
						DXA aBMD & TBS thoracolumbar vertebra	0.718 (0.662-0.773)	Age
						DXA aBMD & TBS thoracolumbar vertebra	0.729 (0.675-0.773)	Age, prevalent vertebral deformity
Hans, 2011[165] Leslie et al, 2013[166] The Manitoba Study Low	Women Baseline mean age: 65.4 years (≥50 years) Canada (N=29,407)	Medical coverage	Lumbar spine TBS: Mean: 1.241 (0.12) Prior major fracture: 13.6%	4.7 years (SD 2.2)	Clinical spine	DXA BMD total hip	0.71 (0.68-0.73)	None
						DXA BMD femoral neck	0.71 (0.68-0.73)	
						DXA BMD spine	0.69 (0.67-0.72)	
						TBS spine	0.66 (0.64-0.69)	
						DXA BMD total hip+TBS spine	0.73 (0.71-0.75)	
						DXA BMD femoral neck+ TBS spine	0.73 (0.71-0.75)	
						DXA BMD spine+TBS spine	0.71 (0.69-0.74)	

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Hans, 2011[165] Leslie et al, 2013[166] (continued					Hip fracture	DXA BMD total hip	0.81 (0.79-0.83)	
						DXA BMD femoral neck	0.80 (0.77-0.82)	
						DXA BMD spine	0.65 (0.62-0.69)	
						TBS spine	0.68 (0.65-0.71)	
						DXA BMD total hip+TBS spine	0.82 (0.79-0.84)	
						DXA BMD femoral neck+TBS spine	0.81 (0.79-0.83)	
						DXA BMD spine+TBS	0.69 (0.66-0.72)	
					Any major osteoporotic fractures (hip, clinical spine, forearm, humerus)	DXA BMD total hip	0.68 (0.66-0.69)	
						DXA BMD femoral neck	0.68 (0.66-0.69)	
						DXA BMD spine	0.64 (0.63-0.66)	
						TBS spine	0.63 (0.61-0.64)	
						DXA BMD total hip+TBS spine	0.69 (0.68-0.71)	
						DXA BMD femoral neck+ TBS spine	0.69 (0.68-0.71)	
						DXA BMD spine+TBS	0.66 (0.65-0.68)	
						DXA BMD spine	0.64 (0.63–0.65)	

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Kwok, 2012[167] Osteoporotic Fractures in Men (MrOS) Study Low	Men Baseline mean age: 72.4 years Hong Kong (n=1921)	Community dwelling, able to walk without assistance, no bilateral hip replacement	Spine BMD: Mean: 0.95 (0.18) Fracture history: 13.9%	Mean 6.5 years	Major fragility fracture including hip, wrist, forearm, or shoulder	QUS SOS heel	0.64 (0.57-0.71)	Age and fracture history
						QUS BUA heel	0.65 (0.58-0.72)	
						QUS QUI heel	0.66 (0.59,0.73)	
						DXA BMD spine	0.71(0.65-0.77)	
						DXA BMD total hip	0.72 0.65-0.78)	
						DXA BMD Femoral neck	0.72 (0.66-0.79)	
Bauer, 2007[163] Osteoporotic Fractures in Men (MrOS) Low	Men Baseline mean age Any non-spine fracture: 76.6 No non-spine fracture: 73.5 Hip fracture: 80.7 No hip fracture: 73.6 United States (N=5,606)	Community dwelling, able to walk without assistance, no bilateral hip replacement, able to provide self-reported data, residence near a clinical site for the duration of the study, absence of a medical condition that could result in imminent death, ability to understand and sign consent.	BMDfn Any non-spine fracture: Mean: 0.72 (0.13) No non-spine fracture: Mean: 0.79 (0.13) Prior non-spine fracture: 4.3% Hip fracture: 0.9%	Mean 4.2 years (SD 1.0)	Non-spine	QUS BUA heel	0.68 (95% CI, NR)	None
					Non-spine	DXA BMD femoral neck	0.68 (95% CI, NR)	
					Non-spine	QUS BUA heel + BMD femoral neck	0.69 (95% CI, NR)	
					Hip	QUS BUA heel	0.84 (95% CI, NR)	
					Hip	DXA BMD femoral neck	0.85 (95% CI, NR)	
					Hip	QUS BUA heel + BMD femoral neck	0.85 (95% CI, NR)	

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Chan et al, 2012[168] Dubbo Osteoporosis Epidemiology Study (DOES) Unclear for AUC, High For NRI	Men and Women Follow up age range (62-89 years old) Australia Men (N=445)	Exclude: malignant disease, Paget disease of bone	FNBMD Nonfracture group: 0.92 (0.14) Any fracture at baseline: 0.86 (0.17) Baseline fracture: 25.8%	Median 13 years, range 11–15	Women Any fracture, excluding from major trauma	DXA BMD femoral neck	0.71 (95% CI, 0.66 to 0.76)	Age, falls, and prior fracture
						QUS BUA heel + DXA BMD femoral neck	0.73 (95% CI, 0.68 to 0.78)	
					Hip Fracture	DXA BMD femoral neck	0.77 (95% CI, 0.69 to 0.86)	
						QUS BUA heel + DXA BMD femoral neck	0.81 (95% CI, 0.73 to 0.88)	
					Vertebral fracture	DXA BMD femoral neck	0.70 (95% CI, 0.62 to 0.77)	
						QUS BUA heel + DXA BMD femoral neck	0.72 (95% CI, 0.65 to 0.79)	
					Men Any fracture, excluding from major trauma	DXA BMD femoral neck	0.71 (95% CI, 0.64 to 0.78)	
						QUS BUA heel + DXA BMD femoral neck	0.71 (95% CI, 0.64 to 0.77)	
					Hip Fracture	DXA BMD femoral neck	0.77 (95% CI, 0.67 to 0.87)	
						QUS BUA heel + DXA BMD femoral neck	0.78 (95% CI, 0.67 to 0.88)	
					Vertebral fracture	DXA BMD femoral neck	0.75 (95% CI, 0.66 to 0.83)	
						QUS BUA heel + DXA BMD femoral neck	0.75 (95% CI, 0.66 to 0.84)	

Appendix F Table 7. Characteristics and Results of Imaging Studies Predicting Fractures: Part 1

Study, Year Cohort Risk of Bias	Participant Characteristics Gender Age Mean (Range) Country Number	Additional Inclusion and Exclusion Criteria	Baseline BMD Fracture Rate	Incident Fracture Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI, or SE)	Characteristics Controlled for in the Model
Fraser et al, 2010[147a]	Men and women Baseline mean age: Women: 65.8 (8.8) Men: 65.3 (9.1) Canada N=6,697	Lived near one of nice Canadian cities, spoke English, French, or chinese	Femoral neck T-score: Women: -1.5 (1.1) Men: -0.5 (1.2) Fracture rate: 9.4%	10 years	Major osteoporotic (hip, clinical spine, humerus, forearm/wrist) Hip fracture	DXA femoral neck DXA femoral neck	0.66 (0.64-0.69) 0.76 (0.72-0.79)	None
Nguyen et al, 2004[144] Dubbo Osteoporosis Epidemiology Study (DOES) unclear	Women Mean age: 63.2 (49-88) Australia N=549	None	NR	NR	Any fracture, excluding from major trauma	DXA BMD lumbar spine	0.77	None
						DXA BMD femoral neck	0.76	
						QUS SOS distal radius	0.71	
						QUS SOS tibia	0.66	
						QUS SOS phalanx	0.67	

[a] Included in Marques et al (2015) meta-analysis report, risk of bias assessment results not reported.

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; DXL=dual x-ray and laser; DXR=digital x-ray radiogrammetry; NRI=net reclassification improvement; QUI=quantitative ultrasound index (combines BUA and SOS); QUS=quantitative ultrasound measured at the calcaneus in all studies; RR=risk ratio; SI=stillness index; SOS=speed of sound; SXA=single x-ray absorptiometry; TBS=trabecular bone score; UBPI=ultrasound bone profile index.

Appendix F Table 8. Characteristics and Results of Risk Prediction Instruments Predicting Fractures

Study, Year Risk of Bias	Participant Characteristics, Sample Size	Baseline BMD and Fracture Rate	Risk Prediction Instruments Evaluated (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Leslie et al, 2012[123] Unclear	Men and women age 50 and older from Manitoba, Canada N=36,730 (92.7%) women N=2,873(7.3%) men Mean age: 65.7 (SD 9.8) women 68.2 (SD 10.1) men	BMD NR History of fracture NR	FRAX (10 year prediction), with and without BMD	Hip and MOF based on hospital discharge abstracts and physician billing claims Number of fractures: 2,543	Mean 5.4 years	*AUC (95% CI) for Fracture Prediction* Women (MOF) Femoral neck BMD alone: 0.682 (0.670-0.693) Without BMD: 0.666 (0.655-0.678) With BMD: 0.698 (0.687-0.708) Men (MOF) Femoral neck BMD alone: 0.645 (0.601-0.689) Without BMD: 0.609 (0.564-0.654 With BMD: 0.661 (0.619-0.703) Women (Hip) Femoral neck BMD alone: 0.802 (0.783-0.820) Without BMD: 0.789 (0.772-0.807) With BMD: 0.822 (0.805-0.838) Men (Hip) Femoral neck BMD alone: 0.798 (0.726-0.870) Without BMD: 0.733 (0.659-0.807) With BMD: 0.789 (0.722-0.855)
Iki et al, 2015 [132] Unclear	Men 65 or older from Japan N=2012 eligible and 1805 for analysis Mean age: 73.0 (SD 5.1)	BMD: 0.741 g/cm^2 (0.114) History of fracture: 22	FRAX, version 3.8 for Japan and TBS	MOF (femoral next, spine, distal forearm, proximal humerus) from low-energy trauma	4.5 years	*AUC* FRAX 10 years (w/BMD) Men MOF : 0.681 (0.586 to 0.776) TBS Men MOF after 4.5 years: 0.669 (0.548 to 0.79)
Van Geel, 2014[124] Unclear	Post-menopausal women ages 50-80 years from 12 practices in southeastern Netherlands N=506 Mean age: 68	Mean(SD) femoral neck BMD T-score Fracture group: −1.7(1.0) Non-fracture group: −1.2(1.0) History of fracture NR	FRAX (10 year prediction), Garvan FRC (5,10 years)	All (included: clinical spine, humerus, forearm, hip, "other"), MOF (all above except other), Hip fractures Self-report with medical record confirmation. Number of fractures: All: 48 MOF: 33	5 years	*AUC for Fracture Prediction* FRAX OF fracture risk without BMD: 0.653 FRAX OF fracture risk with BMD: 0.693 FRAX hip fracture risk with BMD: 0.698 Garvan OF fracture risk without BMD: 0.646 Garvan OF fracture risk with BMD: 0.689 Garvan hip fracture risk with BMD: 0.695

Appendix F Table 8. Characteristics and Results of Risk Prediction Instruments Predicting Fractures

Study, Year Risk of Bias	Participant Characteristics, Sample Size	Baseline BMD and Fracture Rate	Risk Prediction Instruments Evaluated (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Rubin, 2013[128] Unclear	Women ages 40 to 90 living in southern Denmark diagnosed and treated for osteoporosis. N=3614 Mean age: 64 (SD 13)	BMD NR History of OF: 337 (9%) Secondary osteoporosis: 655 (18%)	FRAX 3.0 without BMD(10 year prediction), OST, ORAI, OSIRIS, SCORE, Age alone with follow up BMD testing for fx risk >= 9.3%)- 10 yr horizon	FRAX defined MOF, Any OF from registry. Number of fractures: OF: 225 MOF: 156	3 years	*AUC (95% CI) for Fracture Prediction* *MOF:* FRAX (no BMD): 0.722 (0.686, 0.758) Age alone: 0.720 (0.685, 0.755) OSIRIS: 0.713 (0.677, 0.749) OST: 0.712 (0.675, 0.750) ORAI 0.704 (0.663, 0.745) SCORE 0.703 (0.664, 0.742) *Any OF:* FRAX (no BMD): 0.701 (0.668, 0.735) Age alone: 0.694 (0.660, 0.727) OSIRIS: 0.690 (0.658, 0.723) OST: 0.691 (0.657, 0.725) ORAI: 0.682 (0.646, 0.717) SCORE: 0.681 (0.646, 0.716)
Azagra, 2011[181] & 2012[125] Unclear	Random sample of participations ages 40 to 90 years from the FRIDEX Cohort, comprised of women in Spain referred by general practitioners and specialists for bone density screening. N=770 Mean age: 56.8 (SD8.0)	BMD NR History of fracture: X (22.8%) Use of medication for osteoporosis: X (27.9%)	FRAX version 3.2 (10 year prediction) calibrated for Spain	Incident fragility fractures of hip or MOF, major trauma associated fractures were excluded Self-report confirmed by medical records. Number of fractures: 65	10 years	*AUC (95% CI) for Fracture Prediction* without BMD, Hip: 0.88 (0.82 to 0.95) without BMD, MOF: 0.69 (0.62 to 0.76) with FN BMD, Hip: 0.85 (0.74 to 0.96) with FN BMD, MOF: 0.72 (0.65 to 0.79) with LS BMD, Hip: 0.77 (0.66 to 0.88) with LS BMD, MOF: 0.71 (0.64 to 0.78) BMD FN only, Hip: 0.78 (0.63 to 0.93) BMD FN only, MOF: 0.66 (0.58 to 0.74) BMD LS only, Hip: 0.63 (CI, 0.49 to 0.77) (p=0.067) BMD LS only, MOF: 0.64 (CI, 0.57 to 0.71) without BMD, vertebral: 0.75 (CI, 0.64 to 0.86) with FN BMD, vertebral: 0.82 (CI, 0.73 to 0.91) with LS BMD, vertebral: 0.71 (CI, 0.58 to 0.84) Age alone, hip: 0.89 (no CI, provided, but comparison with FRAX tool reported as p=0.976) Age alone, MOF: 0.67 (no CI, provided, but comparison with FRAX tool reported as p=0.565

Appendix F Table 8. Characteristics and Results of Risk Prediction Instruments Predicting Fractures

Study, Year Risk of Bias	Participant Characteristics, Sample Size	Baseline BMD and Fracture Rate	Risk Prediction Instruments Evaluated (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Leslie, 2012[127] Unclear	Women and men age 50 years and older from Manitoba, Canada N=20,477 Mean age: 65(SD 9) 94.1% women	BMD NR, history of fracture NR	FRAX (10 year prediction)	MOF not associated with major trauma based on hospital discharge abstracts and physician billing claims Number of fractures: 1,845	Mean 8 years	*AUC (95% CI) for Fracture Prediction* With FN BMD: 0.695 (0.683–0.708) Without BMD: 0.668 (0.655–0.681) With LS BMD: 0.685 (0.673–0.698) With minimum BMD: 0.694 (0.681–0.706) With weighted mean BMD: 0.697 (0.685–0.710) With BMD offset: 0.698 (0.685–0.710) *Percent appropriate reclassification:* With FN BMD: reference Without BMD: 44.5% With LS BMD: 41.1% With minimum BMD: 10.5% With weighted mean BMD: 50.6% With BMD offset: 52.4%
Ahmed, 2014[129] Unclear AUCs, High for NRIs	Men and women age 60 years and older from the Norwegian Tromso Cohort N = 2992 55% women	Femoral Neck BMD T-Score Mean: -1.46 (SD 1.19) (Non fracture group) -1.89 (SD 1.10) (Fracture group) History of fracture NR	Garvan Fracture Risk Calculator (FRC) with and without BMD (5 and 10 year prediction)	All fractures except finger, toe, or skull, or vertebral recorded in the fracture registry. Hip fractures were verified through hospital discharge records.	Median 6.9 years	*AUC for Fracture Prediction* 5 yr risk with BMD, nonvertebral fracture (women): 0.61 5 yr risk without BMD, nonvertebral fracture (women): 0.57 5 yr risk with BMD, hip fracture (women): 0.78 5 yr risk without BMD, hip fracture (women): 0.70 5 yr risk with BMD, nonvertebral fracture (men): 0.67 5 yr risk without BMD, nonvertebral fracture (men): 0.56 5 yr risk with BMD, hip fracture (men): 0.79 5 yr risk without BMD, hip fracture (men): 0.69 10 yr risk with BMD, nonvertebral fracture (women): 0.62 10 yr risk without BMD, nonvertebral fracture (women): 0.58 10 yr risk with BMD, hip fracture (women): 0.73 10 yr risk without BMD, hip fracture (women): 0.68 10 yr risk with BMD, nonvertebral fracture: (men) 0.61 10 yr risk without BMD, nonvertebral fracture: (men) 0.57 10 yr risk with BMD, hip fracture (men): 0.74 10 yr risk without, hip fracture (men): 0.65

Appendix F Table 8. Characteristics and Results of Risk Prediction Instruments Predicting Fractures

Study, Year Risk of Bias	Participant Characteristics, Sample Size	Baseline BMD and Fracture Rate	Risk Prediction Instruments Evaluated (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Hippisley-Cox, 2012[130] Unclear	Patients ages 30 to 100 years from a database of 13 million patients in 620 practices nationally representative practices in the United Kingdom using the Egton Medical Information System. N=1,583,373 Mean age: 50 50.8% women	BMD NR, History of fracture: 1.8%	QFracture (10 yr prediction)	OF defined as a hip, vertebral, proximal humerus, or distal radius fracture during follow-up Number of OF: 28,685 Number of hip fractures: 9,610 Fractures were recorded either on the general practice record or the linked death record.	Up to 15 years	*AUC (95% CI) for Fracture Prediction* Women OF: 0.790 (0.787 to 0.793) Women Hip Fracture: 0.893 (0.890 to 0.896) Men OF: 0.711 (0.703 to 0.719) Men Hip Fracture: 0.875 (0.868 to 0.883)
Leslie, 2010[131] Unclear	Men and women age 50 and older from Manitoba, Canada N=36,730 (92.7%) women N=2,873(7.3%) men Mean age: 65.7 (SD 9.8) women 68.2 (SD 10.1) men	14.3% of women have a BMD T score of <=-2.5 based on the female reference; 18.9% of men have a lBMD T-score based on the male reference	CAROC, 10-year prediction	MOF not associated with major trauma based on hospital discharge abstracts and physician billing claims Number of fractures: 2,543	Women, mean 5.4 years, men, mean 4.4 years	*Risk categorization, N fracture/N in category* *Women* With BMD FN Low (<10% 10yr risk): 341/12,878 Moderate (10-20% 10 yr risk): 748/13,813 High (>20% 10 yr risk): 1291/10,039 p<0.001 With minimum site BMD Low (<10% 10 yr risk): 231/9866 Moderate (10-20% 10 yr risk): 599/12,960 High (>20% 10 yr risk): 1550/13,904 p <0.001 *Men* With BMD FN Low (<10% 10 yr risk): 42/1255 Moderate (10-20% 10 yr risk): 71/1187 High (>20% 10 yr risk): 50/431 p <0.001 With minimum site BMD Low (<10% 10 yr risk): 33/1120 Moderate (10-20% 10 yr risk): 70/1199 High (>20% 10 yr risk): 60/554 p <0.001

Appendix F Table 8. Characteristics and Results of Risk Prediction Instruments Predicting Fractures

Study, Year Risk of Bias	Participant Characteristics, Sample Size	Baseline BMD and Fracture Rate	Risk Prediction Instruments Evaluated (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Morin, 2009[102] Unclear	Women age 40–59 years who had baseline BMD testing in Manitoba, Canada N=8,254 Mean age: 52.7	BMD T-Score at any site <=-2.5: 14.9%; history of fracture: 7.1%	Weight, BMI, OST (no prediction time interval specified)	Incident fractures not associated with trauma ascertained by administrative diagnosis codes from longitudinal health record and Number of fractures: 225	Mean 3.3 years	*AUC (95% CI) for Fracture Prediction* Weight: 0.55 (95% CI, 0.51–0.59) BMI: 0.55 (95% CI, 0.51–0.59) OST: 0.56 (95% CI, 0.52–0.60)
Crandall, 2014[58] Unclear	Women ages 50 to 64 years participating in the US Women's Health Initiative Clinical Trials and Observational Studies. Mean Age 57.9(SD 4.1) N=62,492	BMD NR, history of fracture NR	USPSTF Strategy (FRAX 3.0 without BMD with follow up BMD testing for fx risk >= 9.3%); SCORE OST	MOF (clinical vertebral, hip, lower arm/wrist, and upper arm fractures) Hip fractures were centrally adjudicated, other fractures were self-report.	10 years	*AUC (95% CI), Sensitivity (95% CI), Specificity (95% CI) for Fracture Prediction* FRAX without BMD (risk >=9.3%): 0.56 (0.55 to 0.57), 25.8 (24.6 to 27.0), 83.3 (83.0 to 83.6) SCORE: (>7): 0.53 (0.53 to 0.54), 38.6 (37.3 to 39.9), 65.8 (65.4 to 66.2) OST (< 2): 0.52 (0.52 to 0.53), 39.8 (38.5 to 41.1), 60.7 (60.3 to 61.1)

Abbreviations: AUC=area under the curve; BMD=bone mineral density; CI=confidence interval; FN=femoral neck; FRAX=fracture risk assessment tool; FRISK=absolute measure of fracture risk; LS=lumbar spine; MOF=major osteoporotic fracture; NR=not reported; OF=osteoporotic fracture; OST=osteoporosis self-assessment tool; SCORE=simple calculated osteoporosis risk estimate; SD=standard deviation; USPSTF=United States Preventive Services Task Force.

Appendix F Table 9. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Incident Vertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Nonvertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Hip Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Incident Fractures Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Liberman et al, 1995[199]	Women >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	NR	Fair
Cummings et al, 1998[200]	Women least 2 years postmenopausal age 55–80 years; mean age: 67.7 years mean T-score: −2.2 previous fractures: excluded	Alendronate 5 mg/dayfor 2 years, then 10 mg/day for 1 year	43/2214; 78/2218; RR 0.56 (CI, 0.39–0.80; p=0.002)	261/2214; 294/2218; RR 0.88 (CI, 0.74 to 1.04; p=0.13)	19/2214; 24/2218 RR 0.79 (0.43-1.44)	Wrist fractures 83/2214; 70/2218 RR 1.19 (0.87-1.62)	Good
Pols et al, 1999[201]	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)	Wrist fracture: 6/950; 15/958 RR 0.47 (0.19-1.15)	Fair
Hosking et al2003[202]	Postmenopausal women 60-90 years with osteoporosis defined by lumbar spine or total hip BMD T score < -2.5 or both <-2.0; mean age 69 history of fracture 48.5%	Alendronate 70 mg weekly; 12 months	NR	NR	NR	Clinically diagnosed vertebral or nonvertebral 6/172; 2/89 RR 1.55 (0.31 – 7.53)	Fair
Chesnut et al, 1995[203]	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	NR	Fair
Ascott-Evans et al, 2003[204]	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	NR	Fair
Quandt et al, 2005[205]	Women least 2 years postmenopausal age 55–80 years; mean age: 67.7 years femoral neck T-score: −1.6 to -2.5	Alendronate 5 mg/day for 2 years, then 10 mg/day for 1 year	48/1775; 81/1757 RR 0.59 (0.41-0.83)	NR	NR	Clinical vertebral fracture 12/1878; 29/1859 RR 0.41 (0.21-0.80)	Good

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

Appendix F Table 10. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Zoledronic Acid

Study Reference	Participant Characteristics	Intervention; Duration	Incident Vertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Nonvertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Hip Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Incident Fractures Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Reid et al, 2002[217]	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; 12 months	0/174; 0/56 RR not estimable	4/174; 1/59 1.36 (0.15-11.89)	NR	NR	Fair
Boonen, 2012[218]	Men 50 to 85 years of age; median age 66; mean femoral neck T score -2.23 to -2.24; mean total hip T score -1.70 to -1.72. 31.3% vertebral fracture at baseline.	Intravenous infusion of 5mg of Zoledronic acid at baseline and 12 months; 24 months	9/588; 28/611 RR 0.33 (0.16 – 0.70)	5/588; 8/611; RR 0.65 (0.21 to 1.97)	NR	Clinical fractures (vertebral and nonvertebral) 6/588; 11/611; RR 0.57 (0.21-1.52)	Good

Abbreviations: CI=confidence interval; RR=relative risk.

Appendix F Table 11. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Risedronate

Study Reference	Participant Characteristics	Intervention; Duration	Incident Fracture Vertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Fracture Nonvertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Hip Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Incident Fractures Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
McClung et al, 2001[223]	Women 70 years and older;, mean femoral neck T-score -3.7	Risedronate 5 mg/day; 2 years treatment (mean follow-up 2.3 years)	NR	NR	137/6197; 95/3134 [0.73 (0.56 to 0.94)] Subgroup aged 70-79 without prevalent vertebral fracture[b] 14/1773; 12/875 [0.58 (0.27 to 1.24)]	NR	Fair
Mortensen et al, 1998[224]	Women 6-60 months postmenopausal; mean age 51.5 years; mean T-score -1.1; no prior osteoporotic fracture	Risedronate 5 mg/day; 2 years treatment (follow-up 3 years)	1/37; 0/36 [2.92 (CI, 0.12-69.43)] [a]	0/37; 3/36 [0.14 (0.01-2.60)][a]	0/37; 0/36 RR not estimable[a]	NR	Fair
Valimaki et al, 2007[225]	Women ≥5 years postmenopausal; osteoporosis risk factors or low hip BMD; mean age 65.9 years; mean femoral neck T-score -1.2; unknown prior fracture	Risedronate 5 mg/day; 2 years	0/114; 0/56 RR not estimable[a]	2/114; 2/56 0.49 (0.07-3.40) [a]	NR	NR	Fair
[c]Fogelman et al, 2000[226]	Postmenopausal women less than age 80 years, with mean lumbar T-score of -2.0 or less; mean age 65 years; 31 % with vertebral fractures	Risedronate 5 mg/day; 2 years	8/112; 17/125 [0.53 (0.24 to 1.17)] [a]	7/112; 13/125 [0.68 (0.30 to 1.58)] [a]	NR	NR	Fair

[a] Fractures were not primary or secondary efficacy measures in these studies, and studies were not powered based on fracture outcomes.
[b] Results from a post-hoc analysis of women aged 70 to 79 without prevalent vertebral fracture at baseline. The RR in women aged 70-79 with prevalent vertebral fracture at baseline was 0.4 (95% CI, 0.2 to 0.8).
[c] Excluded from previous review because >=20% of study had prior or prevalent fracture; however, this study was considered in the prior review's sensitivity analysis.

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

Appendix F Table 12. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Etidronate

Study References	Participant Characteristics	Intervention; Duration	Incident Fracture Vertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Fracture Nonvertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Hip Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Herd et al, 1997[228]	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 calculable	NR	NR	Fair
Meunier et al, 1997[229]	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

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

Appendix F Table 13. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Raloxifene

Study Reference	Participant Characteristics	Intervention; Duration	Incident Fracture Vertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Fracture Nonvertebral Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Hip Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Multiple Outcomes of Raloxifene (MORE) trial; Ettinger et al, 1999[231], Delmas et al, 2002[232]	Women, ≥ 2 years postmenopausal; mean age 66.9 years (range: 31-80); mean femoral neck or lumbar spine T-score -2.57; 37% with prior vertebral fractures; total 4 year sample includes 1751 women who used 1+ other bone-active agents in year 4 Radiologically-confirmed fracture incidence	Raloxifene 60 or 120 mg/day; 3 and 4 years	3 years 148/2259 (60 mg); 231/2292 (placebo) [0.7 (0.5-0.8)] 4 years 169/2259 (60 mg); 287/2292 (placebo)[a] [0.64 (0.53-0.76)] Subgroup with no use of other bone-active agents in year 4 145/2016 (60 mg); 315/1977 (placebo) [0.63 (0.52-0.77)]	3 years 437/4536 (both doses combined[b]); 240/2292 (placebo) [0.9 (0.8-1.9)] 4 years 548/4536 (both doses combined[b]); 296/2292 (placebo) [0.93 (0.81-1.06)]	3 years 40/4536 (both doses combined[b]); 18/2292 (placebo) [1.1 (0.6-1.9)] 4 years 56/4536 (both doses combined[b]); 29/2292 [0.97 (0.62-1.52)]	3 years Wrist fracture 151/4536 (both doses combined[b]); 86/2292 (placebo) [0.9 (0.6-1.1)] Ankle fracture 34/4536 (both doses combined[b]); 28/2292 (placebo) [0.6 (0.4-1.0)] 4 years Wrist fracture 180/4536 (both doses combined[b]); 109/2292 [0.83 (0.66-1.05)] Ankle fracture 54/4536 (both doses combined[b]); 29/2292 [0.94 (0.60-1.47)]	Good

[a] Figures interpolated by Nelson et al (2010) from in-text graph.[3]
[b] Data available only for combined group of participants receiving dosages of 60 mg/day or 120 mg/day. Recommended dosage is 60 mg/day.

Abbreviations: CI=confidence interval; HR=hazard ratio; mg=milligram; RR=risk ratio.

Appendix F Table 14. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Denosumab

Study Reference	Participant Characteristics	Intervention; Duration	Incident Vertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Nonvertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Hip Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Incident Fractures Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Lewiecki et al, 2007[236a]	Postmenopausal women with lumbar spine BMD T-scores of -1.8 to -4.0 or femoral neck/total hip T-scores of -1.8 to -3.5. Lumbar spine T score of less than −2.5: n=120 (29.1%). Total hip T score of less than −2.5: n=27 (6.6%)	Denosumab for 24 months; dosed at 6, 14, or 30 mg subcutaneously every 3 months, or 14, 60, 100, or 210 mg subcutaneously every 6 months, alternating with placebo	NR	NR	NR	Osteoporotic fractures 12/314; 0/46 (3.73 [0.22 to 61.96]) Clinical fractures 21/314; 1/46 (1.58 [0.68 to 3.63])	Fair
Bone et al, 2008[237a]	Postmenopausal women with a lumbar spine BMD T score between -1.0 and -2.5	Denosumab 60 mg every 6 months for 24 months subcutaneously (last dose at 18 months)	Morphometric 0/164; 1/165	NR	NR	Clinical fractures 2/164; 7/165 (0.29 [0.06 to 1.36])	Fair
Cummings et al, 2009,[238] Simon et al, 2012[346]	Women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip	Denosumab 60 mg every 6 months for 36 months subcutaneously	86/3702; 264/3691 (0.32 [0.26 to 0.41])[b]	238/3902; 293/3906 (0.80 [0.67 to 0.95])[c]	26/3902; 43/3906 (0.60 [0.37 to 0.97])[c]	New clinical vertebral fracture 29/3902; 92/3906 (0.31 [0.20 to 0.47])[c] Multiple (≥2) new vertebral fractures 23/3702; 59/3691 (0.39 [0.24 to 0.63])[b] Wrist fractures 90/3902; 106/3906 (0.84 [0.64 to 1.11])	Fair
Nakamura, 2012[239]	Ambulatory Japenese postmenopausal women 80 years or younger, who had osteoporosis, and a BMD T-score of -2.5 to -4.0 at the lumbar 1 to lumbar 4 spine or -2.5 to -3.5 at either the femoral neck or total hip	Denosumab 14 mg subcutaneously every 6 months for 12 months; or 60 mg subcutaneously every 6 months for 12 months; or 100 mg subcutaneously every 6 months for 12 months; or placebo every 6 months for 12 months	0/212	NA	NA	NA	Fair

[a] Fractures were not primary or secondary efficacy measures 86/in this studies, and studies were not powered based on fracture outcomes.
[b] Risk ratio, adjusted for age-stratification variable.
[c] Hazard ratio, adjusted for age-stratification variable.
Abbreviations: BMD=bone mineral density; CI=confidence interval; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 15. Fracture Outcomes of Placebo-Controlled Primary Prevention Trials of Parathyroid Hormone in Women and Men

Study Reference	Participant Characteristics	Intervention; Duration	Incident Vertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Nonvertebral Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Incident Hip Fracture Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Incident Fractures Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Greenspan et. al, 2007 [36]	Postmenopausal women with mean age of 64.4 years; T-score ≤ -3.0; 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	No baseline fracture: 7/1050/ 21/1011 RR: 0.32 (0.14-0.75) With baseline fracture: 10/236, 21/235; RR 0.47 (0.22-0.98)	72/1286; 72/1246 RR: 0.97 (0.71-1.33)	NR	NR	Fair
Orwoll et. al, 2003[240]	Men with mean age 59 years; mean T-score -2.7; unknown prior fracture	Teriparatide 20 or 40 µg daily injection; mean duration of 11 months	NR	2/151 (20 ug); 1/139 (40 ug); 3/147 (placebo) RR: 0.65 (0.11-3.83) RR: 0.35 (0.04-3.35)	NR	NR	Fair

Abbreviations: CI=confidence interval; NR=not reported; RR=risk ratio; ug=microgram.

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Cummings et al, 1998[200]	Women least 2 years postmenopausal age 55–80 years; mean age: 67.7 years mean T-score: −2.2 previous fractures: excluded	Alendronate 5 mg/day for 2 years, then 10 mg/day for 1 year	221/2214; 227/2218 RR 1.00 (0.84-1.20)	NR	Any upper GI event: 1052/2214; 1047/2218 RR 1.01 (0.95-1.07) Abdominal pain: 322/2214; 325/2218 RR 1.90 (0.86-1.14) Esophagitis: 19/2214; 10/2218; RR 1.90 (0.89-2.08 Esophageal ulcer: 4/2214; 4/2218; RR 1.00 (0.25-4.00) Other esophageal: 44/2214; 41/2218 RR 1.08 (0.71-1.63) Acid regurgitation/reflux: 204/2214; 194/2218 RR 1.05 (0.87 – 1.27)	All-cause mortality: 37/2214; 40/2218 RR 0.93 (0.59 – 1.44)	Good
Liberman et al, 1995[199]	Women >5 years postmenopausal; mean age 64 years; mean T-score -2.2; 21% with prior vertebral fracture	Alendronate 10 mg/day; 3 years	35/597; 24/397 RR 0.97 (0.59 – 1.60)	NR	Abdominal pain: 13/196; 19/397 RR 1.32 (0.66 – 2.62) Dyspepsia: 7/196; 14/397 RR 1.01 (0.42 – 2.37)	NR	Fair
Pols et al, 1999[201]	Women ≥3 years postmenopausal; mean age 63.0 years; mean T-score -2.0; unknown prior fracture	Alendronate 10 mg/day; 1 year	61/950; 54/958 RR 1.14 (0.80-1.62)	NR	NR	NR	Fair
Hosking et al, 2003[202]	Postmenopausal women 60-90 years with osteoporosis defined by lumbar spine or total hip BMD T score < -2.5 or both <-2.0; mean age 69 history of fracture 48.5%	Alendronate 70 mg weekly; 12 months	31/219; 12/108 RR 1.27 (0.68-2.38)	17/219; 12/108 RR 0.70 (0.35-1.41)	Any Upper gastrointenstinal AE 62/219; 29/108 RR 1.05 (0.72-1.54) Any Esophogeal AE 5/219; 0/108 Peptic ulcers, perforations, or bleeds 0/219; 0/108	Any AE 169/219; 76/108 RR 1.10 (0.95-1.26)	Fair

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Johnell et al, 2002[246]	Postmenopausal Women, age <75 yr; >2 yr since their last menstrual period, with femoral neck BMD < -2.0; mean age 63.6; mean femoral neck BMD 0.62	Alendronate 10 mg daily; 12 months	8/83; 4/82 RR 1.98 (0.62 – 6.30)	NR	Abdominal Pain 9/83; 5/82 RR 1.78 (0.62 – 5.08)	Chest Pain substernal 6/83; 2/82 RR 2.96 (0.62 – 14.26)	Good
Sorensen et al, 2008[247]	Cases of women with atrial fibrillation and flutter compared with five controls match on age, sex, and county from Danish registry[a] Osteoporosis rates: 1209 (8.9%) of case participants 5,328 (7.8%) of control participants	Any bisphosphonates	NR	NR	NR	435/13,586 cases (3.2%) and 1,958/68,054 population controls (2.9%) RR for new users: 0.75 (95% CI, 0.49 to 1.16)	Good
Cummings et al, 2008[248]	Women least 2 years postmenopausal age 55–80 years; mean age: 69 years	Alendronate 5 mg qd for 2 years, then 10 mg qd for 1 year; 4 years	NR	NR	NR	Serious Atrial fibrillation[b] 47/3236; 31/3226 RR 1.51 (0.96-2.37) Any atrial fibrillation 81/3236; 71/3226 RR 1.14 (0.83 – 1.56)	Good

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Ascott-Evans et al, 2003[204]	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	10/95; 10/49 RR 0.49 (0.22 – 1.11)	NR	Upper GI Events 15/95; 6/49 RR 1.24 (0.51-2.98)	Any clinical adverse event 60/95; 30/49 RR 0.99 (0.76 – 1.29)	Fair
Chesnut et al, 1995[203]	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	Withdrawals: 18/188 (10%) overall (not stratified by treatment group)	NR	NR	NR	Fair
Greenspan et al, 2003[249]	Women 65-90 years; mean age 71.5; baseline femoral neck T score -1.7; baseline fracture rate not reported	Alendronate 10 mg daily or placebo; 3 years	NR	NR	Esophagitis 26/93; 21/93 RR 1.24 (0.75 – 2.04)	Myocardial infarction 2/93; 1/93 RR 2 (0.18 – 21.68)	Good
Adachi et al, 2001[250]	Postmenopausal women, at least 6 months after last menses, at least 40 years (or 25 years if surgical menopause) with history of osteoporotic fracture or T score < -2.0; mean age 65.5; baseline osteoporotic fracture 6.8%	Alendronate 10 mg daily or placebo; 12 weeks	NR	Serious adverse event: 1.4%(4/291) vs 0.7%(1/147) RR 2.02 (0.23 – 17.91)	Serious upper GI event: 59/291; 19/147 RR 1.57 (0.97 – 2.53) Upper GI event: 66/291; 30/147 RR 1.11 (0.76-1.63) Dyspepsia: 23/291; 0/147 Esophageal spasm: 1/291; 0/147 Non-serious upper GI bleed: 1/291; 0/147	Any adverse event: 166/291; 76/147 RR 1.10 (0.92 – 1.33) Death: 0/291; 0/147	Fair

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Greenspan et al, 2003[254]	Postmenopausal women or men with osteoporosis determined by BMD or clinical diagnosis; mean age 67; 92% female; baseline anti-resorptives 77%; baseline bisphosphonate use 44-50%	Alendronate 70 mg weekly or placebo; 12 weeks	10/224; 11/226 RR 0.92 (0.40 – 2.12)	28/224; 34/226 RR 0.83 (0.52-1.32)	Total upper GI events: 25/224; 30/226 RR 0.84 (0.51 – 1.38) Abdominal Pain 7/224; 8/226 RR 0.88 (0.33 – 2.39) Dyspepsia 4/224; 6/226 RR 0.67 (0.19 – 2.35) GERD 3/224; 1/226 RR 3.03 (0.32 – 28.88) Duodenal ulcer 1/224; 0/226 Gastritis 1/224; 0/226	Any adverse event: 104/224; 97/226 RR 1.08 (0.88 – 1.33)	Fair
Bauer et al, 2000[251]	Women least 2 years postmenopausal age 55–80 years; mean age 69; baseline fracture 40% Baseline mean (SD) BMD in Alendronate group: Lumbar spine: 0.83 (0.13) Femoral neck: 0.58 (0.06) Placebo group: Lumbar spine: 0.83 (0.14) Femoral neck: 0.58 (0.06)	Alendronate 5 mg qd for 2 years, then 10 mg qd for 1 year; 4.5 years	NR	NR	Any upper GI AE 1536/3226; 1490/3223 R 1.03 (0.98 – 1.08) Any gastric or duodenal AE 130/3226; 129/3223 RR 1.01 (0.79 – 1.28) Gastritis 82/3226; 75/3223 RR 1.05 (0.90 – 1.22) Any gastric or duodenal PUB (perforations, ulcers, bleeding) 53/3226; 61/3223 RR 0.87 (0.60 – 1.25) Any esophageal AE 322/3226; 202/3223 RR 1.59 (1.34 – 1.89) Acid regurgitation/ reflux 279/3226; 269/3223 RR 1.04 (0.88 – 1.22)	NR	Good

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Cryer et al, 2005[252]	Postmenopausal women, at least 6 months after last menses, at least 40 years (or 25 years if surgical menopause) with low BMD defined as T score < -2.0 below young mean bone mass at one of any of the following sites: total hip, hip trochanter, femoral neck, total spine; mean age 65 years; mean T score lumbar spine -2.52—2.46; baseline fractures not reported	Alendronate 70 mg weekly or placebo; 6 months	10/224; 18/230 RR 0.57 (0.27 – 1.21)	9/224; 8/230 RR 1.16 (0.45 – 2.94)	Any upper GI event 79/224; 86/230 RR 0.94 (0.74 – 1.20) Dyspepsia 11/224; 9/230 RR 1.26 (0.53 – 2.97) Abdominal Pain 6/224; 3/230 RR 2.05 (0.52 – 8.11) GERD 3/224; 3/230 RR 1.03 (0.21 – 5.03)	Any AE 141/224; 120/230 RR 1.21 (1.03 – 1.42)	Good
Tucci, et al, 1996[253]	Women 42 to 82 years postmenopausal for at least 5 years and have osteoporosis as defined by low lumbar spine BMD <2.5 SD below mean BMD or young white female; mean age 64; baseline fracture rate not reported	Aledronate 10 mg or placebo; 3 years	5/94; 13/192 RR 0.79 (0.29 – 2.14)	20/94; 35/192 RR 1.17 (0.71 – 1.91)	Any Upper GI AE 49/94; 79/192 RR 1.27 (0.98 – 1.64)	Any AE 89/94; 181/192 RR 1.00 (0.95-1.07)	Fair

Appendix F Table 16. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Alendronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Eisman et al,2004[255]	Postmenopausal women and men with osteoporosis (as determined by investigators); mean age 63.6 years; female 93-96%; baseline fracture rate not reported	Alendronate 70 mg weekly or placebo; 12 weeks	NR	NR	Any upper GI event 22/225; 21/224 RR 1.04 (0.59 – 1.84) Abdominal Pain 2/225; 2/224 RR 1.00 (0.14 – 7.01) Dyspepsia 2/225; 1/224 RR 1.99 (0.18 – 21.80) Gastritis 0/225; 2/224 Esophogeal ulcer 0/225; 1/224 GERD 0/225; 1/224	Any AE 91/225; 86/224 RR 1.05 (0.84 – 1.33)	Good

[a] Case control study, comparing cases with atrial fibrillation and flutter with controls without.
[b] Because these data were presented in a letter to the editor, we extracted information on denominators from related citations.[200, 206]

Abbreviations: AE=adverse event; CI=confidence interval; CV=cardiovascular; GI=gastrointestinal; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 17. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Zoledronic Acid

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Reid et al, 2002[217]	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 vs. placebo; 1 year	13/292; 1/59 RR 2.62 (0.35-19.70)	26/292; 3/59 RR 2.67 (0.36 – 20.03)	NR	Any Adverse Event 262/292; 45/59 RR 1.18 (1.02 – 1.36) Myalgia: 41/292; 1/59 RR 8.28 (1.16-59.04) Arthralgia: 46/292; 9/59 RR 1.03 (0.54-1.99)	Fair
Boonen, 2012[218]	Men 50 to 85 years of age; median age 66; mean femoral neck T score -2.23 to -2.24; mean total hip T score -1.70 to -1.72. 31.3% vertebral fracture at baseline.	Intravenous infusion of 5mg of Zoledronic acid at baseline and 12 months; 24 months	NR	149/588; 154/611 RR 1.01 (0.83 – 1.22)	NR	Any Adverse Event 534/588; 466/611 RR 1.19 (1.13- 1.25) Death 15/588; 18/611 RR 0.87 (0.44 – 1.70) Atrial fibrillation 7/588; 5/611 RR 1.45 (0.46-4.56) Myocardial infarction 9/588; 2/611 RR 4.68 (1.015-21.55) Osteonecrosis of the jaw 0/588; 0/611 Arthralgia 123/588; 68/611 RR 1.88 (1.43 – 2.47) Myalgia 129/588; 25/611 RR 5.20 (3.44-7.86)	Good
Grey et al, 2010[274]	Postmenopausal women with osteopenia, BMD -1 to -2 at the lumbar spine or total hip; mean age 62-65; Total hip T score -1.3 to 01.2	Zolendronate 5 mg intravenous vs. Placebo at baseline; 3 years	NR	NR	NR	Atrial fibrillation: 0/25; 0/25 Osteonecrosis of the jaw: 0/25; 0/25 Other fracture: 4/25; 2/25 RR 2.0 (0.40 – 9.95) Symptomatic hypocalcemia 0/25; 0/25	Fair

Appendix F Table 17. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Zoledronic Acid

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations Due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
McClung et al, 2009[275]	Postmenopausal women 45 years or older who had low bone mass, defined as BMD T-score less than -1.0 and more than -2.5 at the lumbar spine and BMD T-score greater than -2.5 at the femoral neck; mean age 59.6 to 60.5; mean baseline femoral neck T score -1.47 to -1.40.	G1: zoledronic acid 5 mg intravenously at randomization and at month 12 G2: zoledronic acid 5 mg intravenously only at randomization and placebo month 12 G3: placebo at randomization and month 12	NR	17/198; 21/181; 23/202 RR (G1/G3) 0.75 (0.42 – 1.37) RR (G2/G3) 1.01 (0.58 – 1.78)	NR	Any Adverse Event 186/198; 173/181; 186/202 RR (G1/G3) 1.02 (0.96 – 1.07) RR (G2/G3) 1.038 (0.99 – 1.09) Myalgia 38/198; 41/181; 14/202 RR (G1/G3) 2.77 (1.55 – 4.95) RR (G2/G3) 3.27 (1.84 – 5.79) Arthralgia 54/198; 34/181; 39/202 RR (G1/G3) 1.41 (0.98-2.03) RR (G2/G3) 0.97 (0.64 – 1.47) Osteonecrosis of the jaw 0/198; 0/181; 0/202 Atrial Fibrillation 0/198; 0/181; 0/202	Fair

Abbreviations: BMD=bone mineral density; CI=confidence interval; G=group; mg=milligram; NR=not reported; RR=risk ratio; vs=versus.

Appendix F Table 18. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Risedronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
McClung et al, 2001[223]	Women 70 years and older; results only reported here for subgroup ages 70-79 with no prevalent vertebral fracture at baseline, mean femoral neck T-score -3.7	Risedronate 5 mg/day; 2 years treatment (mean follow-up 2.3 years)	550/3104; 564/3134 [0.98 (0.89 to 1.10)]	943/3104; 973/3134 [0.98 (0.91 to 1.05)]	Upper GI event: 657/3104; 684/3134 [0.91 (0.88 to 1.07)]	NR	Fair
Mortensen et al,1998[224]	Women 6-60 months postmenopausal; mean age 51.5 years; mean T-score -1.1; no prior osteoporotic fracture	Risedronate 5 mg/day; 2 years treatment (follow-up 3 years)	3/37; 2/36 [1.46 (0.26 to 8.23)]	NR	Dyspepsia 6/37; 10/36 [0.59 (0.24 to 1.44)] Abdominal Pain 3/37; 4/36 [0.73 (0.18 to 3.04)]	NR	Fair
Valimaki et al, 2007[225]	Women ≥5 years postmenopausal; osteoporosis risk factors or low hip BMD; mean age 65.9 years; mean femoral neck T-score -1.2; unknown prior fracture	Risedronate 5 mg/day; 2 years	10/115; 9/55 [0.53 (0.23 to 1.23)]	12/114; 3/56 [1.97 (0.58 to 6.68)]	Upper GI event: 21/115; 14/55 [0.72 (0.40 to 1.30)]	NR	Fair
Fogelman et al, 2000[b226]	Postmenopausal women less than age 80 years, with mean lumbar T-score of -2.0 or less; mean age 65 years; 31% with vertebral fractures	Risedronate 5 mg/day; 2 years	19/175; 14/173 [1.34 (0.70 to 2.59)]	26/173; 27/180 [1.00 (0.61 to 1.65)]	Upper GI event: 40/174; 47/180 [0.88 (0.61 to 1.27)]	NR	Fair
Shiraki et al, 2003[283]	Mostly women ages 40 to 75 years with senile and postmenopausal osteoporosis; mean age 60.3 years; mean number of prevalent vertebral fractures 0.3 (SD 0.8), mean lumbar T-score -2.9	Risedronate 5 mg/d; 36 weeks	NR	0/53; 0/51 RR not calcuable	GI disturbance: 13/53; 7/51 [RR 1.79 (0.78 to 4.11)]	Cardiac disturbances: 2/53; 0/51 RR not estimable Disturbances of skin and subcutaneous tissues: 0/53; 2/51 RR not estimable Disturbances of musculoskeletal, bone and connective tissues 1/53; 0/51 RR not estimable	Fair

Appendix F Table 18. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Risedronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Hosking et al, 2003[202c]	Postmenopausal women; mean age 69 years, 48% with history of fracture	Risedronate 5 mg/day; 3 months	31/222; 12/108 [1.26 (0.67 to 2.35)]	15/222; 12/108 [0.61 (95% CI, 0.30 to 1.25)]	Upper GI event: 1/222; 29/108 [1.02 (0.70 to 1.49)]	NR	Fair

[a] Defined differently in each study, but estimates generally represent a variety of gastrointestinal adverse events including moderate to severe abdominal pain, dyspepsia, esophagitis, gastritis, stomach ulcer, gastrointestinal disorder, esophageal ulcer, duodenal ulcer, unless specifically indicated.
[b] Excluded from previous review because >=20% of study had prior or prevalent fracture; was considered in the prior review's sensitivity analysis.
[c] Not identified for consideration in previous review.

Abbreviations: CI=confidence interval; GI=gastrointestinal; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 19. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Etidronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Herd et al, 1997[228]	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	5/75; 0/77 [11.23 (0.64 to 200.68)]	8/75; 7/77 [1.17 (0.44 to 3.07)]	GI AE events: 9/75; 17/77 [0.54 (0.26 to 1.14)]	Infection 18/74; 22/76 [0.84 (0.49 to 1.43)]	Fair
Meunier et al, 1997[229]	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	0/27; 2/27 [0.20 (0.01 to 3.98)]	NR	Severe GI 0/27; 0/27 RR not calculable Mild abdominal pain 4/27; 1/27 (all had history of GI problems) [4.00 (0.48 to 33.51)]	NR	Fair

Abbreviations: AE=adverse event; CI=confidence interval; GI=gastrointestinal; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 20. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Ibandronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Chapurlat et al, 2013[284]	Women at least 1 year postmenopausal; mean age 63 years; mean T-score -1.4; unknown prior osteoporotic fractures	150 mg ibandronate monthly; 2 years	Due to AEs (including fractures) 4/71; 6/76 [0.71 (0.21 to 2.42)]	15/71; 13/76 [1.23 (0.63 to 2.41)]	NR	NR	Fair
McClung et al, 2004[285]	Women at least 1 year postmenopausal; mean age 58 years; mean T-score 1.0; no prior osteoporotic fractures	0.5, 1.0, 2.5 mg ibandronate daily; 2 years	Any withdrawals because of AEs: 5/161; 5/165; 7/163; 9/159 [0.55 (0.19 to 1.60)] [0.54 (0.18 to 1.56)] [0.76 (0.29 to 1.99)] Percentage of all subjects who withdrew from study medication because of an AE was numerically higher in the placebo group (9%, 5%, 5%, and 7% in the placebo, 0.5-, 1-, and 2.5-mg groups, respectively), although the differences between placebo and ibandronate groups did not reach significance.	Any Serious AEs 6/161; 13/165; 5/163; 8/159 [0.74 (0.26 to 2.09)] [1.57 (0.67 to 3.68)] [0.61 (0.20 to 1.82)] Any drug related serious AEs 0/161; 0/165; 0/163; 0/159 RR not calculable	Dyspepsia 16/161; 14/165; 15/163; 14/159 [1.13 (0.57 to 2.23) [0.96 (0.47 to 1.96)] [1.05 (0.52 to 2.09)] Gastroenteritis 9/161; 4/165; 5/163; 6/159 [1.48 (0.54 to 4.07)] [0.64 (0.18 to 2.23] [0.81 (0.25 to 2.61)] Nausea 6/161; 1/165; 4/163; 3/159 [1.98 (0.50 to 7.76)] [0.32 (0.03 to 3.06)] [1.30 (0.30 to 5.72)] GI Pain 2/161; 0/165; 4/163; 4/159 [0.49 (0.09 to 2.66)] [0.11 (0.01 to 1.98)] [0.98 (0.25 to 3.83)] GI disorder 1/161; 2/165; 0/163; 3/159 [0.33 (0.03 to 3.13)] [0.64 (0.11 to 3.79)] [0.14 (0.01 to 2.68)] Eructation 1/161; 1/165; 1/163; 1/159 [0.99 (0.06 to 15.65)] [0.96 (0.06 to 15.28)] [0.98 (0.06 to 15.47)]	NR	Fair

Appendix F Table 20. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Ibandronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
McClung et al, 2004[285] (continued)					Gastritis 0/161; 1/165; 2/163; 1/159 [0.33 (0.01 to 8.02)] [0.96 (0.06 to 15.28)] [1.95 (0.18 to 21.30)] Dysphagia 2/161; 1/165; 1/163; 0/159 [4.94 (0.24 to 102.06)] [2.89 (0.12 to 70.46)] [2.91 (0.12 to 71.32)] Vomiting 2/161; 0/165; 1/163; 0/159 [4.94 (0.24 to 102.06)] 1mg vs. Placebo: RR not calculable [2.92 (0.12 to 71.32)] Esophagitis 1/161; 0/165; 1/163; 1/159 [0.99 (0.06 to 15.65)] [0.32 (0.01 to 7.83)] [0.98 (0.06 to 15.46)] GI carcinoma 0/161; 0/165; 1/163; 0/159 .5mg vs. Placebo: RR not calculable 1mg vs. Placebo: RR not calculable [0.98 (0.02 to 49.17)] GI hemorrhage 0/161; 0/165; 0/163; 1/159 [0.33 (0.01 to 8.02)] [0.32 (0.01 to 7.83)] [0.33 (0.01 to 7.92)] Hemorrhage gastritis 1/161; 0/165; 0/163; 0/159 [2.96 (0.12 to 72.20)]		

Appendix F Table 20. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Ibandronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
McClung et al, 2004[285] (continued)					1mg vs. Placebo: RR not calculable 2.5mg vs. Placebo: RR not calculable 0.96 (0.02 to 48.29)] [0.98 (0.02 to 48.87)]		
Ravn et al, 1996[286]	Women at least 10 years postmenopausal; mean age 65 years; mean T-score -0.852; no prior osteoporotic fractures	0.25, 0.5, 1.0, 2.5, or 5.0 mg ibandronate daily; 1 year	1/30; 4/30; 2/30; 0/30; 6/30; 2/30 [0.50 (0.05 to 5.22)] [2.00 (0.40 to 10.11)] [1.00 (0.15 to 6.64)] [0.20 (0.01 to 4.00)] [3.00 (0.66 to 13.69)]	1/30; 1/30; 0/30; 2/30; 1/30; 3/30 [0.33 (0.04 to 3.03)] [0.33 (0.04 to 3.03)] [0.14 (0.01 to 2.65)] [0.67 (0.12 to 3.71)] [0.33 (0.04 to 3.03)]	GI AEs 12/30; 17/30; 8/30; 5/30; 17/30; 11/30 [1.09 (0.57 to 2.07)] [1.55 (0.88 to 2.72)] [0.73 (0.34 to 1.55)] [0.45 (0.18 to 1.15)] [1.55 (0.88 to 2.72)] Diarrhea 6/30; 5/30; 2/30; 2/30; 9/30; 2/30 [3.00 (0.66 to 13.69)] [2.50 (0.53 to 11.89)] [1.00 (0.15 to 6.64)] [1.00 (0.15 to 6.64)] [4.50 (1.06 to 19.11)]	Infection 1/26; 0/22; 0/26; 0/24; 0/18; 0/25 [2.8889 (0.12 to 67.76)] [1.13 (0.02 to 54.72)] [0.96 (0.02 to 46.76)] [1.04 (0.02 to 50.43)] [1.37 (0.03 to 65.94)] Death 0/26; 0/22; 0/26; 1/24; 0/18; 1/25 [0.32 (0.01 to 7.53)]	Fair

Appendix F Table 20. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Ibandronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Reginster, et al, 2005[287]	Women at least 3 years postmenopausal; mean age 64 years; mean T-score -1.14; unknown prior fracture	50, 50/100, 100, or 150 mg ibandronate monthly; 3 months	Any AE leading to withdrawal: 0/18; 0/18; 0/36; 1/36; 2/36 [0.39 (0.02 to 7.71)] [0.39 (0.02 to 7.71)] [0.20 (0.01 to 4.03)] [0.50 (0.05 to 5.27)] Any drug-related AE leading to withdrawal: 0/18; 0/18; 0/36; 1/36; 2/36 [0.39 (0.02 to 7.71) [0.39 (0.02 to 7.71) [0.20 (0.01 to 4.03)] [0.50 (0.05 to 5.27)]	0/18; 0/18; 0/36; 0/36; 0/36 RR not calculable	Upper GI AEs within 3 days of treatment: 0/18; 4/18; 8/36; 9/36; 6/36 [0.15 (0.01 to 2.52)] [1.33 (0.43 to 4.13)] [1.33 (0.51 to 3.46)] [1.50 (0.60 to 3.78)] Upper GI AEs anytime during treatment: 3/18; 11/18; 15/36; 15/36; 12/36 [0.50 (0.16 to 1.55)] [1.83 (1.02 to 3.31)] [1.25 (0.68 to 2.28)] [1.25 (0.68 to 2.28)]	Deaths 0/18; 0/18; 0/36; 0/36; 0/36 [1.95 (0.04 to 94.37)] [1.9474 (0.04 to 94.37)] [1.00 (0.02 to 49.08)] [1.00 (0.02 to 49.08)]	Fair
Riis et al, 2001[288]	Women at least 5 years postmenopausal; mean age 67 years; on average spinal T-score was below -3.2; unknown prior fracture	Continuous therapy with 2.5 mg of ibandronate daily or intermittent cyclical therapy with 20 mg of ibandronate every other day for the first 24 days out of every 3 months, followed by a 9-week period without active drug; 2 years	NR	NR	No differences between Continuous treatment, intermittent treatment, and placebo During the first 12 months, the ibandronate treated groups showed a numerically higher incidence of diarrhea compared with the placebo groups. Incidence of diarrhea was lower during the second year	Deaths 1/81; 0/78; 1/81 [1.00 (0.06 to 15.72)] [0.35 (0.01 to 8.37)]	Fair
Tanko et al 2003[289]	Women 1-10 years postmenopausal; mean age 55 years; mean T-score for lumbar spine 1.03; no prior osteoporotic fractures	5, 10, or 20 mg ibandronate weekly; 2 years	Withdrawals due to AEs related to treatment: 8	12% experienced a serious AE, but none were assessed as related to study drug (6 withdrew as a result of serious AE)	Gastrointestinal AEs 6%; 5%; 3%; 3%	NR	Fair

Appendix F Table 20. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Ibandronate

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Thiebaud et al 1997[290]	Women at least 5 years postmenopausal; mean age 64 years; mean T-score 0.71 lumbar spine; no prior osteoporotic fractures	0.25, 0.5, 1.0, or 2.0 mg ibandronate every 3 months; 1 year	7 withdrew because of AEs	3 non-drug related Serious AEs	6/24; 6/27; 7/26; 3/23; 4/26 No differences between the groups emerged [1.63 (0.52 to 5.07] [1.44 (0.46 to 4.54] [1.75 (0.58 to 5.27] [0.85 (0.21 to 3.40)]	NR	Fair

Abbreviations: AE=adverse event; CI=confidence interval; GI=gastrointestinal; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 21. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Raloxifene

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Johnell et al, 2002[246]	Postmenopausal women; mean age 63.6 years (≤75); T-score ≤ -2.0	Raloxifene, 60 mg/day; 1 year	7/82; 4/82 [1.75 (0.53-5.75)]	None reported	Hot flashes 4/82; 4/82 [1.00 (0.26-3.86)] Sweating 1/82; 2/82 [0.50 (0.05-5.41)] Abdominal pain 6/82; 5/82 [1.2 (0.38-3.78)]	Good
Multiple Outcomes of Raloxifene (MORE) trial; Ettinger et al, 1999[231], Delmas et al, 2002[232], Barrett-Connor et al, 2002[311], Barrett-Connor et al, 2004[310], Keech et al, 2005[312]; Cauley et al, 2001[313]; Sontag, Wan & Krege, 2010[242]	Women, ≥ 2 years postmenopausal; mean age 66.9 years (range: 31-80); mean femoral neck or lumbar spine T-score -2.57; 37% with prior vertebral fractures; total 4 year sample includes 1751 women who used 1+ other bone-active agents in year 4	Raloxifene 60 or 120 mg/day; 3 & 4 years	3 years 527/5129 (both doses combined[a]); 227/2576 (placebo) [1.17 (1.01-1.35)] 4 years 327/2557 (60 mg); 285/2576 (placebo) [1.16 (1.00-1.34)]	3 years Venous thromboembolic events 25/2557 (60 mg); 8/2576 (placebo) [3.15 (1.42-6.97)] 4 years Venous thromboembolic events All participants 33/2557 (60 mg); 17/2576 (placebo) [1.78 (0.99-3.19)] Participants without baseline vertebral fracture 17/1574 (60 mg); 13/1629 (placebo) [1.35 (0.66-2.78)] Deep vein thrombosis All participants 20/2557 (60 mg); 8/2576 (placebo) [2.52 (1.11-5.71)] Participants without baseline vertebral fracture 12/1574 (60 mg); 6/1629 (placebo) [21.07 (0.78-5.50)]	3 years Flu syndrome 346/2557 (60 mg); 293/2576 (placebo) [1.19 (1.03-1.38)] Hot flashes 249/2557 (60 mg); 165/2576 (placebo) [1.52 (1.26-1.84)] Leg cramps 178/2557 (60 mg); 96/2576 (placebo) [1.87 (1.47-2.38)] Peripheral edema 134/2557 (60 mg); 114/2576 (placebo) [1.18 (0.93-1.51)] Endometrial cavity fluid 60/2557 (60 mg); 43/2576 (placebo) [1.41 (0.95-2.07)]	Good

Appendix F Table 21. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Raloxifene

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Multiple Outcomes of Raloxifene (MORE) trial; Ettinger et al, 1999[231], Delmas et al, 2002[232], Barrett-Connor et al, 2002[311], Barrett-Connor et al, 2004[310], Keech et al, 2005[312]; Cauley et al, 2001[313]; Sontag, Wan & Krege, 2010[242] (continued)				Coronary heart disease 50/5127 (both doses combined[a]); 28/2576 (placebo) [HR 0.88 (0.56-1.40)] Stroke 22/2557 (60 mg); 32/2576 (placebo) [0.69 (0.40-1.18)] Pulmonary embolism All participants 11/2557 (60 mg); 4/2576 (placebo) [2.77 (0.88-8.69)] Participants without baseline vertebral fracture 6/1574 (60 mg); 3/1629 (placebo) [2.07 (0.52-8.26)] Retinal vein thrombosis 2/2557 (60 mg); 5/2576 (placebo) [0.40 (0.08-2.08)] Any coronary event 45/2557 (60 mg); 55/2576 [0.82 (0.56-1.22)] Any cerebrovascular event 37/2557 (60 mg); 41/2576 (placebo) [0.91 (0.58-1.41)] Any cardiovascular event 82/2557 (60 mg); 96/2576 (placebo) [0.86 (0.63-1.18)]	4 years Flu syndrome 415/2557 (60 mg); 360/2576 (placebo) [1.16 (1.02-1.32)] Hot flashes All participants 272/2557 (60 mg); 183/2576 (placebo) [1.50 (1.25-1.79)] Participants without baseline vertebral fracture 158/1574 (60 mg); 103/1629 (placebo) [1.59 (1.25-2.01)] Leg cramps 234/2557 (60 mg); 154/2576 (placebo) [1.53 (1.26-1.86)] Peripheral edema All participants 182/2557 (60 mg); 158/2576 (placebo) [1.16 (0.94-1.43)] Participants without baseline vertebral fracture 104/1574 (60 mg); 80/1629 (placebo) [1.34 (1.01-1.79)] Endometrial cavity fluid 99/2557 (60 mg); 76/2576 (placebo) [1.31 (0.98-1.76)]	

Appendix F Table 21. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Raloxifene

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Multiple Outcomes of Raloxifene (MORE) trial; Ettinger et al, 1999[231], Delmas et al, 2002[232], Barrett-Connor et al, 2002[311], Barrett-Connor et al, 2004[310], Keech et al, 2005[312]; Cauley et al, 2001[313]; Sontag, Wan & Krege, 2010[242] (continued)				Any cardiovascular event (among women at increased risk) 28/359 (60 mg); 41/317 (placebo) [0.60 (0.38-0.95)] Endometrial cancer 5/2557 (60 mg); 5/2576 (placebo) [1.01 (0.29-3.48)]	Diabetes 38/2557 (60 mg); 17/2576 (placebo) [2.25 (1.27-3.98)]	
McClung et al, 2006[306]	Postmenopausal women; mean age raloxifene group 57.5 years, mean age placebo group 57.5 years (range 47-72); T-score mean -1.0 (range:-2.5 to 2)	Raloxifene, 60 mg/day; 2 years	23/163; 12/83 [0.98 (0.51-1.86)]	Any serious AEs 14/163; 4/83 [1.78 (0.61-5.24)]	Hot flashes 39/163; 17/83 [1.30 (0.68-2.47) Leg cramps 28/163; 11/83 [1.17 (0.70-1.93)] Vaginal bleeding 3/163; 3/83 [0.51 (0.10-2.47)]	Fair
Meunier et al, 1999[307]	Postmenopausal women, mean age 60.2 years (50-75); lumbar T-score mean -2.8 (36% ≤ -2.5); 36% prior nonvertebral fracture	Raloxifene 60 mg/day; 2 years	3/45; 4/40 [0.67 (0.16-2.80)]	Deep venous thromboses 0/45; 0/40 RR not calculable	Hot flashes 4/45; 4/40 [0.89 (0.24-3.32)] Change in endometrial thickness (in millimeters) Mean: 0.49 ± 1.45; Mean: 0.44 ± 1.47 (p = NS)	Good

Appendix F Table 21. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Raloxifene

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Quality Rating
Miller et al, 2008[308]	Postmenopausal women, mean age: 57.6 (≥45); lumbar T-score mean raloxifene group -1.12, placebo group -1.24 (range:-1.0 to -2.5)	Raloxifene 60 mg/day; 2 years	43/311; 48/310 [0.89 (0.61-1.31)]	Any serious AEs 29/311; 28/310 [1.03 (0.63-1.69)] Myocardial infarction 0/311; 1/310 [0.33 (0.01-8.12)] Deep venous thromboses 0/311; 1/310 [0.33 (0.01-8.12)] Retinal vein thrombosis 1/311; 0/310 [2.99 (0.12-73.13)]	Hot flashes 58/311; 44/310 [1.31 (0.92-1.88)] Leg cramps 37/311; 36/310 [1.02 (0.67-1.58)]	Fair
Morii et al, 2003[309]	Postmenopausal women; mean age raloxifene group 65.2 years, mean age placebo group 64.3 years (≤80 years old); lumbar T-score ≤ 2.5; 26% prior vertebral fracture	Raloxifene 60 mg/day; 1 year	7/92; 3/97 [2.36 (0.63-8.85)]	Any serious adverse event 5/92; 7/97 [0.75 (0.25-2.29)] Venous thromboembolic events 0/92; 0/97 RR not calculable Colitis ischaemic 1/92; 1/97 [1.05 (0.07-16.61)] Gastrointestinal disorder NOS 0/92; 0/97 RR not calculable Oesophageal carcinoma NOS 0/92; 1/97 [0.35 (0.01-8.51)] Dissecting aortic aneurysm 1/92; 0/97 [3.16 (0.13-76.63)] Hypertension NOS 0/92; 1/97 [0.35 (0.01-8.51)]	No events of interest reported	Fair

[a] Data available only for combined group of participants receiving dosages of 60 mg/day or 120 mg/day. Recommended dosage is 60 mg/day.
[b] Absolute values calculated by authors from data on percentage per group.

Abbreviations: AE=adverse events; mg=milligram; NR=not reported; NS=not significant; osteo=osteoporosis; RR=relative risk; SD=standard deviation.

Appendix F Table 22. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Denosumab

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Lewiecki et al, 2007[236a]	Postmenopausal women with lumbar spine BMD T-scores of -1.8 to -4.0 or femoral neck/total hip T-scores of -1.8 to -3.5	Denosumab for 24 months; dosed at 6, 14, or 30 mg subcutaneously every 3 months, or 14, 60, 100, or 210 mg subcutaneously every 6 months, alternating with placebo	11/314; 1/46 (1.61 [0.21 to 12.19])	42/314; 4/46 (1.54 [0.58 to 4.09])	1/314; 0/46	Death 1/314; 0/46, Cardiac disorder 6/314; 2/46 (0.45 [0.02 to 10.83]) Serious infections 6/314; 0/46	Fair
Bone et al, 2008[237a]	Postmenopausal women with a lumbar spine BMD T score between -1.0 and -2.5	Denosumab 60 mg every 6 months for 24 months subcutaneously (last dose at 18 months)	1/164; 2/165 (0.50 [0.05 to 5.49])	18/164; 9/165 (2.01 [0.93 to 4.35])	2/164; 0/165	Deaths 0/164; 0/165 RR not calculable Rash 14/164; 5/165 (2.82 [1.04 to 7.64]) Serious infections 8/164; 1/165	Fair
Cummings et al, 2009[238]; Watts et al, 2012[314]	Women between the ages of 60 and 90 years with a bone mineral density T score of less than −2.5 at the lumbar spine or total hip	Denosumab 60 mg every 6 months for 36 months subcutaneously	93/3886; 81/3876 (1.15 [0.85 to 1.54])	1004/3886; 972/3876 (1.03 [0.95 to 1.11])	NR	Deaths 70/3886; 90/3876 (0.78 [0.57 to 1.06]) Osteonecrosis of the jaw 0/3886; 0/3876 RR not calculable Cardiovascular events 186/3886; 178/3876 (1.04 [0.85 to 1.27]) Eczema 118/3886; 65/3876 (1.81 [1.34 to 2.44]) Serious infections 159/3886; 133/3876 (1.19 [0.95 to 1.49]) Serious skin infections (cellulitis and erysipelas) 15/3886; 1/3876 (14.96 [1.98 to 113.21])	Fair

Appendix F Table 22. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Denosumab

Study Reference	Participant Characteristics	Intervention; Duration	Discontinuations due to AE Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Serious AEs Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Gastrointestinal Adverse Events[a] Risk in Treatment Group; Risk in Control Group (RR [95% CI])	Other Adverse Events	Quality Rating
Nakamura et al., 2012[239]	Ambulatory Japenese postmenopausal women 80 years or younger, who had osteoporosis, and a BMD T-score of -2.5 to -4.0 at the lumbar 1 to lumbar 4 spine or -2.5 to -3.5 at either the femoral neck or total hip	Denosumab 14 mg subcutaneously every 6 months for 12 months; or denosumab 60 mg subcutaneously every 6 months for 12 months; or denosumab 100 mg subcutaneously every 6 months for 12 months; or placebo every 6 months for 12 months	NR	Denosumab 14 mg subcutaneously every 6 months for 12 months: 6/53 denosumab 60 mg subcutaneously every 6 months for 12 months: 4/54 denosumab 100 mg subcutaneously every 6 months for 12 months: 2/50 placebo every 6 months for 12 months: 4/55	NR	NR	Fair

Abbreviations: CI=confidence interval; mg=milligram; NR=not reported; RR=risk ratio.

Appendix F Table 23. Harm Outcomes of Placebo-Controlled Primary Prevention Trials of Parathyroid Hormone

Study	Participant Characteristics	Intervention; Duration	Discontinuation	Serious Adverse Events	Other Adverse Events	Quality Rating
Greenspan et. al, 2007[36]	Postmenopausal women with mean age of 64.4 years; T-score ≤ -3.0; 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	389/1286 (100 ug); 306/1246 (placebo) RR 1.22 (1.08-1.40)	None reported	291/1286; 114/1246 RR: 2.47 (2.02-3.03)	Fair
Orwoll et. al, 2003[240]	Men with mean age 59 years; mean T-score -2.7; unknown prior fracture	Teriparatide 20 µg or 40 µg daily injection; mean treatment duration: 11 months	14/151 (20 ug) 18/139 (40 ug) 7/147 (placebo) RR: 1.94 (0.81-4.69) RR: 2.72 (1.17-6.3)	Cancers 3/151 (20 ug) 0/139 (40 ug) 3/147 (placebo) RR: 0.97 (0.2-4.74) RR: 0.15 (0.008-2.9)	Nausea 0/151 5/139 0/147	Fair

Abbreviations: RR=risk ratio; ug=micrograms.

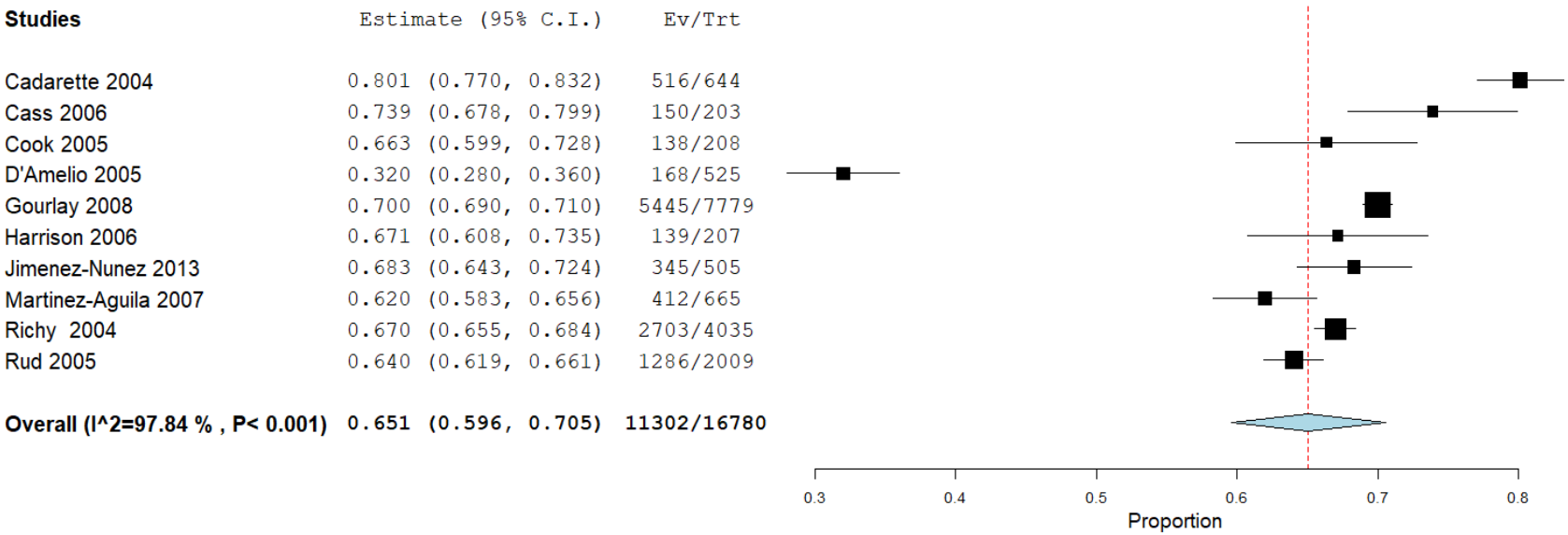
Appendix G Table 1. Completed Trials

Principal Investigators	Location	Population	Approximate Size	Investigations	Outcomes	Status as of 2017
Hyoung-Moo Park	Seoul, Republic of Korea	Women, Postmenopausal	150	Risedronate Cominbe, Risedronate., Placebo, Placebo	Proportion of patients with 25(OH)D level < 20 ng/mL at 16 weeks. [Time Frame: 16 weeks form first drug administration.] [Designated as safety issue: No]	Completed, Not Published
Eli Lilly	United States, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Poland, Singapore, Slovakia, Slovenia, Spain, Sweden, United Kingdom	Women, < 80 years old, Postmenopausal with Osteoporosis		Raloxifene HCL 60 mg, Raloxifene 120mg, Placebo	To establish the effect of long-term treatment with raloxifene, compared with placebo, on the rate of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures by spinal x-ray	Completed, Not Published
Eli Lilly and Company	United States	Female,45 Years to 85 Years (Adult, Senior) With Osteoporosis		Teriparatide and Roloxifene, Roloxifene, Placebo	The study will evaluate any side effects that may be associated with the two drugs and may help to determine whether teriparatide and raloxifene together can help patients with osteoporosis more than **teriparatide** alone	Completed, Not Published
Clifford Rosen, MD St. Joseph Hospital Health Center	United States	Female 45 – 70 years, with osteoporosis	50	Teriparatide, Placebo	Bone mineral density will be measured at 6 and 12 months	Completed, Not Published

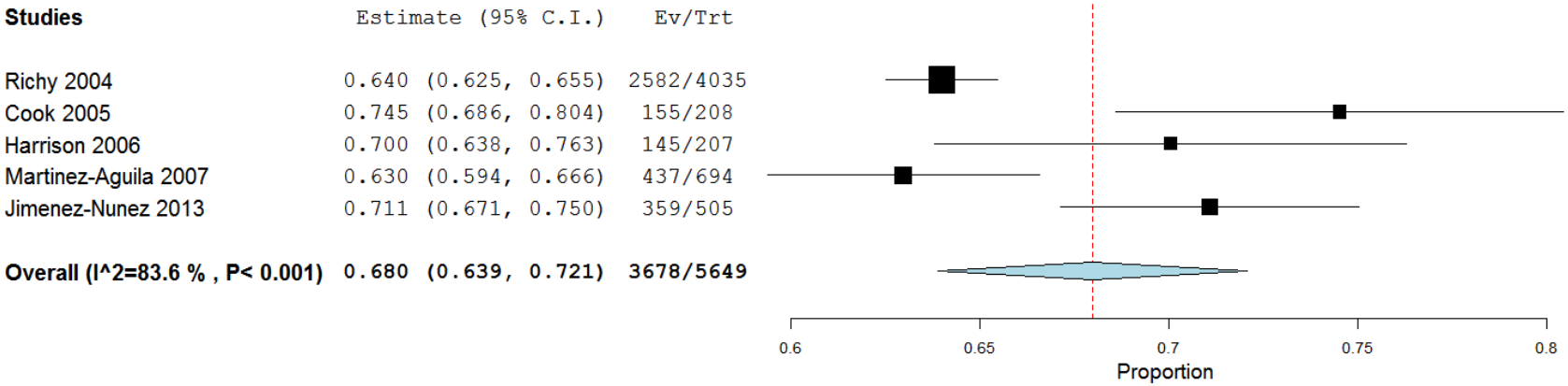
Appendix G Table 2. Ongoing Trials

Principal Investigators	Location	Population	Approx-imate Size	Investigations	Outcomes	Status as of 2017
Sudhaker D Rao, MD, Henry Ford Health System	United States	Women, 50 years and older	1000	(Risedronate) Pathogenesis of Atypical Femur Fractures on Long Term Bisphosphonate Therapy	Determine the prevalence of PBD and/or Atypical Femoral Fractures (AFF) in patients	Recruiting
Susan L. Greenspan, University of Pittsburgh	United States	Women, 65 Years and older	1000	(Zoledronic Acid) **Zoledronic Acid** for Osteoporotic Fracture Prevention (ZEST II)	Total non-traumatic incident clinical fractures (vertebral and nonvertebral)	Recruiting
Elizabeth Shane, Columbia University	United States	Premenopausal Women	40	(Teriparatide) **Forteo** Trial on Idiopathic Osteoporosis in Premenopausal Women	Change in lumbar spine bone mineral density (LS-BMD) [Time Frame: Baseline and 12 months] [Designated as safety issue: Yes]	Recruiting
Susan L. Greenspan, University of Pittsburgh	United States	Men and Women 65 years and older	212	Preventing Osteoporosis Using **Denosumab** (PROUD)	Increased bone density of the total hip/spine	Recruiting

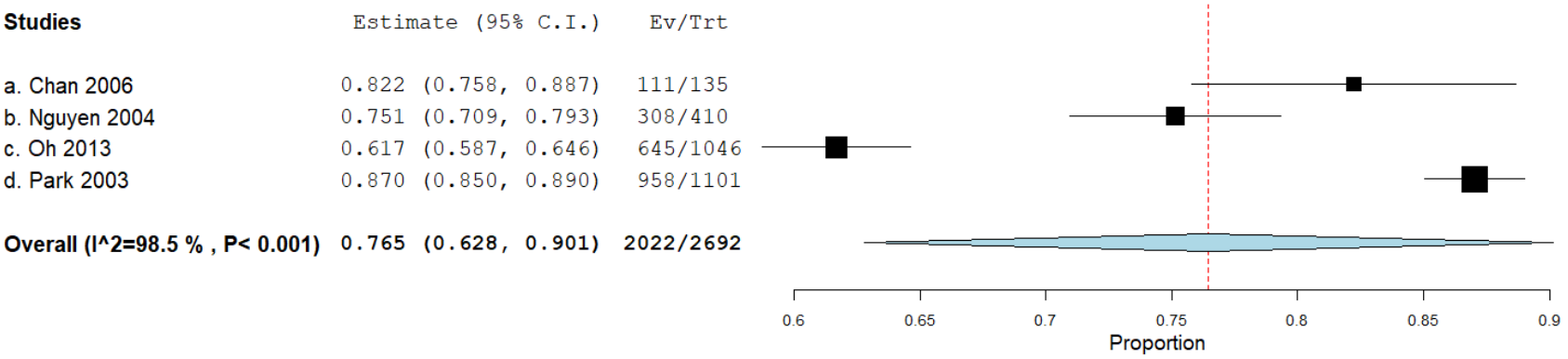
Appendix H Figure 1. Osteoporosis Risk Assessment Instrument (ORAI) in Women



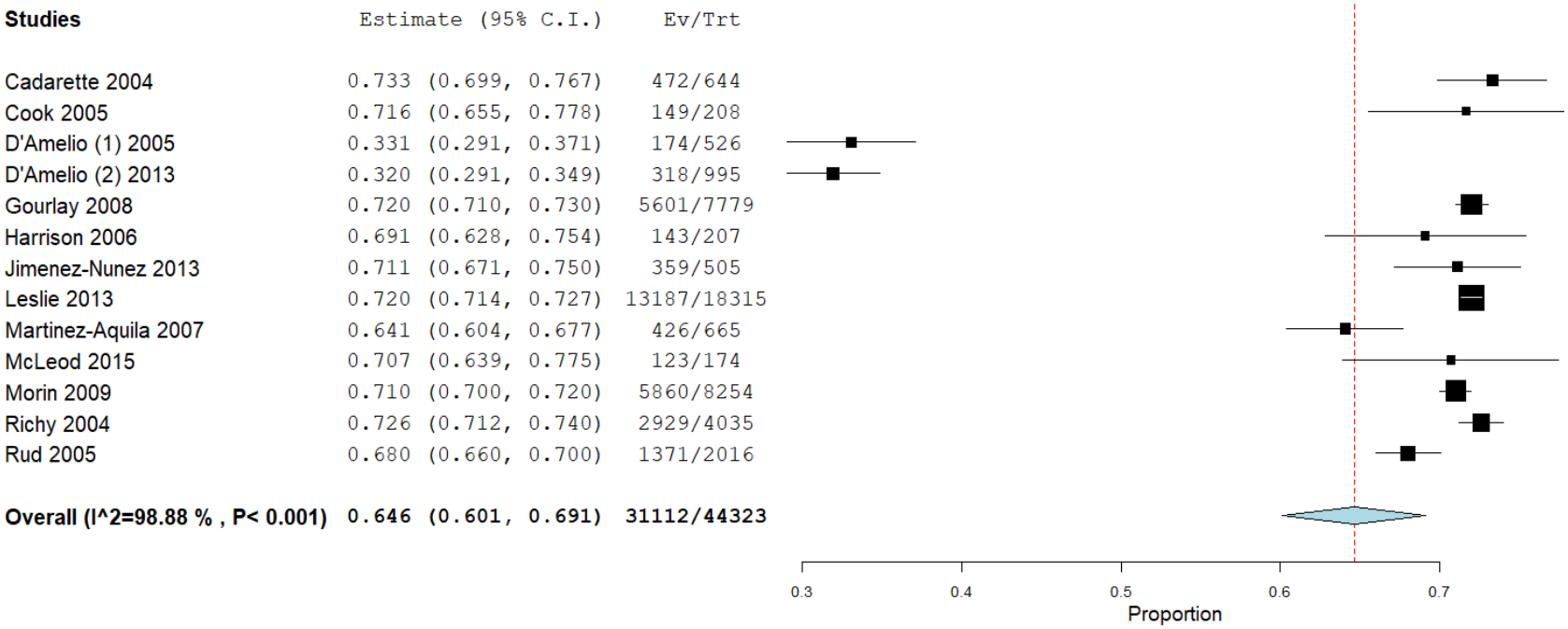
Appendix H Figure 2. Osteoporosis Index of Risk (OSIRIS) in Women



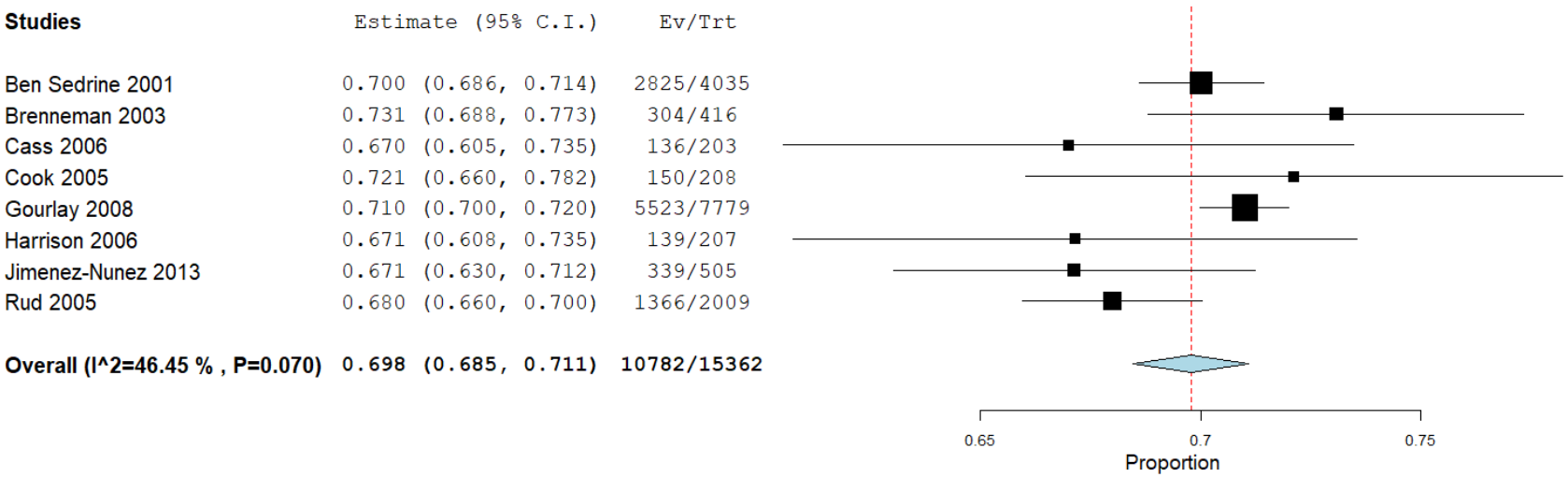
Appendix H Figure 3. Osteoporosis Self-Assessment Tool in Asians (OSTA) in Women



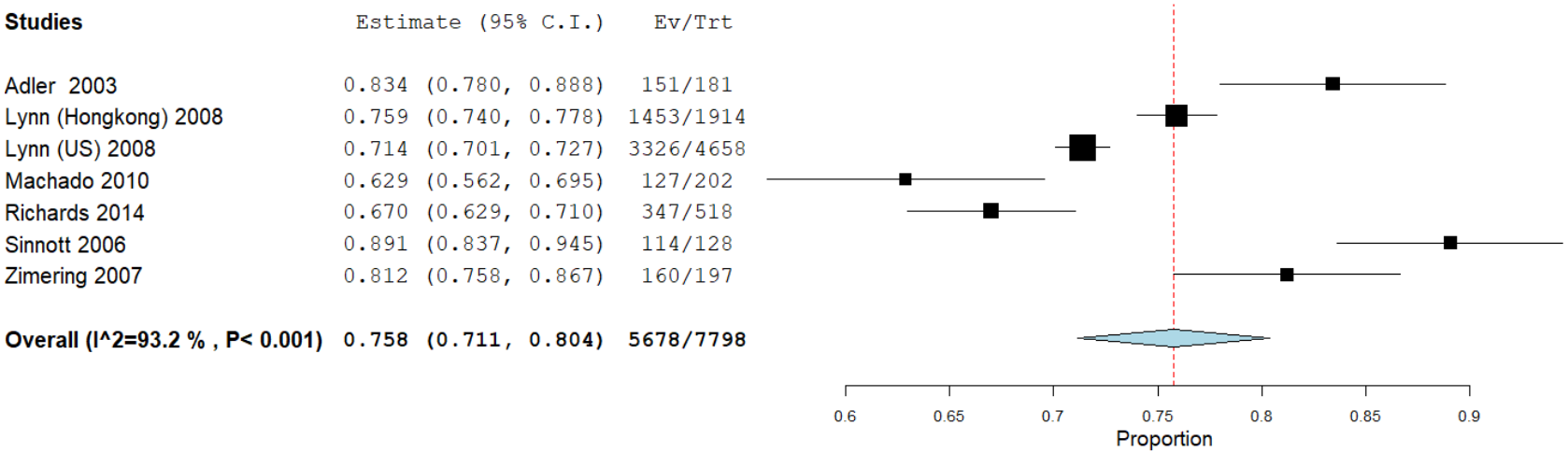
Appendix H Figure 4. Osteoporosis Self-Assessment Tool (OST) in Women



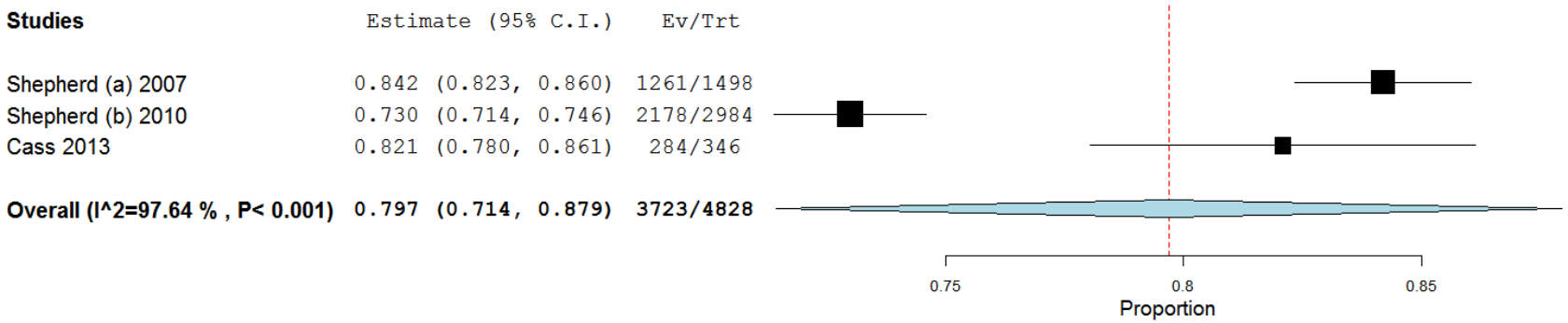
Appendix H Figure 5. Simple Calculated Osteoporosis Risk Estimation (SCORE) in Women



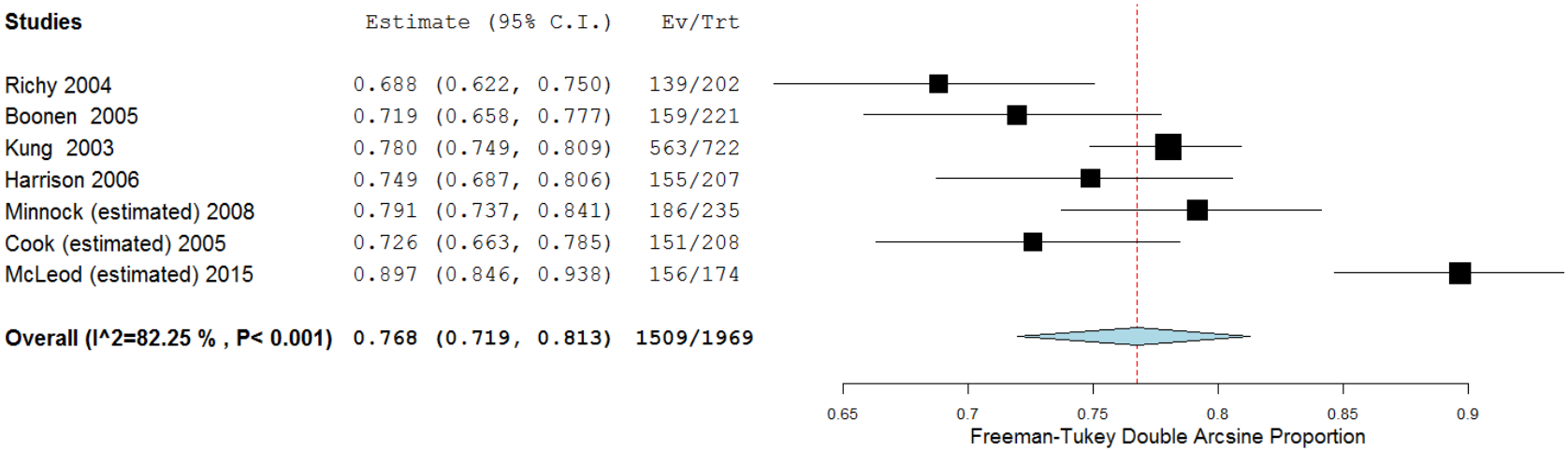
Appendix H Figure 6. OST in Men



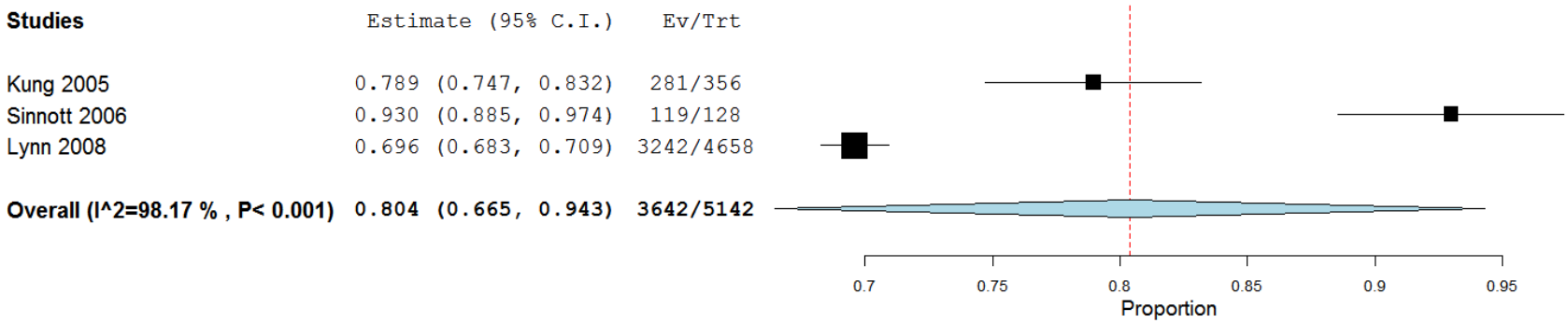
Appendix H Figure 7. Male Osteoporosis Risk Estimation Score (MORES) in Men



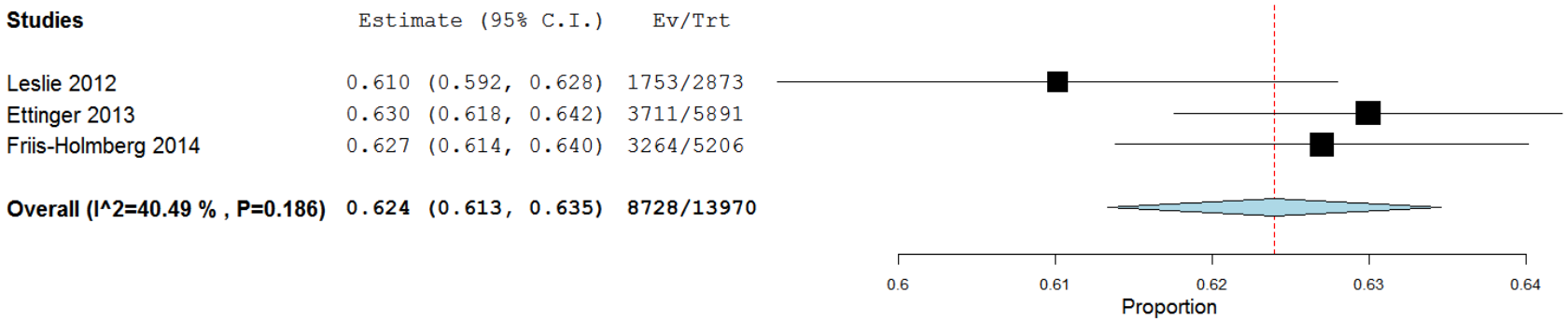
Appendix H Figure 8. Quantitative Ultrasound for Screening Osteoporosis for Women



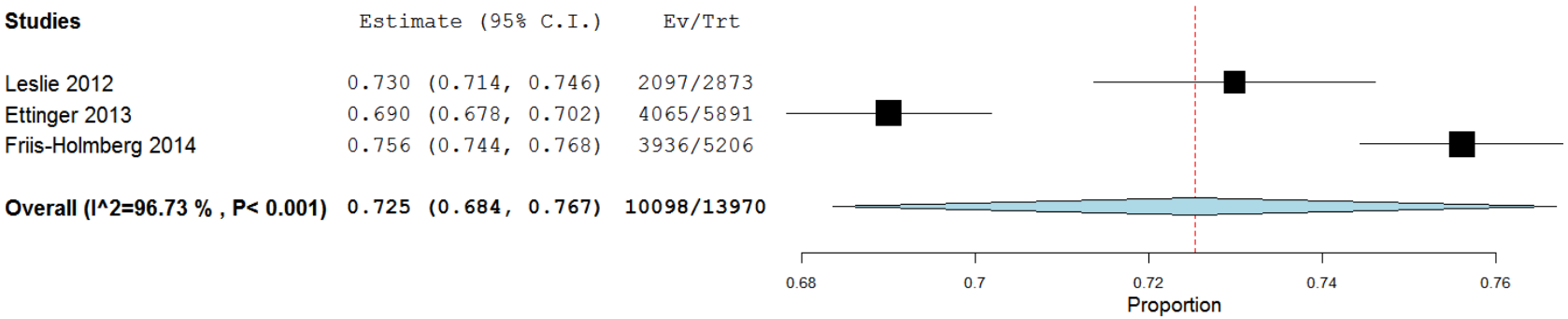
Appendix H Figure 9. Quantitative Ultrasound for Screening Osteoporosis for Men



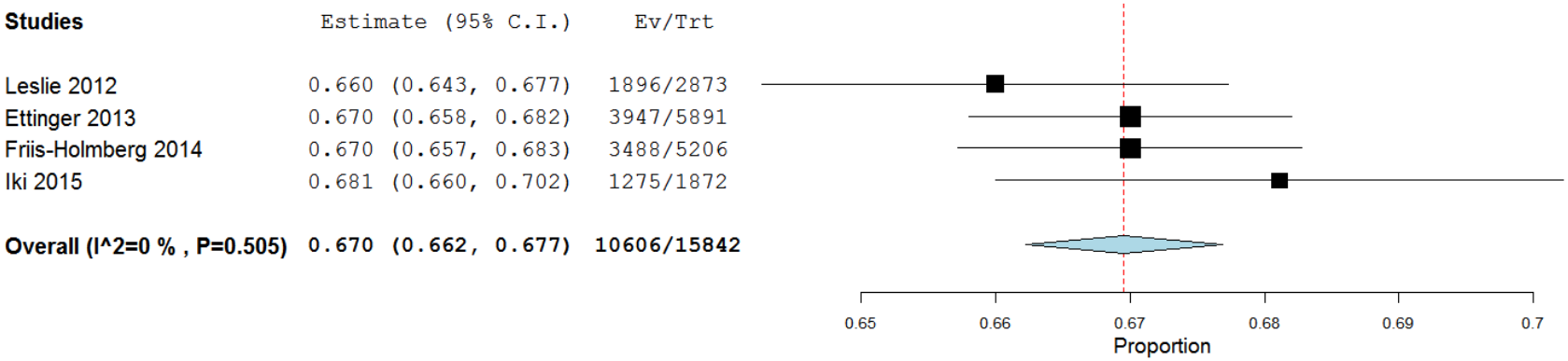
Appendix H Figure 10. FRAX Without Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Men



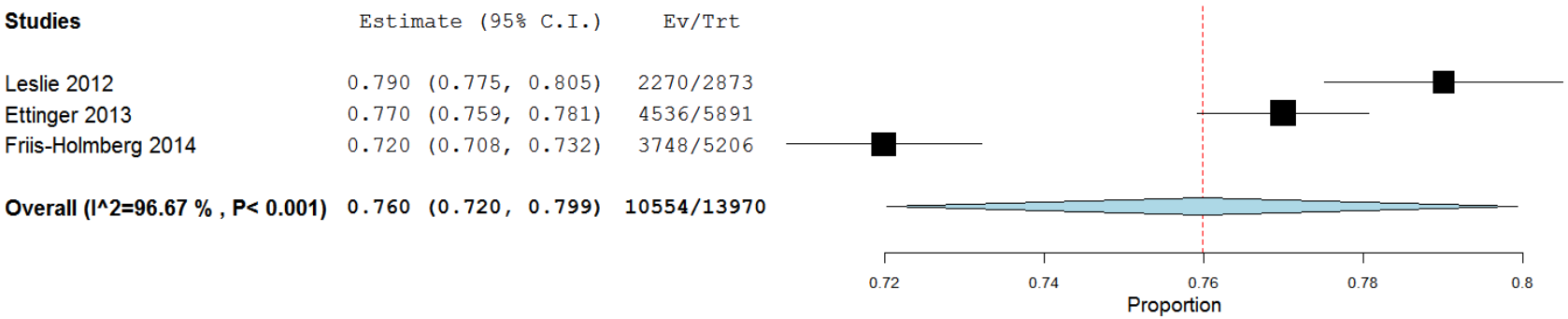
Appendix H Figure 11. FRAX Without Bone Mineral Density Testing for Predicting Hip Fractures in Men



Appendix H Figure 12. FRAX With Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Men

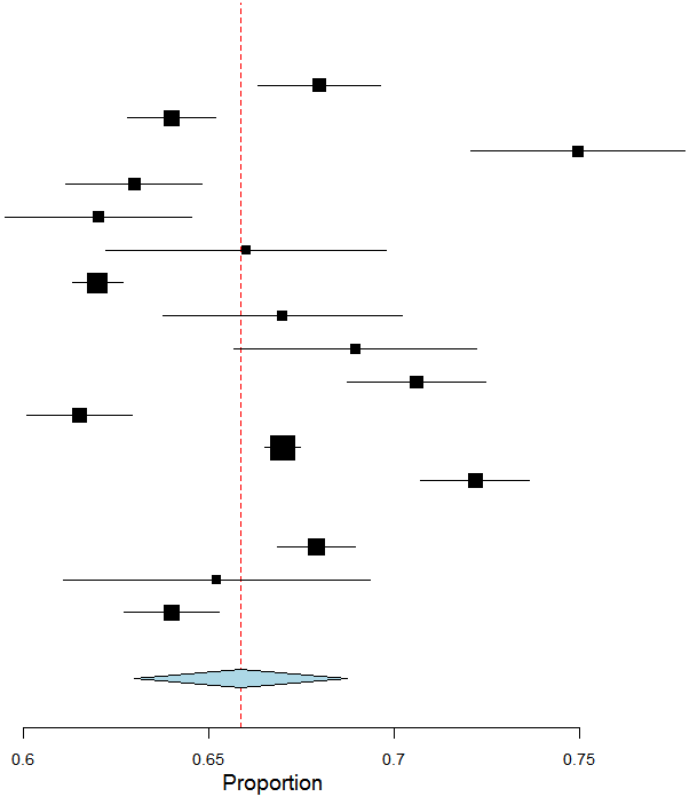


Appendix H Figure 13. FRAX With Bone Mineral Density for Predicting Hip Fractures in Men

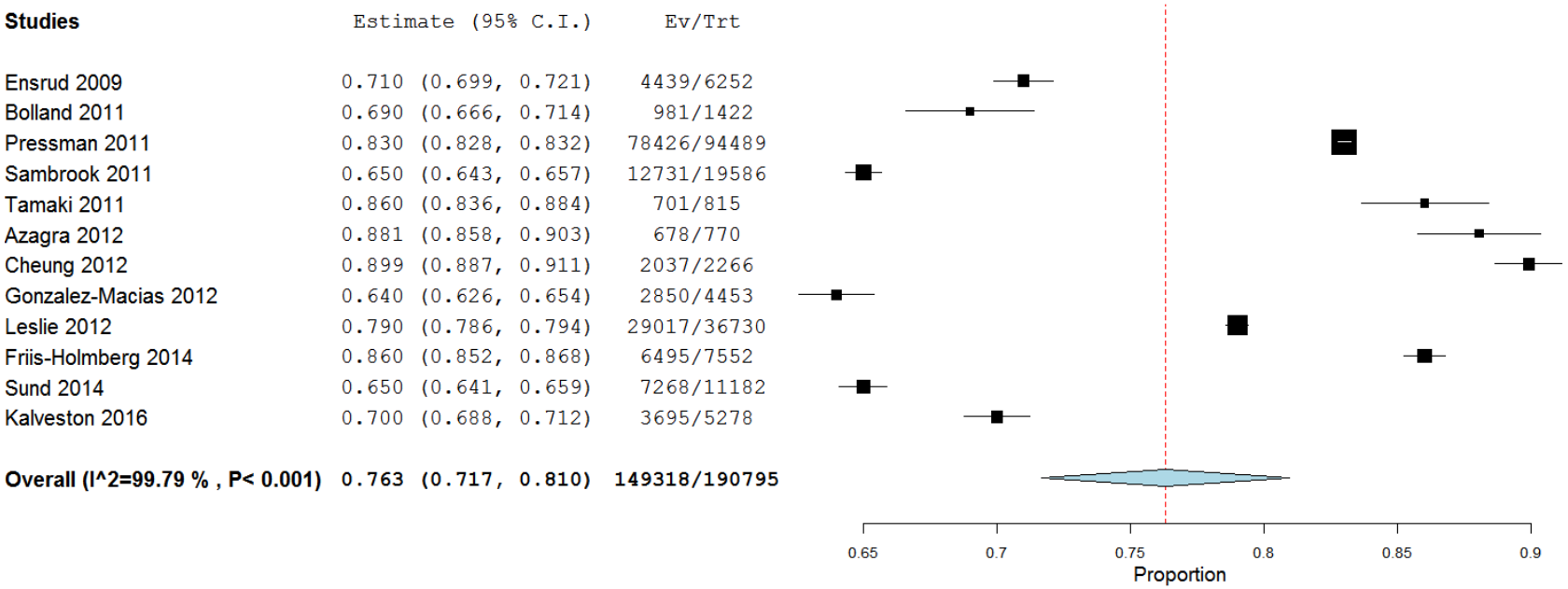


Appendix H Figure 14. FRAX Without Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Women

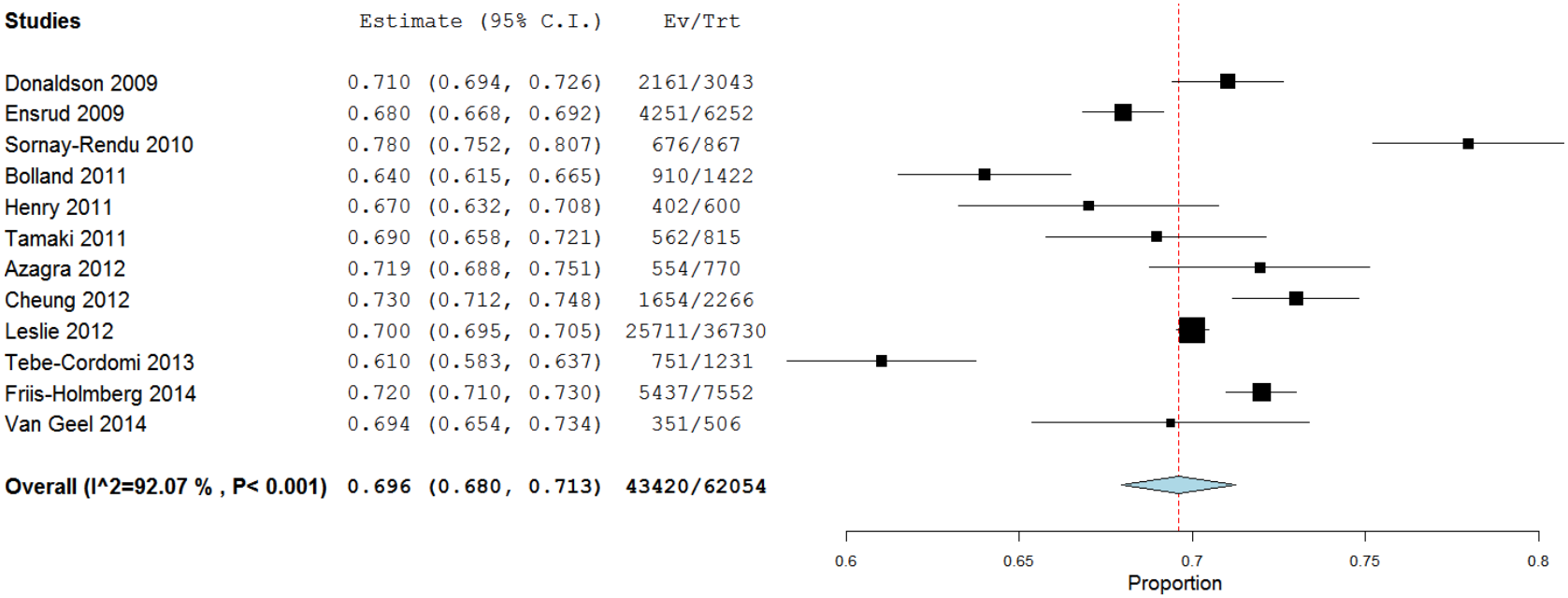
Studies	Estimate (95% C.I.)	Ev/Trt
Donaldson 2009	0.680 (0.663, 0.696)	2069/3043
Ensrud 2009	0.640 (0.628, 0.652)	4001/6252
Sornay-Rendu 2010	0.750 (0.721, 0.779)	650/867
Tremollieres 2010	0.630 (0.612, 0.648)	1670/2651
Bolland 2011	0.620 (0.595, 0.645)	882/1422
Henry 2011	0.660 (0.622, 0.698)	396/600
Sambrook 2011	0.620 (0.613, 0.627)	12143/19586
Tamaki 2011	0.670 (0.638, 0.702)	546/815
Azagra 2012	0.690 (0.657, 0.722)	531/770
Cheung 2012	0.706 (0.687, 0.725)	1600/2266
Gonzalez-Macias 2012	0.615 (0.601, 0.629)	2739/4453
Leslie 2012	0.670 (0.665, 0.675)	24609/36730
Rubin 2013	0.722 (0.707, 0.737)	2609/3614
Crandall 2014	0.560 (0.556, 0.564)	34996/62492
Friis-Holmberg 2014	0.679 (0.668, 0.690)	5128/7552
Van Geel 2014	0.652 (0.611, 0.694)	330/506
Kalveston 2016	0.640 (0.627, 0.653)	3378/5278
Overall (I^2=99.16 % , P< 0.001)	**0.659 (0.630, 0.687)**	**98277/158897**



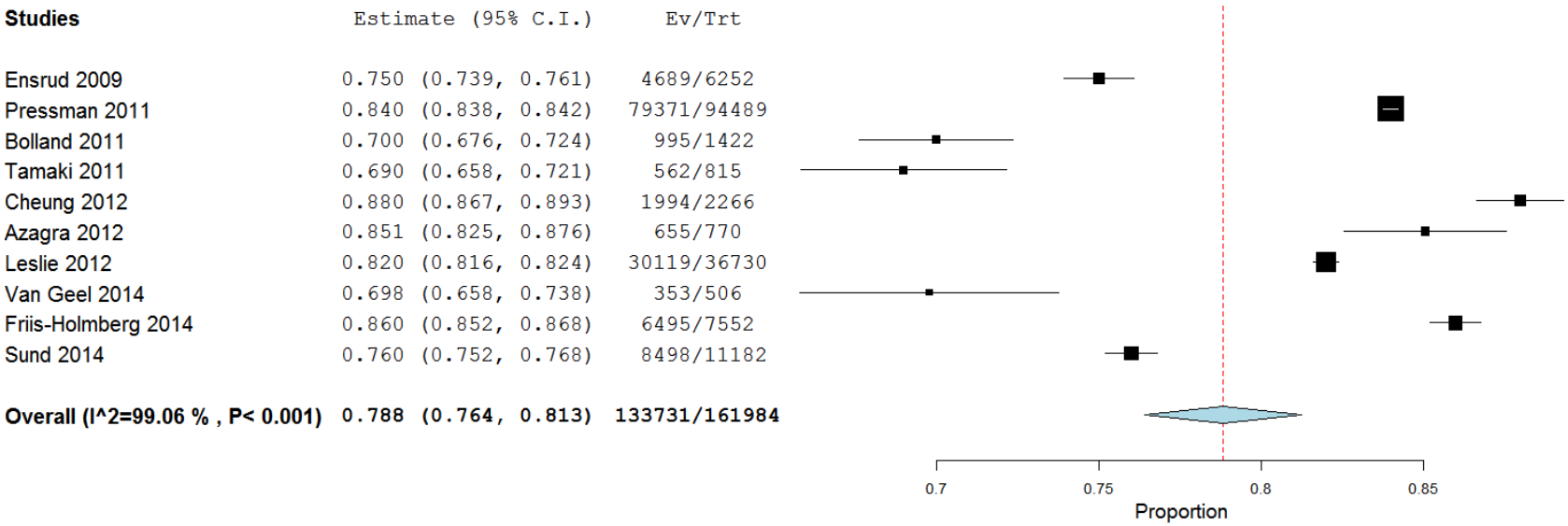
Appendix H Figure 15. FRAX Without Bone Mineral Density Testing for Predicting Hip Fractures in Women



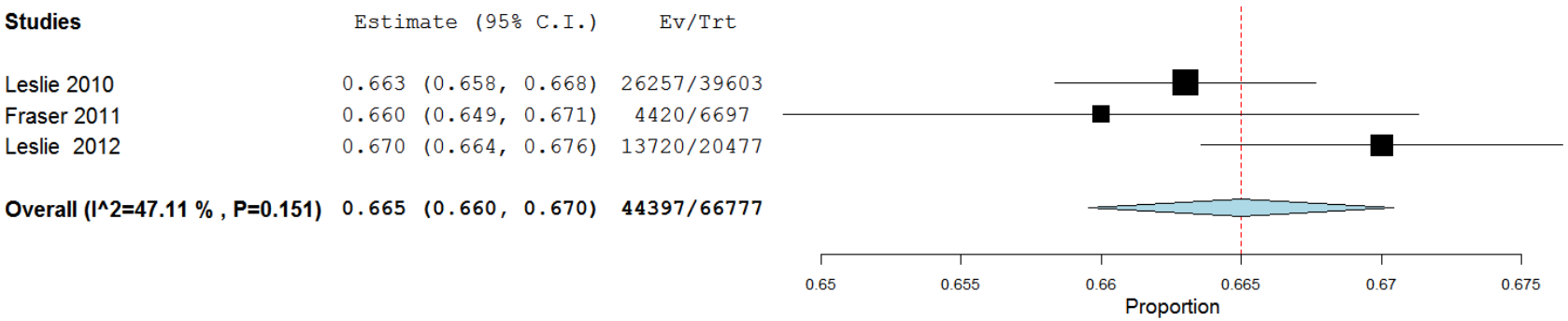
Appendix H Figure 16. FRAX With Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Women



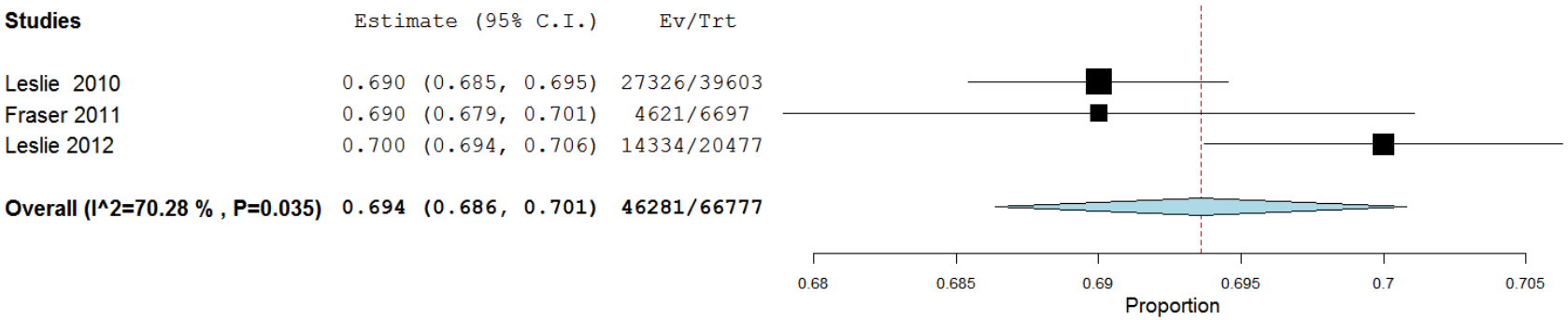
Appendix H Figure 17. FRAX With Bone Mineral Density Testing for Predicting Hip Fractures in Women



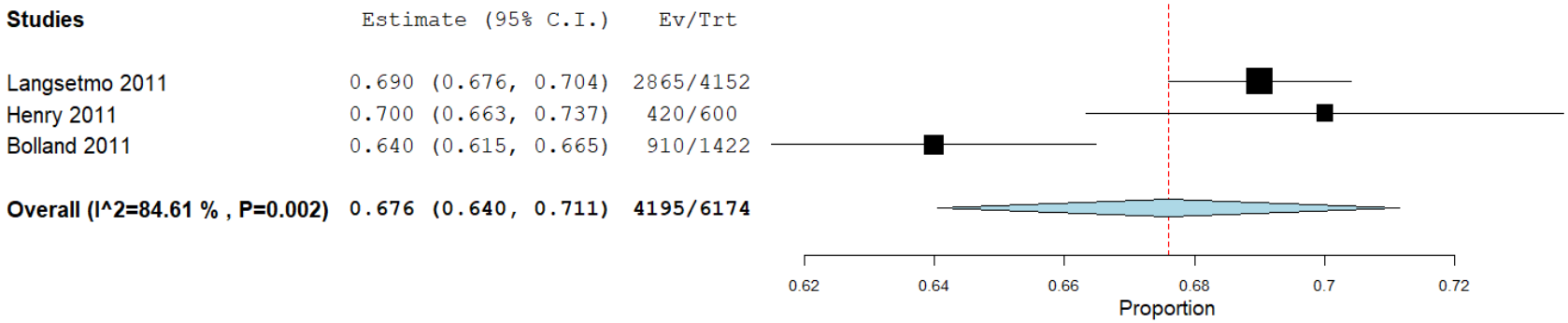
Appendix H Figure 18. FRAX Without Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Both Sexes



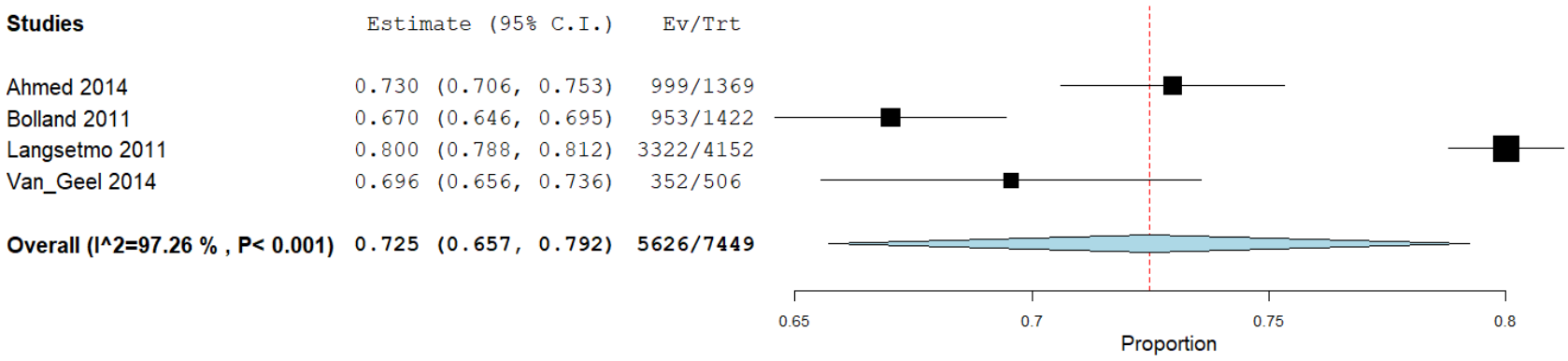
Appendix H Figure 19. FRAX With Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Both Sexes



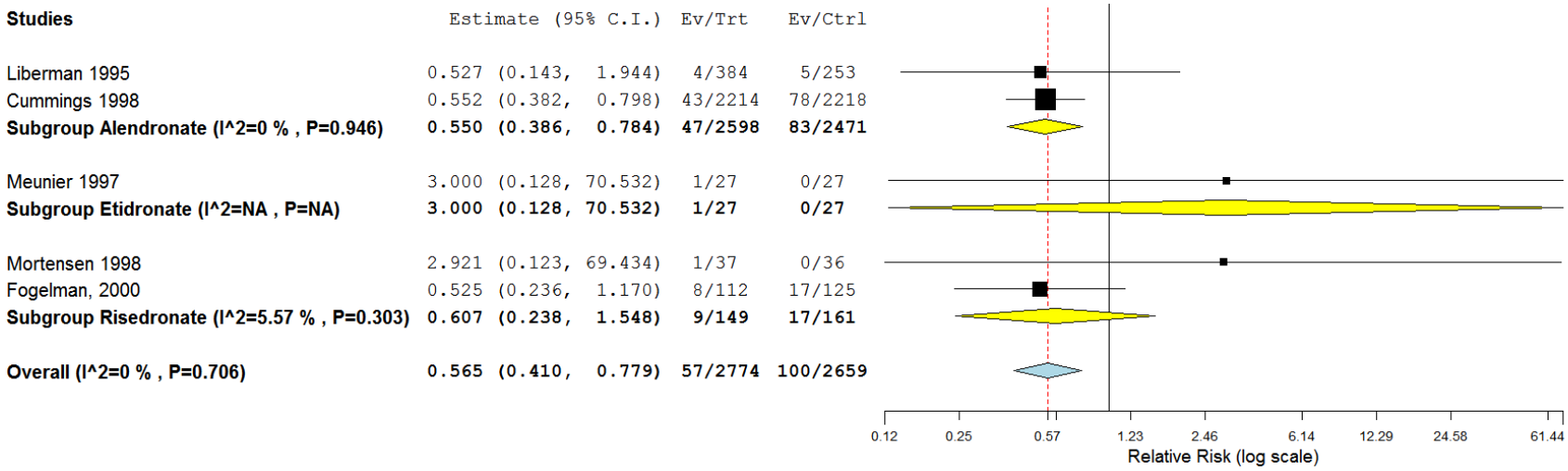
Appendix H Figure 20. Garvan Fracture Risk Calculator With Bone Mineral Density Testing for Predicting Major Osteoporotic Fractures in Women



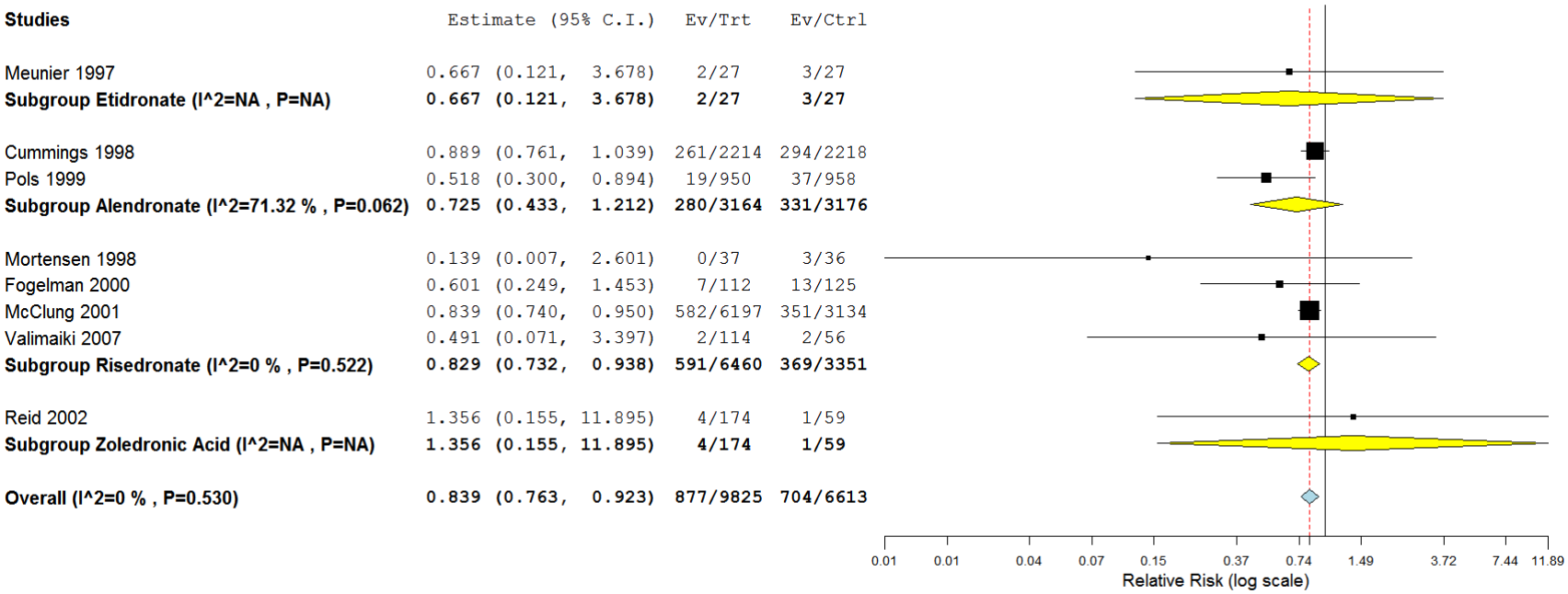
Appendix H Figure 21. Garvan Fracture Risk Calculator With Bone Mineral Density Testing for Predicting Hip Fractures in Women



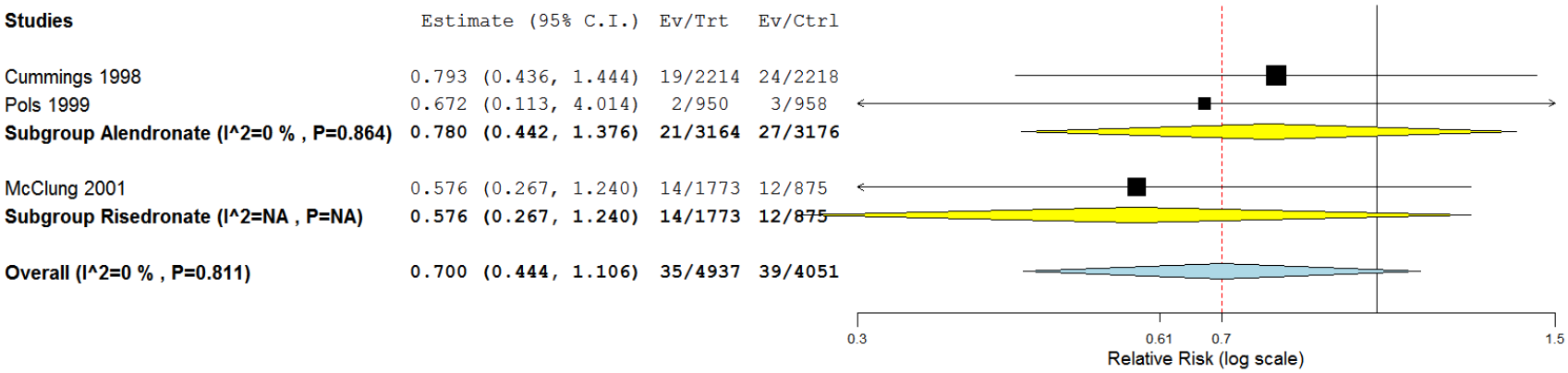
Appendix H Figure 22. Vertebral Fracture Outcomes for Bisphosphonates



Appendix H Figure 23. Nonvertebral Fracture Outcomes for Bisphosphonates

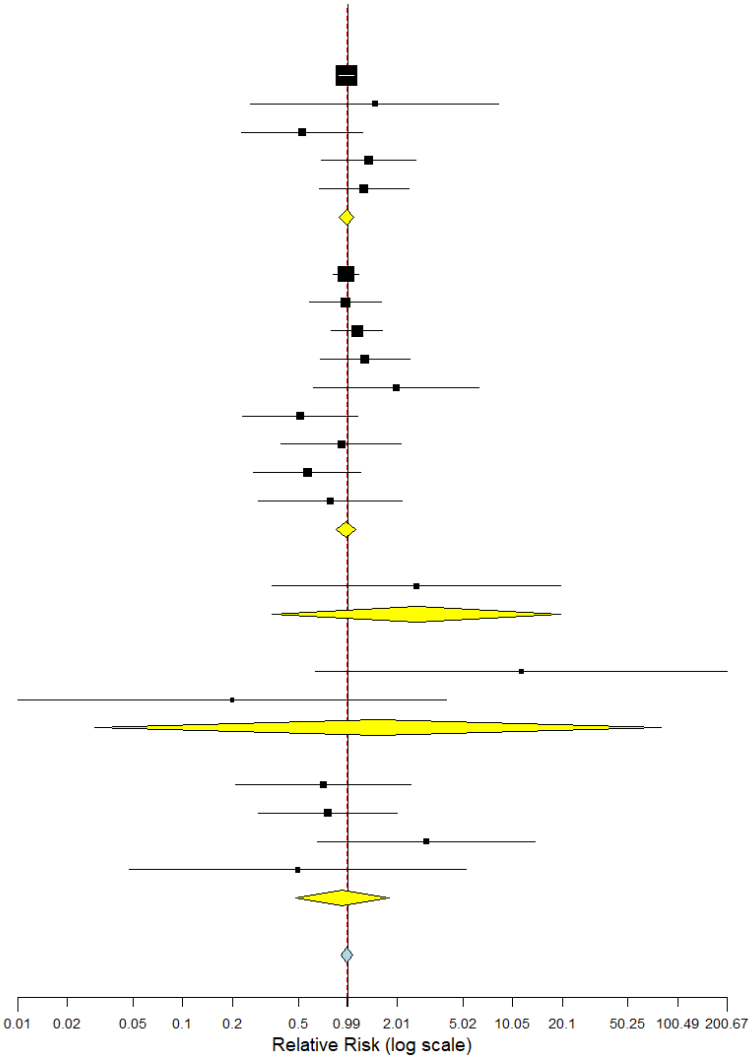


Appendix H Figure 24. Hip Fracture Outcomes for Bisphosphonates

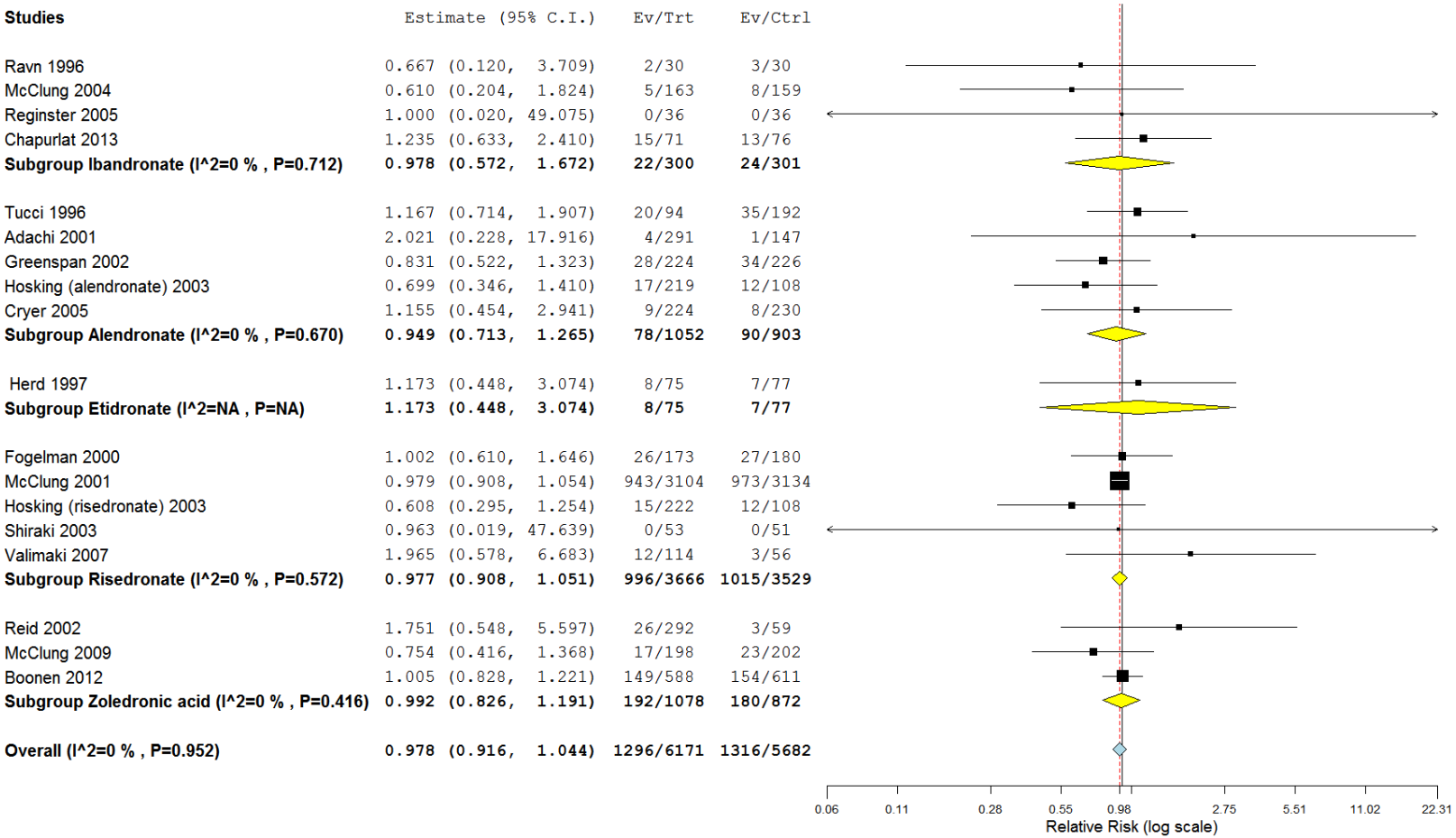


Appendix H Figure 25. Discontinuation Due to Adverse Events for Bisphosphonates vs. Placebo

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
McClung 2001	0.985 (0.885, 1.095)	550/3104	564/3134
Mortensen 1998	1.459 (0.259, 8.227)	3/37	2/36
Valimaki 2007	0.531 (0.229, 1.232)	10/115	9/55
Fogelman 2000	1.342 (0.695, 2.590)	19/175	14/173
Hosking (risedronate) 2003	1.257 (0.672, 2.349)	31/222	12/108
Subgroup Risedronate (I^2=0 % , P=0.450)	**0.991 (0.894, 1.098)**	**613/3653**	**601/3506**
Cummings 1998	0.975 (0.818, 1.163)	221/2214	227/2218
Liberman 1995	0.970 (0.586, 1.605)	35/597	24/397
Pols 1999	1.139 (0.799, 1.625)	61/950	54/958
Hosking (alendronate) 2003	1.274 (0.682, 2.381)	31/219	12/108
Johnell 2002	1.976 (0.619, 6.308)	8/83	4/82
Ascott-Evans 2003	0.516 (0.230, 1.155)	10/95	10/49
Greenspan 2002	0.917 (0.397, 2.117)	10/224	11/226
Cryer 2005	0.570 (0.269, 1.209)	10/224	18/230
Tucci 1996	0.786 (0.289, 2.139)	5/94	13/192
Subgroup Alendronate (I^2=0 % , P=0.492)	**0.979 (0.853, 1.122)**	**391/4700**	**373/4460**
Reid 2002	2.627 (0.350, 19.695)	13/292	1/59
Subgroup Zoledronic acid (I^2=NA , P=NA)	**2.627 (0.350, 19.695)**	**13/292**	**1/59**
Herd 1997	11.289 (0.635, 200.666)	5/75	0/77
Meunier 1997	0.200 (0.010, 3.980)	0/27	2/27
Subgroup Etidronate (I^2=72.43 % , P=0.057)	**1.535 (0.029, 79.916)**	**5/102**	**2/104**
Chapurlat 2013	0.714 (0.210, 2.425)	4/71	6/76
McClung 2004	0.759 (0.290, 1.988)	7/163	9/159
Ravn 1996	3.000 (0.657, 13.692)	6/30	2/30
Reginster 2005	0.500 (0.047, 5.272)	1/36	2/36
Subgroup Ibandronate (I^2=0 % , P=0.407)	**0.930 (0.485, 1.783)**	**18/300**	**19/301**
Overall (I^2=0 % , P=0.534)	**0.988 (0.911, 1.072)**	**1040/9047**	**996/8430**

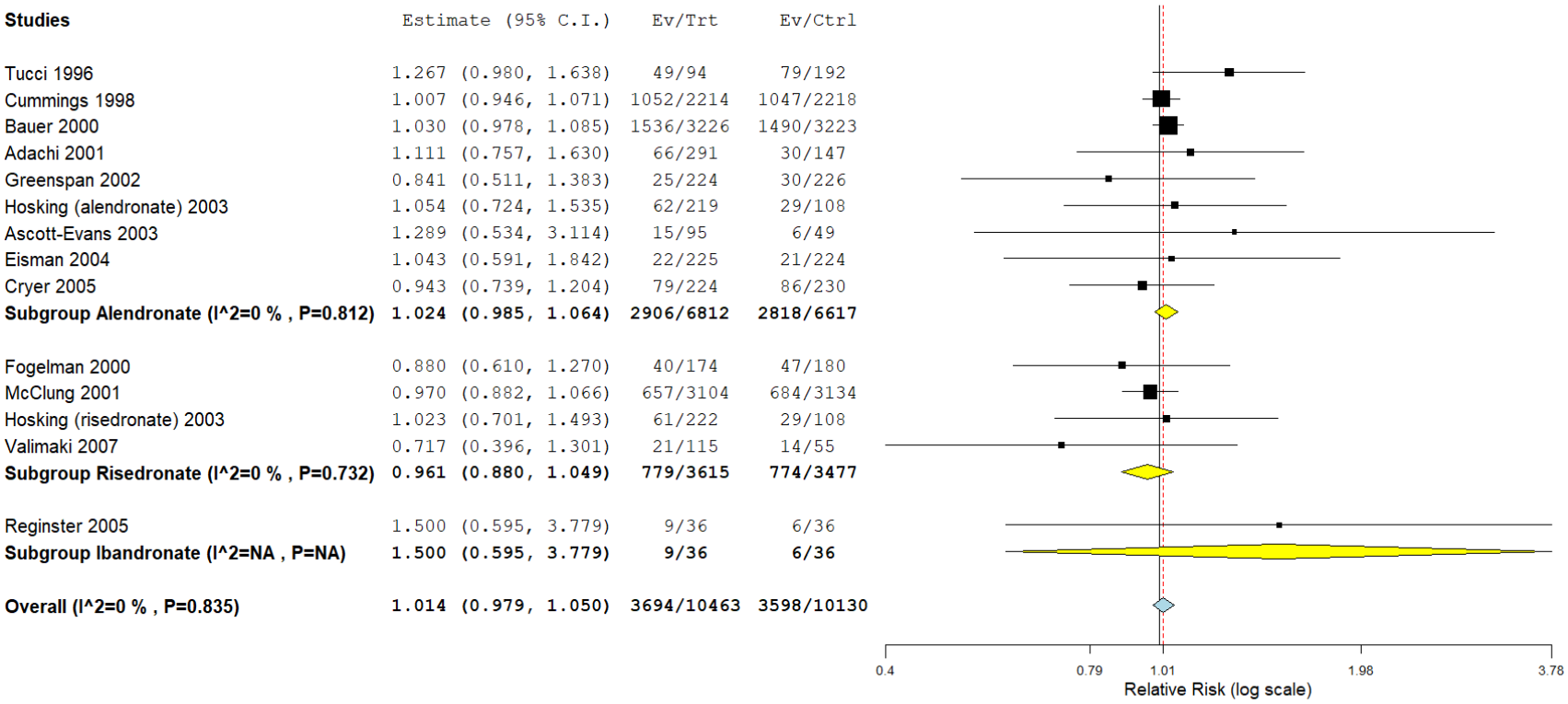


Appendix H Figure 26. Serious Adverse Events for Bisphosphonates vs. Placebo

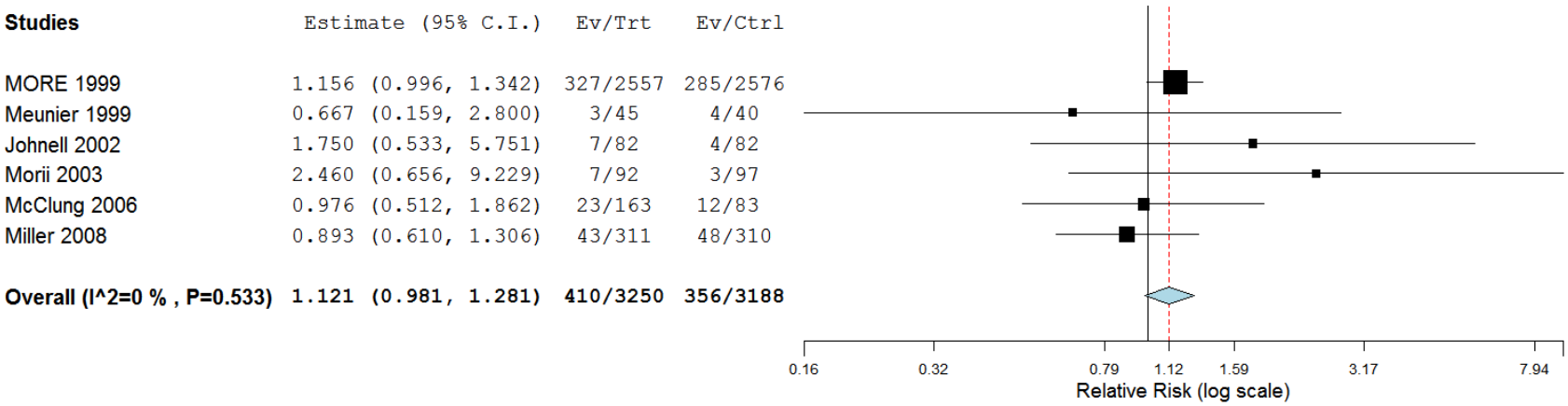


Note: Greenspan et al. present data on drug-related adverse events (serious adverse events were not drug related)

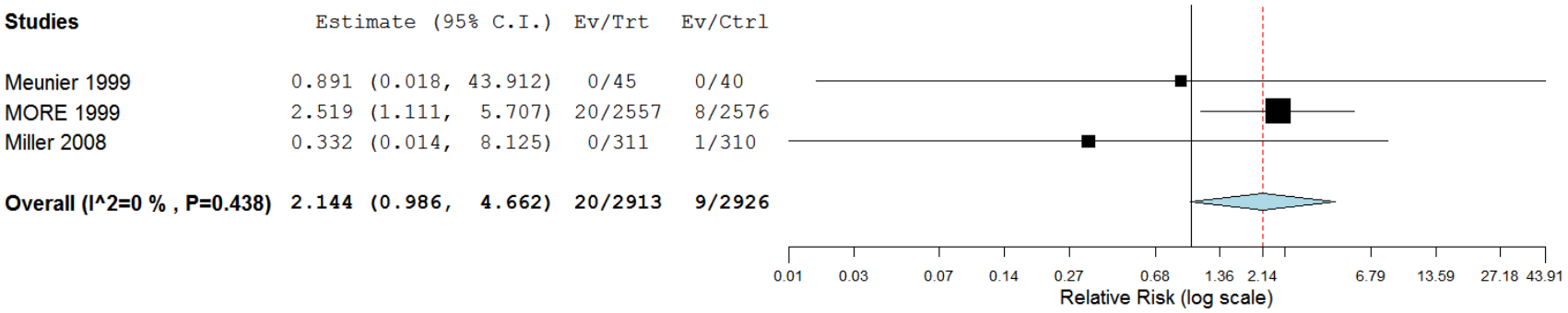
Appendix H Figure 27. Upper Gastrointestinal Events for Bisphosphonates vs. Placebo



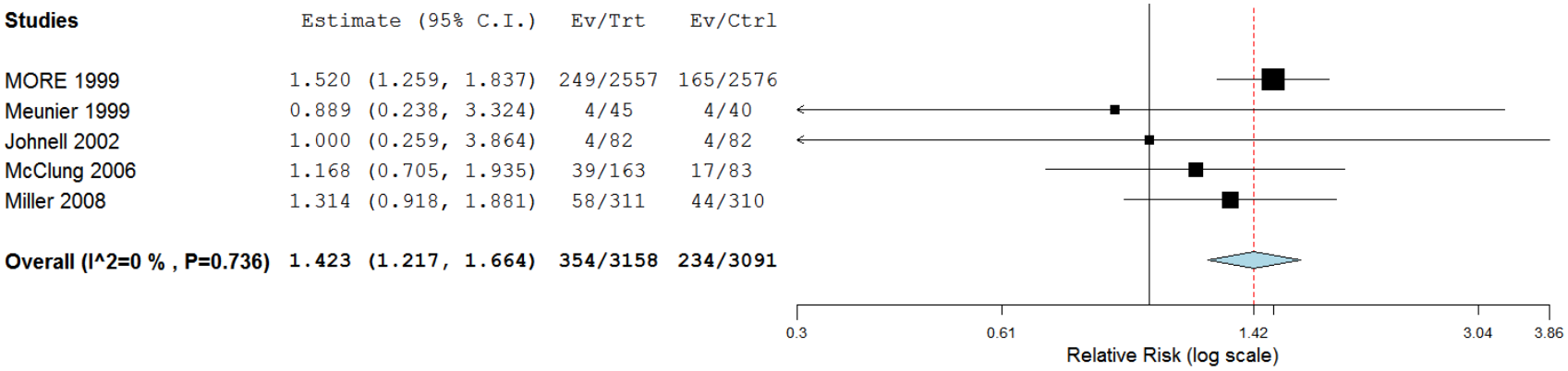
Appendix H Figure 28. Discontinuations Due to Adverse Events for Raloxifene vs. Placebo



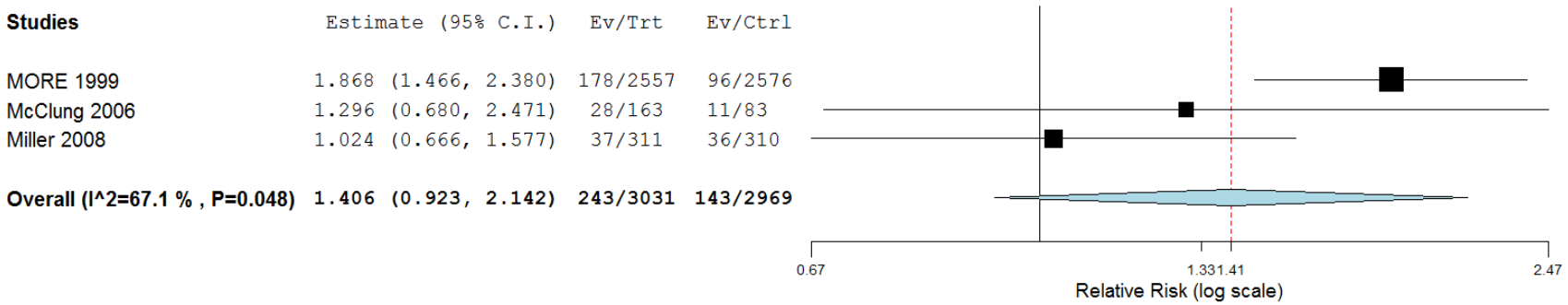
Appendix H Figure 29. Deep Vein Thrombosis for Raloxifene vs. Placebo



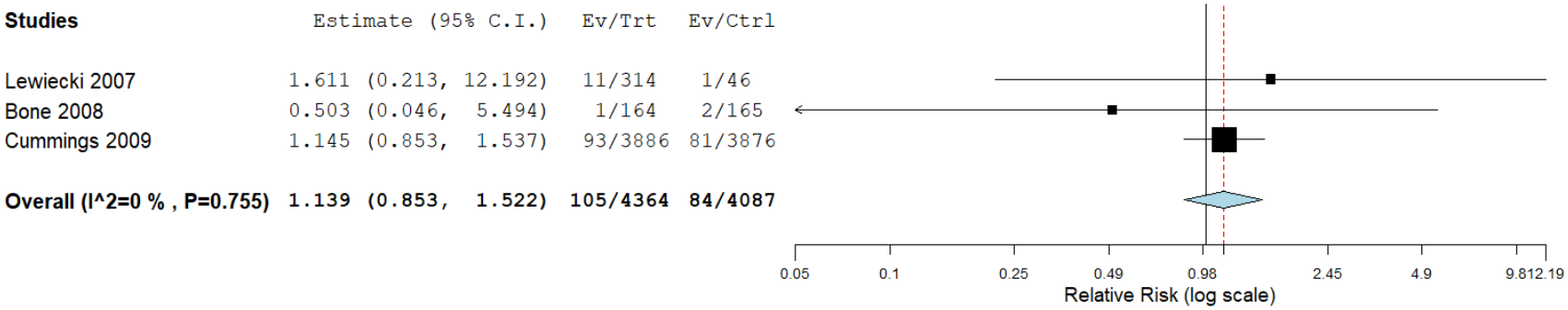
Appendix H Figure 30. Hot Flashes for Raloxifene vs. Placebo



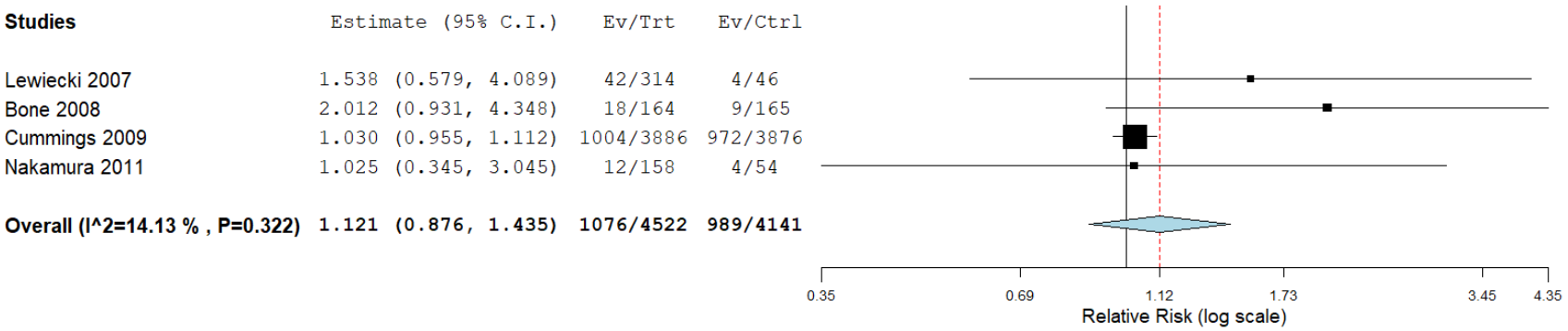
Appendix H Figure 31. Leg Cramps for Raloxifene vs. Placebo



Appendix H Figure 32. Discontinuations Due to Adverse Events for Denosumab vs. Placebo



Appendix H Figure 33. Serious Adverse Events for Denosumab vs. Placebo



Appendix H Figure 34. Serious Infections for Denosumab vs. Placebo