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

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

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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: MEDLINE, the Cochrane Library, Embase, and trial registries from November 1, 2009, through October 1, 2016 and surveillance of the literature through September 26, 2017; 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: We did not identify any fair or good quality studies that compared screening with no screening. We included 153 studies (in 161 articles) of fair or good quality; 96 (in 100 articles) assessed screening accuracy and 61 (in 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 0.70 and for men from 0.75 to 0.80. AUCs for the accuracy of calcaneal quantitative ultrasound in identifying central DXA–measured osteoporosis for women is 0.77 (95% confidence interval [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; 24studies). 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% to 68%. 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% to 20% by bisphosphonates and denosumab (RR: 0.84 and 0.80, respectively). The risk

of hip fractures can be reduced by 40% 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% 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 by lack of information 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: We did not find studies of either good or fair quality evaluating the direct benefits and harms of screening for osteoporotic fracture risk. 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% to 36%, 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 that treatment to increase bone mass and prevent further losses 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 computerized 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 only FDA-approved therapeutic agent with an anabolic mechanism of action is parathyroid hormone (PTH), specifically teriparatide, which is a human recombinant PTH fragment (1-34 N-terminal amino acid sequence).

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.[40] Several other potential targets for increasing bone mass have been identified and several drug candidates are in phase III trials.[41] 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.[42]

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.[43]

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.[44] 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.[45] The 2011 USPSTF recommendation,[1] along with a small minority of other guidelines (Scottish Intercollegiate Guidelines Network,[46] the Michigan Quality Improvement Consortium,[47] the American Academy of Family Physicians,[48] and the Institute for Clinical Systems Improvement)[49] 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.[50] 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)[51] 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;[52] 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.[53] 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.[54] 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.[55] 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 using a lower threshold of FRAX for DXA screening (6.5%) also had an improved sensitivity of nearly 90% for identifying osteoporosis but a poor specificity (37.1%).[56]

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]

We identified one study examining the accuracy of FRAX, including femoral hip BMD, in predicting osteoporosis.[59] Although this study is not eligible for the review of accuracy of instruments identifying osteoporosis because it includes BMD in the FRAX assessment, the authors noted that there was a general concordance between FRAX with BMD and BMD alone, indicating that the use of FRAX may be acceptable to identify patients for treatment even if BMD is not ≤ -2.5.

A Canadian study examined the accuracy of FRAX with and without femoral hip BMD in predicting recurrent fracture[60] among 1,399 men and women, ages 59 to 69 years (median 67

years) enrolled at the time of the incident fracture. FRAX scores were calculated based on prefracture characteristics and after the incident fracture. A high-risk score was FRAX > 20 percent or hip FRAX ≥ 3 percent. FRAX without BMD was calculated for all patients and calculated with BMD among 302 participants. Among patients with major fragility fractures, only 50 percent were estimated at high risk; 43 percent were estimated at moderate or low risk. Postfracture scores were not highly predictive of a recurrent fracture.

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 MEDLINE® (via PubMed), the Cochrane Library, Embase, and the Cumulative Index to Nursing and Allied Health Literature for English-language articles published from November 1, 2009, through October 1, 2016, with active surveillance through September 25, 2017. 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.[61]

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.[62] 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.[63] 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.[64]

For screening studies (KQ 2) assessing diagnostic test accuracy, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool;[65] for diagnostic prediction model studies, we used a preliminary version of the in-development Prediction Model Study Risk of Bias Assessment Tool (PROBAST).[66] 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,[65, 67] 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.[68]

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.[69, 70] 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.[63] 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.[71] All quantitative analyses were conducted using OpenMetaAnalyst.[72] We additionally conducted sensitivity analyses using Comprehensive Meta Analysis.[73]

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.

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 5,203 unique records and assessed 838 full texts for eligibility (**Figure 2**). We excluded 677 studies for various reasons detailed in **Appendix C** and included 153 (in 161 articles) published studies of good or fair quality in our main analyses. In addition to the previous report[2, 3], no included studies were relevant for key question (KQ) 1, 93 studies (in 96 articles) were relevant for KQ 2a, 2 studies were relevant for KQ 2b, 0 studies were relevant for KQ 3, 22 studies (in 26 articles) were relevant for KQ 4, and 49 studies (in 51 articles) were relevant for KQ 5. 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?

As in the previous review,[3] we found no good or fair quality randomized controlled trials (RCTs), controlled clinical trials, or systematic eligible for KQ 1. An unpublished study in process, the Screening for Osteoporosis in Older Women for the Prevention of Fracture [SCOOP] trial)[74, 75] planned to enroll more than11,000 women ages 70 to 85 years and will use the Fracture Risk Assessment Tool (FRAX) tool and dual-energy X-ray absorptiometry (DXA) to assess the 10-year probability of fracture.[74]

Of the studies that did not meet our quality or design criteria, 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) in the subset with data available over the course of followup (calculated rate for screening 3.96% [47/1,184], followup = 9.1 years; calculated rate for control = 4.03% [50/1,241], followup = 8.8 years; calculated relative risk [RR], 1.00, 95% confidence interval [CI], 0.983 to 1.02).[76] We summed hip, wrist, vertebral, and humeral fractures to obtain major osteoporotic fractures and used percentages for the no-fracture category to infer the total numbers for the analysis because the study did not report the denominator directly. The study's attrition exceeded 40 percent.

Additionally, we identified one cohort study that did not meet our prespecified study design criteria for KQ 1.[77] This study, using a nonconcurrent control, evaluated the effectiveness of screening for osteoporosis on reducing hip fractures in 3,107 women and men age 65 years or older. The study collected data prospectively but identified the hypothesis after data collection. As 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.

Participants with osteoporosis, hip fracture, or bisphosphonate use at baseline were excluded. The authors used propensity scores to adjust for baseline differences between the screened and usual care groups; notably, arms differed on several characteristics at baseline. Participants were followed for a mean duration of 4.9 years (range 3 days to 6 years). 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. Subgroup analyses suggest similar benefits of screening for women and men. Among age groups, the largest difference was reported for participants age 85 years or older, with an adjusted hazard of hip fracture 78 percent lower in screened versus usual participants (95% CI, 21 to 94; adjusted hazard ratio [HR] 0.22; 95% CI, 0.06 to 0.79; 3/100 vs. 18/115), although formal statistical testing of the interaction between age group and screening group was not significant.

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) bone measurement tests predicting fracture, and (4) fracture risk prediction instruments 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-five studies (comprising 37 publications)[56, 57, 78-112] provide information on the accuracy of 16 clinical risk assessment instruments in identifying osteoporosis (bone mineral density [BMD] T-score $\leq$-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 (13 studies), Canada (4 studies), the United Kingdom (2 studies), Australia (2 studies), Republic of Korea (3 studies), Italy (3 studies), Belgium (3 studies), Spain (2 studies), Hong Kong (2 studies), Denmark (1 study), the Netherlands (1 study), Singapore (1 study), Portugal (1 study), and one study conducted data in the United States and Hong Kong. Thirty-three reported area under the curve (AUC) and 32 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 (17 in clinics, 17 in community settings, 1 in both) 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%[89]). Four instruments (Mscore,[112] Male Osteoporosis Risk Estimation Score (MORES),[86, 110, 113] Male Osteoporosis Screening Tool (MOST),[98] and Osteoporosis Screening Test [OST]) reported results in men-only samples, with OST reported separately in predominantly Asian (Osteoporosis Screening Tool for Asians [OSTA])[97, 106] and other populations (OST).[78, 98, 99, 108, 111, 112] Two studies reported results for men and women for FRAX[56] and OSTA.[56] 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,[56] among those reporting a mean age (32 studies), the mean in most studies (22 studies, 69%) ranged between 60 and 70 years.

Accuracy of Clinical Risk Assessment Instruments in Identifying Osteoporosis: 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. 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 0.651 (Osteoporosis Risk Assessment Instrument [ORAI]; 10 studies; 16,680 participants) to 0.698 (Simple Calculated Osteoporosis Risk Estimation [SCORE]; 8 studies; 15,262) in women (AUCs from individual studies have a wider range from 0.32[89] to 0.873[107]). AUCs appear to be higher in studies recruiting men, ranging from 0.62[99] to 0.89.[111] The pooled estimate for OSTA is 0.747 (5 studies; 5,687 participants) and for MORES is 0.797 (3; 4,828). Instruments with more risk factors do not report higher AUCs than instruments with fewer risk factors.

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% to 100%, specificity from 10% to 75%, PPV from 20% to 98%, and NPV from 25% to 94%. 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[95-97, 102, 114] and six[88, 94, 98, 111, 115, 116] 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).[117, 118]

Seven of 11 studies included fewer than 250 patients.[88, 94, 102, 111, 114-116] Three studies, including the largest (N=6,572)[98] focused on men in the United States,[111] Hong Kong,[97] or both countries.[98] Studies of women were set in Belgium,[114, 116] Hong Kong,[96] Spain,[95]Canada,[102] and the United Kingdom.[88, 94, 115] Studies varied widely in the degree of restrictiveness of participant inclusion and exclusion. Two studies reported no exclusion criteria.[88, 102] In contrast, two studies set in Hong Kong reported an extensive list of inclusion and exclusion criteria.[96, 97] All were of low or unclear risk of bias.

Studies evaluated quantitative ultrasound (QUS),[88, 94, 96-98, 102, 111, 114, 115] peripheral DXA,[94, 95] digital X-ray absorptiometry (DXR),[114] and radiographic absorptiometry.[114] 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 7**). We were unable to replicate reported confidence intervals in three studies,[88, 102, 115] 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;[94, 95] DXR with an AUC of 0.84 (95% CI, 0.79 to 0.89);[114] and radiographic absorptiometry with an AUC of 0.80 (95% CI, 0.74 to 0.85).[114]

All studies in men focused on comparisons of calcaneal QUS to a centrally-measured DXA BMD T-score cutoff of -2.5 or less.[97, 98, 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 8**).

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,[119, 120] evaluating the performance of various bone measurement tests for predicting fractures (summary in **Table 5**; details in **Appendix F Table 7**).[119-142] 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,[131] and Ensrud et al. did not present risk estimates separately for BMD alone.[138] We rated one other study as high risk of bias and did not include it in our update.[143] 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,[120, 142] one in Scotland,[119] four in Japan,[121, 127, 137, 140] three in Canada,[122, 123, 133, 139] two in Hong Kong,[124, 136] two in Australia,[125, 126, 129] one in Finland,[128] two in France,[130, 132] one in Denmark,[134] one in Sweden,[141]one in New Zealand,[87] and one in Spain.[135]

The Canadian Manitoba study of men and women age 50 years or older was the largest study (N=39,603).[133]

One study only reported data on men and women combined.[139] 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 5**). 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.[141] 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[120, 125] 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,[125] 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.[125] Four studies evaluating the performance of bone measurement tests for predicting fractures in men examined the same bone measurement screening tests used for women.[120, 124, 125, 134] 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.[120, 124] AUC estimates based on combinations of DXA and QUS, reported in two studies, ranged from 0.69 to 0.85.[120, 125]

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),[122, 123] middle phalanges of the second, third, and fourth fingers on the nondominant hand (0.83),[134] and the femoral neck (0.85 and 0.82).[136, 137] Similar results among

women were based on a combination of DXA of the femoral neck and QUS (0.81).[125] 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)[120] but these findings were not replicated in one study based on DXA of the middle phalanges (0.64).[134] AUC point estimates in two studies combined hip fracture results for men and women, based on DXA of the femoral neck (0.80[133] and 0.76[139]). 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,[125] 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.[129]

Accuracy of Fracture Risk Prediction Instruments: Overview

We identified five systematic reviews[117, 144-147] addressing the accuracy of tools to predict fracture in adults. Our synthesis is based on the good-quality Marques et al. systematic review[144] 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, 103, 142, 148-157] 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,[158] Fracture and Mortality Index,[159, 160] a simple clinical score,[161] and simplified system for fracture risk assessment.[162] 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, 142, 149, 154] and nine were studies we identified as eligible but were either not identified or not included by Marques et al.[103, 148, 150-153, 155-157] 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[163] included in the original pooled AUC estimate that was not from an external validation population, and one study[164] 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[165] assessing age, body size, and estrogen use, ORAI, and body weight as risk prediction instruments, and a study[166] assessing FRAX and Garvan FRC. Three studies[126, 167, 168] 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[169] 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 6**, we characterize and report the accuracy of fracture risk prediction at 10 years for 12 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 3-6**). Within that range, pooled estimates were higher for 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 6-10**). 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 11 and 12**). Two studies reported AUC for hip fracture with and without BMD from combined cohorts of men and women; estimates from these two studies[133, 139] 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,[163] 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.[154, 170] The AUC for hip fracture without BMD was 0.65 (95% CI, not reported [NR]; 1,285 men).[154] With BMD, the AUC for hip fracture was 0.74 (95% CI, NR; 1,285 men) in one study[154] and 0.85 (95% CI, NR; 1,606 men) in the other study.[170] Estimates of AUC for nonvertebral fractures were 0.61 and 0.57 with and without BMD, respectively (95% CI, NR for either).[154] Only one of the two studies reported AUC for MOF; the estimate was 0.70 (95% CI, NR; 1,606 men).[170]

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 13**) 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 14**). One study[149] reported an AUC of 0.69 (95% CI, NR; 506 women); a different study[154] 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.[149, 151, 154]

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.[171] A 2012 update to the instrument added previous fall, ethnicity, and 10 additional clinical risk factors.[155] 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.[144] For hip fracture, AUC estimates were 0.86 to 0.89 in men and was 0.89 in women.[144]

Other Fracture Risk Assessment Instruments

The remaining eight fracture risk assessments include the Women's Health Initiative algorithm,[172] OST,[173] SCORE,[174] Fracture and Immobilization Score,[140] Fracture Risk Score,[131] FRC,[175] ORAI,[176] and Osteoporosis Index of Risk (OSIRIS).[177] Of these, all but the Fracture Risk Calculator[175] 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, 103, 151, 153] and from 0.80 to 0.85 for hip fracture.[172, 178, 179]

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.[180] 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.[156] 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.

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).[103, 128, 129, 133, 135, 137, 139, 140, 150, 170, 181-185] Eleven reported calibration outcomes for FRAX (various versions);[128, 129 , 133, 135, 137, 139, 150, 181-185] four reported outcomes for other risk models.[103, 129, 140, 170] 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.[103, 148, 150, 152, 154-156, 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.[138, 156, 162, 186, 187] Others present reclassification rates[148, 188, 189] or net reclassification improvement (NRI).[121, 125, 152, 154, 170, 190, 191] 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.[192]

Other Measures of Test Performance: Findings

FRAX

Five studies evaluate reclassification for FRAX.[152, 170, 188, 189, 193] 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).[193] 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.[148] 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.[188, 189] 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.[189] 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.[189]

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.[188] 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).[188]

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.[152] 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).[190] 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 a 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,[125, 191] 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.[125] Participants been followed for a median of 13 years. The second study restricted analysis to nonosteoporotic participants (BMD T-score >-2.5).[191] 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,[125, 191] and for vertebral fractures in nonosteoporotic women only.[191] 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.[125] In nonosteoporotic women, adding BUA to the model resulted in an NRI of 0.164 for any fractures and 0.338 for hip fracture.[191] 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).[170] 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).[170] 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).[154] 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.[121] 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?

We found no eligible studies that addressed this question.

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.[75, 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 15**).[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 16**).[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 17**). The two large trials dominating this meta-analysis, FIT[200] and the study by McClung et al.[223] also

found no statistically significant effects. 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 safety trial that included an estrogen only arm in comparison with a placebo arm (N=193). It reported a lower 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 trials of denosumab (N=8,565) met eligibility criteria.[236-238] All were conducted in postmenopausal women with low bone mass or osteoporosis. All constituted phase 2 or phase 3 studies for the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. 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]

Denosumab: Findings

Two studies were not powered to look at fractures as benefits and found no statistically significant differences in fractures (clinical or osteoporotic fracture).[236, 237] The third 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, 239] 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[239] 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[240] 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[239] 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.[241]

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.[242, 243] 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).[242] 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).[242] The trial reported no statistically significant differences when comparing combined risk.[243]

Parathyroid Hormone

The two eligible trials did not report subgroup analysis by 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.

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, 244-251] and 2 studies in combined populations of women and men.[252, 253] We excluded several studies that were included in previous reviews for wrong study population,[215, 254-259] wrong intervention,[260] wrong comparator,[261-263] wrong outcome,[264] wrong setting,[265, 266] and wrong study design,[267] an older review that has been subsequently updated,[268] and high risk of bias.[216, 263, 269-271] Nine studies reported on discontinuations because of adverse effects.[199-202, 204, 244, 250-252] Five studies reported serious adverse effects.[202, 248, 250-252] Death was reported as a harm in two studies.[200, 248] 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, 248-253] Three studies reported cardiovascular outcomes, including chest pain,[244] myocardial infarction,[247] and atrial fibrillation.[246]

Zoledronic Acid

Four fair- or good-quality studies reported on harms: three studies in postmenopausal women[217, 272, 273] and one in men.[218] We excluded several studies that were included in previous reviews for wrong study population,[219, 220, 222, 274-278] wrong study design,[279] wrong comparator,[280] and an older review that has been subsequently updated.[268]

Only one study reported on discontinuation of zoledronic acid due to adverse events,[217] while

three studies reported serious adverse events.[217, 218, 273] Three studies reported on osteonecrosis of the jaw[218, 272, 273] and two on atrial fibrillation.[272, 273] Three studies examined myalgia and arthralgia.[218, 272, 273]

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, 281] 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.[281] 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.[228-230] 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).[282-288] All were conducted in postmenopausal women with no prior fractures[283, 284, 287, 288] or with unknown prior fracture history.[283, 285, 286] These studies differed in the menopausal categories of women enrolled: at least 1 year postmenopausal (two studies),[282, 283] at least 3 years postmenopausal (one study),[285] at least 5 years postmenopausal (two studies),[286, 288] at least 10 years postmenopausal (one study),[284] and 1 to 10 years postmenopausal (one study).[287] 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,[285] one evaluated 0.25 mg to 2.0 mg every 3 months over a 1-year period,[288] 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,[283, 286] one that evaluated intermittent dosages of 20 mg,[286] one that evaluated weekly dosages of 5 to 20 mg,[287] and one that evaluated monthly dosages of 150 mg.[282] Six of the included trials were set in Europe[282, 284-288] and one in the United States and Canada.[283] Four trials[282-285] reported on the discontinuation of participants by treatment group and two studies reported only the number of discontinuations overall.[287, 288] Four trials[282-285] reported on serious adverse events by treatment group and two studies reported only serious adverse events overall.[287, 288] Six studies evaluated the risk of GI adverse events.[283-288] Only one trial reported on infection;[284] two reported on deaths.[285, 286]

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 18**). 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 19**). 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 20**). 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, 249, 252, 253] 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 but not statistically significant risk of atrial fibrillation in women (2.5% vs. 2.2%; RR, 1.14 [95% CI, 0.83 to 1.56]),[246] and one study of zoledronic acid in men with a similarly nonsignificant but elevated relative risk 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.[272, 273] 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.[245] Two ineligible systematic reviews[289, 290] sought additional data from two sets of investigators not included in their published results.[236, 291] 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, 272, 273] 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.[276, 279, 280, 292-296]

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).[297] 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,[298, 299] wrong comparator,[300, 301] wrong intervention,[302] wrong design).[261]

Two excluded systematic reviews, published in 2013[300] and 2015[301] 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)[300] to 1.99 (95% CIs, 1.28 to 3.10).[301] Both reviews reported very high heterogeneity (I^2 exceeding 80 percent), but only one review explored heterogeneity in greater detail.[300] 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.

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, 241, 244, 303-310] 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 21**). The pooled analysis suggests a trend toward increased risk for deep vein thromboses (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 22**). However, among the summarized 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.[304, 305] 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 23**) 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 24**).

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 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

Three studies reported on harms.[236-238, 311] 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 (3.1% vs. 2.1%; RR, 1.16 [95% CI, 0.88 to 1.54]; I^2, 0%; **Appendix H Figure 25**) or serious adverse events (23.7% vs. 24.0%; RR, 1.23; 95% CI, 0.78 to 1.93; I^2, 34.5%; **Appendix H Figure 26**). 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 27**). 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]).[311] Two trials evaluated the risk of rash or eczema. Both reported a higher rate 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]

Parathyroid Hormone: Overview of the Evidence

Two fair-quality studies[239, 8402] 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[239] was conducted among 437 men who were randomized to either placebo or one of two dosages of teriparatide (20 µg or 40 µg daily) for an average of 11 months (treatment ranged from less than two 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 (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 a RCT among 437 men,[239] 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-microgram 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

No studies met design or quality criteria for the overarching question on the benefits of screening on fractures and fracture-related morbidity and mortality (KQ 1). Preliminary 5-year results from the Screening for Osteoporosis in Older Women for the Prevention of Fracture (SCOOP) trial, from a conference abstract, suggest a reduced risk of hip fractures (2.6% v 3.5% hazard ratio [HR]=0.73, p=0.003) with routine screening for osteoporosis when compared with no routine screening, but it reported no differences between study arms for overall fracture incidence (12.9% vs. 13.6%, HR=0.93, p=0.199), mortality (8.8% vs. 8.4% HR=1.05, p=0.433) or quality of life (p=0.154). No additional details are available, so the certainty of these findings is unclear.[75]

We found no studies on harms of screening (KQ 3). The evidence on the benefits and harms of screening for osteoporotic fractures is therefore based on the accuracy of screening approaches (KQ 2) and the benefits and harms of treatment (KQs 4 and 5)

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 0.70 and for men from 0.75 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 or type of test. 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]

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);

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 zoledronic acid (RR: 0.33).[218] No studies demonstrate reductions in risk of clinical vertebral fractures or hip fractures for men. 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.[239] We found no studies reporting on 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 or atypical femur fractures, although evidence from excluded studies of populations, designs, and comparators outside the purview of this review suggests a rare but increased risk with bisphosphonates. 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, 312] 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.[312] 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).[313] 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[313] that examined the effectiveness of the DXA, Osteoporosis Self-Assessment Tool (OST), 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.[314]

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.[312] Cost-effectiveness studies suggest benefits from continuing to screen women in older age groups.[315, 316] 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.[315] 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.[316]

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

The evidence base is limited by lack of studies addressing the direct question of the benefits and harms of screening for osteoporotic fractures. In the absence of 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] Furthermore, 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, 317] 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.

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, in whom multiple clinical risk assessment tools perform no better than chance in identifying osteoporosis and predicting fractures and who are unlikely to benefit from frequent rescreening before age 65.Another important limitation of this evidence base is that it focuses on one of many approaches to averting osteoporotic fractures. A comprehensive approach may rely on screening, counseling, medication, physical therapy, and other interventions to prevent falls and improve physical function in older adults.

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.[74]

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

We did not find studies of either good or fair quality evaluating the direct benefits and harms of screening for osteoporotic fracture risk. 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. Screening for osteoporosis: analytic framework

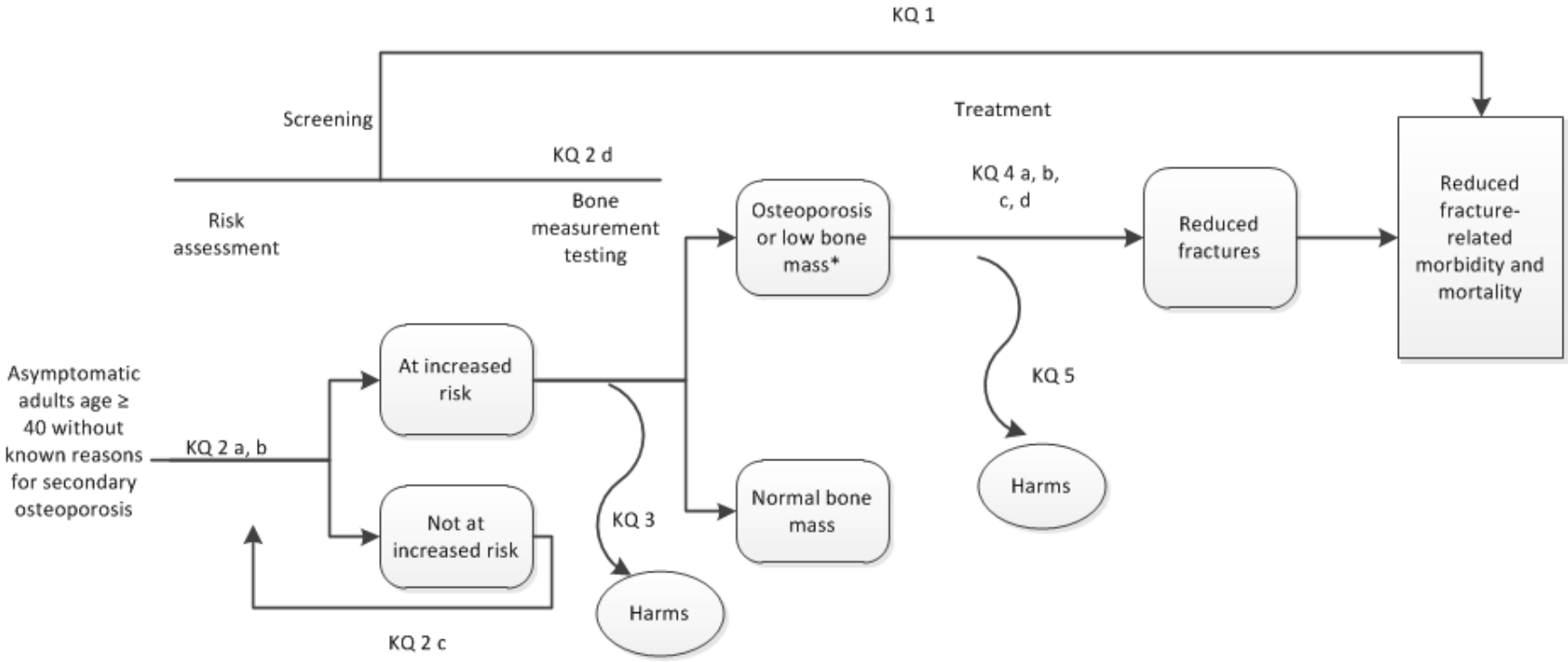
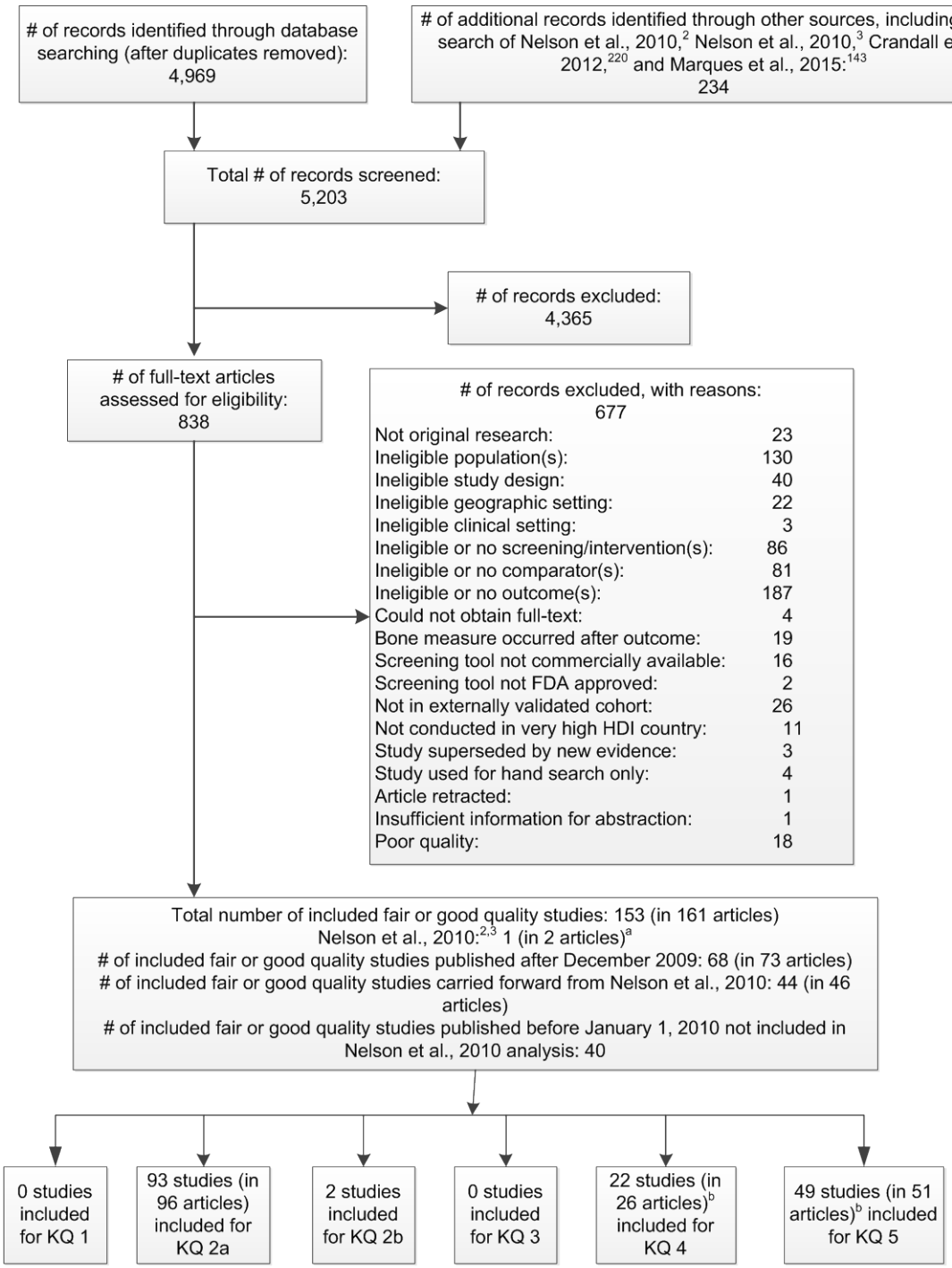


Figure 2. PRISMA Tree



Not included in individual study counts at the bottom level of the diagram.[a]

Not unique citations: studies reporting on both benefits and harms were included in the analysis for both KQ 4 and KQ 5[a]

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[318]	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 ≤-2.5 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 ≤-2.5 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 for hip fracture is ≥3% in the United States or above the country-specific threshold in other countries or regions
AAFP, 2011[319]	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 in men)
ACOG, 2012 (reaffirmed in 2014)[320]	Women	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 ≥9.3% • At intervals not more frequent than every 2 years Recommend FDA-approved therapies for women with BMD diagnosis of osteoporosis or women with osteopenia and 10-year FRAX probability of major osteoporosis risk ≥20% or hip fracture risk ≥3%
ACPM, 2009[321]	Women age 65 years or older Men age 70 years or older	• Recommend BMD testing with DXA for all women age 65 years or older and men age 70 years or older, and not more frequently than every 2 years • Younger postmenopausal women and men ages 50 to 69 years should undergo screening if they have at least 1 major or 2 minor risk factors for osteoporosis • 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

Table 1. Recommendations about screening and treatment of osteoporosis from various professional and health organizations

Organization, Year	Population	Recommendations
ACR, 2016[322]	Asymptomatic BMD screening or persons with established or clinically suspected low BMD, patients with a T-score <-1.0 with additional risk factors, premenopausal women with risk factors, and men ages 20 to 50 years with risk factors	Rate appropriateness and relative radiation levels of various tests for identifying low bone density and fracture risk
Endocrine Society, 2012[323]	Higher-risk men	Recommend BMD testing by central DXA in: • Men age 70 years or older • Men ages 50 to 69 years with risk factors (e.g., low body weight, prior fracture as an adult, smoking)
ISCD, 2015[67]	Men and postmenopausal women	Indications for BMD testing: • Women age 65 years or older • Postmenopausal women younger than age 65 years with risk factors for low bone mass • Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use • Men age 70 years or older • Men younger than age 70 years with clinical risk factors for low bone mass • Adults with a fragility fracture • Adults with a disease or condition associated with low bone mass or bone loss • Adults taking medications associated with low bone mass or bone loss • Anyone being considered for pharmacologic therapy for osteoporosis • Anyone being treated for osteoporosis to monitor treatment effect • Anyone not receiving therapy in whom evidence of bone loss would lead to treatment • Women discontinuing estrogen should be considered for testing according to the indications listed above
NOF, 2014[5]	Men age 50 years or older and postmenopausal women	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 to 69 years based on risk factor profile • Postmenopausal women and men age 50 years or older who have had an adult-age fracture Recommend pharmacologic treatment in those with a T-score <-2.5, in postmenopausal women, and men age 50 years or older with a T-score between -1.0 and -2.5 and a 10-year FRAX probability of major osteoporosis-related fracture ≥20% or hip fracture probability ≥3%
NICE, 2012[324]	Persons presenting in any health care setting	Consider assessment of fracture risk: • In all women age 65 years or older and all men age 75 years or older • In women younger than age 65 years and men younger than age 75 years in the presence of risk factors, such as: o Previous fragility fracture o Current use or frequent recent use of oral or systemic glucocorticoids o History of falls o Family history of hip fracture o Other causes of secondary osteoporosis o Low BMI (<18.5 kg/m^2) o Smoking o Alcohol intake of >14 units per week for women and >21 units per

Table 1. Recommendations about screening and treatment of osteoporosis from various professional and health organizations

Organization, Year	Population	Recommendations
		week for men Do not routinely assess fracture risk in persons younger than age 50 years unless they have major risk factors (e.g., 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. Consider measuring BMD with DXA in persons 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[325]	Postmenopausal women	• Measure height and weight annually and assess chronic back pain, kyphosis, and clinical risk factors • Recommend BMD testing with DXA in postmenopausal women with medical causes of bone loss and all women age 65 years or older • 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 • Vertebral fracture must be confirmed by lateral spine radiographs or vertebral fracture assessment visualization of fracture at the time of BMD testing • 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 • 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-score ≤-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 • Recommend repeating BMD testing 1 to 2 years after treatment • For untreated postmenopausal women, repeat DXA testing is not useful until 2 to 5 years have passed • Recommend bisphosphonates as the first-line drug for treating postmenopausal women with osteoporosis • Recommend SERM raloxifene for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis • Recommend teriparatide (PTH 1-34) for postmenopausal women with osteoporosis at high risk of fracture with therapy indicated for no more than 24 months
Scientific Advisory Council of Osteoporosis Canada, 2010[326]	Men and women older than age 50 years	• Measure height annually and assess for vertebral fracture • Assess history of falls • Perform biochemical testing in select patients to rule out secondary causes of osteoporosis • Perform lateral thoracic and lumbar spine radiography or DXA if clinical evidence suggests fracture • 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 persons with a 10-year risk >20% for major osteoporotic fractures
UKNSC, 2013[327]	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[328]	Men and women ages 40 to 90 years	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 3 high-risk groups: • History of fracture of the hip or spine • BMD in the osteoporosis range (T-score ≤-2.5) • BMD in the low bone mass or osteopenia range with a higher risk of

Table 1. Recommendations about screening and treatment of osteoporosis from various professional and health organizations

Organization, Year	Population	Recommendations
		fracture defined by FRAX score for: o Major osteoporotic fracture 10-year probability ≥20% or o Hip fracture 10-year probability ≥3%

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, sex for U.S. populations of average height and weight

	Age 50		Age 55		Age 60		Age 65		Age 70		Age 75		Age 80 or older	
	MOF	Hip	MOF	Hip	MOF	Hip	MOF	Hip	MOF	Hip	MOF	Hip	MOF	Hip
Caucasian Woman	**Height 163.8 cm, weight 76.1 kg**				**Height 160.3 cm, weight 73.9 kg**									
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
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
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
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	**Height 163.5 cm, weight 88.3 kg**				**Height 160.6 cm, weight 80.7 kg**									
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
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
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
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
Caucasian Man	**Height 178.3 cm, weight 92.9 kg**				**Height 174.6 cm, weight 89.0 kg**									
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
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
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
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	**Height 176.7 cm, weight 92.1 kg**				**Height 174.4 cm, weight 87.8 kg**									
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
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
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
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;[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 PPV; No. of Participants; No. of Participants	Threshold,[b] Range of NPV; No. of Participants; No. of Participants
ABONE[83, 87]	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	Varies by study, no common cutoff	Varies by study, no common cutoff	NR	NR
AMMEB[90]	65	All women	NR	General practices; Italy	Age, BMI, age at menarche, postmenopausal period	Any site: 0.63 (NR); 1; 995	NR	NR	NR	NR
DOEScore[104]	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 (0.691-0.809); 1; 410	>10: 82% (NR); 1; 410	>10: 52% (NR); 1; 410	NR	>10: 55% (NR); 1; 410
FRAX without BMD[57]	57.7	All women	72% white, 17% black, 8% Hispanic	General practice; US	Age, race, rheumatoid arthritis, history of prior fracture, medication use, smoking, alcohol intake, and parental history of hip fracture	Femoral neck: 0.60 (0.56-0.63); 1; 2,857	MOF ≥9.3% 33.3 (26.3-40.4); 1; 2,857	MOF ≥9.3% 86.4 (85.1-87.7); 1; 2,857	MOF ≥9.3% 13.7 (10.4-17.0); 1; 2,857	NR
FRAX without BMD[56]	78.2	45.1% women	NR	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 (0.63-0.74); 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[92]	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: 0.744 (0.699-0.789); 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]: 3.9%; 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;[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 PPV; No. of Participants; No. of Participants	Threshold,[b] Range of NPV; No. of Participants; No. of Participants
Mscore[112]	60.9 to 68.4	All men	Caucasian and African American subgroups	Clinic-based	2 models: Age and weight or Age, weight, gastrectomy, COPD, ≥2 prior fractures	Femoral neck: Age-weight model: Caucasian 0.81 (0.69-0.92); 1, 197 African American[e] 0.99 (0.98-1.01); 1; 134 5-variable model: Caucasian 0.84 (0.74-0.95); 1; 197 NR for African American	Age-weight model: <9 Caucasian 100%; 1, 197 African American[e] 93%; 1; 134 5 variable model: Caucasian 88%; 1; 197 NR African American	Age-weight model: <9 Caucasian 58%; 1; 197 African American[e] 73%; 1; 134 5 variable model: Caucasian 49%; 1; 197 NR African American	NR	NR
MORES[86,110,113]	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 combined with other measures)[d]: 0.797 (0.714-0.879); 3; 4,828	≥6: 66%-95%; 3; 4,828	≥6: 61%-70%; 3; 4,828	≥6 at FN: 11%, 1; 346	≥6 at FN: 99%; 1; 346
MOST[98]	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: 0.799 (0.775-0.823), 1; 4,658 Hong Kong Any site: 0.831 (0.804-0.858); 1; 1,914	NR	NR	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;[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 PPV; No. of Participants; No. of Participants	Threshold,[b] Range of NPV; No. of Participants; No. of Participants
NOF guidelines[83,89,90,101]	57.3 to 69.2	All women	Predominantly white	Majority of studies in general population or general practice; US Canada Italy	Age, weight, personal history of fracture with minimal trauma prior to age 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[80,81,83-85,87-91,93-95,100,101,104,109]	50.5 to 70.5	All women	White participants in majority of studies	Half of the studies conducted in general practice or population settings; US, Australia, Belgium, Canada, Denmark, England, Italy, Singapore, Spain	Age, weight in pounds, current estrogen use	Pooled AUC for any site: 0.651 (0.596-0.705); 10; 16,680	≥9: 50%-100%; 10; 11,173	≥9: 10%-75%; 9; 10,763	≥9: 20%-98%; 6; 7,524	≥9: 25%-94%; 5; 7,114
OSIRIS[81,88,90,94,95,100,109]	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): 0.680 (0.639-0.721) 5; 5,649	<1: 58%-64%; 2; 2,701	<1: 68%-69%; 2; 2,701	<1: 80%-88%; 2; 2,701	<1: 30%-50%; 2; 2,701
OST[78,98,99,108,111,112]	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): 0.747 (0.674-0.821); 5; 5,687; without outlier,[87] pooled AUC: 0.706 (0.691-0.720); 9; 24,213	<2: 62%-89%; 5; 5,366	<2: 36%-74%; 5; 5,366	<2: 10%-38%; 5; 5,366	<2: 40%-97%; 5; 5,366

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;[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 PPV; No. of Participants; No. of Participants	Threshold,[b] Range of NPV; No. of Participants; No. of Participants
OST[57,81,84,88,89,91,93-95,100,102,103,109]	51 to 62	All women	Predominantly Caucasian	11 clinic-based and 1 community based; 2 in US, 3 in Canada, 7 in Northern/ Western Europe	Age and weight	Pooled AUC (any site): 0.667 (0.626-0.708); 10; 24,739	<2: 46.8%-95.3%; 8; 51,158	<2: 39.6%-81.1%; 8; 51,158	<2: 2%-41%; 4; 9,573	<2: 86%-100%; 3; 6,716
OST[56]	78	45.1% men	Predominantly Caucasian	Clinic-based, Australia	Age and weight	Any site: 0.76 (0.71-0.82); 1; 626	≤0: 90.9%	≤0: 39.9%	≤0: 17.5%	≤0: 96.9%
OSTA[97, 105]	63.4 to 54	All men	Asian	Community-based, Hong Kong and South Korea	Age and weight	Any site: AUC ranges from 0.627 to 0.720; 2; 1,466	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[87,90] Kung et al, 2003[96,104,105,107]	59.1 to 70.5	All women	Caucasian and Asian	2 clinic- and 4 community-based studies; Australia, Singapore, Italy, Hong Kong, South Korea	Age and weight	Ranges from 0.617 to 0.75 (any site); 2; 1,768	≤-1: 41%-97%; 5; 3,414	≤-1: 24%-67%; 5; 3,414	≤-1: 24%-49%; 3; 2,557	≤-1: 87%-98%; 2; 2,147
SCORE[57,80-83,85,87,88,91,94,95,101,109]	57.7 to 69.2	All women	Predominantly white	4 clinic-based, 7 community-based; 4 US; 2 UK; Spain; Singapore; Belgium; Denmark; Canada	Age, weight, and estrogen replacement therapy, SCORE instrument includes race/ethnicity, history of rheumatoid arthritis, and history of nontraumatic fractures after age 45	Pooled AUC (any site): 0.698 (0.685-0.711); 8; 15,262	≥6: 54%-100%; 6; 7,455	≥6: 18%-72%; 6; 7,455	≥6: 89%-100%; 3; 4,440	≥6: 19%-41%; 3; 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;[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 PPV; No. of Participants; No. of Participants	Threshold,[b] Range of NPV; No. of Participants; No. of Participants
SOF[82]	69.3	All women	93.5% white	OPRA study, Group Health participant; US	Prior fracture after age 50; ages 60–64 with T-score <-2.5 or age ≥65 with z-score <-0.43; ≥5 risk factors (1st-degree relative with hip fracture, current weight less than at age 25, dementia, using corticosteroids, seizure medication, or benzodiazepines, had a fracture at age ≥50, not taking HRT, on feet <4 h/day, heart rate >80 beats/min, was taller than 5'7 at age 25, age ≥80; 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
SOFSURF[88,91,104]	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;[91,104] Any site: 0.717 (0.777-0.670); 1; 208[88]	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,[86] or thoracic vertebra, lumbar vertebra, arms, ribs, pelvis, or legs.[113]
[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.

Table 3. Characteristics and accuracy of clinical risk assessment tools in identifying osteoporosis

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[88, 94, 96, 102, 114-116]	1,969	AUC ranges from 0.69 to 0.898, pooled estimate: 0.77 (95% CI, 0.72-0.81)
QUS	Calcaneus	Men	Mean age ranges from 61–63	DXA ≤-2.5	Lumbar spine, femoral, or total hip	3[97, 98, 111]	5,142	AUC varies from 0.696 to 0.930, pooled estimate: 0.80 (95% CI, 0.67-0.94)
Peripheral DXA	Calcaneus	Women	61 (SD range, 4–8)	DXA	Lumbar spine, femoral, or total hip	2[94, 95]	1,212	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[114]	221	AUC: 0.84 (95% CI, 0.79-0.89)
RA	Nondominant phalanges	Women	61 (range, 50–75)	DXA	Lumbar spine or total hip	1[114]	221	AUC: 0.80 (95% CI, 0.74-0.85)

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. 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[119, 122, 123, 126]	33,839	Unadjusted: 0.64-0.77 Adjusted: 0.66[a]
			Men	65 to ≥75	1[124]	1,921	Adjusted: 0.71[b]
		Total hip	Women	46-95	2[122, 123, 132]	29,963	Unadjusted: 0.66-0.68
			Men	65 to ≥75	1[124]	1,921	Adjusted: 0.72[b]
		Femoral neck	Women	40-95	10[119, 122, 123, 125, 126, 129, 130, 135-137, 140]	41,294	Unadjusted: 0.59-0.76 Unadjusted by baseline T-score range: -1: 0.54 ≤-1 to >-2.5: 0.57 ≤-2.5: 0.63 Adjusted: 64[a]-0.71[c]
			Men	60 to ≥75	3[120, 124, 125]	7,972	Unadjusted: 0.68 Adjusted: 0.71[c]-0.72[b]
			Combined	≥50	2[133, 139]	46,300	Unadjusted: 0.66-0.68
		Middle phalanges	Women	40-90	2[134,142]	12,830	Unadjusted: 0.71 Adjusted: 0.68[d]
			Men	40-90	1[134]	5,206	Unadjusted: 0.64
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	50-95	3[121-123, 127]	30,837	Unadjusted: 0.61-0.69
		Total hip	Women	50-95	2[122, 123, 125]	29,861	Unadjusted: 0.71 Adjusted: 0.77[c]
		Femoral neck	Women	50-95	2[122, 123, 125]	29,861	Unadjusted: 0.71 Adjusted: 0.70[c]
			Men	≥60	1[125]	445	Adjusted: 0.75[c]
	Hip	Thoracolumbar vertebra, spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.65
		Total hip	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.81
			Men	≥60	1[125]	445	Adjusted: 0.77[c]
		Femoral neck	Women	40-95	7[122, 123, 125, 128, 129, 136, 137]	38,322	Unadjusted: 0.64-0.86 Adjusted: 0.75[d]
			Men	≥65	1[120]	5,606	Unadjusted: 0.85
			Combined	≥50	2[133, 139]	46,300	Unadjusted: 0.76-0.80
		Middle phalanges	Women	40-90	2[134]	12,830	Unadjusted: 0.83
			Men	40-90	1[134]	5,206	Unadjusted: 0.64
DXA TBS	Any osteoporotic	Spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.63
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	53-61; 50-95	2[121-123]	30,072	Unadjusted: 0.66-0.68
	Hip	Spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.68

Table 5. 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	Any osteoporotic	Spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.66
		DXA BMD total hip + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.69
		DXA BMD femoral neck + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.69
	Vertebral, spine	Thoracolumbar vertebra, spine	Women	53-61; 50-95	2[121-123]	30,072	Unadjusted: 0.70-0.71 Adjusted: 0.72[d]-0.73[e]
		DXA BMD total hip + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.73
		DXA BMD femoral neck + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.73
	Hip	Spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.69
		DXA BMD total hip + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.82
		DXA BMD femoral neck + TBS spine	Women	50-95	1[122, 123]	29,407	Unadjusted: 0.81
QUS (BUA)	Any osteoporotic	Heel	Women	44-56	1[119]	775	Adjusted: 0.72[a]
			Men	65 to ≥75; ≥65	2[120, 124]	1,921 + 5,606	Unadjusted: 0.68 Adjusted: 0.65[b]
	Hip	Heel	Men	≥65	1[120]	5,606	Unadjusted: 0.84
QUS (SOS)	Any osteoporotic	Heel	Men	65 to ≥75	1[124]	1,921	Adjusted: 0.64[b]
QUS (QUI)	Any osteoporotic or nonspine	Heel	Men	65 to ≥75	1[124]	1,921	Adjusted: 0.66[b]
QUS (BUA) & DXA BMD	Any osteoporotic or nonspine	QUS: Heel DXA: Femoral neck	Women	≥60	1[125]	454	Adjusted: 0.73[c]
		QUS: Heel DXA: Femoral neck	Men	≥65; ≥60	2[120, 125]	5,606	Unadjusted: 0.69 Adjusted: 0.71[c]
	Vertebral	QUS: Heel DXA: Femoral neck	Women	≥60	1[125]	454	Adjusted: 0.72[c]
			Men	≥60	1[125]	445	Adjusted: 0.75[c]
	Hip	QUS: Heel DXA: Femoral neck	Women	≥60	1[125]	454	Adjusted: 0.81[c]
			Men	≥65; ≥60	2[120, 125]	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]Adusted 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 = duel 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 6. 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[32c]	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]	*Men* MOF: 0.62 (95% CI, 0.61 to 0.64; I^2=40.5%; 3 studies; 13,970 men)[134, 148, 329] Hip: 0.73 (95% CI, 0.68 to 0.77; I^2=96.7%; 3 studies; 13,970 men)[134, 148, 329] *Women* MOF: 0.67 (95% CI, 0.65 to 0.68; I^2=99.2%; 17 studies; 158,897 women)[58, 129, 130, 132, 134, 136-138, 142, 148-151, 153, 184, 330, 331] Hip: 0.76 (95% CI, 0.72 to 0.81; I^2=99.8%; 12 studies; 190,795 women)[128, 129, 134, 136-138, 142, 148, 150, 184, 187, 331] *Both Sexes* MOF: 0.67 (95% CI, 0.66 to 0.67; I^2=47.1%; 3 studies; 66,777)[133,139,152] Hip: 0.77 (95% CI, 0.73 to 0.79; 6,697 participants)[139] 0.79 (95% CI, 0.78 to 0.82; 39,603 participants)[133]	*Men* MOF: 0.67 (95% CI, 0.66 to 0.68; I^2=0%; 4 studies; 15,842 men)[134, 148, 157, 329] Hip: 0.76 (95% CI, 0.72 to 0.80; I^2=96.7%; 3 studies; 13,970 men)[134, 148, 329] *Women* MOF: 0.70 (95% CI, 0.68 to 0.71; I^2=92.1%; 12 studies; 62,054 women)[129, 130, 134-138, 148-151, 330] Hip: 0.79 (95% CI, 0.76 to 0.81; I^2=99.1%; 10 studies; 161,984 women)[128, 129, 134, 136-138, 148-150, 187] *Both Sexes* MOF: 0.69 (95% CI, 0.69 to 0.70; I^2=70.3%; 3 studies; 66,777)[133, 139, 152] Hip: 0.80 (95% CI, 0.77 to 0.83; 6,697 participants)[139] 0.83 (95% CI, 0.82 to 0.85; 39,603 participants)[133]	*Men* Canada, Denmark, U.S., Japan *Women* Australia, Canada, Denmark (2), Finland, France (2), Hong Kong, Japan, multinational European and U.S. cohort, Netherlands, New Zealand, Spain (3), U.S. (4) *Both Sexes* Canada (3)
Garvan nomogram/ FRC[163]	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]	*Men* Hip: 0.65 (95% CI, NR; 1,285 men)[154] Nonvertebral: 0.61 (95% CI, NR; 1,355 men)[154] *Women* MOF: 0.66 (95% CI, 0.61 to 0.72; 600 women)[151] Any OF: 0.65 (95% CI, NR; 506 women)[149] Hip: 0.68 (95% CI, NR; 1,369 women)[154] Nonvertebral: 0.58 (95% CI, NR; 1,637 women)[154]	*Men* MOF[h]: 0.70 (95% CI, NR; 1,606 men)[170] Hip[h]: 0.79 (95% CI, NR; 1,346 men)[154] 0.85 (95% CI, NR; 1,606 men)[170] Nonvertebral: 0.67 (95% CI, NR; 1,346 men)[154] *Women* MOF[h]: 0.68 (95% CI, 0.64 to 0.71; I^2=84.8%; 3 studies;[129, 151, 170] 6,534 women) Any OF: 0.69 (95% CI, NR; 506 women)[149] Hip[h]: 0.73 (95% CI, 0.66 to 0.79; I^2=97.3%; 4 studies;[129, 149, 154, 170] 7,809 women) Nonvertebral: 0.62 (95% CI, NR; 1,646 women)[154]	*Men* Canada, Norway *Women* Australia, Canada, Netherlands, New Zealand, Norway

Table 6. 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[171]	Age, sex, weight, height, smoking, parental fracture or osteoporosis[i], previous fall, glucocorticoid steroid use, rheumatoid arthritis, alcohol use, hormone replacement therapy[i], asthma, endrocrine disease, cardiovascular disease, menopausal symptoms[i], malapsorptive gastrointestinal disease[i], liver disease, type 2 diabetes, tricyclic antidepressant use (or other antidepressant use[i]), ethnicity[j], previous fracture[j], dementia[j], kidney disease[j], epilepsy[j], Parkinson's disease[j], living in a nursing home[j], COPD[j], cancer[j], lupus[j], anticonvulsant use[j], type 1	None	Men and women	30 to 85[k]	1 to 10	2009 version of instrument: *Men* MOF[l]: 0.69 (95% CI, 0.68 to 0.69; 633,764 men)[171] 0.74 (95% CI, NR; 1,108,219 men)[332] Hip: 0.86 (95% CI, 0.85 to 0.86; 633,764 men)[144, 171] 0.86 (95% CI, NR; 1,108,219 men)[332] *Women* MOF[l]: 0.79 (95% CI, 0.79 to 0.79; 642,153 women)[144, 171] 0.82 (95% CI, NR; 1,136,417 women)[332] Hip: 0.89 (95% CI, 0.89 to 0.89; 642,153 women)[171] 0.89 (95% CI, NR; 1,136,417 women)[144, 332] 2012 version of instrument: *Men* MOF[l]: 0.71 (95% CI, 0.70 to 0.72; 778,810 men)[155] Hip: 0.88 (95% CI, 0.87 to 0.88; 778,810, men)[155] *Women* MOF[l]: 0.79 (95% CI, 0.79 to 0.79; 804,563 women)[155] Hip: 0.89 (95% CI, 0.89 to 0.90; 804,563 women)[155]		*Men and Women* France, U.K. *Men and Women* U.K.

Table 6. 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
	diabetes[j]							
WHI[172]	Age, weight, height, self-reported health, prior fracture after age 55, race/ethnicity, physical activity, smoking, parental hip fracture after age 40, diabetes medications, glucocorticoid steroid use	Hip BMD optional	Women	50 to 79	5	Hip: 0.80 (95% CI, 0.77 to 0.82; 10,750 women)[172] 0.82 (95% CI, NR; 13,353 women)[179]	Hip: 0.80 (95% CI, 0.75 to 0.85; 10,750 women)[172]	Denmark, U.S.
OST[173]	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)[103] 0.71 (95% CI, 0.68 to 0.75; 3,614 women)[153] MOF (10-year risk): 0.52 (95% CI, 0.52 to 0.53; 62,492 women)[58]		Canada, Denmark, U.S.
SCORE[174]	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)[153]		Denmark, U.S.
FRISC[140]	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)[140] Long bone and vertebral fracture[o]: 0.69 (95% CI, 0.64 to 0.73; 765 women)[127]	Japan (2)
FRISK[131]	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)[131, 151]	MOF: 0.66 (95% CI, 0.60 to 0.71; 600 women)[151]	Australia

Table 6. 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[175p]	Age, sex, BMI, prior fracture, parental fracture, smoking, alcohol use, glucocorticoid steroid use, rheumatoid arthritis, secondary osteoporosis, race/ethnicity	BMD[q] optional	Men and women[p]	45 to 75	10[p]	MOF: 0.66 (95% CI, NR; 893 men)[190] Hip: 0.71 (95% CI, NR; 893 men)[190] 0.83 (95% CI, 0.82 to 0.84; 94,489 women)[178]	MOF: 0.70 (95% CI, NR; 893 men)[190] Hip: 0.79 (95% CI, NR; 893 men)[190] 0.85 (95% CI, 0.84 to 0.86; 94,489 women)[178]	U.S. (2)
ORAI[176]	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)[153] Any OF (3-year risk): 0.69 (95% CI, 0.66 to 0.72; 3,614 women)[153]		Denmark
OSIRIS[177]	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)[153] Any OF (3-year risk): 0.68 (95% CI, 0.65 to 0.72; 3,614 women)[153]		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[129] uses a broader definition of major osteoporotic fractures and one study[170] 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 years of age; 2012 updated version included up to 100 years of age.
[l] Two studies[155, 171] 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] Thess instruments were initially developed to predict osteoporosis, not incident fracture. S 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] 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.

Table 6. Characteristics and accuracy of fracture risk prediction models in predicting fracture[a]

[q] Based on DXA of the total hip and hip subregions, T-scores based on NHANES reference values for 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; lbs = pounds; 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 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
FRAX with BMD	Pressman et al, 2011[187]	Participants age >50 years with BMD in Kaiser Permanente Northern California, US	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[152]	All adults age ≥50 years 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[190]	Participants age ≥65 years in the Osteoporotic Fractures in Men Study database, US	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 NOF 10-year 20% probability of a major osteoporotic fracture	NRI: 0.085 NRI: 0.04
Dubbo nomogram with calcaneal QUS	Chan et al, 2012[125]	Participants ages 62 to 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 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 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[191]	Participants ages 62 to 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 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 NRI for vertebral fractures: 0 NRI for any fractures: 0.035
Dubbo nomogram	Langsetmo et al, 2011[170]	Participants ages 55 to 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% 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% high: >20%	NRI: 0.192 (95% CI, 0.063 to 0.322)
Garvan nomogram with body weight	Ahmed et al, 2014[154]	Participants age ≥60 years from Tromsø, Norway	1,637 women	Mean: 6.9 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)
			1,355 men	Mean: 7.1 years	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)
Lumbar spine trabecular bone score	Iki et al, 2014[121]	Japanese women age ≥50 years	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, US	Included participants with at least 2 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[a]	0.71 (0.65 to 0.78)	0.68 (0.62 to 0.75)	0.72 (0.66 to 0.79)
							MOF fracture[a]	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, US	Included participants with at least 2 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[b]	0.73 (NR)	0.68 (NR)	0.74 (NR)
							Nonspine fracture[b]	0.65 (NR)	0.61 (NR)	0.65 (NR)
							Spine fracture[b]	0.67 (NR)	0.62 (NR)	0.68 (NR)

[a] Adjusted for age, sex, BMI, weight loss, and history of fracture measured at the time of the second BMD.
[b] 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
KQ 2a	Women[a]	25; 37,154	AUC ranges from 0.32 to 0.87 for all included instruments (pooled AUC ranges from 0.65 to 0.70)	Inconsistent/ imprecise	No evidence of reporting bias	Fair	Heterogeneity in included studies	Low	Unclear whether findings apply to subgroups defined by age or race
KQ 2a	Men	10; 11,108	AUC ranges from 0.62 to 0.89 for all included instruments (pooled AUC ranges from 0.75 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	Women	7; 1,969	BMD tests for identifying osteoporosis: AUC ranges 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
KQ 2a	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	Women	Varies by type of imaging test and site of test	• Centrally measured DXA BMD, TBS, or both predicting fractures, 14 studies, N=46,036: AUC ranges from 0.59 to 0.86 • Other machine-based tests or combination of tests, 2 studies, N=1229: QUS alone predicting fractures: AUC ranges from 0.66 to 0.72; QUS + DXA BMD predicting fractures: AUC ranges 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

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	Men	3; 7,972	• Centrally measured DXA BMD or TBS predicting fractures: AUC ranges from 0.68 to 0.85 • QUS alone predicting fractures: AUC ranges from 0.64 to 0.84; QUS + DXA BMD predicting fractures: AUC ranges 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
KQ 2a	Women and men combined	2; 46,300	Centrally measured DXA BMD predicting fractures: AUC ranges from 0.66 to 0.80	Inconsistent/ precise	No evidence of reporting bias	Fair to good	None identified	Moderate	Findings limited to Canadian samples, unlear whether results are applicable to other populations
KQ 2a	Women	Varies by instrument	• AUC for fracture risk prediction instruments ranges from 0.53 to 0.89 and varies by instrument, type of fracture, and whether BMD is used. Within this range, prediction of hip fracture and predictions that use BMD report higher AUC. • Pooled AUC for FRAX prediction of hip fracture 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	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
			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)						
KQ 2a	Men	Varies by instrument	• AUC for fracture risk prediction instruments ranges from 0.62 to 0.88 and varies by instrument, type of fracture, and whether BMD is used. Within this range, prediction of hip fracture and predictions that use BMD report higher AUC • Pooled AUC for FRAX prediction of hip fracture 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.

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 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, followup period inadequate for women, small N for men, inconsistent screening intervals	Insufficient	Unclear whether all findings apply to subgroups by age, sex, or race
KQ 4a	Women and men	Varies by outcome	Bisphosphonates for women: • RR for vertebral fracture: 0.57 (95% CI, 0.41 to 0.78); 5 trials; N=5,433; 2.1% vs. 3.8% • RR for nonvertebral fracure: 0.84 (95% CI, 0.76 to 0.92); 9 trials; N=16,438; 8.9% vs. 10.6% • RR for hip fracture: 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 fracure: 0.33 (95% CI, 0.16 to 0.70); 1 trial; N=1,199; 1.5% vs. 4.6% • RR for nonvertebral fracture: 0.65 (95% CI, 0.21 to 1.97); 1 trial, N=1,199; 0.9% vs. 1.3%	Consistent/ precise for vertebral and nonvertebral fractures, consistent and imprecise for hip outcomes	No evidence of reporting bias	Fair	Evidence dominated by 1 big study for each drug	Moderate for benefit for bisphosphonate 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
KQ 4a	Women	1; 7,705	Raloxifene: • RR for vertebral fracture: 0.64 (95% CI, 0.53 to 0.76); 7.5% vs. 12.5% • RR for nonvertebral fracture: 0.93 (95% CI, 0.81 to 1.06)[c]; 12.1% vs. 12.9%	Consistency unknown (single trial)/precise for vertebral fracture, imprecise for nonvertebral fracture	No evidence of reporting bias	Good	Single large trial	Moderate for benefit for for vertebral fracture, low for nonvertebral fracture	Unclear whether findings apply to other subgroups defined by age, sex, or race
	Women	1; 7,808	Denosumab: • RR for vertebral fracture: 0.32 (95% CI, 0.26 to 0.41); 2.3% vs. 7.2% • RR for nonvertebral fracture: 0.80 (95% CI, 0.67 to 0.95); 6.1% vs. 7.5% • RR for hip fracture: 0.60 (95% CI, 0.37 to 0.97); 0.7% vs. 1.1%	Consistency unknown (single trial)/precise	No evidence of reporting bias	Fair	Single large trial	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: Women (1 trial, N=2,532): • RR for vertebral fracture: 0.32 (95% CI, 0.14 to 0.75); 0.7% vs. 2.1% • RR for nonvertebral fracture: 0.97 (95% CI, 0.71 to 1.33); 5.6% vs. 5.8% Men (1 trial, N=298): • RR for nonvertebral fracture: 0.65 (95% CI, 0.11 to 3.83); 1.3% vs. 2.0%	Consistency unknown (single trial/precise for women for vertebral fracture Consistency unknown (single trial)/imprecise for men for vertebral fracture	No evidence of reporting bias	Fair	Single trial each for men and women; small trial in men	Low for benefit for vertebral fracture for women, insufficient for men for vertebral fracture	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) • Parathyroid hormone for prior fractures (1 trial; N=1,246).	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
KQ 5	Women and men	Varies by outcome	Bisphosphonates[d]: • RR for discontinuation: 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	Consistent/ precise for discontinuation, serious adverse events, and upper GI events; inconsistent and imprecise for cardiovascular outcomes, osteonecrosis, and atypical femur fractures	No evidence of reporting bias	Fair	Evidence dominated by 1 big study for each drug	Moderate for no harms of bisphosphonate for discontinuation, serious adverse events, and upper GI events; insufficient for cardiovascular events, osteonecrosis, and atypical femur fractures	Unclear whether findings for all drugs apply to subgroups 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
			3 trials that combined results for men and women or included men only had results consistent with trials of women only for discontinuation, serious adverse events, and upper GI events						
KQ 5	Women	Varies by outcome	Raloxifene: • RR for discontinuation: RR, 1.12 (95% CI, 0.98 to 1.28); 6 trials; N=6,438; 12.6% vs. 11.2% • RR for DVT: 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 DVT, leg cramps, and hot flashes; consistent/ imprecise for discontinuation	No evidence of reporting bias	Good	Single large trial dominating results	Low for harm of DVT and hot flashes; low for no harm of discontinuation and leg cramps	Unclear whether findings apply to other subgroups defined by age, sex, or race
	Women	3; 8,451	Denosumab: • RR for discontinuation: 1.16 (95% CI, 0.88 to 1.54); 3.1% vs. 2.1% • RR for serious adverse events: 1.23 (95% CI, 0.78 to 1.93); 23.7% vs. 24.0% • RR for serious infections: 1.89 (95% CI, 0.61 to 5.91); 4.0% vs. 3.3%	Inconsistent/ imprecise for discontinuation, 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 of 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
KQ 5	Women and men	2; 2,830	Parathyroid hormone: Women (1 trial; N=2,532): • RR for discontinuation: 1.22 (95% CI, 1.08 to 1.40); 29.7% vs. 24.6% Men (1 trial; N=298 for 20 µg [FDA-approved dose] vs. placebo): • RR for discontinuation: 1.94 (95% CI, 0.81 to 4.69); 9.2% vs. 4.8% • RR for cancer: 0.97 (95% CI, 0.2 to 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 discontinuation 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).[252]
[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; DVT = deep vein thrombosis; DXA = dual-energy X-ray absorptiometry; EPC = Evidnce-based Practice Center; FDA = Food and Drug Administration; FRAX = Fracture Risk Assessment Tool; GI = gastrointestinal; 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; No. of Studies; No. 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	All women (femoral neck): 0.60 (95% CI, 0.56 to 0.63); 1; 2,857 Both sexes† (any site): 0.68 (95% CI, 0.63 to 0.74); 1; 626	*Men* 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 *Women* 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 *Both Sexes* 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; 15,262	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; 16,680	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): 0.67 (95% CI, 0.63 to 0.71); 10 (with outlier); 24,739; without outlier,[87] pooled AUC: 0.71 (95% CI, 0.69 to 0.72); 9; 24,213	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 fracturesOF = 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)

#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
#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)

#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. 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 glucocorticoid 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 glucocorticoid medications (>5 mg/d oral prednisone [or equivalent] for 3 months or longer)	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 age <40 years KQs 4, 5: Adults with no increased fracture risk
4. Does the study use 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]

Appendix B. Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
5. Does the study include countries with a human developmental 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
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 includes dental bone tests and trabecular bone score[a]* *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 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 KQs 4, 5: Interventions other than those described in the inclusion criteria

Appendix B. Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion 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 U.S. 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, no *comparator, DXA screening at peripheral sites, other noncentral 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
9. Does the study include an outcome of interest?	X9	Wrong or no outcome	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/vertebra (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, AUROC or AUC, positive and 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 c-statistic, 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	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]

Appendix B. Inclusion and Exclusion Criteria

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
			≤-2.5 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. doi: 105/2/432 [pii]. 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. 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. Ann Rheum Dis; 2013.Exclusion Code: X9.
5. 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.
6. 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.
7. 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: 1378033 [pii]; 10.2106/JBJS.K.00774 [doi]. PMID: 23097066.Exclusion Code: X9.

8. 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. doi: 08020338 [pii]. PMID: 18278183.Exclusion Code: X3.
9. 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.
10. 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.
11. 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: S0025-6196(12)00482-X [pii]; 10.1016/j.mayocp.2012.01.020 [doi]. PMID: 22766085.Exclusion Code: X14.
12. 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.
13. 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.
14. 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.
15. 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.
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Appendix D Table 1. KQ 1 Risk of Bias Assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances Suggesting a Problem With Randomization?
Barr, 2010[76]	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.

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Likely to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Barr, 2010[76]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR

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

Author, Year	Confounding of the Effect of Intervention Unlikely?	Participants Analyzed According to Initial Intervention Group Throughout Followup?	Intervention Discontinuations or Switches Unlikely to Be Related to Factors Prognostic for the Outcome?	Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains?
Barr, 2010[76]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort

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

Author, Year	Avoids Adjusting for Postintervention Variables?	Appropriate Analysis Method Adjusting for Time-Varying Confounding?	Bias From Confounding?	Comments
Barr, 2010[76]	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.

Author, Year	Intervention Status Well Defined?	Information on Intervention Status Recorded at Time of Intervention?	Information on Intervention Status Unaffected by Knowledge or Risk of Outcome?	Bias From Measurement of Intervention?	Comments
Barr, 2010[76]	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

AppAuthor, Year	Overall Attrition Attrition by Group Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Barr, 2010[76]	Overall: [%] unclear. Study reports >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

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

Appendix D Table 1. KQ 1 Risk of Bias Assessment

Author, Year	Appropriate Statistical Methods Used to Account for Missing Data?	Bias From Missing Outcome Data?	Comments
Barr, 2010[76]	No	Probably yes	Although this level of attrition would be considered high for trials of treatment, it's not actually unreasonable given the length of followup and that this was a trial of invitation to screening.

Abbreviations: KQ = key question.

Author, Year	Patients Unaware of Intervention Status of Participants?	Trial Personnel and Clinicians Unaware of Intervention Status of Participants?	Intervention Fidelity Adequate?	Crossovers or Contamination That Would Raise Concern for Bias?	Bias From Departures From Intended Interventions?
Barr, 2010[76]	No	No	No information	No information	No information

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

Author, Year	Benefit Outcomes Adequately Described, Prespecified, Valid, and Reliable?	Similar Techniques Used to Ascertain Benefit Outcomes?	Duration of Followup Adequate to Assess Benefit Outcomes?	Harm Outcomes Adequately Described, Valid, and Reliable?
Barr, 2010[76]	Probably yes	Yes	Yes	No information

Abbreviations: KQ = key question; NA = not applicable

Author, Year	Similar Techniques Used to Ascertain Harm Outcomes?	Duration of Followup Adequate to Assess Harm Outcomes?	Bias From Measurement of Outcomes?
Barr, 2010[76]	No information	No information	Probably no

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

Author, Year	Effect Estimate Unlikely to Be Selected From Multiple Outcome Measurements Within the Domain, Multiple Analyses, or Different Subgroups?	Effect Estimate Unlikely to Be Selected From Multiple Definitions of the Intervention?	Bias From Selection of Reposted Results?
Barr, 2010[76]	No	No	No

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

Author, Year	Overall Rating	Rating Justification	Rating Vary by Outcome?	Comments
Barr, 2010[76]	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 followup period; also N and loss-to-followup for per-protocol is unclear but could be at least as high as 40%.	No	Need to pull Torgeson to fully understand randomization procedures (Torgerson DJ, Thomas RE, Campbell MK, Reid DM. Randomized trial of osteoporosis screening: use of hormone replacement therapy and quality-of-life results. *Arch Intern Med*. 1997;157:2121-5.)

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

Appendix D Table 2. KQ 2 systematic review risk of bias assessments

Author, Year	Interventions and Comparators	Adheres to Predefined Objectives and Eligibility Criteria?	Eligibility Criteria Appropriate for the Question?	Eligibility Criteria Unambiguous?
Crandall, 2015[147]	Not applicable	Yes	Yes	Yes
Marques et al, 2015[144]	Fracture risk prediction models	Yes	Yes	Yes
Nayak et al, 2014[117]	Osteoporosis absolute fracture risk assessment instruments	Probably yes	Yes	Yes
Rubin et al, 2013[145]	Risk assessment tools	Yes	Yes	Yes
Steurer et al, 2011[146]	Development of instruments and validation	Yes	Yes	Yes

Abbreviations: KQ = key question

Author, Year	Appropriate Restrictions in Eligibility Criteria Based on Study Characteristics?	Appropriate Restrictions in Eligibility Criteria Based on Sources of Information?	Concerns Regarding Specification of Study Eligibility Criteria?	Searched Appropriate Range of Databases/Electronic Sources for Published and Unpublished Reports?
Crandall, 2015[147]	Yes	Yes	Low	Probably no
Marques et al, 2015[144]	Yes	Yes	Low	Yes
Nayak et al, 2014[117]	Yes	Yes	Low	Yes
Rubin et al, 2013[145]	Yes	Yes	Low	Probably no
Steurer et al, 2011[146]	Yes	Yes	Low	Yes

Abbreviations: KQ = key question

Author, Year	Additional Methods Used to Identify Relevant Reports?	Search Strategy Likely to Retrieve as Many Eligible Studies as Possible?	Appropriate Restrictions Based on Date, Publication Format, or Language?	Minimized Error in Selection of Studies?
Crandall, 2015[147]	Probably no	Yes	Yes	No information
Marques et al, 2015[144]	Yes	Yes	Yes	Yes
Nayak et al, 2014[117]	Yes	Yes	Yes	Yes
Rubin et al, 2013[145]	Yes	Yes	No	Yes
Steurer et al, 2011[146]	Yes	Yes	Yes	Yes

Abbreviations: KQ = key question

Author, Year	Concerns Regarding Methods Used to Identify/Select Studies?	Minimized Error in Data Collection?	Sufficient Study Characteristics to Interpret Results?	All Relevant Results Collected for Synthesis?
Crandall, 2015[147]	Unclear or some concerns	No information	Yes	Yes
Marques et al, 2015[144]	Low	Yes	Probably yes	Yes
Nayak et al, 2014[117]	Low	Yes	Yes	Yes
Rubin et al, 2013[145]	Unclear or some concerns	No information	Yes	Yes
Steurer et al, 2011[146]	Low	Yes	Yes	Yes

Abbreviations: KQ = key question

Appendix D Table 2. KQ 2 systematic review risk of bias assessments

Author, Year	Risk of Bias (or Methodological Quality) Formally Assessed With Appropriate Tool?	Minimized Error in Risk of Bias Assessment?	Concerns Regarding Methods of Data Collection and Study Appraisal?	Synthesis Includes All Studies it Should?
Crandall, 2015[147]	No	No information	Unclear or some concerns	Yes
Marques et al, 2015[144]	Yes	Yes	Low	Yes
Nayak et al, 2014[117]	Probably yes	No information	Low	Yes
Rubin et al, 2013[145]	Yes	Yes	Low	Yes
Steurer et al, 2011[146]	Yes	No information	Low	Yes

Abbreviations: KQ = key question

Author, Year	Predefined Analyses Reported or Departures Explained?	Synthesis Appropriate Given Degree of Similarity in Research Questions, Study Designs, and Outcomes Across Included Studies?	Between-Study Variation Minimal or Addressed?	Robust Findings?
Crandall, 2015[147]	Yes	Yes	Probably yes	No information
Marques et al, 2015[144]	Probably yes	Yes	Probably no	Probably yes
Nayak et al, 2014[117]	Probably yes	Yes	Yes	No information
Rubin et al, 2013[145]	Yes	Yes	Yes	Probably yes
Steurer et al, 2011[146]	Yes	Yes	No information	No information

Abbreviations: KQ = key question

Author, Year	Biases in Primary Studies Minimal or Addressed?	Concerns Regarding the Synthesis?	Interpretation of Findings Address All Concerns Identified in Domains 1–4?	Relevance of Identified Studies to the Research Question Appropriately Considered?	Reviewers Avoid Emphasizing Results on Basis of Statistical Significance?	Risk of Bias in the Review
Crandall, 2015[147]	No	Unclear or some concerns	Probably no	Yes	Yes	Unclear or some concerns
Marques et al, 2015[144]	Probably yes	Low	Yes	Yes	Yes	Low
Nayak et al, 2014[117]	Yes	Low	Yes	Yes	Probably yes	Low
Rubin et al, 2013[145]	Yes	Low	Yes	Yes	Yes	Low
Steurer et al, 2011[146]	Yes	Unclear or some concerns	No	Yes	Yes	Unclear or some concerns

Abbreviations: KQ = key question

Appendix D Table 3. Risk of bias for assessing accuracy of risk prediction instruments for identifying osteoporosis

Author, Year	Patients	Index Test(s)	Reference Standard and Target Condition
Adler, 2003[78]	Men enrolled in a pulmonary clinic (January-May 2001) and a rheumatology clinic (November 2001-March 2002) at a single VA medical center; received questionnaire and DXA scan; patients with previous DXA testing ineligible	Osteoporosis Self-assessment Tool (OST) (risk=[(weight in kg-age in years)*0.2, truncated to integer])	DXA
Ben Sedrine, 2001[79]	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 Liège, Belgium	SCORE	DXA
Brenneman, 2003[82]	Postmenopausal women ages 60-79 years in the OPRA study	SCORE SOF-based screening tool	DXA
Cadarette, 2001[83]	Postmenopausal women in CaMOS	SCORE ABONE ORAI *weight criterion and NOF also evaluated	DXA
Cadarette, 2004[84]	Women age ≥45 years recruited prospectively from university setting and retrospectively analyzed from family practices	ORAI OST	DXA
Cass, 2006[85]	Primary care, women	ORAI and SCORE	DXA
Cass, 2013[86]	Primary care, men	MORES	DXA
Chan, 2006[87]	Community-based elderly women	ORAI, SCORE, ABONE, OSTA	DXA
Cook, 2005[88]	UK, DXA scanning clinics, patients referred from general practitioners 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]	Postmenopausal women enrolled in the WHI observational or clinical trial studies	OST, SCORE, USPSTF criteria (FRAX MOF risk ≥9.3%)	DXA
D'Amelio, 2005[89]	Postmenopausal women referred to a university-based bone metabolic unit for DXA	NOF, OST, ORAI	DXA T score ≤-2.5
D'Amelio, 2013[90]	Postmenopausal women recruited from general practice	NOF ORAI OST AMMEB	DXA
Geusens, 2002 [91]	Postmenopausal women age ≥45 years, US and Netherlands, 81.8% white	OST, ORAI, SCORE, SOFSURF	DXA
Gnudi, 2005[92]	Postmenopausal Italian women requiring a DXA scan	Gnudi et al clinical prediction tool	DXA
Gourlay, 2005[80]	Postmenopausal 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
Gourlay, 2008 [93]	US ambulatory white women age ≥65 years	OST, ORAI, SCORE	DXA
Harrison, 2006[94]	Caucasian females, ages 55-80 years (referred to clinical radiology), intended use of index test (QUS x2), underwent DXA and categorized as nonosteoporosis 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[95]	Women from primary and tertiary care, diagnosis, no prior testing	4 risk scores + PIXI of the heel	DXA of the hip and spine

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Author, Year	Patients	Index Test(s)	Reference Standard and Target Condition
Kung, 2003[96]	Women in Hong Kong recruited from the community	OSTA index and QUI	DXA
Kung, 2005[97]	Community of Asian (Southern Chinese) men; developed index based on clinical factors; compared clinical index with calcaneal QUS in predicting BMD (T score <-2.5) by DXA	Clinical index	Calcaneal QUS; target condition of osteoporosis, as determined by BMD at the hip and spine by DXA
Lynn, 2008[98]	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[99]	Population-based sample of Portugese men age ≥50 years	OST <1, OSTA <2	DXA T score ≤-2.5 at any of the 3 sites (LS, FN, TH) measured
Martinez-Aguila, 2007[100]	Postmenopausal women ages 40-69 years 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 at FN or LS
Mauck, 2005[101]	Population-based sample of postmenopausal women age ≥45 years in Rochester, MN	SCORE ≥6 ORAI ≥9 NOF ≥1	DXA T score ≤-2.5 at FN or LS
McLeod, 2015[102]	Women referred for screening in Canada, no prior testing	QUS and OST	DXA
Morin, 2009[103]	Population-based sample of all women ages 40-59 years and older who received DXA testing in Manitoba, Canada. Note criteria for BMD testing in women age <65 years include premature ovarian failure, history of steroid use, prior fracture, x-ray evidence of osteopenia, and other pertinent clinical risk factors.	OST ≤1	DXA T score ≤-2.5 at FN or LS or total hip
Nguyen, 2004[104]	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)
Oh, 2013[105]	National, population-based health and nutrition cohort	OSTA	DXA
Oh, 2016[106]	Population-based sample of Korean men age ≥50 years	OSTA	DXA
Pang, 2014[56]	Persons age ≥70 years recruited from general practice, excluded persons with history of fracture	OST, FRAX without BMD, MOF, and Hip	DXA
Richards, 2014[108]	Male VA patients	OST	DXA
Richy, 2004[81]	Postmenopausal white women	OST	DXA
Shepherd, 2007[110]	Men age ≥50 years with DXA scan in NHANES III	MORES	DXA
Shepherd, 2010[113]	Men age ≥50 years included in NHANES	MORES	BMD DXA osteo
Sinnott, 2006[111]	African American men, age ≥35 years (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 nondominant foot, outcome is low bone mass	Ultrasound of calcaneous on nondominant foot	BMD by DXA at the 1) lumbar spine (L1-L4) and 2) nondominant hip (femoral neck, trochanter, total hip)
Zimering, 2007[112]	Men age ≥40 years, ambulatory veterans attending general medicine clinics, endocrinology clinics, or osteoporosis clinics	MSCORE OST MSCORE (age-weight)	DXA

Appendix D Table 3. Risk of bias for assessing accuracy of risk prediction instruments for identifying osteoporosis

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

Author, Year	Describes Method of Patient Selection?	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?
Adler, 2003[78]	Yes	Unclear	Yes	Yes
Ben Sedrine, 2001[79]	Yes	Unclear	Yes	Yes
Brenneman, 2003[82]	Yes	Yes	Yes	Unclear
Cadarette, 2001[83]	Yes	Yes	Yes	Yes
Cadarette, 2004[84]	Yes	Yes	Yes	Yes
Cass, 2006[85]	Yes	Yes	Yes	Yes
Cass, 2013[86]	Yes	Yes	Yes	Yes
Chan, 2006[87]	Yes	Unclear	Yes	Unclear
Cook, 2005[88]	Patients referred by general practitioner to DXA screening clinic	Unclear	Yes	Unclear
Crandall, 2014[57]	Yes	Yes	Yes	Yes
D'Amelio, 2005[89]	Yes	Unclear	Yes	Yes
D'Amelio, 2013[90]	Yes	Yes	Yes	Yes
Geusens, 2002 [91]	Postmenopausal women age ≥45 years from US clinics and general practice in the Netherlands	Yes	Yes	Yes
Gnudi, 2005[92]	Yes	Yes	Yes	Yes
Gourlay, 2005[80]	Yes	Yes	Yes	Yes
Gourlay, 2008 [93]	US ambulatory white women age ≥65 years, from population-based listings	Yes	Yes	Yes
Harrison, 2006[94]	White Caucasian females ages 55-70 years (mean age, 61 [SD, 4]) 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[95]	Described as random from 2 sites	Yes	Yes	Yes
Kung, 2003[96]	Women from community, all comers who did not meet exclusion	Unclear	Yes	Yes

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Author, Year	Describes Method of Patient Selection?	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?
Kung, 2005[97]	Men from community, all comers who did not meet exclusion	Yes	Yes	Yes
Lynn, 2008[98]	US participants were recruited using population-based listings at 6 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[99]	Yes	Yes	Yes	Yes
Martinez-Aguila, 2007[100]	Yes	No	Yes	Unclear
Mauck, 2005[101]	Yes	Yes	Yes	Yes
McLeod, 2015[102]	Patients referred for screening to 1 facility	Yes	Yes	Yes
Morin, 2009[103]	Yes	Yes	Yes	Unclear
Nguyen, 2004[104]	Yes	Yes	Yes	Yes
Oh, 2013[105]	Yes	Yes	Yes	Yes
Oh, 2016[106]	Yes	Yes	Yes	Yes
Pang, 2014[56]	Yes	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[81]	Patients seen at an outpatient osteoporosis centre	Unclear	Yes	Yes
Shepherd, 2007[110]	Yes	Unclear	Yes	Unclear
Shepherd, 2010[113]	Yes	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]	Yes	Unclear	Yes	Yes

Abbreviations: AL = Alabama; CA = California; DXA = dual energy x-ray absorptiometry; MN = Minnesota; PA = Pennsylvania; SD = standard deviation; US = United States; VA = Veterans' Administration.

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Author, Year	Could Patient Selection Have Introduced Bias?	Comments	Describes Index Test and How it Was Conducted and Interpreted?	Index Test Results Interpreted Without Knowledge of Results of Reference Standard?
Adler, 2003[78]	Unclear	Risk of spectrum bias used this reference for patient selection methods—appears random, majority of sample (107/181): Adler et al. Osteoporosis in pulmonary clinic patients: does point-of-care screening predict central dual-energy x-ray absorptiometry? *Chest*.	Yes	Unclear
Ben Sedrine, 2001[79]	Unclear	Risk of spectrum bias	Yes	Yes
Brenneman, 2003[82]	Low	Patients recruited by mailing to random sample	Yes	Unclear
Cadarette, 2001[83]	Low	Age-, sex-, and region-stratified random sample of the Canadian population selected using telephone-based sampling frame	Yes	Unclear
Cadarette, 2004[84]	Low	NA	Yes	Unclear
Cass, 2006[85]	Low	NR	Yes	Yes
Cass, 2013[86]	Low	NR	Yes	Yes
Chan, 2006[87]	Unclear	No information on participant inclusion/exclusion criteria	Yes	Unclear
Cook, 2005[88]	Unclear	Sample has potential for bias toward low BMD due to recruitment from DXA clinic (all patients referred by doctor for clinical risk factors)	2 QUS tests: CUBA clinical and Sunlight Omnisense measurements. Performed on nondominant side with same ultrsaound gel. System quality verification tests each day.	Unclear
Crandall, 2014[57]	Low	NA	Yes	Unclear
D'Amelio, 2005[89]	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[90]	Low	NA	Yes	Unclear
Geusens, 2002 [91]	Low	NR	OST: age and weight ORAI: age, weight, estrogen use SCORE: race, rheumatoid arthritis, history of nontraumatic fracture, HRT usage, age, weight SOFSURF: age, weight, current smoker, history of postmenopausal fracture	Unclear
Gnudi, 2005[92]	Low	Patient refered to densitometry unit, possible spectrum bias	Yes	Yes

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Author, Year	Could Patient Selection Have Introduced Bias?	Comments	Describes Index Test and How it Was Conducted and Interpreted?	Index Test Results Interpreted Without Knowledge of Results of Reference Standard?
Gourlay, 2005[80]	Unclear	Potential for spectrum bias, given the study population was referred specifically for DXA testing	Yes	Yes
Gourlay, 2008 [93]	Low	NR	OST: age and weight ORAI: age, weight, estrogen use SCORE: race, rheumatoid arthritis, history of nontraumatic fracture, HRT usage, age, weight	Low
Harrison, 2006[94]	Low	No details on setting or how participants were selected	QUS x2	Unclear
Jimenez-Nunez, 2013[95]	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[96]	Low	Interesting that the study claims to be in early postmenopausal women but the age mean is 62 years, 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[97]	Low	Unclear who chose to participate relative to larger group, excluded abnormal TSH group	Index developed by authors based on characteristics	Unclear
Lynn, 2008[98]	Low	Only exclusions listed were hip replacement and inability to walk without a cane	OST, MOST, QUI	Unclear
Machado, 2010[99]	Low	NR	Yes	Unclear
Martinez-Aguila, 2007[100]	Unclear	Patients were all referred for DXA, so potential for spectrum bias	Yes	Unclear
Mauck, 2005[101]	Low	NR	Yes	Unclear
McLeod, 2015[102]	Low	NA	QUS of BUA and SOS of left calcaneus and personal data based on questionnaire	Yes
Morin, 2009[103]	Unclear	Population is younger women ages 40-59 years who received a DXA; however, in this province, younger women are only eligible for coverage for DXA testing if they have clinical risks for secondary osteoporosis, history of prior fracture, or x-ray evidence of osteoporosis	Yes	Unclear
Nguyen, 2004[104]	Low	NA	Yes	Unclear
Oh, 2013[105]	Low	NA	Yes	Unclear
Oh, 2016[106]	Low	NR	Yes	Unclear
Pang, 2014[56]	Low	NA	Yes	Unclear
Park, 2003[107]	Low	NR	OSTA: age and weight	Unclear
Richards, 2014[108]	Low	NR	OST: age and weight	Unclear

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Author, Year	Could Patient Selection Have Introduced Bias?	Comments	Describes Index Test and How it Was Conducted and Interpreted?	Index Test Results Interpreted Without Knowledge of Results of Reference Standard?
Richy, 2004[81]	Low	NR	SCORE: race, rheumatoid arthritis, history of nontraumatic fracture, HRT usage, age, 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, noninstitutionalized population of the coterminous United States, excluding Indian reservations (i.e., not random or consecutive sampling)	Yes	Unclear
Shepherd, 2010[113]	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 nondominant foot	Unclear
Zimering, 2007[112]	Unclear	Convenience sample. 30% came from specialty clinics (endocrinology or outpatient) 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;

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Author, Year	Threshold Prespecified?	Could Conduct or Interpretation of Index Test Have Introduced Bias?	Comments	Describes Reference Standard and How it Was Conducted and Interpreted?
Adler, 2003[78]	Yes	Low	Used 3 cutoffs for OST: 2 based on published literature, 1 based on what they thought was appropriate	Yes
Ben Sedrine, 2001[79]	Yes	Low	Authors reported on outcomes of clinical prediction tools using a priori cutoffs but also calibrated tool for this population using AUC curve	Yes
Brenneman, 2003[82]	Yes	Low	SCORE cutoff was recalibrated using study data to achieve sensitivity of about 90%. Developer cutoff ≥6 Study cutoff ≥8	Yes
Cadarette, 2001[83]	Yes	Low	Used cutoffs based on those of the developers of the study	Yes
Cadarette, 2004[84]	Yes	Low	Unclear timing of DXA, reference test, in relationship to index test in prospective and retrospective parts of the study sample	Yes
Cass, 2006[85]	Yes	Low	NR	Unclear
Cass, 2013[86]	Yes	Low	NR	Yes
Chan, 2006[87]	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, 2005[88]	Yes	Unclear	Threshold question: yes and no, used a 90% sensitivity threshold, but also created a cutoff level based on the highest combined value of sensitivity and specificity	DXA. Unclear. Were all scans done on the same DXA machine? Were machine readings standardized? Did multiple radiologists read? Agreement? Also, unclear if radiologist reading DXA blinded to QUS results.
Crandall, 2014[57]	Unclear	Unclear	Study mentions the existing thresholds used for the instruments from the literature, but outcomes are not reported by these thresholds	Yes
D'Amelio, 2005[89]	Yes	Low	NR	Yes
D'Amelio, 2013[90]	Yes	Low	Thresholds mentioned in study do not correspond entirely to thresholds used by other studies	Unclear
Geusens, 2002 [91]	Yes	Low	NR	DXA, femoral neck or lumbar spine

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Author, Year	Threshold Prespecified?	Could Conduct or Interpretation of Index Test Have Introduced Bias?	Comments	Describes Reference Standard and How it Was Conducted and Interpreted?
Gnudi, 2005[92]	Yes	Low	Does not report on blinded index test assessment. Had 3 apriori cutoffs from development cohort to achieve 97%, 98%, and 99% sensitivity.	Yes
Gourlay, 2005[80]	No	Unclear	Did not use prespecified cutoffs for ORAI, OST, or SCORE. Instead, picked cutoff to achieve sensitivity of 90% for each age group under and over 65 years.	Yes
Gourlay, 2008 [93]	Yes	Low	NR	DXA, femoral neck or lumbar spine
Harrison, 2006[94]	Yes	Low	NR	Yes
Jimenez-Nunez, 2013[95]	Yes	Low	NR	DXA of the hip and spine
Kung, 2003[96]	Yes	Low	Index based on characteristics can be biased based on analysis decisions	DXA: BMD of the lumbar spine, femoral neck
Kung, 2005[97]	Yes	Low	The authors are developing their own index test and so by definition are playing with their data. QUI is okay.	DXA: BMD of the lumbar spine, femoral neck
Lynn, 2008[98]	Yes	Low	NR	Yes
Machado, 2010[99]	Yes	Low	NR	Yes
Martinez-Aguila, 2007[100]	Yes	Low	NR	Yes
Mauck, 2005[101]	Yes	Low	NR	Yes
McLeod, 2015[102]	Yes	Low	NR	DXA: BMD of the lumbar spine, left and right femoral neck
Morin, 2009[103]	Yes	Low	Sensitivity and specificity reported for multiple thresholds; threshold of ≤1 is what has been used in other studies, so data were only extracted for this threshold	Yes
Nguyen, 2004[104]	Yes	Low	Validation cohort only	Yes
Oh, 2013[105]	No	Unclear	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	Yes
Oh, 2016[106]	Unclear	Unclear	Unclear whether OSTA threshold used was prespecified	Yes
Pang, 2014[56]	No	Unclear	Thresholds were not prespecified, rather they were chosen to maximize discriminative ability.	Yes
Park, 2003[107]	Yes	Low	NR	DXA, femoral neck BMD was measured using DXA, GE Lunar Model DPQ-IQ, no other details

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Author, Year	Threshold Prespecified?	Could Conduct or Interpretation of Index Test Have Introduced Bias?	Comments	Describes Reference Standard and How it Was Conducted and Interpreted?
Richards, 2014[108]	Yes	Low	NR	DXA, femoral neck and total hip
Richy, 2004[81]	Yes	Low	NR	DXA, total hip, femoral neck, lumbar spine, any site
Shepherd, 2007[110]	Yes	Low	Does not report on blinded index test assessment. Threshold is determined in development cohort in this study. Applied to validation cohort.	Yes
Shepherd, 2010[113]	Yes	Low	NR	Yes
Sinnott, 2006[111]	Unclear	Low	NR	Yes
Zimering, 2007[112]	Yes	Low	Does not report on blinded index test assessment. Threshold is determined in development cohort in this study. Applied to validation cohort.	Yes

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.

Author, Year	Reference Standard Likely to Correctly Classify Target Condition?	Reference Standard Results Interpreted Without Knowledge of Results of Index Test?	Could Reference Standard or Its Conduct or Interpretation Have Introduced Bias?	Comments
Adler, 2003[78]	Yes	Unclear	Low	NR
Ben Sedrine, 2001[79]	Yes	Yes	Low	From discussion: "All of our DXA tests come from the same densitometers and from the same clinical unit“
Brenneman, 2003[82]	Yes	Unclear	Low	NR
Cadarette, 2001[83]	Yes	Unclear	Low	NR
Cadarette, 2004[84]	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[85]	Yes	Yes	Low	Specific reference range for T-scores not reported, but used manufacturer's ranges, so likely NHANES
Cass, 2013[86]	Yes	Yes	Low	NR
Chan, 2006[87]	Unclear	Unclear	Unclear	No information on the specific reference ranges used to determine T-score
Cook, 2005[88]	Yes	Unclear	Unclear	NR
Crandall, 2014[57]	Yes	Unclear	Low	NR
D'Amelio, 2005[89]	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

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Author, Year	Reference Standard Likely to Correctly Classify Target Condition?	Reference Standard Results Interpreted Without Knowledge of Results of Index Test?	Could Reference Standard or Its Conduct or Interpretation Have Introduced Bias?	Comments
D'Amelio, 2013[90]	Unclear	Unclear	Unclear	Reference range for T-score NR
Geusens, 2002 [91]	Yes	Unclear	Low	NR
Gnudi, 2005[92]	Yes	Yes	Low	Does not report on blinded reference test assessment
Gourlay, 2005[80]	Yes	Yes	Low	NR
Gourlay, 2008 [93]	Yes	Unclear	Low	NR
Harrison, 2006[94]	Yes	Unclear	Low	NR
Jimenez-Nunez, 2013[95]	Yes	Yes	Low	NR
Kung, 2003[96]	Yes	Unclear	Low	NR
Kung, 2005[97]	Yes	Yes	Low	NR
Lynn, 2008[98]	Yes	Unclear	Low	All obtained from MrOS (sequence of data collection not described)
Machado, 2010[99]	Yes	Unclear	Low	NR
Martinez-Aguila, 2007[100]	Yes	Unclear	Low	Did not use NHANES reference standards, but may be appropriate since conducted in a Spanish population
Mauck, 2005[101]	Yes	Unclear	Low	Used a local reference range for T-score values
McLeod, 2015[102]	Yes	Yes	Low	NR
Morin, 2009[103]	Yes	Yes	Low	NR
Nguyen, 2004[104]	Yes	Unclear	Low	Used a local reference range for young Australian women at the FN or LS
Oh, 2013[105]	Yes	Unclear	Low	NR
Oh, 2016[106]	Yes	Unclear	Low	NR
Pang, 2014[56]	Yes	Unclear	Low	NR
Park, 2003[107]	Yes	Unclear	Unclear	NR
Richards, 2014[108]	Yes	Yes	Unclear	NR
Richy, 2004[81]	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[113]	Yes	Unclear	Low	NR
Sinnott, 2006[111]	Yes	Unclear	Low	Threshold values not explicity provided
Zimering, 2007[112]	Yes	Unclear	Low	Does 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.

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Author, Year	Any Patients Not Receiving Index Test, Reference Standard, or Excluded?	Time Interval and Interventions Between Index Test and Reference Standard	Appropriate Interval Between Index Test and Reference Standard?	All Patients Received Reference Standard?	Patients Received Same Reference Standard?	All Patients Included in Analysis?
Adler, 2003[78]	Excluded patients with previous DXA scan (i.e., the reference test)	1 month	Yes	Unclear	Yes	Yes
Ben Sedrine, 2001[79]	NR	NR: gathered retrospective medical data on BMD measurement and risk factors between January 1996 and 1999	Unclear	Yes	Yes	Unclear
Brenneman, 2003[82]	1,986 recruited, 428 consented, 416 had complete data	Occurred concurrently	Yes	Yes	Yes	Yes
Cadarette, 2001[83]	69 participants missing data to calculate clinical decision rules	Not specifically reported. All baseline data collected 2/2016 to 9/2017, presumably includes questionnaire and DXA testing	Unclear	Yes	Yes	No
Cadarette, 2004[84]	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[85]	Yes	Yes	Yes	Yes	Yes	No
Cass, 2013[86]	Yes	Yes	Yes	Yes	Yes	No
Chan, 2006[87]	No	Yes	Yes	Yes	Yes	Unclear
Cook, 2005[88]	None	None	Yes	Yes	Yes	Yes
Crandall, 2014[57]	No	Yes	Yes	Yes	Yes	Yes
D'Amelio, 2005[89]	NR	Clinical risk factors collected at time of DXA scan	Yes	Yes	Yes	Yes
D'Amelio, 2013[90]	Yes	Yes	Yes	Yes	Yes	No
Geusens, 2002 [91]	NA	Unclear	Unclear	Yes	Yes	Yes
Gnudi, 2005[92]	NR	NR	Unclear	Yes	Yes	Unclear
Gourlay, 2005[80]	NR	NR	Unclear	Yes	Yes	Unclear
Gourlay, 2008 [93]	NA	Unclear	Unclear	Yes	Yes	Yes
Harrison, 2006[94]	NR	NR	Unclear	Yes	Yes	Unclear
Jimenez-Nunez, 2013[95]	Nursing home, homebound, prior diagnosis of osteoporosis, taking osteoporosis drugs, serious acute or chronic disease, hip replacement, steroids	Same day	Unclear	Yes	Yes	Unclear

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Author, Year	Any Patients Not Receiving Index Test, Reference Standard, or Excluded?	Time Interval and Interventions Between Index Test and Reference Standard	Appropriate Interval Between Index Test and Reference Standard?	All Patients Received Reference Standard?	Patients Received Same Reference Standard?	All Patients Included in Analysis?
Kung, 2003[96]	History or evidence of metabolic bone disease, menopause before age 40 years, history of cancer, evidence of significant renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride, or calcitonin	NR	Unclear	Yes	Yes	Yes
Kung, 2005[97]	History or evidence of metabolic bone disease, hightory of cancer, evidence of significant 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, 2008[98]	NR	NR	Unclear	Yes	Yes	NA
Machado, 2010[99]	NR	NR	Unclear	Yes	Yes	Yes
Martinez-Aguila, 2007[100]	Yes	NR	Unclear	Yes	Yes	No
Mauck, 2005[101]	NR	Yes	Yes	Yes	Yes	Yes
McLeod, 2015[102]	Previous diagnosis, progressive terminal illness	Within 3 weeks	Yes	Yes	Yes	Yes
Morin, 2009[103]	NR	Unclear	Unclear	Yes	Yes	Yes
Nguyen, 2004[104]	NR	Not explicitly, but given study design presume it was concurrent	Yes	Yes	Yes	Yes
Oh, 2013[105]	Yes	Yes	Yes	Yes	Yes	Yes
Oh, 2016[106]	Yes	Yes	Yes	Yes	Yes	Yes
Pang, 2014[56]	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[81]	NA	Unclear	Unclear	Yes	Yes	Yes
Shepherd, 2007[110]	From Looker et al. Bone mineral measurements were performed on 3,176 older men in NHANES III, but 86 (3%) were rejected for technical reasons after review, leaving 3,090 with acceptable data	NR	Unclear	Yes	Yes	Yes
Shepherd, 2010[113]	Yes	Yes	Yes	Yes	Yes	Yes

Appendix D Table 3. Risk of bias for assessing accuracy of risk prediction instruments for identifying osteoporosis

Author, Year	Any Patients Not Receiving Index Test, Reference Standard, or Excluded?	Time Interval and Interventions Between Index Test and Reference Standard	Appropriate Interval Between Index Test and Reference Standard?	All Patients Received Reference Standard?	Patients Received Same Reference Standard?	All Patients Included in Analysis?
Sinnott, 2006[111]	NR	NR	Unclear	Yes	Yes	Yes
Zimering, 2007[112]	NR	NR, presumably concurrent testing	Unclear	Yes	Yes	No

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

Author, Year	Could Patient Flow Have Introduced Bias?	Comments	Overall Judgement	Overall Comments
Adler, 2003[78]	Low	From Adler et al. Osteoporosis in pulmonary clinic patients: does point-of-care screening predict central dual-energy x-ray absorptiometry? *Chest*. 2003;123(6): 2012-8. 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.
Ben Sedrine, 2001[79]	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[82]	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[83]	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[84]	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	The difference in recruitment could be an issue; unclear on assessment timing; unclear on blinding; looks like those with missing data were excluded
Cass, 2006[85]	Low	23 enrolled patients did not undergo DXA scan so were not included. 173 eligible patients declined to participate.	Low	NR
Cass, 2013[86]	Low	40 patients did not undergo DXA so were dropped from the analysis.	Low	NR
Chan, 2006[87]	Unclear	Number eligible and number of dropouts are 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 unclear
Cook, 2005[88]	Low	NR	Unclear	Patient selection has the potential to skew the sample toward low BMD
Crandall, 2014[57]	Low	Analysis was restricted to a subgroup of non-HRT users by design	Low	NR

Appendix D Table 3. Risk of bias for assessing accuracy of risk prediction instruments for identifying osteoporosis

Author, Year	Could Patient Flow Have Introduced Bias?	Comments	Overall Judgement	Overall Comments
D'Amelio, 2005[89]	Low	NR	Low	NR
D'Amelio, 2013[90]	Low	Some patients initially enrolled were excluded because it was determined they did not meet study criteria	Low	NR
Geusens, 2002[91]	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 test
Gnudi, 2005[92]	Low	While authors don't report on timing between reference and index test, validation cohort was recruited over 6 months (<2 years)	Low	NR
Gourlay, 2005[80]	Unclear	NR	Unclear	NR
Gourlay, 2008[93]	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 test
Harrison, 2006[94]	Unclear	Participants underwent DXA and were 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[95]	Low	Random sample done with some sort of cards	Low	NR
Kung, 2003[96]	Low	NR	Low	NR
Kung, 2005[97]	Low	Not clear what the time frame between clinical assessment of risk factors and QUS is; however, should be little impact; all participants received the same reference standard (referring to the validated group)	Low	NR
Lynn, 2008[98]	Low	NR	Low	Data were collected prospectively from MrOS study and then analyzed as part of this study focus
Machado, 2010[99]	Low	Interval between clinical risks and BMD inferred to be <2 years	Low	NR
Martinez-Aguila, 2007[100]	Unclear	30 eligible patients were excluded for missing data. Clinical risk factors assessed retrospectively by asking participants to answer based on the date of their BMD testing.	Unclear	NR
Mauck, 2005[101]	Low	NR	Low	NR
McLeod, 2015[102]	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[103]	Unclear	Unclear for timing between DXA and index test	Unclear	NR
Nguyen, 2004[104]	Low	NR	Low	NR

Appendix D Table 3. Risk of bias for assessing accuracy of risk prediction instruments for identifying osteoporosis

Author, Year	Could Patient Flow Have Introduced Bias?	Comments	Overall Judgement	Overall Comments
Oh, 2013[105]	Low	Some patients meeting preliminary 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[106]	Low	Excluded some men for probably valid reasons	Low	NR
Pang, 2014[56]	Low	Some patients meeting preliminary 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 test
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 test
Richy, 2004[81]	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 test
Shepherd, 2007[110]	Low	NR	Low	NR
Shepherd, 2010[113]	Low	Excluded men without DXA available, though not specifically reported, NHANES enrolls subjects prospectively, so clinical risks and DXA likely collected concurrently	Low	NR
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 Nutrition examination Survey; NR = not reported; OST = osteoporosis self-assessment tool; QUS = quantitative ultrasound; ROB = risk of bias.

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Patients	Index Test	Reference Standard and Target Condition	Methods of Patient Selection	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?	Could Selection of Patients Have Introduced Bias?	Comments
Boonen, 2005[114]	Commmunty-dwelling postmenopausal women	QUS	T-score <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, 2005[88]	UK, DXA scanning clinics, patients referred from general practitioners based on ≥1 clinical risk factors for OP	2 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 for clinical risk factors)
Harrison, 2006[94]	Caucasian females, ages 55-80 years (referred to clinical radiology, intended use of index test [QUS x2]), underwent DXA and categorized as nonosteoporosis 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
Jimenez-Nunez, 2013[95]	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

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Patients	Index Test	Reference Standard and Target Condition	Methods of Patient Selection	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?	Could Selection of Patients Have Introduced Bias?	Comments
Kung, 2003[96]	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 postmenopausal women, age mean is 62 years
Kung, 2005[97]	Community of Asian (Southern Chinese) men; developed index based on clinical factors; compared clinical index with calcaneal QUS in predicting BMD (T-score <-2.5) by DXA	Clinical index	Calcaneal QUS; target condition: osteoporosis as 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
Lynn, 2008[98]	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; 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	Low	NR
McLeod, 2015[102]	Women referred for screening in Canada, no prior testing	QUS and OST	DXA	Patients referred for screening to 1 facility	Y es	Yes	Yes	Low	NA

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Patients	Index Test	Reference Standard and Target Condition	Methods of Patient Selection	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?	Could Selection of Patients Have Introduced Bias?	Comments
Minnock, 2008[115]	Causian women underwent clinical risk factor questionnaire, QUS, and DXA 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, 2004[116]	2 cohorts of postmenopasual women, age ≥45 years; purpose of study #1 was to develop a 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 2nd 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 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Patients	Index Test	Reference Standard and Target Condition	Methods of Patient Selection	Enrolls Consecutive or Random Sample of Patients?	Avoids Case-Control Design?	Avoids Inappropriate Exclusions?	Could Selection of Patients Have Introduced Bias?	Comments
Sinnott, 2006[111]	African American men, age ≥35 years (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 nondominant foot, outcome is low bone mass	Ultrasound of calcaneous on nondominant 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.

Author, Year	Index Test	Results Interpreted Without Knowledge of Reference Standard Results?	Threshold Prespecified?	Could Conduct or Interpretation of Index Test Have Introduced Bias?	Comments
Boonen, 2005[114]	QUS, DXR, RA	Yes	Yes	Low	NR
Cook, 2005[88]	2 QUS tests- CUBA Clinical and Sunlight Omnisense measurements. Performed on nondominant 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 cutoff level based on the highest combined value of sensitivity and specificity. ROB assessment–depends if QUS studies read independently of DXA imaging.

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Index Test	Results Interpreted Without Knowledge of Reference Standard Results?	Threshold Prespecified?	Could Conduct or Interpretation of Index Test Have Introduced Bias?	Comments
Harrison, 2006[94]	QUS x2	Unclear	Yes	Unclear	Osteoporosis status determined before index tests conducted, but unclear if results available
Jimenez-Nunez, 2013[95]	4 risk scores + PIXI of the heel, algorithms were developed	Yes	Yes	Low	NR
Kung, 2003[96]	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, 2005[97]	Index developed by authors based on characteristics	Unclear	Yes	Low	NR
Lynn, 2008[98]	OST, MOST, QUI	Unclear	Yes	Low	NR
McLeod, 2015[102]	QUS of BUA and SOS of left calcaneus and personal data based on questionnaire	Yes	Yes	Low	NR
Minnock, 2008[115]	Combined clinical risk facors + QUS	Unclear	Yes	Low	NR
Richy, 2004[116]	Clinical algorithm; QUS	Unclear	Yes	Low	NR
Sinnott, 2006[111]	Ultrasound of calcaneous on nondominant 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

Author, Year	Reference Standard	Reference Standard Likely to Correctly Classify Target Condition?	Results Interpreted Without Knowledge of Index Test Results?	Could Reference Standard or Its Conduct/Interpretation Have Introduced Bias?	Comments
Boonen, 2005[114]	DXA, BMD of the lumbar spiine and proximal femur	Yes	Unclear	Low	NR
Cook, 2005[88]	DXA, BMD of the lumbar spine and total hip	Yes	Unclear	Unclear	NR
Harrison, 2006[94]	DXA, BMD of the femoral neck and total hip	Yes	Unclear	Low	NR
Jimenez-Nunez, 2013[95]	DXA, BMD of the hip and spine	Yes	Yes	Low	NR
Kung, 2003[96]	DXA, BMD of the lumbar spine, femoral neck	Yes	Unclear	Low	NR

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Reference Standard	Reference Standard Likely to Correctly Classify Target Condition?	Results Interpreted Without Knowledge of Index Test Results?	Could Reference Standard or Its Conduct/Interpretation Have Introduced Bias?	Comments
Kung, 2005[97]	DXA, BMD of the lumbar spine, femoral neck	Yes	Yes	Low	NR
Lynn, 2008[98]	DXA, lumbar spine and proximal femur	Yes	Unclear	Low	All obtained from MrOS (sequence of data collection not described)
McLeod, 2015[102]	DXA, BMD of the lumbar spine, left and right femoral neck	Yes	Yes	Low	NR
Minnock, 2008[115]	DXA, BMD of the lumbar spine, femoral neck, and total hip	Yes	Unclear	Low	NR
Richy, 2004[116]	DXA, BMD of the femoral neck	Yes	Yes	Low	NR
Sinnott, 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.

Author, Year	Patients Not Receiving Index Test, Reference Standard, or Were Excluded?	Time Interval and Interventions Between Index Test and Reference Standard	Appropriate Interval Between Index Test and Reference Standard?	All Patients Received Reference Standard?	Patients Received Same Reference Standard?	All Patients Included in Analysis?
Boonen, 2005[114]	On treatment for osteoporosis, peripheral oedema	Same day	Yes	Yes	Yes	Yes
Cook, 2005[88]	None	None	Yes	Yes	Yes	Yes
Harrison, 2006[94]	NR	NR	Unclear	Yes	Yes	Unclear
Jimenez-Nunez, 2013[95]	Nursing home, homebound, prior diagnosis of osteoporosis, on osteoporosis drugs, serious acute or chronic disease, hip replacement, steroids	Same day	Unclear	Yes	Yes	Unclear
Kung, 2003[96]	History or evidence of metabolic bone disease, menopause before age 40 years, history of cancer, evidence of significant renal impariment, both hips previously fractured or replaced, prior use of any bisphosphonates, fluoride, or calcitonin	NR	Unclear	Yes	Yes	Yes
Kung, 2005[97]	History or evidence of metabolic bone disease, history of cancer, evidence of significant renal impairment, 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, 2008[98]	NR	NR	Unclear	Yes	Yes	NA

Appendix D Table 4. Risk of bias assessment for KQ2a imaging studies predicting bone density status

Author, Year	Patients Not Receiving Index Test, Reference Standard, or Were Excluded?	Time Interval and Interventions Between Index Test and Reference Standard	Appropriate Interval Between Index Test and Reference Standard?	All Patients Received Reference Standard?	Patients Received Same Reference Standard?	All Patients Included in Analysis?
McLeod, 2015[102]	Previous diagnosis, progressive terminal illness	Within 3 weeks	Yes	Yes	Yes	Yes
Minnock, 2008[115]	NR	NR	Unclear	Yes	Yes	No
Richy, 2004[116]	NR	NR	Unclear	Yes	Yes	Yes
Sinnott, 2006[111]	NR	NR	Unclear	Yes	Yes	Yes

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

Author, Year	Could Patient Flow Have Introduced Bias?	Comments	Overall Judgement	Overall Comments
Boonen, 2005[114]	Low	NR	Low	Not a community-based sample. Women referred for bone densitometry.
Cook, 2005[88]	Low	NR	Unclear	Patient selection has the potential to skew the sample toward low BMD
Harrison, 2006[94]	Unclear	Participants underwent DXA and were categorized as nonosteoporosis or osteoporosis prior to QUS or risk indices	Unclear	Osteoporosis status determined first
Jimenez-Nunez, 2013[95]	Low	Random sample done with some sort of cards	Low	NR
Kung, 2003[96]	Low	NR	Low	NR
Kung, 2005[97]	Low	It is not clear what the time frame was between clinical assessment of risk factors and QUS; however, should be little impact; all participants received the same reference standard (referring to the validated group)	Low	NR
Lynn, 2008[98]	Low	NR	Low	NR
McLeod, 2015[102]	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
Minnock, 2008[115]	Low	NR	Unclear	Initial sample is 274 but number in analysis is 235 because of missing data, impact of missing data unclear
Richy, 2004[116]	Low	NR	Low	NR
Sinnott, 2006[111]	Low	The flow was not specifically described, but appears sequence was clinical assessment followed 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 5. KQ 2a prediction studies risk of bias

Author, Year	Interventions and Comparators	Prediction Model Development and External Validation in Same Publication?	Tests Performance of a Previously Developed Prediction Model in Other Individuals	Appropriate Data Sources Used?
Ahmed, 2014[154]	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[120]	QUS	No	No	Yes
Berry, 2013[195]	Assess contribution of repeat BMD in 4 years to Fx risk: 1. BMD at baseline and Fx risk 2. BMD percent change and Fx risk 3. BMD at baseline, BMD percent change, and Fx risk	No	Yes- Val only	Yes
Chan, 2012[125]	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[191]	1. FN plus 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 3 screening strategies for women ages 50-64 year: 1. USPSTF strategy (FRAX 3.0 without BMD, with followup BMD testing for Fx risk ≥9.3%)-10 yr horizon 2. OST-horizon unknown, developed to identify osteoporosis, not fracture 3. SCORE-horizon unknown, developed to identify osteoporosis, not fracture	No	Yes- Val only	Yes
Hans, 2011[122]	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[155]	QFracture updated with additional clinical predictors and outcomes	Yes- Dev and Val	Yes- Val only	Yes
Iki, 2014[121]	DXA- spine areal BMD, trabecular bone score	No	No	Yes
Iki, 2015[157]	FRAX and TBS	no	Yes- Val only	yes
Kalveston, 2016[142]	FRAX and BMD	Yes- Val only	Yes- Val only	Yes
Kanis, 2007[32]	FRAX	Yes- Dev and Val	No	Yes
Kwok, 2012[124]	Imaging screening: QUS (BUA, SOS, QUI measures), DXA (tHIP, fnHIP, spine BMD)	No	No	Yes
Leslie, 2010[156]	CAROC	No	Yes	Yes
Leslie, 2012[152]	FRAX	No	Yes- Dev and Val	Yes
Leslie, 2012[148]	FRAX with and without DXA	No	Yes	Yes
Leslie, 2013[123]	Trabecular bone score	No	No	Yes
Lo, 2011[178]	FRC	No	Yes- Val only	Probably yes

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Interventions and Comparators	Prediction Model Development and External Validation in Same Publication?	Tests Performance of a Previously Developed Prediction Model in Other Individuals	Appropriate Data Sources Used?
Lundin, 2015 [141]	FRAX and BMD	No	Yes- Val only	yes
Melton, 2005[333]	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[143]	Heel SXR, Heel QUS, forearm DXA, finger DXA; NORA study	No	No	Yes
Morin, 2009[103]	Body weight, BMI, OST	No	Yes	Yes
Nguyen, 2004[126]	QUS, DOES	No	No	Yes
Rubin, 2013[153]	FRAX (no BMD), OST, ORAI, OSIRIS, SCORE, age alone	No	Yes- Val only	Yes
Stewart, 2006[119]	DXA	No	Yes- Val only	Yes
van Geel, 2014[149]	FRAX, Garvan FRCr	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.

Author, Year	Inclusion/Exclusion of Participants Appropriate?	Participants Enrolled at Similar Health State or Considered Predictors to Account for Dissimilarities?	Risk of Bias Introduced by Selection of Participants?	Justification of Bias Rating	Comments
Ahmed, 2014[154]	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[120]	Yes	Yes	Low	NR	NR
Berry, 2013[195]	Yes	Yes	Low	NR	NR
Chan, 2012[125]	Yes	Yes	Low	NR	NR
Chan, 2013[191]	No	Yes	High	High concern for spectrum bias in the subgroup analysis, since participants were limited to those with BMD <-2.5	NR
Crandall, 2014[58]	Yes	Yes	Low	NR	NR
Hans, 2011[122]	Probably yes	Probably yes	Low	NR	NR

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Inclusion/Exclusion of Participants Appropriate?	Participants Enrolled at Similar Health State or Considered Predictors to Account for Dissimilarities?	Risk of Bias Introduced by Selection of Participants?	Justification of Bias Rating	Comments
Hillier, 2007[194]	Probably yes	Yes	Low	NR	NR
Hippisley-Cox, 2012[155]	Probably yes	Probably yes	Low	NR	NR
Iki, 2014[121]	Yes	Yes	Low	NR	NR
Iki, 2015 [157]	yes	yes	low	Population-based cohort	None
Kalvesten, 2016[142]	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[124]	Yes	Yes	Low	NR	NR
Leslie, 2010[156]	No information	Probably no	Low	Database covers population in Manitoba age 50 years with a first bone density measurement, and all citizens of Manitoba have university access to publicly funded medical care, including BMD.	NR
Leslie, 2012[152]	No information	Probably no	Low	Database covers population in Manitoba age 50 years with a first bone density measurement, and all citizens of Manitoba have university access to publicly funded medical care, including BMD.	NR
Leslie, 2012[148]	No information	Probably no	Low	Database covers population in Manitoba age 50 years with a first bone density measurement, and all citizens of Manitoba have university access to publicly funded medical care, including BMD.	NR
Leslie, 2013[123]	No information	Probably no	Low	Database covers all women in Manitoba age 50 years with a first bone density measurement, and all citizens of Manitoba have university access to publicly funded medical care, including BMD.	NR

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Inclusion/Exclusion of Participants Appropriate?	Participants Enrolled at Similar Health State or Considered Predictors to Account for Dissimilarities?	Risk of Bias Introduced by Selection of Participants?	Justification of Bias Rating	Comments
Lo, 2011[178]	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 ages 50 to 85 years referred to bone density scanning. Women without continuous membership both prior to and following DXA scans, and those for whom DXA results were not electronically accessible and those with missing race/ethnicity.
Lundin, 2015 [141]	Yes	Yes	Low	Population-based recruitment strategy	None
Melton, 2005[333]	No information	No information	Unclear	NR	NR
Miller, 2002[143]	Yes	No information	Unclear	It is unclear whether sites selected people with similar underlying characteristics	NR
Morin, 2009[103]	No information	Probably no	Low	Database covers all women in Manitoba ages 40 to 59 years with a first bone density measurement, and all citizens of Manitoba have university access to publicly funded medical care, including BMD.	NR
Nguyen, 2004[126]	No information	No information	Unclear	Unclear whether patients selected from database have similar underlying characteristics	NR
Rubin, 2013[153]	Yes	Yes	Low	NR	NR
Stewart, 2006[119]	Yes	No information	Low	NR	NR
van Geel, 2014[149]	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 5. KQ 2a prediction studies risk of bias

Author, Year	Predictors Defined and Assessed in Similar Way for All Participants?	Predictors Defined and Assessed in Similar Way to Those in Development Model?	Risk of Bias Introduced by Predictors or Their Assessment?	Justification of Bias Rating	Comments
Ahmed, 2014[154]	1. Garvan FRC with BMD, adjusted for age, prior fracture, prior fall 2. Garvan FRC, adjusted for body weight, age, prior fracture, prior fall	Yes	Yes	NR	NR
Azagra, 2011[181]	FRAX (Spain)	Yes	Yes	NR	NR
Bauer, 2007[120]	QUS	Yes	Yes	NR	NR
Berry, 2013[195]	Assess contribution of repeat BMD in 4 years to Fx risk: 1. BMD at baseline and Fx risk 2. BMD percent change and Fx risk 3. BMD at baseline, BMD percent change, and Fx risk	Yes	Yes	NR	NR
Chan, 2012[125]	1. FNBMD (adjusted for age, falls, prior fracture) 2. QUS (BUA) plus FNBMD (adjusted for age, falls, prior fracture)	Yes	Yes	NR	NR
Chan, 2013[191]	1. FN plus BMD (adjusted for age, falls, prior fracture) 2. QUS (BUA) plus FNBMD (adjusted for age, falls, prior fracture)	Yes	Yes	NR	NR
Crandall, 2014[58]	Comparison of 3 screening strategies for women ages 50-64 years: 1. USPSTF strategy (FRAX 3.0 without BMD, with followup BMD testing for Fx risk ≥9.3%)-10 yr horizon 2. OST-horizon unknown, developed to identify osteoporosis, not fracture 3. SCORE-horizon unknown, developed to identify osteoporosis, not fracture	Yes	Yes for FRAX and OST, probably no for SCORE	Authors show that use of different age cutoff for prior history of fracture would likely have little impact	NR
Hans, 2011[122]	TBS alone, DXA alone, TBS plus DXA	NA-NOT VAL	NA-NOT VAL	NR	NR
Hillier, 2007[194]	Imaging screening: DXA, initial BMD, repeat BMD, change in BMD, initial BMD plus change in BMD	NA-NOT VAL	NA-NOT VAL	NR	NR
Hippisley-Cox, 2012[155]	QFracture updated with additional clinical predictors and outcomes	Yes	Yes	NR	NR
Iki, 2014[121]	DXA- spine areal BMD, trabecular bone score	Yes	NA-NOT VAL	NR	NR
Iki, 2015 [157]	Yes	Yes	Low	In-person interviews	None

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Predictors Defined and Assessed in Similar Way for All Participants?	Predictors Defined and Assessed in Similar Way to Those in Development Model?	Risk of Bias Introduced by Predictors or Their Assessment?	Justification of Bias Rating	Comments
Kalvesten, 2016[142]	Yes	Yes	Low	Questionnaire-based assessment, all relevant predictors assessed	None
Kanis, 2007[32]	FRAX	Probably yes	Probably yes	NR	NR
Kwok, 2012[124]	Imaging screening: QUS (BUA, SOS, QUI measures), DXA (tHIP, fnHIP, spine BMD)	NA-NOT VAL	NA-NOT VAL	Imaging prediction of fracture, not clinical preduction tool	NR
Leslie, 2010[156]	CAROC	Yes	No	The final risk category was modified to reflect the presence of additional risk factors: any prior osteoporotic fracture (from 1987 to date of BMD testing) and/or recent systemic corticosteroid use (in the year before BMD testing)	NR
Leslie, 2012[152]	FRAX	Yes	No	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[148]	FRAX with and without DXA	Yes	No	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, 2013[123]	TBS	Yes	NA	TBS assessed the same way for all	NR
Lo, 2011[178]	FRC	Yes	Probably yes	NR	NR

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Predictors Defined and Assessed in Similar Way for All Participants?	Predictors Defined and Assessed in Similar Way to Those in Development Model?	Risk of Bias Introduced by Predictors or Their Assessment?	Justification of Bias Rating	Comments
Lundin, 2015 [141]	Yes for DXA No for FRAX	Yes for DXA No information for FRAX	Low for DXA Unclear for FRAX	Study does not describe how inputs to FRAX were obtained	NR
Melton, 2005[333]	NOF model including femoral neck BMD and clinical risk factors (personal Fx history, FHx, low BWT, smoking status)	Yes	Probably yes	NR	NR
Miller, 2002[143]	Heel SXR, heel QUS, forearm DXA, finger DXA; NORA study	Yes	NA	Peripheral bone densitometry done in similar ways for all	NR
Morin, 2009[103]	Body weight, BMI, OST	Yes	No information	Unclear whether data for OST (age, weight) was collected before fracture for all participants	NR
Nguyen, 2004[126]	QUS, DOES	Yes	NA	QUS done in similar ways for all	NR
Rubin, 2013[153]	FRAX (no BMD), OST, ORAI, OSIRIS, SCORE, age alone	Yes	No information	NR	NR
Stewart, 2006[119]	DXA	Yes	Yes	NR	NR
van Geel, 2014[149]	FRAX, Garvan Fracture Risk Calculator	Probably yes	Probably yes	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.

Author, Year	Outcome Definition Prespecified?	Outcome Defined and Determined in Similar Way for All?	Outcome Defined and Determined in Similar Way to Those in Development Model?	Outcome Determined Without Knowledge of Predictor Information?
Ahmed, 2014[154]	Yes	Yes	Yes	No information
Azagra, 2011[181]	Yes	Yes	Yes	Yes
Bauer, 2007[120]	Yes	Yes	Yes	No information
Berry, 2013[195]	Yes	Yes	Yes	No information
Chan, 2012[125]	Yes	Yes	Probably yes	No information
Chan, 2013[191]	Yes	Yes	Probably yes	No information
Crandall, 2014[58]	Yes	Yes	No for OST and SCORE, yes for FRAX	No information
Hans, 2011[122]	Yes	Yes	NA-NOT VAL	Yes

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Outcome Definition Prespecified?	Outcome Defined and Determined in Similar Way for All?	Outcome Defined and Determined in Similar Way to Those in Development Model?	Outcome Determined Without Knowledge of Predictor Information?
Hillier, 2007[194]	Yes	Yes	NA-NOT VAL	Yes
Hippisley-Cox, 2012[155]	Yes	Yes	Yes	Yes
Iki, 2014[121]	Yes	Yes	NA-NOT VAL	Yes
Iki, 2015 [157]	Yes	Yes	Yes	No information
Kalvesten, 2016[142]	Yes	Yes	Yes	No information
Kanis, 2007[32]	No information	No	Probably yes	No information
Kwok, 2012[124]	Yes	Yes	NA-NOT VAL	Yes
Leslie, 2010[156]	Yes	Yes	No information	Probably yes
Leslie, 2012[152]	Yes	Yes	No information	Probably yes
Leslie, 2012[148]	Yes	Yes	No information	Probably yes
Leslie, 2013[123]	Yes	Yes	Yes	Yes
Lo, 2011[178]	Yes	Yes	Probably yes	No information
Lundin, 2015[141]	Yes	Yes	Yes	No Information
Melton, 2005[333]	Yes	Yes	Probably no	Yes
Miller, 2002[143]	Yes	Yes	Yes	Yes
Morin, 2009[103]	Yes	Yes	No information	No information
Nguyen, 2004[126]	Yes	Yes	Yes	Yes
Rubin, 2013[153]	Yes	Yes	No information	Yes
Stewart, 2006[119]	Yes	Yes	Yes	No information
van Geel, 2014[149]	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.

Author, Year	Risk of Bias Introduced by Outcome or Its Determination?	Justification of Bias Rating	Comments
Ahmed, 2014[154]	Low	NR	NR
Azagra, 2011[181]	Low	NR	NR
Bauer, 2007[120]	Low	NR	NR
Berry, 2013[195]	Low	NR	NR
Chan, 2012[125]	Low	NR	NR
Chan, 2013[191]	Low	NR	NR
Crandall, 2014[58]	Unclear	NR	Both OST and SCORE were initially developed and validated for prediction of low BMD; in this study they were used to predict fracture. It's unclear what impact this will have.
Hans, 2011[122]	Low	NR	NR
Hillier, 2007[194]	Low	NR	NR
Hippisley-Cox, 2012[155]	Low	NR	NR
Iki, 2014[121]	Low	NR	NR

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Risk of Bias Introduced by Outcome or Its Determination?	Justification of Bias Rating	Comments
Iki, 2015[157]	Low	Fractures were confirmed	None
Kalvesten, 2016[142]	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[124]	Low	Did not exclude traumatic fractures; would have to use just number of fragility fractures	NR
Leslie, 2010[156]	Low	NR	NR
Leslie, 2012[152]	Low	NR	NR
Leslie, 2012[148]	Low	NR	NR
Leslie, 2013[123]	Low	NR	NR
Lo, 2011[178]	Low	NR	NR
Lundin, 2015[141]	Low	Identification of fractures from population-based claims/diagnosis data	None
Melton, 2005[333]	High	13.3% of fractures were due to severe trauma, another 18.3% had unclear cause	NR
Miller, 2002[143]	High	Self-reported factures	NR
Morin, 2009[103]	Unclear	Unclear whether OST variables collected for all women before fracture outcome	NR
Nguyen, 2004[126]	Low	NR	NR
Rubin, 2013[153]	Low	NR	NR
Stewart, 2006[119]	Low	NR	NR
van Geel, 2014[149]	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.

Author, Year	Missing Data on Predictors and Outcomes?	Reasonable Number of Outcome Events?	Appropriate Time Interval Between Predictor Assessment and Outcome Determination?	All Enrolled Participants Included in Analysis?
Ahmed, 2014[154]	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[120]	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[125]	No missing data described	Yes	Yes	Probably no
Chan, 2013[191]	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.	No information	Yes	Yes
Hans, 2011[122]	N eligible NR (>34,000, see comments) N included 29,407	Yes	Probably yes	Probably yes

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Missing Data on Predictors and Outcomes?	Reasonable Number of Outcome Events?	Appropriate Time Interval Between Predictor Assessment and Outcome Determination?	All Enrolled Participants Included in Analysis?
Hillier, 2007[194]	9704 enrolled in SOF, 8141 women had followup (93%), 4124 had repeat BMD measurement, excluded patients with incident hip or nonspine fractures between BMD measurement (72,513 respectively)	Yes	Yes	Probably no
Hippisley-Cox, 2012[155]	Did not report amount of missing data (particularly for BMI, smoking status, alcohol intake), though reports multiple imputation was used. Qresearch database >13,000,000 patients but only 4,726,046 used for development and validation cohorts.	Yes	Probably yes	No
Iki, 2014[121]	789 eligible 665 analyzed 112 lost to followup 4 unassessable VFA 8 developed disease affecting bone metabolism	Yes	Yes	Probably yes
Iki, 2015[157]	No information about the men excluded from the analysis	Probably No	Probably No	Probably Yes
Kalvesten, 2016[142]	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
Kwok, 2012[124]	N (eligible)=2000, N (analyzed)=1921, those missing QUS or DXA readings excluded, invalid QUS readings excluded	Probably yes	Probably yes	No
Leslie, 2010[156]	Unclear	Yes	Yes	Yes
Leslie, 2012[152]	Unclear	Yes	Yes	Yes
Leslie, 2012[148]	Unclear	Yes	Yes	Yes
Leslie, 2013[123]	Not reported	Yes	Yes	Probably yes
Lo, 2011[178]	Women with missing data on race/ethnicity and BMD were excluded from analysis	Yes	Yes	Yes
Lundin, 2015[141]	Missing data for 5 participants	Yes	Yes	Yes
Melton, 2005[333]	1,479 approached, 1,315 eligible, 655 consented, only 393 included in analysis - unclear why	Probably yes	Yes	No
Miller, 2002[143]	Not reported	Yes	No	Unclear
Morin, 2009[103]	Not reported	Yes	Yes	Unclear
Nguyen, 2004[126]	Not reported	Yes	Unclear	Unclear
Rubin, 2013[153]	Eligible: 5000 Analysis: 3614 Exclusion: 334 Missing questionnaire data, 246 diagnosed with/ treated for OP, reported "near complete followup"	Probably yes	Probably no	Yes

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Missing Data on Predictors and Outcomes?	Reasonable Number of Outcome Events?	Appropriate Time Interval Between Predictor Assessment and Outcome Determination?	All Enrolled Participants Included in Analysis?
	in registry			
Stewart, 2006[119]	Nonresponse analysis done	Yes	Yes	Yes
van Geel, 2014[149]	Random sample: 1686, analysis sample: 506 Missing: no coop with MD (272), no coop with patient (448), untraceable/deceased (207), age <60 years (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.

Author, Year	Participants With Missing Data Handled Appropriately?	Risk of Bias Introduced by Sample Size or Participant Flow?	Justification of Bias Rating	Comments
Ahmed, 2014[154]	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[120]	Yes	Low	NR	No mention of missing data
Berry, 2013[195]	Yes	Low	NR	NR
Chan, 2012[125]	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[191]	Yes	Unclear	NR	NR
Crandall, 2014[58]	Yes	Low	NR	NR
Hans, 2011[122]	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[155]	Probably yes	Unclear	Unclear exclusion criteria	Over 13 million in database, only 4.7 million used
Iki, 2014[121]	Probably yes	Low	NR	NR
Iki, 2015 [157]	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

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Participants With Missing Data Handled Appropriately?	Risk of Bias Introduced by Sample Size or Participant Flow?	Justification of Bias Rating	Comments
Kalvesten, 2016[142]	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[124]	Probably yes	Low	2.5% excluded for missing data (small)	NR
Leslie, 2010[156]	No information	Unclear	NR	NR
Leslie, 2012[152]	No information	Unclear	NR	NR
Leslie, 2012[148]	No information	Unclear	NR	NR
Leslie, 2013[123]	Probably yes	Low	99% accuracy and completeness	NR
Lo, 2011[178]	Probably yes	Low	NR	NR
Lundin, 2015 [141]	yes	low	No concerns	NR
Melton, 2005[333]	No information	High	Only about 50% of eligible patietns consented, and of those only 2/3rd included for analysis	NR
Miller, 2002[143]	No information	Unclear	Unclear whether followup window is sufficient	NR
Morin, 2009[103]	No information	Unclear	Unclear what proportion of cohort did not have information on predictors	NR
Nguyen, 2004[126]	No information	Unclear	The average time between imaging and fractures is unclear	NR
Rubin, 2013[153]	No information	Unclear	Only 3 year follow-up while FRAX predicts 10 year fracture for women over 40 years old	NR
Stewart, 2006[119]	Probably yes	Low	NR	NR
van Geel, 2014[149]	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.

Author, Year	Nonbinary Predictors Handled Appropriately?	Complexities in Data Accounted for Appropriately?	Model Recalibrated or Likely Not Needed?	Risk of Bias Introduced by Analysis?
Ahmed, 2014[154]	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[120]	Yes	No information	No information	Low
Berry, 2013[195]	Yes	No information	Probably yes	Low
Chan, 2012[125]	Probably yes	No information	Yes	Varies by outcome
Chan, 2013[191]	Probably yes	No information	Yes	Varies by outcome

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Nonbinary Predictors Handled Appropriately?	Complexities in Data Accounted for Appropriately?	Model Recalibrated or Likely Not Needed?	Risk of Bias Introduced by Analysis?
Crandall, 2014[58]	Yes	No information	No information	Unclear
Hans, 2011[122]	Yes	Probably yes	Probably yes	Low
Hillier, 2007[194]	Probably yes	Yes	Yes	Low
Hippisley-Cox, 2012[155]	Probably yes	Yes	Yes	Low
Iki, 2014[121]	Yes	Probably yes	Yes	Low
Iki, 2015 [157]	Yes	no information	yes	low
Kalvesten, 2016 [142]	yes	no information	yes	low
Kanis, 2007[32]	Yes	Probably yes	Probably yes	Low
Kwok, 2012[124]	Yes	Yes	NA-NOT VAL	Low
Leslie, 2010[156]	Yes	No information	No	Low
Leslie, 2012[152]	Yes	No information	No	Low
Leslie, 2012[148]	Yes	No information	No	Low
Leslie, 2013[123]	Yes	No information	No	Low
Lo, 2011[178]	Yes	No information	Probably yes	Low
Lundin, 2015 [141]	yes	no	yes	low
Melton, 2005[333]	Yes	Probably yes	Yes	Low
Miller, 2002[143]	Yes	No information	No	Low
Morin, 2009[103]	Yes	No information	No	Low
Nguyen, 2004[126]	Yes	No information	No	Low
Rubin, 2013[153]	Yes	Yes	Yes	Low
Stewart, 2006[119]	NA	Probably no	Na	Low
van Geel, 2014[149]	Yes	Probably yes	Yes	Low

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

Author, Year	Justification of Bias Rating	Comments	Overall Judgement of Risk of Bias	Justification of Bias Rating
Ahmed, 2014[154]	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 followup 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 followup.
Bauer, 2007[120]	NR	NR	Low	NR
Berry, 2013[195]	NR	NR	Low	NR

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Justification of Bias Rating	Comments	Overall Judgement of Risk of Bias	Justification of Bias Rating
Chan, 2012[125]	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[191]	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 devleoped and validated to predict fractures; they were developed and validated to predict low BMD/osteoporosis.
Hans, 2011[122]	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[155]	NR	NR	Unclear	Unclear because of partipant flow
Iki, 2014[121]	NR	NR	Low	NR
Iki, 2015 [157]	Evidence of good calibration	None	unclear	Length of follow-up only 4.5 years for a 10-year prediction.
Kalvesten, 2016 [142]	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.
Kanis, 2007[32]	NR	NR	Low	NR
Kwok, 2012[124]	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[156]	NR	NR	Unclear	Effect of adjustment to final risk category unclear
Leslie, 2012[152]	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[148]	Model demonstrates the effect of not using BMD	NR	Unclear	Effect of adjustments of absence of data on parental hip fractures unclear

Appendix D Table 5. KQ 2a prediction studies risk of bias

Author, Year	Justification of Bias Rating	Comments	Overall Judgement of Risk of Bias	Justification of Bias Rating
Leslie, 2013[123]	NR	NR	Low	NR
Lo, 2011[178]	NR	NR	Unclear	Selection bias and spectrum bias due to how cohort was assembled.
Lundin, 2015 [141]	Most of the items are NA.	None	low	No serious risks of bias
Melton, 2005[333]	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[143]	NR	NR	High	Self-reported fracture outcomes
Morin, 2009[103]	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
Nguyen, 2004[126]	NR	NR	Unclear	Proportion and management of missing data unclear
Rubin, 2013[153]	NR	NR	Unclear	For short follow-up duration to predict 10 year risk.
Stewart, 2006[119]	NR	NR	Low	NR
van Geel, 2014[149]	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 6. KQ4 and KQ5 systematic review risk of bias assessments

Author, Year	Interventions and Comparators	Adhered to Predefined Objectives and Eligibility Criteria?	Eligibility Criteria Appropriate for Review Question?	Eligibility Criteria Unambiguous?
Crandall et al, 2012[221]	Treatments to prevent fractures vs. placebo	Yes	Yes	Yes

Abbreviations: KQ = key question; vs= versus

Author, Year	Appropriate Restrictions in Eligibility Criteria Based on Study Characteristics?	Appropriate Restrictions in Eligibility Criteria Based on Sources of Information?	Concerns Regarding Specification of Study Eligibility Criteria?	Searched 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

Author, Year	Used Methods in Addition to Database Searching to Identify Relevant Reports?	Search Likely to Retrieve as Many Eligible Studies as Possible?	Appropriate Restrictions Based on Date, Publication Format, or Language?	Minimized Error in Selection of Studies?
Crandall et al, 2012[221]	Yes	Yes	Probably yes	Yes

Abbreviations: KQ = key question

Author, Year	Concerns Regarding Methods Used to Identify and/or Select Studies?	Minimized Error in Data Collection?	Sufficient Study Characteristics for Authors and Readers to Interpret the Results?	All Relevant Study Results Collected?
Crandall et al, 2012[221]	Low	No information	Yes	Yes

Abbreviations: KQ = key question

Author, Year	Risk of Bias Formally Assessed Using an Appropriate Tool?	Minimized Error in Risk of Bias Assessment?	Concerns Regarding Methods Used to Collect Data and Appraise Studies?	Synthesis Includes All Studies That It Should?
Crandall et al, 2012[221]	Yes	No information	Low	Yes

Abbreviations: KQ = key question

Author, Year	Predefined Analyses Reported or Departures Explained?	Synthesis Appropriate Given the Degree of Similarity in the Research Questions, Study Designs, and Outcomes Across Included Studies?	Between-Study Variation Minimal or Addressed?	Findings Robust?
Crandall et al, 2012[221]	Yes	Yes	Yes	Yes

Abbreviations: KQ = key question

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

Abbreviations: KQ = key question

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances That Suggest a Problem With Randomization?
Abrahamsen, 2010[271]	G1: Alendronate G2: Untreated	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Adachi, 2009[248]	G1: Alendronate 10 mg/day (generic preparation) G2: Placebo	RCT parallel	Yes	Yes	Probably yes
Barrett-Connor, 2002[308]	G1: Raloxifene (60 mg/day) G2: Raloxifene (120 mg/day) G2: Placebo	Post-hoc or subgroup analysis of RCT	Yes	Yes	No
Barrett-Connor, 2004[307]	G1: Raloxifene (60 or 120 mg/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[295]	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[282]	G1: Ibandronate G2: Placebo	RCT parallel	Probably yes	Yes	No
Cryer, 2005[250]	G1: Alendronate 70 mg weekly G2: Placebo	RCT parallel	Yes	Yes	No
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	G1: Alendronate 5 mg/day for 2 years, then 10 mg/day for 3 years G2: Placebo	RCT parallel	Yes	Yes	No
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	G1: Denosumab G2: Placebo	RCT parallel	Probably yes	Probably yes	No
Eisman, 2004[253]	G1: Alendronate 70 mg weekly G2: Placebo	RCT parallel	Yes	Yes	No
Fogelman, 2000[226]	G1: Risedronate 5 mg/day x 24 months G2: Placebo	RCT parallel	No information	No information	No
Greenspan, 2002[252]	G1: Alendronate 70 mg weekly G2: Placebo	RCT parallel	No information	No information	No

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances That Suggest a Problem With Randomization?
Greenspan, 2003[247]	G1: Alendonate 10 mg/day G2: Conjugated equine estrogen 0.625 mg/day with or without medroxyprogesterone 2.5 mg/day based on uterus presence G3: Alendronate + CEE G4: Placebo	RCT parallel	Yes	Yes	No
Grey, 2010[272]	G1: Zolendronate 5 mg IV x 1 dose G2: Placebo	RCT parallel	Yes	Yes	Probably yes
Hosking, 2003[202]	G1: Risedronate 5 mg/day x 3 months G2: Alendronate 70 mg weekly x 3 months G3: Placebo	RCT parallel	Yes	Yes	No
Hosking, 2003[202]	G1: Alendronate 70 mg weekly G2: Risendronate 5 mg/day G3: Placebo	RCT parallel	Yes	Yes	No
Johnell, 2002[244]	RLX 60, placebo	RCT parallel	Yes	Yes	Probably no
Keech, 2005[309]	G1: Raloxifene 60 mg/day G2: Placebo	Post-hoc or subgroup analysis of RCT	Yes	Yes	No
Kung, 2000[334]	G1: Alendronate 10 mg/day G2: Placebo	RCT parallel	No information	No information	No
Lasco, 2011[240]	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: Alendronate G3: Placebo	RCT parallel	Probably yes	Probably yes	No
McCloskey, 2012[335]	G1: 60 mg denosumab SC q 6 months for 36 months G2: Placebo	RCT parallel	No information	No information	No
McClung, 2004[283]	G1: 0.5 mg ibandronate daily G2: 1.0 mg ibandronate daily G3: 2.5 mg ibandronate daily G4: Placebo	RCT parallel	No information	No information	No
McClung, 2006[303]	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 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances That Suggest a Problem With Randomization?
McClung, 2006[209]	G1: Denosumab 6 mg q 3 months G2: Denosumab 14 mg q 3 months G3: Denosumab 30 mg q 3 months G4: Denosumab 14 mg q 6 months G5: Denosumab 60 mg q 6 months G6: Denosumab 100 mg q 6 months G7: Denosumab 210 mg q 6 months G8: Alendronate 70 mg weekly G9: Placebo	RCT parallel	No information	No information	No
McClung, 2009[273]	G1: Zoledronic acid 5 mg IV q 12 months for 2 doses G2: Zoledronic acic 5 mg IV once and placebo at 12 months G3: Placebo at baseline and 12 months	RCT parallel	Yes	Yes	No
Meunier, 1999[304]	Raloxifene 60 mg, 150 mg, or placebo	RCT parallel	No information	Probably yes	No
Miller, 2008[305]	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[306]	Raloxifene, 2 dosage amounts vs. placebo	RCT parallel	No information	No information	Probably no
Murphy, 2001[270]	G1: MK-677 25 mg/day G2: Alendronate 10 mg/day G3: MK-677 and alendronate G4: Placebo **G2 and G4 data only for KQ5	RCT parallel	Yes	Yes	No
Nakamura, 2012[336]	G1: Denosumab 14 mg G2: Denosumab 60 mg G3: Denosumab 100 mg G4: Placebo	RCT parallel	No information	No information	No
Orwoll, 2003[239]	G1: 20 µg teriparatide: 151 G2: 40 µg teriparatide: 139 G3: Placebo: 147	RCT parallel	Yes	Yes	No
Pazianas, 2008 [296]	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
Ravn, 1996[284]	G1: 0.25 mg ibandronate daily G2: 0.5 mg ibandronate daily G3: 1.0 mg ibandronate daily G4: 2.5 mg ibandronate daily G5: 5.0 mg ibandronate daily G6: Placebo	RCT parallel	No information	No information	No

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances That Suggest a Problem With Randomization?
Reginster, 2005[285]	G1: 50 mg ibandronate monthly for 1 month, followed by 50 mg monthly for 2 months for half the sample and 100 mg monthly for 2 months for the other half G2: 100 mg ibandronate monthly for 3 months G3: 150 mg ibandronate monthly for 3 months G4: Placebo for 3 months	RCT parallel	No information	No information	Yes
Rhee, 2012[337]	G1: Bisphosphonate use G2: Nonbisphosphonate use	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Riis, 2001[286]	G1: 2.5 mg ibandronate daily continuous therapy G2: 20 mg ibandronate intermittent cyclical therapy G3: Placebo	RCT parallel	No information	No information	No
Samelson, 2014[338]	G1: 60 mg denosumab SC q 6 months for 36 months G2: Placebo	Post-hoc or subgroup analysis of RCT	No information	No information	Probably no
Shiraki, 2003[281]	G1: Risedronate 5 mg/day x 36 weeks G2: Placebo	RCT cluster	No information	No information	No
Simon, 2013[339]	G1: 60 mg Denosumab SC q 6 mos for 36 mos G2: Placebo	RCT parallel	No information	No information	No
Sontag, 2010[241]	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[245]	G1: Bisphosphonate therapy* G2: Placebo *Study examined all bisphosphonates 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[287]	G1: 5 mg ibandronate weekly G2: 10 mg ibandronate weekly G3: 20 mg ibandronate weekly G4: Placebo	RCT parallel	No information	No information	No
Thiebaud, 1997[288]	G1: 2.5 mg ibandronate IV every 3 months G2: 0.5 mg ibandronate IV every 3 months G3: 1 mg ibandronate IV every 3 months G4: 2 mg ibandronate IV every 3 months G5: Placebo	RCT parallel	No information	No information	No

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Interventions and Comparators	Study Design	Method of Randomization Adequate?	Allocation Concealment Adequate?	Baseline Imbalances That Suggest a Problem With Randomization?
Tucci, 1996[251]	G1: Alemg/ndronate 5 mg daily G2: Alendronate 10 mg daily G3: Alendronate 20 mg/day for 2 years then 5 mg/day for 1 year G4: Placebo	RCT parallel	Yes	Yes	No
Van Staa, 1997[340]	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[341]	Gastric and esophagus events	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2011[342]	Stroke	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2012[343]	Cardiac and atherosclerosis	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2011[344]	Femoral shaft and subtrochanteric fractures	Cohort study	NA-not an RCT	NA-not an RCT	NA-not an RCT
Vestergaard, 2012[345]	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.

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Used to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Using Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Abrahamsen, 2010[271]	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[248]	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.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Used to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Using Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Barrett-Connor, 2002[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Barrett-Connor, 2004[307]	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[295]	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[282]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Cryer, 2005[250]	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[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	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[253]	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[252]	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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Used to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Using Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Greenspan, 2003[247]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Grey, 2010[272]	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[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Keech, 2005[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Kung, 2000[334]	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[240]	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.
McCloskey, 2012[335]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No information	NR
McClung, 2004[283]	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[303]	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[273]	No	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Meunier, 1999[304]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Miller, 2008[305]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Morii, 2003[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	Some missing information
Murphy, 2001[270]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Nakamura, 2012[336]	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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Used to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Using Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Orwoll, 2003[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Pazianas, 2008[296]	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[284]	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[285]	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
Rhee, 2012[337]	Yes	No	No information	NA-not a case-control	Probably yes	Although the authors attempt to create an new user cohort by excluding 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[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
Samelson, 2014[338]	Yes	Yes	No information	NA-not a case-control	Probably no	NR
Shiraki, 2003[281]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	Probably no	NR
Simon, 2013[339]	Yes	Yes	Probably yes	NA-not a case-control	Probably no	No detail on method of randomization and allocation concealment.
Sontag, 2010[241]	yes	yes	NA	NA-not a case-control	Probably no	NR
Sorensen, 2008[245]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Yes	No	NR
Tanko, 2003[287]	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[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 Slight differences length of menopause

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Study Selection Unrelated to Intervention or Outcome?	Start of Followup and Intervention Coincide for Most Subjects?	Adjustment Techniques Used to Correct for Presence of Selection Biases?	Controls Sampled From Population That Gave Rise to Cases, or Using Another Method That Avoids Selection Bias?	Bias From Randomization or Selection?	Comments
Tucci, 1996[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a case-control	No	NR
Van Staa, 1997[340]	Yes	Yes	Yes	NA-not a case-control	Probably no	NR
Vestergaard, 2010[341]	Yes	Yes	Irrelevant, claim there is no missing data	NA-not a case-control	No	NR
Vestergaard, 2011[342]	Yes	Yes	Irrelevant, claim there is no missing data	Yes	No	NR
Vestergaard, 2012[343]	Yes	Yes	Irrelevant, claim there is no missing data	NA-not a case-control	No	NR
Vestergaard, 2011[344]	Yes	Yes	Irrelevant, claim there is no missing data	NA-not a case-control	No	NR
Vestergaard, 2012[345]	Yes	Yes	Irrelevant, claim there is no missing data	NA-not a case-control	No	NR

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

Author, Year	Confounding of Effect of Intervention Unlikely?	Participants Analyzed According to Their Initial Intervention Group Throughout Followup?	Intervention Discontinuations or Switches Unlikely to Be Related to Factors That Are Prognostic for the Outcome?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains?
Abrahamsen, 2010[271]	Probably no	Yes	No information	Probably yes
Adachi, 2009[248]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Barrett-Connor, 2002[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Barrett-Connor, 2004[307]	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 [295]	Probably no	NA-not a cohort	NA-not a cohort	No information
Chapurlat, 2013[282]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cryer, 2005[250]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Cummings, 1998[200]; Quandt, 2005[205]; Bauer, 2000[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Confounding of Effect of Intervention Unlikely?	Participants Analyzed According to Their Initial Intervention Group Throughout Followup?	Intervention Discontinuations or Switches Unlikely to Be Related to Factors That Are Prognostic for the Outcome?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains?
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Eisman, 2004[253]	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[252]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Greenspan, 2003[247]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Grey, 2010[272]	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[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Keech, 2005[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Kung, 2000[334]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Lasco, 2011[240]	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[335]	Probably yes	Yes	Yes	Probably yes
McClung, 2004[283]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
McClung, 2006[303]	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[273]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Meunier, 1999[304]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Miller, 2008[305]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Morii, 2003[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Murphy, 2001[270]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Nakamura, 2012[336]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Orwoll, 2003[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Pazianas, 2008 [296]	Probably no	NA-not a cohort	NA-not a cohort	Yes
Ravn, 1996[284]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Reginster, 2005[285]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Rhee, 2012[337]	Yes	Yes	Unclear, all switches dropped from analysis	NA
Riis, 2001[286]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Samelson, 2014[338]	Probably yes	Yes	Yes	Probably yes
Shiraki, 2003[281]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Simon, 2013[339]	Probably yes	Yes	Yes	Probably yes
Sontag, 2010[241]	Yes	NA	Yes	No
Sorensen, 2008[245]	No	NA-not a cohort	NA-not a cohort	Yes
Tanko, 2003[287]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Thiebaud, 1997[288]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Confounding of Effect of Intervention Unlikely?	Participants Analyzed According to Their Initial Intervention Group Throughout Followup?	Intervention Discontinuations or Switches Unlikely to Be Related to Factors That Are Prognostic for the Outcome?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains?
Tucci, 1996[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA-not a cohort
Van Staa, 1997[340]	Yes	NA	NA	NA
Vestergaard, 2010[341]	No	No information	No information	No
Vestergaard, 2011[342]	No	No information	No information	No
Vestergaard, 2012[343]	No	No information	No information	No
Vestergaard, 2011[344]	No information	No information	No	Yes
Vestergaard, 2012[345]	No	No information	No information	No

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

Author, Year	Avoid Adjusting for Postintervention Variables?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains and Time-Varying Confounding?	Bias From Confounding?	Comments
Abrahamsen, 2010[271]	yes	Probably yes	Probably yes	NR
Adachi, 2009[248]	NA-not a cohort	NA-not a cohort	No	NR
Barrett-Connor, 2002[308]	NA-not a cohort	NA-not a cohort	NA	NR
Barrett-Connor, 2004[307]	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 [295]	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[282]	NA-not a cohort	NA-not a cohort	N/A	NR
Cryer, 2005[250]	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	NA-not a cohort	NA-not a cohort	No	NR
Eisman, 2004[253]	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[252]	NA-not a cohort	NA-not a cohort	No	NR
Greenspan, 2003[247]	NA-not a cohort	NA-not a cohort	No	NR
Grey, 2010[272]	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[244]	NA-not a cohort	NA-not a cohort	Probably no	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Avoid Adjusting for Postintervention Variables?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains and Time-Varying Confounding?	Bias From Confounding?	Comments
Keech, 2005[309]	NA-not a cohort	NA-not a cohort	NA	NR
Kung, 2000[334]	NA-not a cohort	NA-not a cohort	No	NR
Lasco, 2011[240]	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[335]	Probably yes	NA	No information	Analysis was prespecified according to the methods and does not appear to be a subgroup. Looks at efficacy across the range of baseline FRAX risk.
McClung, 2004[283]	NA-not a cohort	NA-not a cohort	NA	NA, Not a cohort or case control
McClung, 2006[303]	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[273]	NA-not a cohort	NA-not a cohort	No	RCT design mitigates risk of confounding from known and unknown factors.
Meunier, 1999[304]	NA-not a cohort	NA-not a cohort	Probably no	NR
Miller, 2008[305]	NA-not a cohort	NA-not a cohort	No	NR
Morii, 2003[306]	NA-not a cohort	NA-not a cohort	Probably no	NR
Murphy, 2001[270]	NA-not a cohort	NA-not a cohort	No	NR
Nakamura, 2012[336]	NA-not a cohort	NA-not a cohort	NA	NR
Orwoll, 2003[239]	NA-not a cohort	NA-not a cohort	No	Not a cohort study
Pazianas, 2008 [296]	NA-not a cohort	NA-not a cohort	Probably no	Possible patients could have been taking other treatments that were not documented
Ravn, 1996[284]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Reginster, 2005[285]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Rhee, 2012[337]	No	No	Yes	Dropped all patients with switches, which potentially selectively drops patients with reactions to initial drug therapy
Riis, 2001[286]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Samelson, 2014[338]	Yes	NA, if item 10 is yes/probably yes	Probably no	Treatment assignment is random; CV risks were balanced between groups.
Shiraki, 2003[281]	NA-not a cohort	NA-not a cohort	No information	NR
Simon, 2013[339]	Probably yes	NA	Probably no	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Avoid Adjusting for Postintervention Variables?	Used an Appropriate Analysis Method Adjusting for All Critically Important Confounding Domains and Time-Varying Confounding?	Bias From Confounding?	Comments
Sontag, 2010[241]	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 agents
Sorensen, 2008[245]	NA-not a cohort	NA-not a cohort	No	NR
Tanko, 2003[287]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Thiebaud, 1997[288]	NA-not a cohort	NA-not a cohort	NA, Not a cohort or case control	NR
Tucci, 1996[251]	NA-not a cohort	NA-not a cohort	No	NR
Van Staa, 1997[340]	NA	NA	No	NR
Vestergaard, 2010[341]	Yes	Probably no	Probably yes	Given the results, it's likely there were other underlying variables not fully accounted for. For example, are all NSAIDS in the drugs registry? What about OTC NSAIDS?
Vestergaard, 2011[342]	Yes	Probably no	Probably yes	NR
Vestergaard, 2012[343]	Yes	Probably no	Probably yes	Given the results it's likely there were other underlying variables not fully accounted for. For example, did they fully control for all other causes of MI, such as smoking and hypertension?
Vestergaard, 2011[344]	Probably no	Probably yes	No	NR
Vestergaard, 2012[345]	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.

First Author, Year	Intervention Status Well Defined?	Information on Intervention Status Recorded at Time of Intervention?	Information on Intervention Status Unaffected by Knowledge or Risk of Outcome?	Bias From Measurement of Intervention?	Comments
Abrahamsen, 2010[271]	Yes	Yes	Yes	Probably no	NR
Adachi, 2009[248]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Barrett-Connor, 2002[308]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Barrett-Connor, 2004[307]	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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

First Author, Year	Intervention Status Well Defined?	Information on Intervention Status Recorded at Time of Intervention?	Information on Intervention Status Unaffected by Knowledge or Risk of Outcome?	Bias From Measurement of Intervention?	Comments
Cartsos, 2008 [295]	No	No	Probably yes	Yes	Intervention based on dispensing information from claims data, information on dose not available
Chapurlat, 2013[282]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Cryer, 2005[250]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Eisman, 2004[253]	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[252]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Greenspan, 2003[247]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Grey, 2010[272]	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[244]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Keech, 2005[309]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Kung, 2000[334]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Lasco, 2011[240]	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[335]	Yes	Yes	Yes	No	It was prespecified.
McClung, 2004[283]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
McClung, 2006[303]	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
McClung, 2009[273]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	RCT design so all items NA.
Meunier, 1999[304]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Miller, 2008[305]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Morii, 2003[306]	NA-not a cohort	NA-not a cohort	NA-not a cohort	Probably no	NR
Murphy, 2001[270]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Nakamura, 2012[336]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA	NR
Orwoll, 2003[239]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Pazianas, 2008 [296]	No	No	Probably yes	Yes	intervention based on dispensing information from claims data, information on dose, etc. not available

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

First Author, Year	Intervention Status Well Defined?	Information on Intervention Status Recorded at Time of Intervention?	Information on Intervention Status Unaffected by Knowledge or Risk of Outcome?	Bias From Measurement of Intervention?	Comments
Ravn, 1996[284]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Reginster, 2005[285]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Rhee, 2012[337]	Yes	Yes	Yes	No	NR
Riis, 2001[286]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Samelson, 2014[338]	Probably yes	Yes	Yes	Probably no	NR
Shiraki, 2003[281]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No information	NR
Simon, 2013[339]	Yes	Yes	Yes	Probably no	NR
Sontag, 2010[241]	Yes	Yes	Yes	Probably no	NR
Sorensen, 2008[245]	Yes	Yes	Yes	No	NR
Tanko, 2003[287]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Thiebaud, 1997[288]	NA-not a cohort	NA-not a cohort	NA-not a cohort	NA, not a cohort or case control	NR
Tucci, 1996[251]	NA-not a cohort	NA-not a cohort	NA-not a cohort	No	NR
Van Staa, 1997[340]	No	Yes	Yes	Yes	Intervention status defined as patients who had received a prescription
Vestergaard, 2010[341]	No	No information	Yes	Probably yes	NR
Vestergaard, 2011[342]	No	No information	Yes	Probably yes	NR
Vestergaard, 2012[343]	No	No information	Yes	Probably yes	NR
Vestergaard, 2011[344]	Yes	Probably yes	None	No	NA, no attrition
Vestergaard, 2012[345]	No	No information	Yes	Probably yes	NR

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

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Abrahamsen, 2010[271]	Overall: NR G1: 3.1% G2: 3.0% Vary by outcome: Probably no	No	Yes	NA-not a case-control
Adachi, 2009[248]	Overall: 16.2 [%] G1: 18.6 [%] G2: 11.6% [%] Vary by outcome: No	No	Yes	NA-not a case-control

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Barrett-Connor, 2002[308]	Overall: 26% G1: 26% G2: 25% G3: 26% Vary by outcome: No	Yes	No	NA
Barrett-Connor, 2004[307]	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 consent, lost to followup, protocol violations, no signficant variation 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[295]	NA- no attrition	NA- no attrition	NA- no attrition	NA- no attrition
Chapurlat, 2013[282]	Overall: 0.67 G1: 0 G2: 1.3 Vary by outcome: No *Followup* Overall: Unclear G1: Unclear G2: Unclear	No	Yes	NA- no attrition
Cryer, 2005[250]	Overall: 13.7 [%] G1: 13.8 [%] G2: 13.5[%] G3: [%] Vary by outcome: No	No	Probably yes	NA-not a case-control

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Patients missing followup x-ray Overall: 379/6459 (5.9%) G1: 198/3195 (6.2%) G2: 181/3183 (5.75)	No	Yes	NA-not a case-control
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	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[253]	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[252]	Overall: 6.9% G1: 6.3% G2: 7.5% Vary by Outcome: No	No	Yes	NA-not a case-control
Greenspan, 2003[247]	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
Grey, 2010[272]	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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
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.	Yes	Yes	No
Johnell, 2002[244]	Overall: 17%; differences by group NR	No	Yes	NA- no attrition
Keech, 2005[309]	Overall: NR G1: 29% G2: 33% Vary by outcome: No	Yes	No	NA
Kung, 2000[334]	Overall: 80 [%] G1: 80 [%] G2: 80 [%] G3: [%] Vary by outcome: No	Yes	Yes	NA-not a case-control
Lasco, 2011[240]	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
McCloskey, 2012[335]	Overall: 82% G1: NR G2: NR Vary by outcome: Probably no	No	No information	NA-not a case-control
McClung, 2004[283]	Overall: 16% G1: 15% G2: 13% G3: 18% G4: 17% Vary by outcome: No	No	Yes	NA-not a case-control

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
McClung, 2006[303]	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 [%] NR by group overall. For below, only reported by drug (not dosing group) Vary by outcome: Yes *Withdrawal 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[273]	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[304]	Overall: 20/129 (19%) at 24 months, of these, 14 in year 1; differences by group NR	No	Yes	NA- no attrition
Miller, 2008[305]	Overall: 29.7% (N=470) discontinued treatment, another 2.9% (46) failed to return. The flow chart shows patients who did not complete because of "subject request" and "other."	Yes	Yes	NA-not a case-control
Morii, 2003[306]	Overall: 13%; differences by group NR	No	Yes	NA- no attrition
Murphy, 2001[270]	Overall:15% at 6 months, 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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Nakamura, 2012[336]	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[239]	Overall: 77 [17.6%] G1: 17 [12%] G2: 28 [19%] G3: 36 [26%] No information by outcome	Yes	No	NA- no attrition
Pazianas, 2008[296]	NA- no attrition	NA- no attrition	NA- no attrition	NA- no attrition
Ravn, 1996[284]	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%) Vary by outcome: No	Yes	Yes	NA-not a case-control
Reginster, 2005[285]	Overall: 3% G1: 0 G2: 0 G3: 0 G4: 3% G5: 8% Vary by outcome: No	No	Yes	NA-not a case-control
Rhee, 2012[337]	No attrition because data are from registry	NA- no attrition	NA- no attrition	NA- no attrition
Riis, 2001[286]	Overall: 14% G1: 15% G2: 15% G3: 11% Vary by outcome: No	No	Yes	NA-not a case-control

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Samelson, 2014[338]	Overall: 82% for the main FREEDOM trial, but this was a subgroup analysis of patients at increased CV risk with adequate imaging studies. Only 1045/2363 patients eligible had evaluation data at baseline and followup. G1: NR G2: NR	Yes	No information	NA-not a case-control
Shiraki, 2003[281]	G1: 9/56 = 16% G2: 9/54 = 17%	No	No information	NA-not a case control
Simon, 2013[339]	Overall: 82% (for 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[241]	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[245]	NA-not an RCT	NA-not an RCT	NA-not an RCT	Yes
Tanko, 2003[287]	Overall: 14% G1: NR G2: NR G3: NR G4: NR G5: NR Vary by outcome: No	No	Yes	NA-not a case-control
Thiebaud, 1997[288]	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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Overall Attrition? Attrition by Group? Did Attrition Vary for Different Outcomes?	High Attrition Raising Concern for Bias?	Proportion of Participants and Reasons for Missing Data Similar Across Interventions?	Proportion of Participants and Reasons for Missing Data Similar Across Cases and Controls?
Tucci, 1996[251]	Overall: 29/478 = 6.0% (from numbers in Table 4) G1: 9.2% G2: 6.4% G3: 8.5% G4: 3.1%	No	No information	NA-not a case-control
Van Staa, 1997[340]	No attrition	NA- no attrition	NA	NA
Vestergaard, 2010[341]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2011[342]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2012[343]	None	No	NA, no attrition	NA, no attrition
Vestergaard, 2011[344]	NA, no attrition	NA, no attrition	No	NA-not an RCT
Vestergaard, 2012[345]	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 Month; G = group; KQ = key question; NA = not applicable; NR = not reported; QCT = Quantitative computed tomography; RCT = randomized controlled trials.

Author, Year	Appropriate Statistical Methods Used to Account for Missing Data?	Bias From Missing Outcome Data?	Comments
Abrahamsen, 2010[271]	Yes	No	NR
Adachi, 2009[248]	No information	Probably no	Authors do not specifically say they performed an ITT analysis.
Barrett-Connor, 2002[308]	Yes	Probably yes	Overall attrition a little high
Barrett-Connor, 2004[307]	Yes	No	NR
Bone, 2000[216]	Yes	Probably yes	>20% attrition, and >30% attrition in one of the arms.
Bone, 2008[237]	Yes	No	NR
Boonen, 2012[218]	Yes	No	NR
Cartsos, 2008 [295]	NA- no attrition	No information	No mention of how missing data was handled
Chapurlat, 2013[282]	Yes	Probably no	NR
Cryer, 2005[250]	Yes	Probably no	There is a small difference in reasons for discontinuation. More patients in placebo group dropped out due to any clinical AE; however, this difference is judged to be small.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Appropriate Statistical Methods Used to Account for Missing Data?	Bias From Missing Outcome Data?	Comments
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Yes	No	Missing data = missing x-ray at followup 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[311]; McClung, 2012[242]; Boonen, 2011[243]	Yes	No	NR
Eisman, 2004[253]	Yes	Probably no	More withdrawals for clinical AE in alendronate group vs. placebo, but no testing. Results show no difference in discontinuation for UGI AE.
Fogelman, 2000[226]	Yes	Probably no	NR
Greenspan, 2002[252]	Yes	No	NR
Greenspan, 2003[247]	Yes	No	ITT analysis
Grey, 2010[272]	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[244]	Yes	Probably no	NR
Keech, 2005[309]	Yes	Probably yes	NR
Kung, 2000[334]	Yes	Probably yes	NR
Lasco, 2011[240]	NA- no attrition	Probably no	NR
Lewiecki, 2007[236]	No information	No	NR
McCloskey, 2012[335]	Probably yes	Probably no	It is discussed in the main study.
McClung, 2004[283]	Yes	No	NR
McClung, 2006[303]	Yes	Probably yes	17, not a case-control; overall attrition a little high
McClung, 2006[209]	Yes	No	NR
McClung, 2009[273]	Probably no	Unclear	Risk of bias for harms data because it is limited to ITT analysis.
Meunier, 1999[304]	Yes	No	Harms analysis is only relevant information. All participants taken into account
Miller, 2008[305]	Yes	Probably no	Table 3 appears to have an event for almost the whole sample, so individuals weren't missed.
Morii, 2003[306]	Yes	Probably no	NR
Murphy, 2001[270]	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.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Appropriate Statistical Methods Used to Account for Missing Data?	Bias From Missing Outcome Data?	Comments
Nakamura, 2012[336]	Yes	Probably no	NR
Orwoll, 2003[239]	Yes	Probably yes	Differential attrition between arms
Pazianas, 2008 [296]	NA- no attrition	No information	No mention of how missing data was handled
Ravn, 1996[284]	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[285]	Yes	No	NR
Rhee, 2012[337]	NA- no attrition	No	NR
Riis, 2001[286]	Yes	No	NR
Samelson, 2014[338]	No	Probably yes	NR
Shiraki, 2003[281]	Yes	Probably no	NR
Simon, 2013[339]	Yes	Probably no	NR
Sontag, 2010[241]	Yes	Probably yes	Overall attrition a little high
Sorensen, 2008[245]	Yes	No	Authors report Danish registry information is complete.
Tanko, 2003[287]	Yes	Probably no	Not able to calculate group attrition
Thiebaud, 1997[288]	Yes	Probably no	Used ITT, but 1 patient who dropped out before treatment because of inability to administer the drug was not included. Missing values were not replaced.
Tucci, 1996[251]	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[340]	NA	No information	The study did not provide any information on attrition or missing data.
Vestergaard, 2010[341]	NA, no attrition	No	NR
Vestergaard, 2011[342]	NA, no attrition	No	NR
Vestergaard, 2012[343]	NA, no attrition	No	NR
Vestergaard, 2011[344]	NA-not an RCT	No information	No information
Vestergaard, 2012[345]	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.

Author, Year	Patients unaware of intervention status?	Trial personnel and clinicians unaware of intervention status of participants?	Intervention fidelity adequate?	Enough crossovers or contamination that would raise concern for bias?	Bias from departures from intended interventions?	Comments
Abrahamsen, 2010[271]	NA-not an RCT	NA-not an RCT	Probably yes	No information	Probably no	NR
Adachi, 2009[248]	Yes	Yes	No information	No information	Probably no	No data on adherence
Barrett-Connor, 2002[308]	Yes	Yes	Probably yes	Probably no	Probably no	In year 4 could take additional medications.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Patients unaware of intervention status?	Trial personnel and clinicians unaware of intervention status of participants?	Intervention fidelity adequate?	Enough crossovers or contamination that would raise concern for bias?	Bias from departures from intended interventions?	Comments
Barrett-Connor, 2004[307]	Yes	Yes	Yes	No	No	Stated in larger study that 92% of women took >80% of study medication
Bone, 2000[216]	Yes	Yes	No information	No information	No	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 [295]	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 crossovers but not clear if other treatments were allowed
Chapurlat, 2013[282]	Yes	Yes	Yes	No	No	NR
Cryer, 2005[250]	Yes	Yes	Yes	No	No	
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Yes	Yes	Yes	No	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
Eisman, 2004[253]	NR	Yes	Yes	No	No	Mean compliance 95% and 96% for alendronate and placebo groups
Fogelman, 2000[226]	Yes	Yes	No information	Probably no	Probably no	NR
Greenspan, 2002[252]	Yes	Yes	Probably yes	Probably no	Probably no	NR
Greenspan, 2003[247]	Yes	Yes	Yes	No	No	NR
Grey, 2010[272]	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[244]	Yes	Yes	Yes	No	Probably no	NR
Keech, 2005[309]	Yes	Yes	Yes	No	No	NR
Kung, 2000[334]	Yes	Yes	No information	No information	Probably no	NR
Lasco, 2011[240]	NA-not an RCT	NA-not an RCT	Probably yes	Probably no	Probably no	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Patients unaware of intervention status?	Trial personnel and clinicians unaware of intervention status of participants?	Intervention fidelity adequate?	Enough crossovers or contamination that would raise concern for bias?	Bias from departures from intended interventions?	Comments
Lewiecki, 2007[236]	Probably no	Probably no	NA (subcutaneous)	No information	Probably no	NR
McCloskey, 2012[335]	Yes	Yes	Yes	No information	No	NR
McClung, 2004[283]	Yes	Yes	Yes	No	No	Compliance in mid- to high-80s
McClung, 2006[303]	Yes	Yes	No information	No information	probably yes	Adherence unknown
McClung, 2006[209]	Yes	Yes	Yes	No	No	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[273]	Yes	Yes	Probably yes	Probably no	Probably no	NR
Meunier, 1999[304]	Yes	Yes	Probably yes	No	No	NR
Miller, 2008[305]	Yes	Probably yes	No information	No information	Probably no	NR
Morii, 2003[306]	Yes	No information	Probably yes	No	No	NR
Murphy, 2001[270]	Yes	Yes	Yes	No	No	Only 4 patients failed to take >75% of assigned drug
Nakamura, 2012[336]	Probably yes	Probably yes	Yes	No	No	NR
Orwoll, 2003[239]	Yes	Yes	Yes	Probably no	Probably no	Patient-administered injections of placebo or drug
Pazianas, 2008[296]	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 crossovers but not clear if other treatments were allowed
Ravn, 1996[284]	Yes	No	No information	No	Probably no	Data safety review committee was not blinded to treatment, and it monitored adverse events during each step. Information on compliance was not provided.
Reginster, 2005[285]	NA-not an RCT	NA-not an RCT	Probably no	No	Probably yes	No way to determine if participants took dose
Rhee, 2012[337]	Yes	Yes	Yes	No	No	NR
Riis, 2001[286]	Probably yes	Probably yes	Yes	No	Probably no	NR
Samelson, 2014[338]	Yes	Yes	Probably yes	No information	Probably no	NR
Shiraki, 2003[281]	Yes	Yes	No information	Probably no	Probably no	NR
Simon, 2013[339]	Yes	Yes	Probably yes	No information	No	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Patients unaware of intervention status?	Trial personnel and clinicians unaware of intervention status of participants?	Intervention fidelity adequate?	Enough crossovers or contamination that would raise concern for bias?	Bias from departures from intended interventions?	Comments
Sontag, 2010[241]	Probably yes	Probably yes	No	Probably no	Probably no	Study was reported as double-blind but no other details were 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[245]	NA-not an RCT	NA-not an RCT	Probably yes	No information	Probably no	NR
Tanko, 2003[287]	Yes	Yes	No information	No	Probably no	Large proportion of patients in each study group took at least 75% of study medication: 89% (placebo), 88.8% (5 mg), 90.1% (10 mg) and 88.7% (20 mg) patients.
Thiebaud, 1997[288]	Yes	No	No information	No	Probably no	Information on compliance was not provided. Investigator was not blind for all arms.
Tucci, 1996[251]	Yes	Yes	Yes	No	No	Investigators only evaluated blinded results (excluded patients who declined blinding for third year)
Van Staa, 1997[340]	NA-not an RCT	NA-not an RCT	No information	No	No information	Did not evaluate adherence
Vestergaard, 2010[341]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2011[342]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2012[343]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR
Vestergaard, 2011[344]	No information	NA-no benefits outcomes	NA-no benefits outcomes	NA-no benefits outcomes	Probably no	NR
Vestergaard, 2012[345]	NA-not an RCT	NA-not an RCT	No information	No information	No information	NR

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

Author, Year	Benefit Outcomes Adequately Described, Prespecified, Valid, and Reliable?	Similar Techniques Used Among Groups to Ascertain Harm Outcomes?	Duration of Followup Adequate to Assess Harm Outcomes?	Bias from Measurement of Outcomes?	Comments
Abrahamsen, 2010[271]	NA-no benefits outcomes	Probably yes	Probably yes	Probably yes	Not able to identify atypia.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Benefit Outcomes Adequately Described, Prespecified, Valid, and Reliable?	Similar Techniques Used Among Groups to Ascertain Harm Outcomes?	Duration of Followup Adequate to Assess Harm Outcomes?	Bias from Measurement of Outcomes?	Comments
Adachi, 2009[248]	NA-no benefits outcomes	Yes	Yes	Probably no	No specific information about how often patients were assessed for harms, though did describe adequate blinding of patients.
Barrett-Connor, 2002[308]	NA-no benefits outcomes	Yes	Yes	No	NR
Barrett-Connor, 2004[307]	Yes	Yes	Yes	No	NR
Bone, 2000[216]	Probably Yes	Probably yes	Yes	Probably yes	Patients were seen at 3, 6, 12, 18, and 24 months, but doesn'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[295]	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[282]	Yes	Probably yes	Yes	No	NR
Cryer, 2005[250]	Yes	Yes	Yes	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Yes	Yes	Yes	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	Yes	Yes	Probably yes	Probably no	NR
Eisman, 2004[253]	Yes	Yes	Yes	No	NR
Fogelman, 2000[226]	Probably Yes	Yes	Yes	Probably no	NR
Greenspan, 2002[252]	NA-no benefits outcomes	Yes	Yes	No	NR
Greenspan, 2003[247]	Yes	Yes	Yes	No	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Benefit Outcomes Adequately Described, Prespecified, Valid, and Reliable?	Similar Techniques Used Among Groups to Ascertain Harm Outcomes?	Duration of Followup Adequate to Assess Harm Outcomes?	Bias from Measurement of Outcomes?	Comments
Grey, 2010[272]	Probably yes	Probably yes	Yes	Probably no	Looked at parent article to identify clinical assessment of harms-no information.
Hosking, 2003[202]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Johnell, 2002[244]	NA-no benefits outcomes	Yes	Probably yes	Probably no	12-month study
Keech, 2005[309]	NA-no benefits outcomes	Yes	Yes	No	NR
Kung, 2000[334]	NA-no benefits outcomes	Yes	Yes	Probably yes	No information on how harms were ascertained
Lasco, 2011[240]	NA-no benefits outcomes	No information	No information	Probably no	NR
Lewiecki, 2007[236]	Yes	Yes	Probably yes	Probably no	NR
McCloskey, 2012[335]	Yes	NA-no harms outcomes	NA-no harms outcomes	No	NR
McClung, 2004[283]	NA-no benefits outcomes	Yes	Yes	No	NR
McClung, 2006[303]	NA-no benefits outcomes	Yes	Yes	No	NR
McClung, 2006[209]	Yes	Yes	Yes	No	NR
McClung, 2009[273]	NA-no benefits outcomes	yes	Yes	Probably no	NR
Meunier, 1999[304]	NA-no benefits outcomes	Yes	Yes	Probably no	Followup was 2 years
Miller, 2008[305]	NA-no benefits outcomes	Yes	Yes	Probably no	NR
Morii, 2003[306]	NA-no benefits outcomes	Yes	Yes	Probably no	NR
Murphy, 2001[270]	Yes	Yes	Yes	No	NR
Nakamura, 2012[336]	Yes	Yes	Probably yes	No	NR
Orwoll, 2003[239]	Yes	Yes	Probably no	Probably no	NR
Pazianas, 2008[296]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Ravn, 1996[284]	NA-no benefits outcomes	Yes	Yes	No	NR
Reginster, 2005[285]	NA-no benefits outcomes	Yes	Yes	No	NR

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Benefit Outcomes Adequately Described, Prespecified, Valid, and Reliable?	Similar Techniques Used Among Groups to Ascertain Harm Outcomes?	Duration of Followup Adequate to Assess Harm Outcomes?	Bias from Measurement of Outcomes?	Comments
Rhee, 2012[337]	NA-no benefits outcomes	Yes	Yes	No	NR
Riis, 2001[286]	NA-no benefits outcomes	Yes	Yes	No	NR
Samelson, 2014[338]	NA-no benefits outcomes	Yes	Yes	Probably yes	Post hoc analysis and 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[281]	NA-no benefits outcomes	Yes	Yes	Probably yes	NR
Simon, 2013[339]	Probably Yes	NA-no harms outcomes	NA-no harms outcomes	Probably no	NR
Sontag, 2010[241]	Yes	Yes	Yes	Probably no	NR
Sorensen, 2008[245]	NA-no benefits outcomes	Yes	Probably yes	Probably no	Case-control; harms only identified in the case group
Tanko, 2003[287]	NA-no benefits outcomes	Yes	Yes	No	NR
Thiebaud, 1997[288]	NA-no benefits outcomes	Yes	Yes	No	NR
Tucci, 1996[251]	Yes	Yes	Yes	No	Some data on reduction of vertebral fractures, but investigators have planned another arm with future reporting. Study not powered for fracture reduction.
Van Staa, 1997[340]	NA-no benefits outcomes	Yes	Yes	No	NR
Vestergaard, 2010[341]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Vestergaard, 2011[342]	NA-no benefits outcomes	Yes	Probably yes	Probably no	NR
Vestergaard, 2012[343]	NA-no benefits outcomes	Yes	Probably yes	Probably yes	NR
Vestergaard, 2011[344]	Probably Yes	Probably no	Yes	Probably yes	NR
Vestergaard, 2012[345]	NA-no benefits outcomes	Yes	Probably yes	Probably yes	NR

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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Effect Estimate Unlikely to Be Selected, on the Basis of Results, From Multiple Outcome Measurements Within the Domain, Multiple Analyses, or Different Subgroups?	Effect Estimate Unlikely to Be Selected, on the Basis of Results, From Multiple Definitions of the Intervention?	Bias From Selection of Reposted Results?	Comments
Abrahamsen, 2010[271]	Probably yes	NA-not a case-control	Probably no	NR
Adachi, 2009[248]	Yes	NA-not a case-control	No	NR
Barrett-Connor, 2002[308]	No	NA-not a case-control	No	NR
Barrett-Connor, 2004[307]	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[295]	NA-not an RCT	Probably yes	Probably no	None
Chapurlat, 2013[282]	No	NA-not a case-control	No	NR
Cryer, 2005[250]	Yes	NA-not a case-control	No	NR
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Yes	NA-not a case-control	No	NR
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	Probably no	NA-not a case-control	Probably no	NR
Eisman, 2004[253]	Yes	NA-not a case-control	No	NR
Fogelman, 2000[226]	Yes	NA-not a case-control	No	NR
Greenspan, 2002[252]	Yes	NA-not a case-control	No	NR
Greenspan, 2003[247]	Yes	NA-not a case-control	No	NR
Grey, 2010[272]	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[346]	Probably yes	NA-not a case-control	Probably no	NR
Keech, 2005[309]	No	NA-not a case-control	No	NR
Kung, 2000[334]	Yes	NA-not a case-control	No	NR
Lasco, 2011[240]	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[335]	No	NA-not a case-control	Probably no	NR
McClung, 2004[283]	No	No	No	NR
McClung, 2006[303]	No	NA-not a case-control	No	NR
McClung, 2006[209]	Yes	NA-not a case-control	No	Study was powered for primary outcome of urinary markers, not harms. Reports nominal p-values for harms.

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Effect Estimate Unlikely to Be Selected, on the Basis of Results, From Multiple Outcome Measurements Within the Domain, Multiple Analyses, or Different Subgroups?	Effect Estimate Unlikely to Be Selected, on the Basis of Results, From Multiple Definitions of the Intervention?	Bias From Selection of Reposted Results?	Comments
McClung, 2009[273]	Probably yes	NA-not a case-control	Probably no	NR
Meunier, 1999[304]	Yes	NA-not a case-control	Probably no	NR
Miller, 2008[305]	Probably no	NA-not a case-control	Probably no	NR
Morii, 2003[306]	Yes	NA-not a case-control	Probably no	NR
Murphy, 2001[270]	Yes	NA-not a case-control	No	NR
Nakamura, 2012[336]	No	NA-not a case-control	No	NR
Orwoll, 2003[239]	Probably yes	NA-not a case-control	Probably no	NR
Pazianas, 2008[296]	NA-not an RCT	Probably yes	Probably no	NR
Ravn, 1996[284]	No	No	No	NR
Reginster, 2005[285]	No	No	No	NR
Rhee, 2012[337]	No	NA-not a case-control	No	NR
Riis, 2001[286]	No	No	No	NR
Samelson, 2014[338]	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 reported in the main FREEDOM trial. This appears to be a post-hoc analysis.
Shiraki, 2003[281]	Yes	NA-not a case-control	No	NR
Simon, 2013[339]	Probably yes	NA-not a case-control	Probably no	NR
Sontag, 2010[241]	Probably no	NA-not a case-control	Probably no	NR
Sorensen, 2008[245]	NA-not an RCT	Yes	No	NR
Tanko, 2003[287]	No	No	No	NR
Thiebaud, 1997[288]	No	No	No	NR
Tucci, 1996[251]	Yes	NA-not a case-control	No	Stepwise Tukey trend test to adjust for multiple comparisons.
Van Staa, 1997[340]	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 were handled was not reported.
Vestergaard, 2010[341]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2011[342]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2012[343]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2011[344]	Probably no	NA-not a case-control	Probably no	NR
Vestergaard, 2012[345]	Probably no	NA-not a case-control	Probably no	NR

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

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Abrahamsen, 2010[271]	Poor	Risk of bias from residual confounding and measurement of outcomes.	No
Adachi, 2009[248]	Fair	Baseline differences between groups raise some concerns for risk of bias.	No
Barrett-Connor, 2002[308]	Fair	About 25% lost to followup. Also year 4 data allows additional therapy for osteoporosis, which was different per group, athough a small number (<7%)--this study included year 4 participants but didn't report concomitant medications. Additionally, there was differential loss to followup due to excessive bone loss in the placebo group (3% vs. 1%).	No
Barrett-Connor, 2004[307]	Fair	About 25% lost to followup. Also year 4 data allows additional therapy for osteoporosis, which was different per group, although a small number (<7%)--this study included year 4 participants but didn't report concomitant medications. (No sensitivity analysis looked at 3 years of data where there was no additional medications.) Additionally, there was differential loss to followup 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, and blinding.	No
Boonen, 2012[218]	Good	NR	No
Cartsos, 2008 [295]	Poor	Unclear how outcomes were measured. Fidelity: not sure if participants took medication correctly; no information on crossovers but unclear 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[282]	Fair	Considering IVR with minimization scheme to be just adequate; unclear how dropouts were handled.	No
Cryer, 2005[250]	Good	Fair for differential attrition, no information on contamination.	No
Cummings, 1998[200] Quandt, 2005[205] Bauer, 2000[249]	Good	NR	No
Cummings, 2009[238]; Watts, 2012[311]; McClung, 2012[242]; Boonen, 2011[243]	Fair	Some uncertainties in reporting of randomization, allocation concealment, and blinding.	No
Eisman, 2004[253]	Good	NR	No
Fogelman, 2000[226]	Fair	NR	No
Greenspan, 2002[252]	Fair	Missing information on randomization. No washout period for patients previously on bisphosphonates.	No
Greenspan, 2003[247]	Good	NR	No
Grey, 2010[272]	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 attrition was modeled.	No
Johnell, 2002[244]	Good	NR	No
Keech, 2005[309]	Fair	About 25% lost to followup. Also year 4 data allows additional therapy for osteoporosis, which was different per group, though a small number (<7%)--this study included year 4 participants but didn't report concomitant medications. (No sensitivity analysis looked at 3 years of data where there were no additional medications.) Additionally, there was differential loss to followup due to excessive bone loss in the placebo group (3% vs. 1%).	No

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Kung, 2000[334]	Poor	No information on randomization methods, fidelity, or contamination; 20% attrition with not enough information to judge differential attrition; and poorly specified harms outcomes (very specific patient self-reported AEs, with no indication as to seriousness or whether it resulted in discontinuation); data offered are number of events, not number of women, making it difficult to know whether the risk is higher in one group vs. the other.	No
Lasco, 2011[240]	Poor	Potential for confounding.	No
Lewiecki, 2007[236]	Fair	Some uncertainties in reporting of randomization, allocation concealment, and blinding.	No
McCloskey, 2012[335]	Fair	No detail on randomization and allocation concealment prevents this from being rated as good. No fatal flaws.	No
McClung, 2004[283]	Fair	No information provided on method of randomization or concealment.	No
McClung, 2006[303]	Fair	Overall attrition high, not a lot of information provided on randomization process; fidelity issue: no information whether participants actually took their assigned doses.	No
McClung, 2006[209]	Good	Good for denosumab. Poor for alendronate for lack of blinding.	No
McClung, 2009[273]	Fair	Higher risk of bias for harms than benefits (ITT analysis understates harms).	No
Meunier, 1999[304]	Good	Documentation on randomization missing, outcomes mostly self reported.	No
Miller, 2008[305]	Fair	Cannot 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[306]	Fair	NR	No
Murphy, 2001[270]	Poor	Very poor attrition at 12 and 18 months, unable to assess differential attrition, and missing information on randomization.	No
Nakamura, 2012[336]	Fair	Article was lacking information on method of randomization and concealment; lack of information on participants who discontiuned study.	No
Orwoll, 2003[239]	Fair	Differential attrition; higher in treatment arm; used ITT to adjust for analysis.	No
Pazianas, 2008 [296]	Poor	Fidelity: not sure if participants took medication correctly; no information on crossovers 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
Ravn, 1996[284]	Fair	High attrition; however, safety data 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[285]	Fair	No information provided on method of randomization or concealment. Information on compliance was not provided.	No
Rhee, 2012[337]	Poor	Potential bias arising from creation of a new user cohort and from restriction to those without switches.	No
Riis, 2001[286]	Fair	No information provided on method of randomization or concealment.	No
Samelson, 2014[338]	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 substudy make this analysis at high risk of bias, thus poor quality.	No
Shiraki, 2003[281]	Fair	NR	No
Simon, 2013[339]	Fair	In the end, the only outcome that is of interest is wrist fractures in subgroups based on baseline risk.	No

Appendix D Table 7. KQ4 and KQ5 risk of bias assessment

Author, Year	Rating Overall	Rating Justification	Does Quality Rating of Study Vary by Outcome?
Sontag, 2010[241]	Poor	The open-label portion of the trial allowed patient choice, and as a result, outcomes could be the result of confounding because of prognostic variables.	No
Sorensen, 2008[245]	Good	NR	No
Tanko, 2003[287]	Fair	No information provided on method of randomization or concealment. Not able to calculate group attrition.	No
Thiebaud, 1997[288]	Fair	No information provided on method of randomization or concealment. Slight differences in length of menopause. Information on compliance was not provided. Investigator was not blinded for all arms.	No
Tucci, 1996[251]	Fair	Randomization methods, fidelity, and contamination missing information.	No
Van Staa, 1997[340]	Poor	NR	No
Vestergaard, 2010[341]	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[342]	Poor	Concerns include lack of adjustment for all potential confounders. For example, smoking, hypertension, or 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[343]	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[344]	Poor	Concerns include lack of adjustment for all potential confounders, particularly underlying disease that might also be related to the choice of medication for osteoporosis and the outcome. Additionally, the outcome did not distinguish between typical and atypical fractures.	No
Vestergaard, 2012[345]	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. Overview of 2010 included studies and inclusion/exclusion status in current report

Author, Year	Status in Current Report	Reasons for Exclusion
Adler, 2003[78]	Include	NA
Alexandersen, 2005[347]	Exclude	BMD screening after identification of fractures
Anderson, 2003[348]	Exclude	Not osteoporotic women, WHI
Anderson, 2004[349]	Exclude	Wrong population
Ascott-Evans, 2003[204]	Include	NA
Barrett-Connor, 2006[233]	Exclude	Wrong population
Bauer, 1997[350]	Exclude	No AUCs
Bauer, 2007[120]	Include	NA
Ben Sedrine, 2001[79]	Include	NA
Black, 2001[168]	Exclude	Wrong or no outcome
Black, 2007[219]	Exclude	Wrong population
Brenneman, 2003[82]	Include	NA
Cadarette, 2001[83]	Include	NA
Cadarette, 2004[84]	Include	NA
Cadarette, 2008[351]	Exclude	Not a relevant comparison
Cass, 2006[85]	Include	NA
Cauley, 2003[352]	Exclude	Not osteoporotic women, WHI
Chesnut, 1995[203]	Include	NA
Chesnut, 2000[353]	Exclude	Wrong intervention
Chesnut, 2004[354]	Exclude	Wrong population
Chlebowski, 2003[355]	Exclude	Not osteoporotic women, WHI
Colon-Emeric, 2002[167]	Exclude	Wrong or no outcome
Cook, 2005[88]	Include	NA
Crabtree, 2002[356]	Exclude	Wrong or no intervention
Cranney, 2002[357]	Exclude	Calcitonin was not an included intervention
Cryer, 2002[358]	Exclude	Wrong study design
Cummings, 1998[200]	Include	NA
Cummings, 2006[359]	Exclude	Wrong or no outcome
Curb, 2013[360]	Exclude	Not osteoporotic women, WHI
Cushman, 2004[361]	Exclude	Not osteoporotic women, WHI
D'Amelio, 2005[89]	Include	NA
Dargent-Molina, 2003[362]	Exclude	Not in externally validated cohort
Delmas, 2002[232]	Include	NA
Diez-Perez, 2007[363]	Exclude	Not in externally validated cohort
Donaldson, 2009[330]	Include	NA
Dursun, 2001[207]	Exclude	Wrong or no comparator
Ensrud, 2009[138]	Include	NA
Ettinger, 1999[231]	Include	NA
Frediani, 2006[364]	Exclude	BMD screening after identification of fractures
Gennari, 1985[365]	Exclude	Calcitonin was not an included intervention
Girman, 2002[169]	Exclude	Wrong clinical setting
Gluer, 2003[366]	Exclude	Not original research
Gnudi, 2005[92]	Include	NA
Goh, 2007[267]	Exclude	Wrong study design
Gonnelli, 2005[367]	Exclude	Not a key question reviewed in the current report (DXA in men)
Gourlay, 2005[80]	Include	NA
Grbic, 2008[279]	Exclude	Wrong population
Greenfield, 2007[368]	Exclude	Wrong population Note: the authors of Nelson, 2010 have a discrepancy in the author names in references vs. tables.
Greenspan, 2005[369]	Exclude	Superseded by the current meta-analysis in this update.
Greenspan, 2007[36]	Include	NA
Hans, 1996[370]	Exclude	No AUCs
Hans, 2008[371]	Exclude	Not in externally validated cohort
Harris, 2008[372]	Exclude	Superseded by the current meta-analysis in this update.
Harrison, 2006[94]	Include	NA

Appendix E. Overview of 2010 included studies and inclusion/exclusion status in current report

Author, Year	Status in Current Report	Reasons for Exclusion
Heckbert, 2008[254]	Exclude	Wrong population
Herd, 1997[228]	Include	NA
Hillier, 2007[194]	Include	NA
Hippisley-Cox, 2009[171]	Include	NA
Hizmetli, 1996[373]	Exclude	Calcitonin was not an included intervention
Hooper, 2005[227]	Include	NA
Hosking, 1998[215]	Include	NA
Hsia, 2006[374]	Exclude	Not osteoporotic women, WHI
Kanis, 2007[32]	Include	NA
Karam, 2007[291]	Exclude	Superseded by the current meta-analysis in this update.
Kaufman, 2005[375]	Exclude	Wrong or no intervention
Khaw, 2004[376]	Exclude	No AUCs
Kurland, 2000[377]	Exclude	Wrong population
LaCroix, 2005[378]	Exclude	Wrong or no comparator
Lenart, 2008[261]	Exclude	Wrong or no comparator
Lynn, 2008[98]	Include	NA
MacLean, 2008[268]	Exclude	Superseded by new evidence
Manson, 2003[379]	Exclude	Not osteoporotic women, WHI
Martinez-Aguila, 2007[100]	Include	NA
Masoni, 2005[380]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Mauck, 2005[101]	Include	NA
McClung, 2004[283]	Include	NA
Meunier, 1997[229]	Include	NA
Minnock, 2008[115]	Exclude	Not in an externally validated cohort
Mortensen, 1998[224]	Include	NA
Mulleman, 2002[381]	Exclude	Not a key question reviewed in the current report (DXA in men)
Nayak, 2006[118]	Exclude	Superseded by the current meta-analysis in this update.
Neer, 2001[382]	Exclude	Wrong population
Nelson, 2009[383]	Include	NA
Nelson, 2009[384]	Include	NA
Nguyen, 2004[104]	Include	NA
Odvina, 2005[262]	Exclude	Wrong or no comparator
Office of Drug Safety, 2004[255]	Exclude	Wrong population
Orwoll, 2003[239]	Include	NA
Overgaard, 1992[385]	Exclude	Wrong intervention
Pols, 1999[201]	Include	NA
Pouilles, 1997[230]	Exclude	Wrong population
Reid, 2002[217]	Include	NA
Richards, 2008[386]	Exclude	Not in externally validated cohort
Richy, 2004[81]	Include	NA
Rico, 1995[387]	Exclude	Calcitonin was not an included intervention
Robbins, 2007[172]	Exclude	Not osteoporotic women, WHI
Rossouw, 2002[388]	Exclude	Not osteoporotic women, WHI
Rossouw, 2007[389]	Exclude	Not osteoporotic women, WHI
Rud, 2005[109]	Include	NA
Rud, 2007[390]	Exclude	Study does not look at fracture outcomes
Russell, 2001[391]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Salaffi, 2005[392]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Sandhu, 2010[166]	Include	NA
Sawka, 2005[393]	Exclude	Superseded by the current meta-analysis in this update.
Schuit, 2004[23]	Exclude	Wrong or no outcome
Sedrine, 2002[177]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Shepherd, 2007[110]	Include	NA

Appendix E. Overview of 2010 included studies and inclusion/exclusion status in current report

Author, Year	Status in Current Report	Reasons for Exclusion
Shiraki, 2003[281]	Include	NA
Sinnott, 2006[111]	Include	NA
Sorensen, 2008[245]	Include	NA
Stefanick, 2006 [394]	Exclude	Not osteoporotic women, WHI
Stewart, 2006[119]	Include	NA
Tracz, 2006[395]	Exclude	Wrong or no intervention-- testosterone
Valimaki, 2007[225]	Include	NA
Van der Klift, 2002[396]	Exclude	Not a key question reviewed in the current report (DXA in men)
Van Staa, 1997[340]	Include	NA
Varenna, 2005[376]	Exclude	No AUCs
Vestergaard, 2007[397]	Exclude	Wrong or no comparator
Wallace, 2004[398]	Exclude	Risk prediction instruments predicting BMD with no information on imaging tests screening for BMD.
Wassertheil-Smoller, 2003[399]	Exclude	Not osteoporotic women, WHI
Wei, 2004[165]	Exclude	Bone measurement happens after outcome
Wells, 2008[400]	Exclude	Wrong population
Wells, 2008[401]	Exclude	Wrong population
Wells, 2008[402]	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: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Cadarette, 2001[83] Low	ABONE	ABONE	CaMOS- Canadian study of women from the general population (97% white) Canada	ABONE: Age Body size No estrogen use or no estrogen use for ≥6 months
Chan, 2006[87] Unclear	ABONE	ABONE	Free-living ambulant Chinese postmenopausal women age ≥55 years (Tanjong Rhu community in Singapore) Singapore	ABONE: Age Body size No estrogen use or no estrogen use for ≥6 months
D'Amelio, 2013[90] Low	AMMEB	AMMEB	Female and menopausal (general practices in Italy). Race not reported. Italy	AMMEB: Age BMI Age at menarche Postmenopausal period
Nguyen, 2004[104] Low	DOESCore	DOESCore	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia (98.6% white) Australia	DOESCore
Pang, 2014[56] Low	NA	FRAX: 10-year hip FRAX without BMD >3%	Men and women age ≥70 years who presented to a participating GP, excluded persons with prior h/o fracture Australia	FRAX: Height Weight
Pang, 2014[56] Low	NA	FRAX: 10-year MOF FRAX without BMD >6.5%	Men and women age ≥70 years who presented to a participating GP, excluded persons with prior h/o fracture Australia	FRAX: Height Weight
Gnudi, 2005[92] 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 Maternal fracture history Arm help to get up from sitting
Cass, 2013[86] Low	MORES	MORES	Men who attended unviersity-based primary care clinics for usual care; age >60 years United States	Age Weight History of COPD
Shepherd, 2007[110] Low	MORES	MORES	Men age ≥50 years with DXA scan in NHANES III United States	MORES: Age Weight COPD

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Shepherd, 2010[113] Low	MORES	MORES	Men age ≥50 years from NHANES III cohort United States	Race/ethnicity COPD Age Weight
Lynn, 2008[98] Low	MOST	MOST	Community-dwelling, ambulatory men age ≥65 years United States and Hong Kong	Weight QUI
Zimering, 2007[112] Unclear	MSCORE (age-weight)	MSCORE (age-weight)	Men age ≥40 years, ambulatory veterans attending general medicine, endocrinology, or osteoporosis clinics United States	MSCORE (age-weight)
Zimering, 2007[112] Unclear	MSCORE	MSCORE	Men age ≥40 years, ambulatory veterans attending general medicine, endocrinology, or osteoporosis clinics United States	MSCORE: Age Weight Gastrectomy Emphysema Prior fracture
D'Amelio, 2013[90] Low	NOF	NOF	Female and menopausal (general practices in Italy). Race not reported. Italy	NOF: Weight Age Previous fracture Smoking Family history
Cadarette, 2001[83] Low	NOF guidelines	NOF guidelines	CaMOS- Canadian study of women from the general population (97% white) Canada	NOF guidelines
Mauck, 2005[101] Low	NOF guidelines	NOF guidelines	Population-based sample of postmenopausal women age ≥45 years in Rochester, MN United States	NOF ≥1
D'Amelio, 2005[89] Low	NOF, OST, ORAI (Note: "weight" and "AMMEB" are not eligible interventions.)	NOF-specified risk factors	Postmenopausal Italian women referred to university bone metabolic unit within the Department of Internal Medicine for DXA. 13% were noted to have secondary osteoporosis. Italy	NOF-specified risk factors
Cadarette, 2001[83] Low	ORAI	ORAI	CaMOS- Canadian study of women from the general population (97% white) Canada	ORAI: Age Weight in pounds Current estrogen use

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Cadarette, 2004[84] Low	ORAI	ORAI	Caucasian women age ≥45 years recruited prospectively from university setting and retrospectively analyzed from family practices in Canada Canada	ORAI: Age Weight in pounds Current estrogen use
Cass, 2006[85] Low	ORAI	ORAI	Postmenopausal women age ≥45 years (receiving usual care at U.S. university-based family practice clinic). Diverse practice: 29% white, 43% black, 28% Hispanic United States	ORAI: Age Weight in pounds Current estrogen use
Cook et al, 2005[88] Unclear	ORAI	ORAI	Postmenopausal UK women through natural or unnatural causes, referred by GPs or hospital-based clinics because of ≥1 clinical risk factors for osteoporosis. Race not reported. United Kingdom	ORAI: Age Weight in pounds Current estrogen use
D'Amelio, 2005[89] Low	NOF, OST, ORAI (Note: "weight" and "AMMEB" are not eligible interventions.)	ORAI	Postmenopausal Caucasian Italian women referred to university bone metabolic unit within the Departmen of Internal Medicine for DXA. 13% were noted to have secondary osteoporosis. Italy	ORAI: Age Weight in pounds Current estrogen use
D'Amelio, 2013[90] Low	ORAI	ORAI	Female and menopausal (general practices in Italy). Race not reported. Italy	ORAI: Age Weight in pounds Current estrogen use
Gourlay, 2005[80] Unclear	ORAI	ORAI	Postmenopausal Caucasian women ages 45 to 96 years referred for DXA scans at an outpatient osteoporosis center in Belgium, based on suspicion of osteoporosis. Belgium	ORAI: Age Weight in pounds Current estrogen use
Harrison et al, 2006[94] Low	ORAI	ORAI	White women ages 55 to 70 years (mean, 61 [SD, 4]) referred to University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on radiography. United Kingdom	ORAI: Age Weight in pounds Current estrogen use

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Jimenez-Nunez, 2013[95] Low	ORAI	ORAI	Caucasian women age ≥50 years with menopausal status for ≥12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialty clinics in Spain Spain	ORAI: Age Weight in pounds Current estrogen use
Martinez-Aguila, 2007[100] Unclear	ORAI	ORAI	Postemenopausal women ages 40 to 69 years 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 in pounds Current estrogen use
Mauck, 2005[101] Low	ORAI	ORAI	Population-based sample of postmenopausal women age ≥45 years in Rochester, MN (99% white) United States	ORAI: Age Weight in pounds Current estrogen use
Nguyen, 2004[104] Low	ORAI	ORAI	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia (98.6% white) Austrailia	ORAI: Age Weight in pounds Current estrogen use
Richy, 2004[81] Unclear	ORAI	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 in pounds Current estrogen use
Rud, 2005[109] Low	Screening tool: SCORE, ORAI, OST Comparator: DXA	ORAI	White women from the genreal population recruited for the Danish Osteoporosis Prevention Study (DOPS) Denmark	ORAI: Age Weight in pounds Current estrogen use
Chan, 2006[87] Unclear	ORAI (femoral neck)	ORAI	Free-living ambulant Chinese postmenopausal women age ≥55 years (Tanjong Rhu community in Singapore) Singapore	ORAI: Age Weight in pounds Current estrogen use
Gourlay, 2008[93]	OST, ORAI, SCORE	ORAI	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age ≥65 years. United States	Age Weight Estrogen use

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Geusens, 2002[91]	OST, ORAI, SOFSURF, SCORE	ORAI	4 cohorts were evaluated, including a clinic-based U.S. population, 1 population-based cohort and 1 clinic-based sample in the Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the United States. United States	Age Weight Estrogen use
Cook et al, 2005[88] Unclear	OSIRIS	OSIRIS	Postmenopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of ≥1 clinical risk factors for osteoporosis United Kingdom	Age Weight HRT use History of low-trauma fracture
Harrison et al, 2006[94] Low	OSIRIS	OSIRIS	White women ages 55 to 70 years (mean, 61 [SD, 4]) referred to University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on radiography. United Kingdom	Age Weight HRT use History of low-trauma fracture
Jimenez-Nunez, 2013[95] Low	OSIRIS	OSIRIS	Caucasian women age ≥50 years with menopausal status for ≥12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialty clinics in Spain. Spain	Age Weight HRT use History of low-trauma fracture
Martinez-Aguila, 2007[100] Unclear	OSIRIS	OSIRIS	Postemenopausal women ages 40 to 69 years referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture. Race not reported. Spain	Age Weight HRT use History of low-trauma fracture
Richy, 2004[81] Unclear	OSIRIS	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	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: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Adler, 2003[78] Low	Screening tool: OST Comparator: DXA	OST	Men enrolled in a pulmonary clinic (January-May 2001) and a rheumatology clinic (November 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 Risk=[(weight in kg-age in years)*0.2, truncated to integer]
Cadarette, 2004[84] Low	OST	OST	Caucasian women age ≥45 years recruited prospectively from university setting and retrospectively analyzed form family practices in Canada. Canada	OST: Age Weight
Crandall, 2014[57] Low	OST	OST	Postmenopausal women ages 50 to 64 years free from serious medical conditions (WHI) and not using menopausal hormone therapy United States	OST- calculation using weight and age
D'Amelio, 2005[89] Low	NOF, OST, ORAI (Note: "weight" and "AMMEB" are not eligible interventions.)	OST	Postmenopausal Caucasian Italian women referred to university bone metabolic unit within the Departmen of Internal Medicine for DXA. 13% were noted to have secondary osteoporosis. Italy	Age Weight
Gourlay, 2005[80] Unclear	OST	OST	Postmenopausal Caucasian women ages 45 to 96 years referred for DXA scans at an outpatient osteoporosis center in Belgium, based on suspicion of osteoporosis. Belgium	OST
Machado, 2010[99] Low	OST	OST	Population-based sample of Portugese men age ≥50 years Portugal	OSTA <2 (threshold previously validated in postmenopausal women) OST <2 (threshold previously validated in postmenopausal women)
Martinez-Aguila, 2007[100] Unclear	OST	OST	Postmenopausal women ages 40 to 69 years referrred to a local bone densitometry unit from local gynecologists in Spain; 24% with history of prior fracture. Race not reported. Spain	Age Weight
Richards, 2014[108] Unclear	OST	OST	Male VA patients age >50 years attending primary care clinics at 4 participating VA medical centers United States	Age Weight

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Richy, 2004[81] Unclear	OST	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	Age Weight
Rud, 2005[109] Low	Screening tool: SCORE, ORAI, OST Comparator: DXA	OST	White women from the general population recruited for the Danish Osteoporosis Prevention Study (DOPS). Denmark	OST: Age Weight
Zimering, 2007[112] Unclear	OST	OST	Men age ≥40 years, ambulatory veterans attending general medicine, endocrinology, or osteoporosis clinics United States	OST: Age Weight
Gourlay, 2008[93]	OST, ORAI, SCORE	OST	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age ≥65 years. United States	Age Weight
Geusens, 2002[91]	OST, ORAI, SOFSURF, SCORE	OST	4 cohorts were evaluated, including a clinic-based U.S. population, 1 population-based cohort and 1 clinic-based sample in the Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the United States. United States	Age Weight
Morin, 2009[103] Unclear	OST	OST ≤1	Population-based sample of all women ages 40 to 59 and older who received DXA scans in Manitoba, Canada. Note: criteria for BMD testing in women age <65 years include premature ovarian failure, history of steroid use, prior fracture, and x-ray evidence of osteopenia. Canada	NR
Cook et al, 2005[88] Unclear	OST	OST	Postmenopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of ≥1 clinical risk factors for osteoporosis United Kingdom	Age Weight

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Harrison et al, 2006[94] Low	OST	OST	White women ages 55 to 70 years (mean, 61 [SD, 4]) referred to University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on radiography. United Kingdom	Age Weight
Jimenez-Nunez, 2013[95] Low	OST	OST	Caucasian women age ≥50 years with menopausal status for ≥12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialty clinics in Spain. Spain	Age Weight
Lynn, 2008[98] Low	OST	OST	Community-dwelling, ambulatory men age ≥65 years. Hong Kong and United States	Age Weight
McLeod, 2015[102] Low	OST	OST	Women referred for screening in Canada, no prior testing. Canada	Age Weight
Sinnott, 2006[111] Low	OST	OST	African American men age ≥35 years. United States	Age Weight
Pang, 2014[56] Low	NA	OST <0	Men and women age ≥70 years who presented to a participating GP, excluded persons with history of fracture. Australia	FRAX: Height Weight
Nguyen, 2004[104] Low	OSTA	OSTA	Women from the Dubbo Osteoporosis Epidemiology Study, a population-based cohort of men and women from Dubbo, Australia (98.6% white) Australia	OSTA
D'Amelio, 2013[90] Low	OSTA	OSTA	Female and menopausal (general practices in Italy). Race not reported. Italy	OSTA- calculation using weight and age
Kung, 2005[97] Low	OSTA	OSTA	Community of Asian (Southern Chinese) men; developed index based on clinical factors; compared clinical index with calcaneal QUS in predicting BMD (T<-2.5) by DXA. Hong Kong	Age Weight
Machado, 2010[99] Low	OSTA	OSTA	Population-based sample of Portugese men age ≥50 years. Portugal	OSTA <2 (threshold previously validated in postmenopausal women) OST <2 (threshold previously validated in postmenopausal women)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Oh, 2016[106] Low	OSTA	OSTA	Population-based sample of Korean men (KNHANES) age ≥50 years. Republic of Korea	Age Body weight
Oh, 2016[106] Low	OSTA	OSTA	Population-based sample of Korean men (KNHANES) age ≥50 years. Republic of Korea	Age Body weight
Oh, 2013[105] Low	Data from validation cohort only	OSTA (≤0)	Postmenopausal women age ≥50 years, KNHANES data set Republic of Korea	OSTA - calculation using weight and age
Oh, 2013[105] Low	Data from validation cohort only	OSTA (≤-1)	Postmenopausal women age ≥50 years, KNHANES data set Republic of Korea	OSTA - calculation using weight and age
Kung, 2003[96] Low	OSTA	OSTA	Postmenopausal women in Hong Kong recruited from the community Hong Kong	Age Weight
Park, 2003[107] Unclear	osteoporosis self-assessment tool for Asians (OSTA)	OSTA	Postmenopausal women at a menopause clinic in Korea not currently using HRT Republic of Korea	Age Weight
Chan, 2006[87] Unclear	OSTA, NR (femoral neck)	OSTA, NR (femoral neck)	Free-living ambulant Chinese postmenopausal women age ≥55 years (Tanjong Rhu community in Singapore) Singapore	OSTA - calculation using weight and age
Ben Sedrine, 2001[79] Low	Comparator: DXA	SCORE	Liege (Belgian cohort) Belgium	SCORE: Race Rheumatoid arthritis Low-trauma fracture Never received HRT Age Weight
Brenneman, 2003[82] Low	Postmenopausal women in OPRA study	SCORE	OPRA study, Group Health participants United States	Race Rheumatoid arthritis Low-trauma fracture Never received HRT Age Weight
Crandall, 2014[57] Low	SCORE	SCORE	Ages 50-64 years, postmenopausal, and free from serious medical conditions (WHI) and not using menopausal hormone therapy United States	SCORE - age, weight, and estrogen replacement therapy, the SCORE instrument includes race/ethnicity, history of rheumatoid arthritis, and history of nontraumatic fractures after age 45 years

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Gourlay, 2005[80] Unclear	SCORE	SCORE	Postmenopausal Caucasian women ages 45-96 years referred for DXA scans at an outpatient osteoporosis center in Belgium, based on suspicion of osteoporosis. Belgium	SCORE
Mauck, 2005[101] Low	SCORE	SCORE	Population-based sample of postmenopausal women age ≥45 years in Rochester, MN (99% white) United States	SCORE ≥6
Gourlay, 2008[93]	OST, ORAI, SCORE	SCORE	Study of Osteoporotic Fractures (SOF) inception cohort; a population-based cohort of women age ≥65 years. United States	Race Rheumatoid arthritis Fracture Age Estrogen use Weight
Geusens, 2002[91]	OST, ORAI, SOFSURF, SCORE	SCORE	4 cohorts were evaluated, including a clinic-based U.S. population, 1 population-based cohort and 1 clinic-based sample in the Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the United States. The Netherlands and United States	Race Rheumatoid arthritis Fracture Age Estrogen use Weight
Cadarette, 2001[83] Low	SCORE *weight criterion and NOF also evaluated but not abstracted	SCORE	CaMOS- Canadian study of women from the general population (97% white) Canada	SCORE Race Rheumatoid arthritis Low-trauma fracture Never received HRT Age Weight
Cook et al, 2005[88] Unclear	SCORE	SCORE	Postmenopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of ≥1 clinical risk factors for osteoporosis United Kingdom	Race Rheumatoid arthritis History of nontraumatic fracture HRT usage Age Weight
Harrison et al, 2006[94] Low	SCORE	SCORE	White Caucasian females ages 55-70 years (mean, 61 [SD, 4]) referred to University of Manchester for routine bone densitometry scans. Risk factors include suggested osteopenia on radiography. United Kingdom	Race Rheumatoid arthritis History of nontraumatic fracture HRT usage Age Weight

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Jimenez-Nunez, 2013[95] Low	SCORE	SCORE	Caucasian women age ≥50 years with menopausal status for ≥12 months, in good general health, without prior diagnosis of osteoporosis. 60% of women recruited from primary care, 40% from specialty clinics in Spain Spain	Race Rheumatoid arthritis History of nontraumatic fracture HRT usage Age Weight
Richy, 2004[81] Unclear	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	Race Rheumatoid arthritis History of nontraumatic fracture HRT usage Age Weight
Rud, 2005[109] Low	Screening tool: SCORE, ORAI, OST Comparator: DXA	SCORE	White women from the general population recruited for the Danish Osteoporosis Prevention Study (DOPS) Denmark	SCORE: Race Rheumatoid arthritis Low-trauma fracture Never received HRT Age Weight
Cass, 2006[85] Low	SCORE, NR	SCORE, NR	Postmenopausal women age ≥45 years receiving usual care at university-based family practice clinic in the United States. Diverse practice, 29% white, 43% black, 28% Hispanic. United States	SCORE - age, weight, and estrogen replacement therapy, the SCORE instrument includes race/ethnicity, history of rheumatoid arthritis, and history of nontraumatic fractures after age 45 years
Chan, 2006[87] Unclear	SCORE, NR (femoral neck)	SCORE, NR (femoral neck)	Free-living ambulant Chinese postmenopausal women age ≥55 years (Tanjong Rhu community in Singapore) Singapore	SCORE - age, weight, and estrogen replacement therapy, the SCORE instrument includes race/ethnicity, history of rheumatoid arthritis, and history of nontraumatic fractures after age 45 years
Brenneman, 2003[82] Low	Postmenopausal women in the OPRA study	SOF-based screening tool	OPRA study, Group Health participants United States	1 point each: 1st-degree relative with hip fracture; current weight less than at age 25 years; diagnosed with dementia; using corticosteroids, seizure medication, or benzodiazepines; had a fracture at age 50 years; not taking HRT; on feet <4 hours/day; heart rate
Nguyen, 2004[104] Low	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

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	Interventions and Comparators	Tool and Risk Prediction Horizon	Cohort or Study Population and Country	Risk Prediction Variables
Geusens, 2002[91]	OST, ORAI, SOFSURF, SCORE	SOFSURF	4 cohorts were evaluated, including a clinic-based U.S. population, 1 population-based cohort and 1 clinic-based sample in the Netherlands, and 1 clinic-based sample enrolled in a clinical trial of alendronate (FIT) in the United States. United States and the Netherlands	Age Weight Smoker History of fracture
Cook et al, 2005[88] Unclear	SOFSURF: risk index derived using data from SOF	SOFSURF: risk index derived using data from SOF	Postmenopausal women through natural or unnatural causes, referred by GPs or hospital-based clinics because of ≥1 clinical risk factors for osteoporosis United Kingom	Age Weight Smoking History of postmenopausal fracture
Crandall, 2014[57] Low	USPSTF	USPSTF	Ages 50-64 years, postmenopausal, and free from serious medical conditions (WHI) and not using menopausal hormone therapy United States	USPTSF - FRAX 10-yearr risk of MOF without BMD of ≥9.3%

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

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Cadarette, 2001[83] Low	2434	2365	240 (10%) based on femoral neck	66.4 (SD, 8.8)	2365 (100)	Femoral neck
Chan, 2006[87] Unclear	135	135	Femoral neck: 33 (24) Spine: 37 (27)	68.4 (SD, 5.5)	135 (100)	Primary was femoral neck; spine was also analyzed
D'Amelio, 2013[90] Low	NR	995	335 (33.7) Unclear what BMD site this is based on	65	995 (100)	Lumbar spine and femoral neck
Nguyen, 2004[104] Low	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) Femoral neck: 30.0% (95% CI, 25.8 to 34.6) Lumbar spine: 26.1% (95% CI, 22.1 to 30.6)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Pang, 2014[56] Low	626	626	Lumber 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

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Gnudi, 2005[92] Low	478	478	37.2% based on femoral neck or lumbar spine	64.3 (7.6)	100	Lumbar spine and femoral neck
Cass, 2013[86] Low	386	346	15 (4.3)	70.2 (, 6.9)	0 (0)	Femoral neck and total hip
Shepherd, 2007[110] Low	1498	1498	4.4% based on total hip	64.2 (9.7)	0	Total hip
Shepherd, 2010[113] Low	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, other sites not specifically reported.
Lynn, 2008[98] Low	U.S.: 4658 Hong Kong: 1914	U.S.: 4658 Hong Kong: 1914	U.S. Femoral neck: 5% Lumbar spine: 3% Total spine: 10% Hong Kong Femoral neck: 5% Lumbar spine: 2% Total spine: 5%	All age ≥65 years	0	Femoral neck, lumbar spine, or total hip
Zimering, 2007[112] Unclear	197	197	11% based on femoral neck	68.2 (10.2)	0	Femoral neck
Zimering, 2007[112] Unclear	197	197	11% based on femoral neck	68.2 (10.2)	0	Femoral neck
D'Amelio, 2013[90] Low	NR	995	335 (33.7), unclear what BMD site this is based on	65	995 (100)	Lumbar spine and femoral neck
Cadarette, 2001[83] Low	2434	2365	239 (10%) based on femoral neck	66.4 (SD, 8.8)	2365 (100)	Femoral neck
Mauck, 2005[101] Low	Unclear how many were eligible in the stated age group of interest	202	Overall: 69 (34%) (based on femoral neck T-score, would have been 7% if based on lumbar spine T- score) Ages 45-64: 11 (5%) Age ≥65: 58 (29%)	Mean, 69.2 (SD, 11.9) N (%) Ages 45-64: 79 (39%) Age ≥65: 123 (61%)	202 (100%)	Femoral neck and lumbar spine
D'Amelio, 2005[89] Low	553 (estimated based on 95% paticipation rate)	525	249 (47.4)	(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

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Cadarette, 2001[83] Low	2434	2365	241 (10%) based on femoral neck	66.4 (SD, 8.8)	2365 (100)	Femoral neck
Cadarette, 2004[84] Low	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 and lumbar spine
Cass, 2006[85] Low	399 eligible, 226 enrolled (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.
Cook et al, 2005[88] Unclear	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine and proximal femur
D'Amelio, 2005[89] Low	555 (estimated based on 95% paticipation rate)	525	251 (47.4)	(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[90] Low	NR	995	335 (33.7), unclear what BMD site this is based on	65	995 (100)	Lumbar spine and femoral neck
Gourlay, 2005[80] Unclear	4035	4035	380 (9.4)	61.5 (8.8)	4035 (100)	Femoral neck
Harrison et al, 2006[94] Low	207	207	70 (33.8) at any site	61	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[95] Low	505	505	20% at any site	61	505 (100)	Total femur, femoral neck, and lumbar spine
Martinez-Aguila, 2007[100] Unclear	694	665	117 (17.6) based on lowest BMD at spine or femoral neck 16.7% based on lumbar spine 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
Mauck, 2005[101] Low	Unclear how many were eligible in the stated age group of interest	202	Overall: 69 (34) (based on femoral neck T-score, would have been 7% if based on lumbar spine T-score) Ages 45-64: 11 (5) Age ≥65: 58 (29)	Mean, 69.2 (SD, 11.9) N (%) Ages 45-64: 79 (39) Age ≥65: 123 (61)	202 (100)	Femoral neck and lumbar spine

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Nguyen, 2004[104] Low	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) Femoral neck: 30.0% (95% CI, 25.8 to 34.6) Lumbar spine: 26.1% (22.1 to 30.6)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Richy, 2004[81] Unclear	4035	4035	32% at one or more site	61.5	4035 (100)	Total femur, femoral neck, and lumbar spine
Rud, 2005[109] Low	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)	100	Femoral neck, total hip, and lumbar spine
Chan, 2006[87] Unclear	135	135	Femoral neck: 33 (24) Spine: 37 (27)	68.4 (SD, 5.5)	135 (100)	Primary was femoral neck; spine was also analyzed
Gourlay, 2008[93]	7779	7679	20.5% (based on femoral neck)	Age ≥75: 2714 (34.9%) Ages 67-74: 5065 (65.1%)	1	Lumbar spine and femoral neck
Geusens, 2002[91]	US clinic sample NR	1102 US clinic sample 3374 Netherlands population sample 23,833 US trial sample	US clinic sample (based on femoral neck): 14% US trial sample (site not specified, presumably femoral neck): 21% Netherlands population sample (site not specified, presumably femoral neck): 19%	US clinic sample: 61.3 (SD, 9.6) NR for other samples	1	Lumbar spine and femoral neck (femoral neck not measured in Netherlands clinic-based sample)
Cook et al, 2005[88] Unclear	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine and proximal femur
Harrison et al, 2006[94] Low	207	207	70 (33.8) at any site	61	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[95] Low	505	505	20% at any site	61	505 (100)	Total femur, femoral neck, and lumbar spine
Martinez-Aguila, 2007[100] Unclear	694	665	117 (17.6%) based on lowest BMD at spine or femoral neck 16.7% based on lumbar spine 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
Richy, 2004[81] Unclear	4035	4035	32% at one or more site	61.5	4035 (100)	Total femur, femoral neck, and lumbar spine
Adler, 2003[78] Low	Unknown	181	15.6% based on lowest T-score of spine, total hip, or femoral neck	64.3 (12.3)	0	Spine, femoral neck, and total hip
Cadarette, 2004[84] Low	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 and lumbar spine

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Crandall, 2014[57] Low	2857	2857	NR (5)	57.7 (based on entire sample of 5167)	2857 (100)	3 sites: femoral neck, total hip and lumbar spine; outcomes reported are based on femoral neck BMD
D'Amelio, 2005[89] Low	554 (estimated based on 95% paticipation rate)	526	25,049 (47.4) (site not specified but implied to be the lowest of either femoral neck or lumbar spine)	(Provided by bone density status) Normal BMD: 57.3 (6.6) Osteopenic BMD: 60.2 (7.8) Osteoporotic BMD: 62.2 (6.7)	526 (100)	Lumbar spine and femoral neck
Gourlay, 2005[80] Unclear	4035	4035	380 (9.4) at femoral neck	61.5 (8.8)	4,035 (100)	Femoral neck
Machado, 2010[99] Low	202	202	35 (16.8) based on lowest T-score at any site 30 (14.9) based on lumbar spine 10 (5) based on femoral neck 2 (1) based on total hip	63.8 (8.2) 75.7% were age <70	0 (0)	Femoral neck, total hip, and lumbar spine, but the lowest value at any site was used to determine osteoporosis
Martinez-Aguila, 2007[100] Unclear	694	665	117 (17.6) based on lowest BMD at spine or femoral neck 16.7% based on lumbar spine 3.8% based on femoral neck	54.2 (5.4)	665 (100)	Femoral neck or lumbar spine
Richards, 2014[108] Unclear	520	518	92 (17.8)	66	0	Femoral neck and total hip
Richy, 2004[81] Unclear	4035	4035	32% at one or more site	61.5	4035 (100)	Total femur, femoral neck, and lumbar spine
Rud, 2005[109] Low	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)	100	Femoral neck, total hip, and lumbar spine
Zimering, 2007[112] Unclear	197	197	11% based on femoral neck	68.2 (10.2)	0	Femoral neck
Gourlay, 2008[93]	7779	7617	20.5% based on femoral neck	Age ≥75; 2714 (34.9%) Ages 67-74: 5065 (65.1%)	1	Femoral neck and lumbar spine
Geusens, 2002[91]	US clinic sample NR	1102 US clinic sample 3374 Netherlands population sample 23,833 US trial sample	US clinic sample (based on femoral neck): 14% US trial sample (site not specified, presumably femoral neck): 21% Netherlands population sample (site not specified, presumably femoral neck): 19%	US clinic sample: 61.3 (SD, 9.6) NR for other samples	1	Femoral neck and lumbar spine (femoral neck not measured in Netherlands clinic-based sample)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Morin, 2009[103] Unclear	8254	8254	1226 (14.9) at any site	52.7 (4.9)	8254 (100)	Femoral neck, total hip, proximal femur, lumbar spine
Cook et al, 2005[88] Unclear	208	208	45 (21.6) at any site	59.7 (29-87)	208 (100)	Lumbar spine and proximal femur
Harrison et al, 2006[94] Low	207	207	70 (33.8) at at any site	61	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[95] Low	505	505	20% at any site	61	505 (100)	Total femur, femoral neck, and lumbar spine
Lynn, 2008[98] Low	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	0	Femoral neck, lumbar spine, or total hip
McLeod, 2015[102] Low	174	174	18 (10.3)	59	100	Femoral neck and lumbar spine
Sinnott, 2006[111] Low	128	128	7% (any site)	63.8	0	Lumbar spine (L1–L4) and nondominant hip (femoral neck, trochanter, total hip)
Pang, 2014[56] Low	626	626	Lumber 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
Nguyen, 2004[104] Low	2095 (entire cohort)	410 (validation cohort)	Any site: 41.5% (95% CI, 36.7 to 46.3) Femoral neck: 30.0% (95% CI, 25.8 to 34.6) Lumbar spine: 26.1% (95% CI, 22.1 to 30.6)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
D'Amelio, 2013[90] Low	NR	995	335 (33.7), unclear what BMD site this is based on	65	995 (100)	Lumbar spine and femoral neck
Kung, 2005[97] Low	356	356	Femoral neck: 11.2% Lumbar spine: 10.1% Either region: 15.8%	64	0	Femoral neck, lumbar spine, or either
Machado, 2010[99] Low	202	202	34 (16.8) based on lowest T-score at any site 30 (14.9) based on lumbar spine 10 (5) based on femoral neck 2 (1) based on total hip	63.8 (8.2) 75.7% age <70	0 (0)	Femoral neck, total hip, and lumbar spine, but the lowest value at any site was used to determine osteoporosis
Oh, 2016[106] Low	1353	1110	Based on -2.5 at femoral neck: 35 (3.2) Based on -2.5 at lumbar spine: 73 (6.6) Based on lowest at any site: 91 (8.2)	63.5 (8.3)	0 (0)	Total femur, femoral neck, and lumbar spine (L1-L4)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Oh, 2016[106] Low	1353	1110	Based on -2.5 at femoral neck: 35 (3.2) Based on -2.5 at lumbar spine: 73 (6.6) Based on lowest at any site: 91 (8.2)	63.5 (8.3)	0 (0)	Total femur, femoral neck, and lumbar spine (L1-L4)
Oh, 2013[105] Low	1046	1046	Based on T-score at lumbar spine: 252 (24.1) Based on T-score at femoral neck: 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 lumbar spine (L1-L4)
Oh, 2013[105] Low	1046	1046	Based on T-score at lumbar spine: 252 (24.1) Based on T-score at femoral neck: 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 lumbar spine (L1-L4)
Kung, 2003[96] Low	722	722	Femoral neck: 21.5% Lumbar spine: 30.6% Either region: 37.7%	62	100	Femoral neck, lumbar spine, or either
Park, 2003[107] Unclear	1101	1101	119 (11)	59.1	100	Femoral neck
Chan, 2006[87] Unclear	135	135	Femoral neck: 33 (24) Spine: 37 (27)	68.4 (SD, 5.5)	135 (100)	Primary was femoral neck; spine was also analyzed
Ben Sedrine, 2001[79] Low	NR	4035	18.5% based on femoral neck 9.5% based on total hip 24.3% based on spine	61.5 (8.8)	100	Femoral neck, total hip, and lumbar spine
Brenneman, 2003[82] Low	428	416	126 (30.3) based on lowest T-score of hip or lumbar spine	69.3 (5.5)	100	Hip and lumbar spine
Crandall, 2014[57] Low	2857	2857	NR (5)	57.7 (based on entire sample of 5167)	2857 (100)	3 sites: femoral neck, total hip, and lumbar spine; outcomes reported are based on femoral neck BMD.
Gourlay, 2005[80] Unclear	4035	4035	380 (9.4)	61.5 (8.8)	4035 (100)	Femoral neck
Mauck, 2005[101] Low	Unclear how many were eligible in the stated age group of interest	202	Overall: 69 (34) (based on femoral neck T-score, would have been 7% if based on lumbar spine T-score) Age 45-64: 11 (5) Age ≥65: 58 (29)	Mean, 69.2 (SD, 11.9) N (%) Ages 45-64: 79 (39) Age ≥65: 123 (61)	202 (100)	Femoral neck and lumbar spine
Gourlay, 2008[93]	7779	7235	20.5% (based on femoral neck)	Age ≥75: 2714 (34.9) Ages 67-74: 5065 (65.1)	1	Femoral neck and lumbar spine

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
Geusens, 2002[91]	US clinic sample NR	1102 US clinic sample 3374 Netherlands population sample 23,833 US trial sample	US clinic sample (based on femoral neck): 14% US trial sample (site not specified, presumably femoral neck): 21% Netherlands population sample (site not specified, presumably femoral neck): 19%	US clinic sample: 61.3 (SD, 9.6) NR for other samples	1	Femoral neck and lumbar spine (femoral neck not measured in Netherlands clinic-based sample)
Cadarette, 2001[83] Low	2434	2365	239 (10) based on femoral neck	66.4 (SD, 8.8)	2365 (100)	Femoral neck
Cook et al, 2005[88] Unclear	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine and proximal femur
Harrison et al, 2006[94] Low	207	207	70 (33.8) at any site	61	207 (100)	Hip (femoral neck and total hip) and lumbar spine (L1-L4)
Jimenez-Nunez, 2013[95] Low	505	505	20% at any site	61	505 (100)	Total femur, femoral neck, and lumbar spine
Richy, 2004[81] Unclear	4035	4035	32% at one or more site	61.5	4035 (100)	Total femur, femoral neck, and lumbar spine
Rud, 2005[109] Low	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)	100	Femoral neck, total hip, and lumbar spine
Cass, 2006[85] Low	399 eligible, 226 enrolled (remainder declined enrollment)	203	Hip only: 1.0% Spine only: 7.9% Both: 2.0%	60.2 (SD, 9.6)	226 (100)	Total hip or total lumbar spine; lowest T-score from either was used.
Chan, 2006[87] Unclear	135	135	Femoral neck: 33 (24) Spine: 37 (27)	68.4 (SD, 5.5)	135 (100)	Primary was femoral neck; spine was also analyzed
Brenneman, 2003[82] Low	428	416	126 (30.3) based on lowest T-score of hip or lumbar spine	69.3 (5.5)	100	Hip and lumbar spine
Nguyen, 2004[104] Low	2095 (entire cohort)	410 (validation cohort)	At any site: 41.5% (95% CI, 36.7 to 46.3) Femoral neck: 30.0% (95% CI, 25.8 to 34.6) Lumbar spine: 26.1% (95% CI, 22.1 to 30.6)	70.5 (7.5)	410 (100)	Lumbar spine and femoral neck
Geusens, 2002[91]	US clinic sample NR	1102 US clinic sample 3374 Netherlands population sample 23,833 US	US clinic sample (based on femoral neck): 14% US trial sample (site not specified, presumably femoral neck): 21% Netherlands population sample (site not specified, presumably femoral neck): 19%	US clinic sample: 61.3 (SD, 9.6) NR for other samples	1	Lumbar spine and femoral neck (femoral neck not measured in Netherlands clinic-based sample)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	N Eligible	N for Analysis	N (%) With Osteoporosis Report for Each Site	Age	N (%) Female	Location of BMD
		trial sample				
Cook et al, 2005[88] Unclear	208	208	45 (21.6)	59.7 (29-87)	208 (100)	Lumbar spine and proximal femur
Crandall, 2014[57] Low	2857	2857	NR (5)	57.7 (based on entire sample of 5167)	2857 (100)	3 sites: femoral neck, total hip, and lumbar spine; outcomes reported are based on femoral neck BMD.

Abbreviations: BMD= body mass index; L1-L4= lumber 1 to lumbar 4; N= number; NR= not reported; SD= standard deviation; US= United States

Author, Year Risk of Bias	T-Score Reference Range	Machine and Software Version	Other Comments on BMD Test	Analysis Include Additional Adjustments?	Adjustment Variables
Adler, 2003[78] Low	NHANES reference database for hip Hologic reference source for spine Age, gender, race of reference group not reported	Hologic QDR 4500	NR	No	NA
Ben Sedrine, 2001[79] Low	Hologic QDR reference values specifically established for the population of Liege, Belgium (local reference values)	Hologic	NR	No	NA
Brenneman, 2003[82] Low	NHANES III Does not specify age or gender of reference group	Hologic QDR 2000	NR	No	NA
Brenneman, 2003[82] Low	NHANES III Does not specify age or gender of reference group	Hologic QDR 2000	NR	No	NA
Cadarette, 2001[83] Low	Canadian young adult normal values at the femoral neck (Authors note that Canadian young adult normal reference at the femoral neck (mean, 0.857 g/cm^3 [SD, 0.125]) is similar to that reported by NHANES III for non-Hispanic w hite Americans (mean, 0.858 g/cm^3 [SD, 0.120]).	Hologic QDR 4500 Hologic QDR 2000 Hologic QDR 1000 Lunar DPX	BMD at femoral neck used to determine T-score	No	NA
Cadarette, 2004[84] Low	Not reported	Hologic Lunar Norland Unknown	Lowest BMD at femoral neck, or lumbar spine used to determine T-score.	No	NA
Cass, 2006[85] Low	NHANES III non-Hispanic white women ages 20-29 years	DXA (Hologic QDR 4500A), NR	"Positive" test is a T-score of -2.5 at the femoral neck or total hip	Unclear	NA
Cass, 2013[86] Low	NHANES III non-Hispanic white women ages 20-29 years	DXA (Hologic QDR 4500A), NR (standardized conversion formulas furnished by GE	"Positive" test is a T-score of -2.5 at the femoral neck or total hip	Unclear	NA

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	T-Score Reference Range	Machine and Software Version	Other Comments on BMD Test	Analysis Include Additional Adjustments?	Adjustment Variables
		Health Care)			
Chan, 2006[87] unclear	Reference ranges used NR	DXA (Hologic QDR 4500A), NR	BMD at femoral neck used to determine T-score	Unclear	NA
Cook, 2005[88] Unclear	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	NHANES III normative reference database (presumably young non-Hispanic white females ages 20-29 years, though this is not specifically reported)	DXA (Hologic QDR 4500A), NR	Femoral neck	Unclear	NA
D'Amelio, 2005[89] Low	Reference values for T-scores NR. Site of measurement used for T-score NR.	Hologic QDR 4500	NR	No	NA
D'Amelio, 2013[90] Low	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[91]	Femoral neck: Non-Hispanic female white women ages 20-29 years (NHANES) Lumbar spine: Unclear	Brand of DXA manufacturer varied among centers; included Norland, Hologic, and Lunar	NR	No	NA
Gnudi, 2005[92] Low	"Reference values were those reported by Norland for the European female population." Age not given.	Norland XR 36	NR	No	NA
Gourlay, 2005[80] Unclear	T-score reference range was NHANES III Non-Hispanic white women ages 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[93]	Femoral neck: Non-Hispanic female white women ages 20-29 years (NHANES) Lumbar spine: Manufacturers norms for women age 30 years	Hologic	NR	No	NA
Harrison et al, 2006[94] Low	Hologic reference data for the T- and z-scores calculated using Hologic reference data for the lumbar spine and NHANES reference data for the proximal femur	GE Lunar Prodigy (GE Lunar, Madison, WI) or Hologic Discovery (Hologic, Bedford, MA)	Value of -2.5 or less at the total hip, femoral neck, or lumbar spine	No	NA
Jimenez-Nunez, 2013[95] Low	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 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	T-Score Reference Range	Machine and Software Version	Other Comments on BMD Test	Analysis Include Additional Adjustments?	Adjustment Variables
Kung, 2003[96] Low	Peak young Chinese mean values used for calculating T-scores: L1–L4 BMD 1.02±0.11 g/cm^2, femoral neck 0.77±0.09 g/cm^2, total hip BMD 0.86±0.10 g/cm^2	Sahara ultrasound bone densitometer (Hologic)	Results presented for femoral neck, or femoral neck or lumbar spine	no	NA
Kung, 2005[97] Low	NR	QDR 2000 Plus, Hologic	Results presented for femoral neck, lumbar spine, or femoral neck or lumbar spine	no	NA
Lynn, 2008[98] Low	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[99] Low	NHANES III young normal references values (sex unspecified) for femoral neck; manufacturer's database for male Caucasian references values for lumbar spine (age unspecified)	Hologic QDR 4500/c bone densitometer	NR	No	NA
Martinez-Aguila, 2007[100] Unclear	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[101] Low	T-scores based on references ranges for young healthy women ages 20-29 years in the local community area	QDR2000; Hologic (Waltham, MA)	NR	Yes	Age
McLeod, 2015[102] Low	NHANES III	GE Lunar Prodigy densitometer	Results presented for femoral neck and lumbar spine	No	NA
Morin, 2009[103] Unclear	T-scores for lumbar spine used manufacturer‘s US white female reference ranges, based on revised NHANES III, but these are only applicable to femoral neck	Lunar Prodigy; GE Lunar (Madison, WI)	NR	No	NA
Nguyen, 2004[104] Low	Reference ranges for calculation of T-scores not described. 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[105] Low	Sex-specific normal values for young Japanese women	QDR Discovery fan-beam densitometer (Hologic), Hologic Discovery software (version 13.1)	NR	Unclear	NA

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	T-Score Reference Range	Machine and Software Version	Other Comments on BMD Test	Analysis Include Additional Adjustments?	Adjustment Variables
Oh, 2016[106] Low	Sex-specific norms for young Japanese men	Hologic	Defined osteoporosis as BMD of -2.5 or -2.0 at the femoral neck or lumbar spine.	No	NA
Pang, 2014[56] Low	Manufactuer's sex-specific normative databse and an ethnic database	Lunar Prodigy limited fan-beam machine, NR	NR	Unclear	NA
Park, 2003[107] Unclear	Reference range for young Korean women	GE Lunar Model DPQ-IQ	NR	No	NA
Richards, 2014[108] Unclear	NHANES III	DXA on either Hologic (Hologic, Bedford, MA) or 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 data.	NR	No	NA
Richy, 2004[81] Unclear	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	T-scores for the femoral neck and total hip calculated using NHANES III reference values. Hologic reference 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
Shepherd, 2007[110] Low	T-scores derived from race/ethnicity and sex-specific BMD for Hispanic, non-Hispanic white, and non-Hispanic black men ages 20-29 years.	Hologic QDR	NR	No	NA

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	T-Score Reference Range	Machine and Software Version	Other Comments on BMD Test	Analysis Include Additional Adjustments?	Adjustment Variables
Shepherd, 2010[113] Low	White men ages 20-29 years;	Whole body DXA Hologic QDR-4500A	NR	No	No
Sinnott, 2006[111] Low	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 (GE, Madison, WI)	Results presented for total hip, femoral neck, or trochanter	No	NA
Zimering, 2007[112] Unclear	T-score ≤-2.5 compared to NHANES III young male, ethnicity/race specific reference data	Hologic QDR 4500 SL	NR	No	NA

Abbreviations: BMD= body mass index; cm= centimeter; G= gram; NA= not applicable; NHANES= National Health And Nutrition examination Survey; NR= not reported; SD= standard deviation.

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Adler, 2003[78] Low	Yes	1 month	AUROC for DXA outcome of T-score <-2.5 for any of 3 sites (LS, FN, TH) (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 (OST <2): 82% Cutoff used for white women (OST <1): 75% All compared to DXA outcome of any T-score <-2.5 (LS, FN, TH)	Cutoff used by study authors (OST <3): 66% Cutoff used for older men (OST <2): 74% Cutoff used for white women (OST <1): 80% All compared to DXA outcome of any T-score <-2.5 (LS, FN, TH)
Ben Sedrine, 2001[79] Low	Yes	NR	AUC (SE) for DXA T-score <-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)	A priori cutoff ≥6, T-score <-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-score <-2.5 Total hip: 93.7 Femoral neck: 88.4 Lumbar spine: 81.0 Any site: 82.4 Hip (total or neck) or spine: 89.6 All sites: 93.5	A priori cutoff ≥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

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Brenneman, 2003[82] Low	Yes	Concurrent	AUROC for DXA outcome of T-score <-2.5 for total hip or lumbar spine: 0.73 (SE, 0.03)	SCORE cutoff ≥7: 93.7 (88.3-99.1)	SCORE cutoff ≥7: 23.8 (9.6-38.0)
Brenneman, 2003[82] Low	Yes	Concurrent	AUROC for DXA outcome of T-score <-2.5 for total hip or lumbar spine: 0.54 (SE, 0.03)	SOF cutoff ≥5: 32.6 (26.6-38.6)	SOF cutoff ≥5: 76.0 (63.5-88.6)
Cadarette, 2001[83] Low	Yes	NR. Likely <2 years	AUROC for DXA outcome of T-score <-2.5 at femoral neck ABONE: 0.72 (0.02)	Cutoffs determined by original developers of clinical decision rules (ABONE ≥2) ABONE: 83.3 (78.5-88.0)	Cutoffs determined by original developers of clinical decision rules (ABONE ≥2) ABONE: 47.7 (45.6-49.8)
Cadarette, 2001[83] Low	Yes	NR. Likely <2 years	AUROC for DXA outcome of T-score <-2.5 at femoral neck (NOF cutoff ≥1 risk factor) NOF: 0.70 (0.02)	NOF cutoff ≥1 risk factor NOF: 96.2 (93.8-98.6)	NOF cutoff ≥1 risk factor NOF: 17.8 (16.2-19.4)
Cadarette, 2001[83] Low	Yes	NR. Likely <2 years	AUROC for DXA outcome of T-score <-2.5 at femoral neck ORAI: 0.79 (0.01)	Cutoffs determined by original developers of clinical decision rules (ORAI ≥9) ORAI: 97.5 (95.5-99.5)	Cutoffs determined by original developers of clinical decision rules (ORAI ≥9) ORAI: 27.8 (25.9-29.7)
Cadarette, 2001[83] Low	Yes	NR. Likely <2 years	AUROC for DXA outcome of T-score <-2.5 at femoral neck SCORE: 0.80 (0.01)	Cutoffs determined by original developers of clinical decision rules (SCORE ≥6) SCORE: 99.6 (98.8-100)	Cutoffs determined by original developers of clinical decision rules (SCORE ≥6) SCORE: 17.9 (16.2-19.5)
Cadarette, 2004[84] Low	Yes	Unknown	AUROC for DXA outcome of T-score <-2.5 by lowest value at femoral neck or lumbar spine: 0.802 (SE, 0.02)	Cutoff determined by original developer (ORAI >8) 92.5 (85.6-96.7)	Cutoff determined by original developer (ORAI >8) 38.7 (34.5-42.9)
Cadarette, 2004[84] Low	Yes	Unknown	AUROC for DXA outcome of T score <-2.5 by lowest value at femoral neck or lumbar spine: 0.733 (SE, 0.02)	Cutoff determined by original developer (OST <2) 95.3 (89.3-98.5)	Cutoff determined by original developer (OST <2) 39.6 (35.4-43.9)
Cass, 2006[85] Low	Yes	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 (0.596-0.73)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cass, 2006[85] Low	Yes	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)
Cass, 2013[86] Low	Yes	Concurrent	SCORE ≥6 0.82 (0.71-0.92)	SCORE ≥6 0.80 (0.52-0.96)	SCORE ≥6 0.70 (0.64-0.74)
Chan, 2006[87] Unclear	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	AUROC for DXA outcome of T-score <-2.5 at femoral neck 0.70 (0.63-0.78)	ABONE ≥3 81.8% (NR)	ABONE ≥3 55.9% (NR)
Chan, 2006[87] Unclear	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	AUC for ORAI ≥9 was NR ORAI ≥20: 0.76 (0.68-0.84)	ORAI ≥9 100% (NR)	ORAI ≥9 9.8% (NR)
Chan, 2006[87] Unclear	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	0.82 (0.75-0.90)	OSTA ≤-1 97% (NR)	OSTA ≤-1 18.6% (NR)
Chan, 2006[87] Unclear	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled	0.80 (0.72-0.87)	SCORE ≥6 100% (NR)	SCORE ≥6 30.4% (NR)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
		prospectively.			
Cook et al, 2005[88] Unclear	Yes	None	0.664 (0.739 to 0.595)	ORAI <14 0.43	ORAI <14 0.86
Cook et al, 2005[88] Unclear	Yes	None	0.747 (0.805 to 0.702)	OSIRIS <0 70	OSIRIS <0 73
Cook et al, 2005[88] Unclear	Yes	None	0.716 (0.775 to 0.669)	OST ≤-1 52	OST ≤-1 82
Cook et al, 2005[88] Unclear	Yes	None	0.720 (0.674 to 0.779)	SCORE <12 0.5	SCORE <12 0.83
Cook et al, 2005[88] Unclear	Yes	None	0.717 (0.777 to 0.670)	SOFSURF <1 0.72	SOFSURF <1 0.67
Crandall, 2014[57] Low	Yes	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)
Crandall, 2014[57] Low	Yes	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)
Crandall, 2014[57] Low	yes	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)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Amelio, 2005[89] Low	Yes	NR	AUROC for DXA outcome of lowest T-score <-2.5 of all sites (NOF cutoff ≥1 risk factor) NOF: 0.60 (NR)	NR	NR
D'Amelio, 2005[89] Low	Yes	NR	ORAI 0.32 (NR)	NR	NR
D'Amelio, 2005[89] Low	Yes	NR	OST <2 0.33 (NR)	NR	NR
D'Amelio, 2013[90] Low	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	SCORE ≥10 0.63 (NR)	NR	NR
D'Amelio, 2013[90] Low	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	AUROC for DXA outcome of lowest T-score <-2.5 of all sites (NOF cutoff ≥1 risk factor) 0.60 (NR)	NR	NR
D'Amelio, 2013[90] Low	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	SCORE >8 0.68 (NR)	NR	NR
D'Amelio, 2013[90] Low	yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled	SCORE <2 0.32 (NR)	NR	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
		prospectively.			
Geusens, 2002[91]	Yes	NR	NR	US clinic sample ORAI >8: 90% (85-95) US trial sample ORAI >9: 137/593=23.1% Netherlands population study OST ≤1: 4903/20,820=23.5%	US clinic sample ORAI >8: 52% (49-55) US trial sample NR Netherlands population sample NR
Geusens, 2002[91]	Yes	NR	NR	US clinic sample OST <2 (FN site): 88% (83-93) US trial sample OST ≤1: (94+39)/(67+525)=22.3% Netherlands population study OST ≤1: (3648+1134)/(16059+1974)= 26.5%	US clinic sample OST <2 (FN site): 52% (49-55) US trial sample NR Netherlands population sample NR
Geusens, 2002[91]	Yes	NR	NR	US clinic sample SCORE >7: 89% (84-94) US trial sample SCORE ≥7: 143/628=22.8% Netherlands population sample: 4819/18724=25.7%	US clinic sample SCORE >7: 58% (55-61) US trial sample NR Netherlands population sample NR
Geusens, 2002[91]	Yes	NR	NR	US clinic sample SOFSURF ≥-1: 92% (88-96) US trial sample: 140/736=19.0% Netherlands population sample: 5007/23,033=21.7%	US clinic sample SOFSURF ≥-1: 37% (34-40) US rrial sample NR Netherlands population sample NR
Gnudi, 2005[92] Low	Yes	NR	Compared to T-score ≤-2.5 at either FN or LS: 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 (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 (1) 16.9% (2) 27.7% (3) 31.0%
Gourlay, 2005[80] Unclear	Yes	NR	Reported by age groups: Ages 45-64, ORAI: 0.75 (0.71-0.79) Age ≥65+, ORAI: 0.75 (0.71-0.78)	Reported by age groups: Ages 45-64, ORAI (higher risk ≥8): NR Age ≥65, ORAI (higher risk ≥13): 89.2 (84.6-92.8)	Reported by age groups: Ages 45-65, ORAI (higher risk ≥8) 46.2 (44.2-48.2) Age ≥65, ORAI (higher risk ≥13): 44.7 (42.0-47.5)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gourlay, 2005[80] Unclear	Yes	NR	Reported by age groups: Ages 45-64: OST 0.77 (0.73-0.81) Age ≥65: OST 0.76 (0.73-0.79)	Reported by age groups: Ages 45-64: OST (higher risk ≤1) 89.2 (82.8-93.8) 88.5 (82.0-93.3) Age ≥65: OST (higher risk ≤-1) 84.6 (79.5-89.0)	Reported by age groups: Ages 45-64: OST (higher risk ≤1) 45.0 (43.0-47.0) Age ≥65: OST (higher risk ≤-1) 47.5 (44.7-50.3)
Gourlay, 2005[80] Unclear	Yes	NR	Reported by age groups: Ages 45-64: SCORE 0.76 (0.72-0.80) Age ≥65: SCORE 0.75 (0.71-0.78)	Reported by age groups: Ages 45-65: SCORE (higher risk ≥7) 88.5 (82.0-93.3) Age ≥65: SCORE (higher risk ≥11) 88.8 (84.1-92.5)	Reported by age groups: Ages 45-66: SCORE (higher risk ≥7) 39.8 (37.8-41.7) Age ≥65: SCORE (higher risk ≥11) 42.3 (39.6-45.1)
Gourlay, 2008[93]	Yes	NR	ORAI ≥9 0.70 (0.69-0.71) for lowest site (FN or LS)	NR (wrong T-score threshold used)	NR (wrong T-score threshold used)
Gourlay, 2008[93]	Yes	NR	OST ≤-1 0.76 (0.74-0.77) for FN site 0.72 (0.71-0.73) for lowest site (FN or LS)	OST ≤-1 85% (83-87)	48% (inferred from 1-Specificity)
Gourlay, 2008[93]	Yes	NR	SCORE ≥6 0.71 (0.70-0.72) for lowest site (FN or LS)	NR (wrong T-score threshold used)	NR (wrong T-score threshold used)
Harrison, 2006[94] Low	Yes	Unclear	0.67	NR	NR
Harrison, 2006[94] Low	Yes	Unclear	0.7	NR	NR
Harrison, 2006[94] Low	Yes	Unclear	0.69	NR	NR
Harrison, 2006[94] Low	Yes	Unclear	0.67	NR	NR
Jimenez-Nunez, 2013[95] Low	Yes	None	0.684	Threshold for risk set at ≥9 points: 78	Threshold for risk set at ≥9 points: 52
Jimenez-Nunez, 2013[95] Low	yes	None	0.711	Threshold for risk set at ≤-3: 81	Threshold for risk set at ≤-3: 54

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Jimenez-Nunez, 2013[95] Low	Yes	None	0.71	Threshold for risk set at ≤-1: 83	Threshold for risk set at ≤-1: 52
Jimenez-Nunez, 2013[95] Low	Yes	None	0.672	Threshold for risk set at ≥6 points: 68	Threshold for risk set at ≥6 points: 60
Kung, 2003[96] Low	Yes	Unclear	Femoral neck: 0.80 (0.78-0.84) Femoral neck or lumbar spine: 0.75 (0.72-0.79)	Threshold set at ≤-1 for high risk Femoral neck: 88% Femoral neck or lumbar spine: 79%	Threshold set at ≤-1 for high risk Femoral neck: 54% Femoral neck or lumbar spine: 60%
Kung, 2005[97] Low	Yes	Unclear	Femoral neck: 0.85 (0.80-0.89) Lumbar spine: 0.79 (0.74-0.83) Femoral neck or lumbar spine: 0.78 (0.73-0.82)	Threshold set at ≤-1 for high risk Femoral neck: 83% Lumbar spine: 72% Femoral neck or lumbar spine: 73%	Threshold set at ≤-1 for high risk Femoral neck: 67% Lumbar spine: 65% Femoral neck or lumbar spine: 68%
Lynn, 2008[98] Low	Yes	Unclear	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
Lynn, 2008[98] Low	Yes	Unclear	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%
Machado, 2010[99] Low	Yes	NR	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OST <2: 0.627 (0.524-0.731)	OST <2: 61.8% (NR)	OST <2: 63.7% (NR)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Machado, 2010[99] Low	Yes	NR	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OSTA <2: 0.62 (0.51-0.72)	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OSTA <2: 55.9% (NR)	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OSTA <2: 67.9% (NR)
Martinez-Aguila, 2007[100] Unclear	Yes	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	ORAI ≥9: 0.62 (0.56-0.67)	Based on a priori thresholds ORAI ≥9: 64.1 (54.7-72.7)	Based on a priori thresholds ORAI ≥9: 58.9 (54.7-63.1)
Martinez-Aguila, 2007[100] Unclear	Yes	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	OSIRIS ≤1: 0.63 (0.57-0.69)	Based on a priori thresholds OSIRIS ≤1: 58.1 (48.6-67.2)	Based on a priori thresholds OSIRIS ≤1: 67.9 (63.8-71.8)
Martinez-Aguila, 2007[100] Unclear	Yes	NR, but study was done restrospectively so assumption is clinical risks were collected at the time of the BMD measurement.	OST ≤1: 0.64 (0.59-0.69)	Based on a priori thresholds OST <2: 69.2 (60.0-77.4)	Based on a priori thresholds OST <2: 58.8 (54.5-62.9)
Mauck, 2005[101] Low	Yes	Concurrent	AUROC for DXA outcome of T-score <-2.5 at femoral neck NOF cutoff ≥1 risk factor Unadjusted analyses NOF Overall: 0.70 (0.63-0.77) Ages 45-64: 0.69 (0.51-0.70) Age ≥65: 0.60 (0.51-0.70)	NOF cutoff ≥1 risk factor NOF overall: 100% (95-100) Ages 45-64: 100% (72-100) Age ≥65: 100% (94-100)	NOF cutoff ≥1 risk factor NOF overall: 10% (5-16) Ages 45-64: 19% (11-31) Age ≥65: 0% (0-6)
Mauck, 2005[101] Low	Yes	Concurrent	Unadjusted analyses ORAI Overall: 0.84 (0.78-0.89) Ages 45-64: 0.82 (0.71-0.94) Age ≥65: 0.79 (0.71-0.87)	ORAI ≥9 Overall: 99% (92 to 100) Ages 45-64: 91% (59 to 100) Age ≥65: 100% (94 to 100)	ORAI ≥9 Overall: 36% (28 to 44) Ages 45-64: 69% (57 to 80) Age ≥65: 0% (0 to 6)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mauck, 2005[101] Low	Yes	Concurrent	Unadjusted analyses SCORE Overall: 0.87 (0.81-0.92) Ages 45-64: 0.85 (0.72-0.99) Age ≥65: 0.80 (0.72-0.88)	SCORE ≥6 Overall: 100% (95 to 100) Ages 45-64: 100% (72 to 100) Age ≥65: 100% (94 to 100)	SCORE ≥6 Overall: 25% (18 to 33) Ages 45-64: 41% (29 to 54) Age ≥65: 8% (3 to 17)
McLeod, 2015[102] Low	Yes	3 weeks	Femoral neck: 0.807 (0.692-0.985) Lumbar spine: 0.706 (0.559-0.852)	OST <2 for femoral neck: 87.5 OST <21 for lumbar spine: 78.6	OST <2 for femoral neck: 62.7 OST <2 for lumbar spine: 63.7
Morin, 2009[103] Unclear	Yes	Unclear	Using lowest T-score from femoral neck: 0.77 (0.75 to 0.79) Using T-score from any site: 0.71 (0.69 to 0.72)	Only values associated with OST <2 are extracted (a priori threshold) Using lowest T-score from any site: 46.8% (45.7 to 47.9) Using FN T-score: 60.2% (59.2 to 61.3)	Only values associated with OST <2 are extracted (a priori threshold) Using lowest T-score from any site: 81.1% (80.3 to 82.0) Using FN T-score: 78.8 (77.9 to 79.6)
Nguyen, 2004[104] Low	Data presented for both -2.0 and -2.5 thresholds.	Concurrent	DOEScore: 0.75 (SE, 0.03) NR for FOSTA, SOFSURF, or ORAI	DOEScore >10 : 82% (NR)	DOEScore >10: 52% (NR)
Nguyen, 2004[104] Low	Data presented for both -2.0 and -2.5 thresholds.	Concurrent	NR	ORAI >15: 61% (NR)	ORAI >15: 68% (NR)
Nguyen, 2004[104] Low	Data presented for both -2.0 and -2.5 thresholds.	Concurrent	NR	OSTA <-1: 41% (NR) FN	OSTA <-1: 24% (NR) FN
Nguyen, 2004[104] Low	Data presented for both -2.0 and -2.5 thresholds.	Concurrent	NR	SOFSURF >10 : 78% (NR)	SOFSURF >10 : 36% (NR)
Oh, 2013[105] Low	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	OST ≤0 0.646 (SE, 0.013)	OST ≤0 94.2 (91.0-96.5)	OST ≤0 29.2 (26.0-32.6)
Oh, 2013[105] Low	yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were	OST ≤-1 0.617 (SE, 0.11)	OST ≤-1 76.1 (71.0-80.8)	OST ≤-1 67.1 (63.6-70.5)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
		enrolled prospectively.			
Oh, 2016[106] Low	Yes	Not specifically reported, but prospective enrollment so presumed to be at the same time.	SCORE ≤0 0.665 (SE, 0.021)	SCORE ≤0 84.6 (75.5 to 91.3)	SCORE ≤0 48.4 (45.3 to 51.5)
Oh, 2016[106] Low	Yes	NR	0.627 (SE, 0.016)	Score ≤1 92.3 (84.8 to 96.9)	Score ≤1 33.2 (30.3 to 36.2)
Pang, 2014[56] Low	Yes	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) 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
Pang, 2014[56] Low	Yes	Not specifically indicated but appears to have been done shortly after enrollment since subjects were enrolled prospectively.	Based on lowest BMD at any site 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
Pang, 2014[56] Low	Yes	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 of 0 (not clear if this means ≤0 or <0) 90.9	Based on lowest BMD at any site OST threshold of 0 (not clear if this means ≤0 or <0) 39.9
Park, 2003[107] Unclear	Yes	Unclear	0.873	OSTA ≤-1: 87%	OSTA ≤-1: 67%
Richards, 2014[108] Unclear	Yes	Unclear	0.67	OST ≤-6: 82.6% OST ≤0: 40.2%	OST >-6: 33.6% OST ≤0: 85.4%

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Richy, 2004[81] Unclear	Yes	Unclear	Total hip: 74.1 Femoral neck: 70.6 Lumbar spine: 64.4 Any site: 67	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
Richy, 2004[81] Unclear	Yes	Unclear	Total hip: 81.7 Femoral neck: 77.2 Lumbar spine: 69 Any site: 73	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
Richy, 2004[81] Unclear	Yes	Unclear	OST <2 Total hip: 81.3 Femoral neck: 76.8 Lumbar spine: 68.6 Any site: 72.6	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
Richy, 2004[81] Unclear	Yes	Unclear	Total hip: 78.5 Femoral neck: 74.9 Lumbar spine: 66.6 Any site: 70.8	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	Yes	NR	AUROC for DXA outcome of T-score <-2.5 for any of3 sites (femoral neck, total hip, lumbar spine) ORAI: 0.64 (0.58-0.70)	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield sensitivity close to 90% and DXA outcome of lowest T-score at FN, TH, LS <-2.5 ORAI 1) >8: 50 (44-56) (<-2.0) 2) >2: 81 (76-86) (<-2.0) 3) >2: 82 (72-89) (<-2.5)	ORAI 1) >8: 75 (73-77) (<-2.0) 2) >2: 39 (37-41) (<-2.0) 3) >2: 37 (35-39)(<-2.5)
Rud, 2005[109] Low	Yes	NR	AUROC for DXA outcome of T-score <-2.5 for any of 3 sites (femoral neck, total hip, lumbar spine) OST ≤1 0.68 (0.63-0.74)	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield sensitivity close to 90% and DXA outcome of lowest T-score at FN, TH, LS <-2.5 OST 1) <2: 92 (64-100) (<-2.5) 2) <5: 92 (89-95) (<-2.0)	OST 1) <2: 71 (69-73) (<-2.5) 2) <5: 24 (22-26) (<-2.0) 3) <5: 23 (21-25) (<-2.5)

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	BMD Threshold for Osteoporosis Defined as T-Score <-2.5?	Time Between Risk Prediction Measurement and BMD Measurement	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
				3) <5: 94 (86-98) (<-2.5)	
Rud, 2005[109] Low	Yes	Not reported	AUROC for DXA outcome of T-score <-2.5 for any of 3 sites (femoral neck, total hip, lumbar spine) SCORE 0.68 (0.63-0.73)	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield sensitivity close to 90% and DXA outcome of lowest T-score at FN, TH, LS <-2.5 SCORE 1) NA (wrong DXA threshold) 2) >3: 90 (86-93) (<-2.0) 3) >3: 89 (81-95) (<-2.5)	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield sensitivity close to 90% and DXA outcome of lowest T-score at FN, TH, LS <-2.5 SCORE 1) NA (wrong DXA threshold) 2) >3: 28 (25-29)
Shepherd, 2007[110] Low	Yes	Unknown	AUROC for DXA outcome of T-score <-2.5 at total hip 0.842 (0.811-0.873)	MORES ≥6 0.95 (0.81-0.99)	MORES ≥6 0.61 (0.57-0.64)
Shepherd, 2010[113] Low	Yes	Not specifically reported	SCORE ≥6 at any site: 0.73 SCORE ≥6 at lumbar spine: 0.66	SCORE ≥6 at any site: 0.66 (0.58 to 0.72) SCORE ≥6 at lumbar spine: 0.58 (0.46 to 0.69)	SCORE ≥6 at any site: 0.68 (0.65 to 0.70) SCORE ≥6 at lumbar spine: 0.65 (0.63 to 0.68)
Sinnott, 2006[111] Low	Yes	Unclear	0.89 (0.75-1.03)	OST <4 at femoral neck, total hip, or trochanter: 89 OST ≤1: 89%	OST <4 fat femoral neck, total hip, or trochanter: 54 OST <2: 71%
Zimering, 2007[112] Unclear	Yes	Unknown	AUROC for DXA outcome of T-score <-2.5 at FN MSCORE age-weight: 0.84 (0.74-0.95)	MSCORE age-weight (>9): 85	MSCORE age-weight (>9): 58
Zimering, 2007[112] Unclear	Yes	Unknown	AUROC for DXA outcome of T-score <-2.5 at FN MSCORE: 0.84 (0.74-0.95)	MSCORE (>9): 88	MSCORE (>9): 57
Zimering, 2007[112] Unclear	Yes	Unknown	AUROC for DXA outcome of T-score <-2.5 at FN OST: 0.81 (0.70-0.92)	OST (<2 [established in elderly male population]): 75 OST (<3 [established in male veteran population]): 75	OST (<2 [established in elderly male population]): 68 OST (<3 [established in male veteran population]): 59

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; 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;

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

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

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Adler, 2003[78] Low	Cutoff used by study authors (OST <3): 98% Cutoff used for older men (OST <2): 97% Cutoff used for white women (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 (OST <2): 38% Cutoff used for white women (OST <1): 41% All compared to DXA outcome of any T-score (LS, FN, TH) <-2.5	None	Subgroup analyses for race, age deciles, corticosteroid treatment (Table 4: AUC, Sn, Sp, PPV, NPV) AUC (no CI): White: 0.848 Black: 0.800 Ages 50-59: 0.938 Ages 60-69: 0.894 Ages 70-79: 0.696 Age ≥80: 0.993 Current CS treatment: 0.786 No current CS: 0.803
Ben Sedrine, 2001[79] Low	A priori cutoff ≥6, T-score <-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-score <-2.5 Total hip: 98.3 Femoral neck: 93.7 Lumbar spine: 86.5 Any site: 83.4	A priori cutoff ≥6, T-score <-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-score <-2.5 Total hip: 13.5 Femoral neck: 25.0 Lumbar spine: 30.0 Any site: 40.6	NR	A priori cutoff >6, T-score <-2.5 Sn in women age ≥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 in women age ≥65 Total hip: 4.4 Femoral neck: 5.1 Lumbar spine: 4.7 Any site: 5.7 Hip (total or neck) or spine: 4.5 All sites: 4.1 PPV in women age ≥65 Total hip: 16.2 Femoral neck: 30.3 Lumbar spine: 31.6 Any site: 44.8 Hip (total or neck) or spine: 18.8 All sites: 10.4 NPV in women age ≥65 Total hip: 100.0 Femoral neck: 98.2 Lumbar spine: 89.1 Any site: 87.3 Hip (total or neck) or spine: 100.0

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
				All sites: 100.0 Sn in women age <65 Total hip: 95.3 Femoral neck: 92.9 Lumbar spine: 88.9 Any site: 88.9 Hip (total or neck) or spine: 95.5 All sites: 94.8 Sp in women age <65 Total hip: 27.7 Femoral neck: 29.1 Lumbar spine: 30.3 Any site: 31.7 Hip (total or neck) or spine: 28.3 All sites: 27.2 PPV in women age<65 Total hip: 7.6 Femoral neck: 15.5 Lumbar spine: 24.8 Any site: 31.0 Hip (total or neck) or spine: 10.3 All sites: 4.9 NPV in women age <65 Total hip: 99.0 Femoral neck: 96.7 Lumbar spine: 91.3 Any site: 89.3 Hip (total or neck) or spine: 98.7 All sites: 99.3
Brenneman, 2003[82] Low	NR	NR	NR	SCORE cutoff recalibrated for older population of this study compared to development cohort (≥6 to ≥7)
Brenneman, 2003[82] Low	NR	NR	NR	NR
Cadarette, 2001[83] Low	NR	NR	NR	NR
Cadarette, 2001[83] Low	NR	NR	NR	NR
Cadarette, 2001[83] Low	NR	NR	NR	NR
Cadarette, 2001[83] Low	NR	NR	NR	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Cadarette, 2004[84] Low	NR	NR	NR	Study also looked at weight criterion and OST-chart tool that was developed just for this study (not validated)
Cadarette, 2004[84] Low	NR	NR	NR	Study also looked at weight criterion and OST-chart tool that was developed just for this study (not validated)
Cass, 2006[85] Low	ORAI ≥9 0.94 (0.90-0.98)	ORAI ≥9 0.20 (0.11-0.29)	NR	Has subgroup analysis for non-Hispanic white, Hispanic, and African American
Cass, 2006[85] Low	SCORE ≥6 0.93 (0.89-0.97)	SCORE ≥6 0.19 (0.09-0.29)	NR	Has subgroup analysis for non-Hispanic white, Hispanic, and African American
Cass, 2013[86] Low	SCORE ≥6 0.99 (0.96-1.00)	SCORE ≥6 0.11 (0.06-0.18)	NR	None
Chan, 2006[87] Unclear	NR	NR	NR	This is just for the femoral neck
Chan, 2006[87] Unclear	NR	NR	NR	This is just for the femoral neck
Chan, 2006[87] Unclear	NR	NR	NR	This is just for the femoral neck
Chan, 2006[87] Unclear	NR	NR	NR	This is just for the femoral neck
Cook, 2005[88] Unclear	ORAI <14 0.84	ORAI <14 0.48	NR	None
Cook, 2005[88] Unclear	OSIRIS <0 89	OSIRIS <0 42	NR	None
Cook, 2005[88] Unclear	OST ≤-1 56	OST ≤-1 44	NR	None
Cook, 2005[88] Unclear	SCORE <12 0.85	SCORE <12 0.46	NR	None
Cook, 2005[88] Unclear	SOFSURF <1 0.89	SOFSURF <1 0.42	NR	None
Crandall, 2014[57] Low	NR	OST <2 14.7 (12.4-16.9)	NR	Other cutpoints are also available
Crandall, 2014[57] Low	NR	SCORE >7 14.1 (11.9-16.4)	NR	Other cutpoints are also available
Crandall, 2014[57] Low	NR	FRAX MOF risk ≥9.3% 13.7 (10.4-17.0)	NR	Other cutpoints are also available
D'Amelio, 2005[89] Low	NR	NR	NR	NR
D'Amelio, 2005[89] Low	NR	NR	NR	NR
D'Amelio, 2005[89] Low	NR	NR	NR	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
D'Amelio, 2013[90] Low	NR	NR	NR	NR
D'Amelio, 2013[90] Low	NR	NR	NR	NR
D'Amelio, 2013[90] Low	NR	NR	NR	NR
D'Amelio, 2013[90] Low	NR	NR	NR	NR
Geusens, 2002[91]	NR	NR	NR	NR
Geusens, 2002[91]	NR	NR	NR	NR
Geusens, 2002[91]	NR	NR	NR	NR
Geusens, 2002[91]	NR	NR	NR	NR
Gnudi, 2005[92] Low	Cutoffs based on predicted probability to have low BMD (PPL-BMD) 1) PPL-BMD = 0.090 2) PPL-BMD = 0.132 3) PPL-BMD = 0.156 1) 90.9% 2) 91.2% 3) 86.1%	Cutoffs based on predicted probability to have low BMD (PPL-BMD) 1) PPL-BMD = 0.090 2) PPL-BMD = 0.132 3) PPL-BMD = 0.156 1) 40.9% 2) 43.9% 3) 44.1%	NR	NR
Gourlay, 2005[80] Unclear	NR	NR		Same study cohort as reported in Richy and Ben Sedrine, reports findings by age groups instead of overall.
Gourlay, 2005[80] Unclear	NR	NR		Same study cohort as reported in Richy and Ben Sedrine, reports findings by age groups instead of overall.
Gourlay, 2005[80] Unclear	NR	NR		Same study cohort as reported in Richy and Ben Sedrine, i reports findings by age groups instead of overall.
Gourlay, 2008[93]	NR	NR	NR	NR
Gourlay, 2008[93]	NR	NR	LR-: 0.31 LR+: 1.64	NR
Gourlay, 2008[93]	NR	NR	NR	NR
Harrison et al, 2006[94] Low	NR	NR	NR	None
Harrison et al, 2006[94] Low	NR	NR	NR	None

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Harrison et al, 2006[94] Low	NR	NR	NR	None
Harrison et al, 2006[94] Low	NR	NR	NR	None
Jimenez-Nunez, 2013[95] Low	NR	NR	NR	None
Jimenez-Nunez, 2013[95] Low	NR	NR	NR	None
Jimenez-Nunez, 2013[95] Low	NR	NR	NR	None
Jimenez-Nunez, 2013[95] Low	NR	NR	NR	None
Kung, 2003[96] Low	NR	NR	NR	None
Kung, 2005[97] Low	NR	NR	NR	None
Lynn, 2008[98] Low	NR	NR	NR	None
Lynn, 2008[98] Low	OST <2: 97.4%	OST <2: 9.7%	NR	None
Machado, 2010[99] Low	OST <2: 89.2%	OST <2: 25.6% (NR)	NR	NR
Machado, 2010[99] Low	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OSTA <2: 88.4% (NR)	Based on a priori thresholds (data for other thresholds are also presented in Table 4) OSTA <2: 26.0% (NR)	NR	
Martinez-Aguila, 2007[100] Unclear	Based on a priori thresholds ORAI ≥9: 25.0 (20.2 to 30.3)	Based on a priori thresholds ORAI ≥9: 88.5 (84.8 to 91.6)	NR	NR
Martinez-Aguila, 2007[100] Unclear	Based on a priori thresholds OSIRIS ≤1: 88.4 (84.9 to 91.3)	Based on a priori thresholds OSIRIS ≤1: 27.9 (22.3 to 33.9)	NR	NR
Martinez-Aguila, 2007[100] Unclear	Based on a priori thresholds OST <2: 89.9 (86.3 to 92.9)	Based on a priori thresholds OST <2: 26.4 (21.5 to 31.7)	NR	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Mauck, 2005[101] Low	NOF ≥1 risk factor NOF overall: 100% (75 to 100) Ages 45-64: 100% (75 to 100) Age ≥65: NA	NOF overall: 37% (30 to 44) Ages 45-64: 17% (9 to 28) Age ≥65: 48% (38 to 57)	+LR and -LR are also presented in Table 3.	Age-adjusted analysis: AUC: 0.65 (0.58 to 0.71) Sn: 100% (55 to 100) Sp: 10% (4 to 29) NPV: 100% (30 to 100) PPV: 27% (17 to 41)
Mauck, 2005[101] Low	ORAI ≥9 Overall: 44% (36 to 53) Ages 45-64: 32% (17 to 51) Age ≥65: 48% (38 to 57)	ORAI ≥9 Overall: 98% (89 to 100) Ages 45-64: 98% (89 to 100) Age ≥65: NA	+LR and -LR are also presented in Table 3.	Age-adjusted analysis: AUC: 0.79 (0.74 to 0.83) Sn: 98% (51 to 100) Sp: 40% (30 to 56) NPV: 77% (46 to 100) PPV: 29% (18 to 59)
Mauck, 2005[101] Low	SCORE ≥6 Overall: 100% (89 to 100) Ages 45-64: 100% (88 to 100) Age ≥65: 100% (48 to 100)	SCORE ≥6 Overall: 41% (34 to 39) Ages 45-64: 22% (11 to 35) Age ≥65: 50% (40 to 59)	+LR and -LR are also presented in Table 3.	Age-adjusted analysis: AUC: 0.85 (0.80 to 0.89) Sn: 100% (55 to 100) Sp: 29% (18 to 48) NPV: 100% (51 to 100) PPV: 27% (17 to 48)
McLeod, 2015[102] Low	NR	NR	NR	Score of <2 considered to be optimal to achieve close to 90% sensitivity
Morin, 2009[103] Unclear	NR	NR	NR	NR
Nguyen, 2004[104] Low	NR	DOEScore >10: 55% (NR)	LR+ are also reported.	NR
Nguyen, 2004[104] Low	NR	ORAI >15: 57% (NR)	LR+ are also reported.	NR
Nguyen, 2004[104] Low	NR	OSTA <-1: 28% (NR) FN	LR+ are also reported.	NR
Nguyen, 2004[104] Low	NR	SOFSURF >10: 47% (NR)	LR+ are also reported.	NR
Oh, 2013[105] Low	OST ≤0 92.3 (88.1-95.4)	OST ≤0 35.9 (32.6-39.3)	OST <0 LR+: 1.33 (1.26-1.40) LR-: 0.20 (0.13-0.32)	Provides information from development dataset, day for <2.0 or Tls <-2.0, p-values for differences between models and OSTA
Oh, 2013[105] Low	OST ≤-1 87.0 (83.9-89.6)	OST ≤-1 49.4 (44.8-54.0)	OST ≤-1 LR+: 2.32 (2.05-2.61) LR-: 0.36 (0.29-0.44)	Provides information from development dataset, day for <2.0 or Tls <-2.0, p- values for differences between models and OSTA
Oh, 2016[106] Low	Score ≤0 97.2 (95.4 to 98.5)	Score ≤0 12.8 (10.2 to 15.0)	NR	Only extracted values for validation dataset for threshold BMD -2.5
Oh, 2016[106] Low	Score ≤1 98.0 (95.9 to 99.2)	Score ≤1 11.0 (8.9 to 13.4)	NR	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Pang, 2014[56] Low	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 2 hip sites.	NR
Pang, 2014[56] Low	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 2 hip sites.	NR
Pang, 2014[56] Low	Based on lowest BMD at any site (OST cutoff of 0, not clear if this means ≤0 or <0): 96.9	Based on lowest BMD at any site (OST cutoff of 0, not clear if this means ≤0 or <0): 17.5	Also reports based on BMD at each individual site, and lowest of the 2 hip sites.	NR
Park, 2003[107] Unclear	OSTA ≤-1: 98%	OSTA ≤-1: 24%	NR	NR
Richards, 2014[108] Unclear	NR	NR	NR	This study also reported sensivity and specifity 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.
Richy, 2004[81] Unclear	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	NR
Richy, 2004[81] Unclear	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	NR
Richy, 2004[81] Unclear	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	NR
Richy, 2004[81] Unclear	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	NR
Rud, 2005[109] Low	ORAI 1) >8: 91 (90-93) (<-2.0) 2) >2: 17 (15-19) (<-2.0) 3) f>2: 6 (5-7) (<-2.5)	ORAI 1) >8: 23 (1926) (<-2.0) 2) >2: 93 (91-95) (<-2.0) 3) >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	NR

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
			population of women that was generally younger (by >10 years)	
Rud, 2005[109] Low	OST 1) <2: 100 (99-100) (<-2.5) 2) <5: 96 (93-97) (<-2.0) 3) <5: 99 (97-100) (<-2.5)	OST 1) <2: 2 (1-3) (<-2.5) 2) <5: 15 (14-17) (<-2.0) 3) <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)	NR
Rud, 2005[109] Low	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield Sn close to 90% and DXA at FN, TH, LS <-2.5 SCORE 1) NA (wrong DXA threshold) 2) Cutoff >3: 95 (92-97)	1) A priori cutoff based on developer cutoff and DXA outcome of T-score at FN <-2.5 2) Cutoff based on ROC analysis to yield Sn close to 90% and DXA outcome of lowest T-score at FN, TH, LS <-2.5 SCORE 1) NA (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)	NR
Shepherd, 2007[110] Low	NR	NR	Simulation study yielding number needed to screen to prevent 1 additional hip fracture in 10,000 men age ≥50 years (Table 5)	Abstracted data for validation cohort only.
Shepherd, 2010[113] Low	NR	NR	NR	Outcomes by race/ethnicity also provided
Sinnott, 2006[111] Low	OST <4 at femoral neck, total hip, or trochanter: 13 OST <2: 40%	OST <4 at femoral neck, total hip, or trochanter: 98 OST <2: 19%	NR	Score of 4 considered optimal for African American men
Zimering, 2007[112] Unclear	MSCORE age-weight (>9): 97	MSCORE age-weight (>9): 18	NR	Abstracted data for Caucasian validation cohort only. Also data for African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort so not pure external validation cohort.

Appendix F Table 1. Characteristics and results of studies of risk prediction instruments for identifying osteoporosis: KQ2

Author, Year Risk of Bias	NPV	PPV	Other Outcomes	Comments
Zimering, 2007[112] Unclear	MSCORE (>9): 98	MSCORE (>9): 16	NR	Abstracted data for Caucasian validation cohort only. Also data for African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort so not pure external validation cohort.
Zimering, 2007[112] Unclear	OST (<2 [established in elderly male population]): 96 OST (<3 [established in male veteran popualation]): 95	OST (<2 [established in elderly male population]): 22 OST (<3 [established in male veteran popualation]): 17	NR	Abstracted data for Caucasian validation cohort only. Also data for African American validation cohort, but combined data from 95 new subjects and 39 subjects from development cohort so not pure external validation cohort.

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 2. Characteristics and results of imaging studies predicting fractures

Study, Year Risk of Bias	Participant Characteristics	BMD Status; Baseline Fracture Rate	Inclusion/Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI)
Boonen et al, 2005[114] Low	Women Baseline mean age: 61 (50-75) Belgium N=221	41/221 (18.5%) had T-score <-2.5; proportion with baseline fractures NR	Included community-dwelling postmenopausal women consecutively referred to Leuven University Center for Metabolic Bone Diseases for bone densitometry. Excluded if receiving therapy for osteoporosis, including HRT, SERM, 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 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 (nondominant 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 nondominant hand against hip or spine T- score <-2.5	0.80 (SE, 0.03)
Kung et al, 2003[96] 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	Community-based study of Southern Chinese women ≤6 months postmenopausal. Excluded if history or evidence of metabolic bone disease (other than postmenopausal bone loss, hyper- or hypoparathyroidism, Paget's disease, osteomalacia, renal osteodystrophy, or osteogenesis imperfecta), menopause before age 40 years, presence of cancer with known metastasis to bone, evidence of significant renal impairment, ≥1 ovary removed, both hips previously fractured or replaced, and prior use of any bisphosphonates,	QUS, using Sahara ultrasound bone densitometer (Hologic, Waltham, MA) 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 2. Characteristics and results of imaging studies predicting fractures

Study, Year Risk of Bias	Participant Characteristics	BMD Status; Baseline Fracture Rate	Inclusion/Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI)
			fluoride, or calcitonin; abnormal biochemistry.				
Kung et al, 2005[97] 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	Community-based study of southern Chinese men in Hong Kong age ≥50 from 1999-2003. Excluded if history or evidence of metabolic bone disease (hyper- or hypoparathyroidism, Paget's disease, osteomalacia, renal osteodystrophy, or osteogenesis imperfecta), history of cancer in 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, MA) 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)
Jimenez-Nunez et al, 2013[95] Low	Women Mean age: 61 (SD, 8) Spain N=505	T-score: -1.01 (SD, 1.05); no nontraumatic fractures	Included Caucasian women age ≥50 years, menopausal ≥12 months, from tertiary care referred for routine bone density screening by DXA (recruited consecutively) at the Rheumatology Department of Carlos Haya University Hospital.	PIXI on nondominant heel, using GE Lunar PIXI densitometer (software 50699)	GE Lunar Prodigy Advance DXA densitometer (software ENCORE 2006, PA+ 300274; GE, 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)

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Risk of Bias	Participant Characteristics	BMD Status; Baseline Fracture Rate	Inclusion/Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI)
			Excluded if nursing home resident, homebound, or had any of the following: previous diagnosis of osteoporosis or history of >12 months with any potential antiosteoporotic drug (bisphosphonate, parathormone, estrogen, strontium ranelate, calcitonin, SERM), serious acute or chronic disease, steroid treatment in last 6 months, or bilateral hip replacement				
McLeod et al, 2015[102] Low	Women Mean age: 59.0 (50-80) Canada N=174	57.4% had osteoporosis or osteopenia; 22.4% with fracture after age 40 years	Included if referred by health care provider for DXA screening to the Regina General Hospital, Saskatchewan, Canada, July 2010 to 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)
						QUS T-score based on lumbar spine DXA T-score ≤-2.5	0.698 (0.077; 0.548-0.848)
Cook et al, 2005[88] unclear	Women Baseline mean age: 59.7 (29-87) UK 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 postmenopausal women recruited through DXA clinics at Great Western Hospital, Swindon, UK. All were referred due to presence of 1+ clinical risk factors for osteoporosis. No exclusion criteria.	QUS using Sunlight Omnisense ultrasound, measured at the distal radium proximal phalanx of the middle finger, and the midshaft 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 midshaft 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)

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Risk of Bias	Participant Characteristics	BMD Status; Baseline Fracture Rate	Inclusion/Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI)
						VOS calcaneus based on DXA T-score ≤-2.5	0.723 (0.781-0.676)
Harrison et al, 2006[94] Low	Women Mean age: 61 (SD, 4) UK N=207	Mean BMD at hip, FN, TH, LS (L1-L4) Non-osteoporotic patients: 0.463 (SD, 0.46) Osteoporotic patients: 0.369 (SD, 1.64)	Included 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 Corp, Madison, WI)	Central DXA of the hip, FN, TH, and LS (L1-L4) on the GE Lunar Prodigy (GE Lunar Corp, Madison, WI) or Hologic Discovery (Hologic Inc., Bedford, MA); T- and Z-scores from the 2 DXA scanners merged, then transformed into Hologic BMD values before calculation of T- and Z-scores using Hologic reference data for LS and NHANES reference data for 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[98] Low	Men Mean age NR US and Hong Kong N=6572 (4,658 US Caucasian men and 1914 Hong Kong Chinese men)	NR	Included community-dwelling older men (age >65 years) in the U.S. Similar for Hong Kong. Excluded if bilateral hip replacement or unable to walk without assistance.	Sahara clinical bone sonometer (Hologic Inc.) of the right calcaneus	BMD 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)
						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[115]	Women Baseline mean age: 59.7 (29-87)	23.8% had BMD T-score <-2.5 at any site; 32.3% had	Included postmenopausal Caucasian women recruited through DXA	QUS using Sunlight Omnisense ultrasound, measured at the distal radium proximal phalanx	BMD as measured by DXA at the lumbar spine; BMD values determined for the	Sunlight SOS distal radius based on DXA T-score ≤-2.5	0.72 (0.63-0.80)
						Sunlight proximal phalanx	0.68 (0.60-

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Risk of Bias	Participant Characteristics	BMD Status; Baseline Fracture Rate	Inclusion/Exclusion Criteria	Index Bone Measurement Test	Gold Standard Test	Location and Threshold of Index Test	AUC (95% CI)
Unclear	UK N=235	a history of nontraumatic fracture	clinics at Great Western Hospital, Swindon, UK. Excluded if disease known to cause secondary osteoporosis.	of the middle finger, and the midshaft tibia using SOS QUS using CUBA Clinical ultrasound measured by BUA and VOS at the calcaneus	lumbar spine, femoral neck, and total hip and the corresponding T-score calculated based on the NHANES database	SOS based on DXA T-score ≤-2.5	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[116] 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 healthy postmenopausal women age ≥45 years. 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., US)	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)
Sinnott et al, 2006[111] Low	Men Mean age: 63.8 (SD, 14.8) Chicago N=128	FN BMD (g/cm^2): 1.02 (SD, 0.18); 40% had prior traumatic fractures	Included African American men age ≥35 years, recruited from general medicine clinics at Jesse Brown VA Medical Center. Excluded if history or evidence of metabolic bone disease, traumatic fractures, history of any medical condition predisposing to low bone mass, history of cancer in prior 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 obtained using an Achilles Plus System (Lunar, Madison, WI); results include SOS, BUA, and a clinical index named the SI which is a linear combination of SOS and BUA	GE lunar machine (GE, Madison, WI) at the lumbar spine (L1–L4) and the nondominant 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;

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

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.

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
Cheung et al, 2012[136a] Hong Kong Osteoporosis Study	Women Baseline mean age: 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	0.711 (0.66-0.763) 0.855 (0.791-0.919)	None
Bolland et al, 2011[129a]	Women Baseline mean age: 74.2 (>55) New Zealand (N=1422)	Postmenopause, no major medical conditions, normal lumbar spine BMD for 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	0.64 (0.57-0.72) 0.59 (0.56-0.62)	None
Friis-Holmberg et al, 2014[134a] Danish Health Examination Survey cohort	Women and men Baseline age: 49.0 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	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
Kalvesten et al, 2016 [142] Study of Osteoporotic Fracture Low	Women Baseline mean age: 71 (65-80+) US (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

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
Leslie et al, 2010[133a] 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	DXA BMD femoral neck	0.801 (0.783-0.819)	None
					Osteoporotic: Hip, clinical vertebral, forearm, or humerus	DXA BMD femoral neck	0.679 (0.668-0.690)	
Lundin et al, 2015 [141] 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 and 1930, able to come to the health center	NR	Mean: 9.9	Hip	DXL BMD Heel DXA Femoral neck	0.61 0.66	None
Stewart et al, 2006[119] 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)	Postmenopause, may have received any treatment 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[128a] Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE)	Women Baseline mean age: 59.1 (47-56) Finland (N=2,755)	Postmenopause, 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

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
Tamaki et al, 2011[137a] 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: 0.706 (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[127a] Nagano Cohort Study	Women Baseline mean: 63.3 (SD, 10.8) Japan (N=765)	Postmenopausal outpatients at a medical institute receiving treatment for primary and secondary osteoporosis	Lumbar BMD Mean: 1.010 (0.191) Fracture rate: 11.6%	10 years; median followup 5.1 years	Long bone and vertebral fracture	DXA lumbar spine	0.598 (0.551-0.646)	None
					Vertebral fracture	DXA lumbar spine	0.613 (0.560-0.666)	
Tanaka et al, 2010[140a] 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[135a] 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[132a] Menopause et Os (MENOS) Study	Women Baseline age: >45 France (N=556)	Postmenopausal. 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

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
Sornay-Rendu et al, 2010[130a] Os des Femmes de Lyon (OFELY) cohort	Women Baseline mean Age: 58.8 (SD, 10.3) France (N=867; of these, N=680 postmenopausal	Post and premenopausal, age ≥40 years	Femoral neck Mean BMD: 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
Iki et al, 2014[121] Japanese Population-Based Osteoporosis (JPOS) Baseline Study Low	Women Followup mean age: 64.1 Baseline: (53-61) Japan (N=665)	Excluded: history or present condition affecting bone metabolism including glucocorticoids, 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 Mean BMD: 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 followup image vs baseline height; and satisfied McCloskey-Kanis criteria or grade 2 or 3 fracture criteria in Genant's method on followup 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[122] Leslie et al, 2013[123] The Manitoba Study Low	Women Baseline mean age: 65.4 years (≥50 years) Canada (N=29,407)	Medical coverage	Lumbar spine: Mean TBS: 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	0.71 (0.69-0.74)	

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
						spine		
					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 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
Kwok, 2012[124] 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 Mean BMD: 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[120] 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 (NR)	None
					Non-spine	DXA BMD femoral neck	0.68 (NR)	
					Non-spine	QUS BUA heel + BMD femoral neck	0.69 (NR)	
					Hip	QUS BUA heel	0.84 (NR)	
					Hip	DXA BMD femoral neck	0.85 (NR)	
					Hip	QUS BUA heel + BMD femoral neck	0.85 (NR)	
Chan et al, 2012[125] Dubbo Osteoporosis Epidemiology Study (DOES) Unclear for AUC, high For NRI	Men and Women Followup age range (62-89 years old) Australia Men (N=445) Women (N=454)	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 (0.66 to 0.76)	Age, falls, and prior fracture
						QUS BUA heel + DXA BMD femoral neck	0.73 (0.68 to 0.78)	
					Hip Fracture	DXA BMD femoral neck	0.77 (0.69 to 0.86)	
						QUS BUA heel + DXA BMD femoral neck	0.81 (0.73 to 0.88)	
					Vertebral fracture	DXA BMD femoral neck	0.70 (0.62 to 0.77)	
						QUS BUA heel + DXA BMD femoral neck	0.72 (0.65 to 0.79)	
					Men	DXA BMD femoral neck	0.71 (0.64 to 0.78)	Age, falls, and prior fracture

Appendix F Table 2. Characteristics and results of imaging studies predicting fractures

Study, Year Cohort Risk of Bias	Participant Characteristics	Additional Inclusion/ Exclusion Criteria	Baseline BMD Fracture Rate	Length of Followup	Type of Incident Fracture	Bone Measurement Test	AUC (95% CI)	Controlled Characteristics in Model
					Any fracture, excluding from major trauma	QUS BUA heel + DXA BMD femoral neck	0.71 (0.64 to 0.77)	
					Hip Fracture	DXA BMD femoral neck	0.77 (0.67 to 0.87)	
						QUS BUA heel + DXA BMD femoral neck	0.78 (0.67 to 0.88)	
					Vertebral fracture	DXA BMD femoral neck	0.75 (0.66 to 0.83)	
						QUS BUA heel + DXA BMD femoral neck	0.75 (0.66 to 0.84)	
Fraser et al, 2010[139a]	Men and women Baseline mean age: Women: 65.8 (8.8) Men: 65.3 (9.1) Canada N=6,697	Lived near one of 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[126] Dubbo Osteoporosis Epidemiology Study (DOES) Unclear	Women Mean age: 63.2 (49-88) Australia N=549	None	NR	Not reported	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 3. 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 Instrument (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Leslie et al, 2012[148] Unclear	Men and women age ≥50 years 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 [157] Unclear	Men age ≥65 yearsr 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 neck, 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[149] Unclear	Postmenopausal 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) Nonfracture 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 3. 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 Instrument (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Rubin, 2013[153] Unclear	Women ages 40 to 90 years 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 followup BMD testing for Fx risk ≥9.3% (10 year 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] and 2012[150] 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 (SD, 8.0)	BMD NR History of fracture: 22.8% Use of medication for osteoporosis: 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 (0.49 to 0.77) (p=0.067) BMD LS only, MOF: 0.64 (0.57 to 0.71) Without BMD, vertebral: 0.75 (0.64 to 0.86) With FN BMD, vertebral: 0.82 (0.73 to 0.91) With LS BMD, vertebral: 0.71 (0.58 to 0.84) Age alone, hip: 0.89 (p=0.976) Age alone, MOF: 0.67 (p=0.565)

Appendix F Table 3. 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 Instrument (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Leslie, 2012[152] Unclear	Women and men age ≥50 years 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[154] Unclear AUC, high for NRI	Men and women age ≥60 years from the Norwegian Tromso Cohort N=2992 55% women	Femoral neck BMD T-score Mean: -1.46 (SD, 1.19) (Nonfracture 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 3. 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 Instrument (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Hippisley-Cox, 2012[155] Unclear	Patients ages 30 to 100 years from a database of 13 million patients in 620 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 followup Number of OF: 28,685 Number of hip fractures: 9,610 Fractures recorded on 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[156] Unclear	Men and women ages 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 BMD 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% 10 yr 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 3. 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 Instrument (Prediction Interval)	Fracture Definition Used, Number of Fracture Events	Length of Cohort Followup	Summary of Results
Morin, 2009[103] Unclear	Women ages 40 to 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 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 followup 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 4. 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 Fracture Risk in Treatment Group; Risk in Control Group RR (95% C])	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; RR, 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 (0.39-0.80; p=0.002)	261/2214; 294/2218; RR, 0.88 (0.74-1.04; 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 al, 2003[202]	Postmenopausal women ages 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, 1995[203]	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
Hosking et al, 1998[215]	Women ≥6 months postmenopausal; mean age 53.3 years; mean T-score -0.1; prior fracture unknown	Alendronate 5 mg/day; 2 years	0/498; 0/502[§] RR not estimable	22/498;14/502[§] RR, 1.58 (0.82-3.06)	NR	NR	Fair
Quandt et al, 2005[205]	Women at least 2 years postmenopausal, ages 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 5. 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 Fracture Risk in Treatment Group; Risk in Control Group RR (95% CI)	Quality Rating
Reid et al, 2002 (#8413)	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 RR, 1.36 (0.15-11.89)	NR	NR	Fair
Boonen, 2012[218]	Men ages 50-85 years; 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 5 mg 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 (0.21-1.97)	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 6. Fracture outcomes of placebo-controlled primary prevention trials of risedronate

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)	Hip Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Incident Fracture Risk in Treatment Group; Risk in Control Group RR (95% CI)	Quality Rating
Hooper et al, 2005[227]	Women 6-36 months postmenopausal; mean age 53 years; mean lumbar T-score -0.7; unknown prior fracture	Risedronate 5 mg/day; 2 years	10/129; 10/125 RR, 0.97 (0.42-2.25)[a]	5/129; 6/125 RR, 0.81 (0.25-2.58)[a]	NR	NR	Fair
McClung et al, 2001[223]	Women age ≥70 years, mean femoral neck T-score -3.7	Risedronate 5 mg/day; 2 years treatment (mean followup 2.3 years)	NR	NR	137/6197; 95/3134 RR, 0.73 (0.56 to 0.94) Subgroup ages 70-79 without prevalent vertebral fracture[b] 14/1773; 12/875 RR, 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 (followup 3 years)	1/37; 0/36 RR, 2.92 (0.12-69.43)[a]	0/37; 3/36 RR, 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 RR, 0.49 (0.07-3.40)[a]	NR	NR	Fair
Fogelman et al, 2000[226c]	Postmenopausal women age <80 years, with mean lumbar T-score of ≤-2.0; mean age 65 years; 31% with vertebral fractures	Risedronate 5 mg/day; 2 years	8/112;17/125 RR, 0.53 (0.24 to 1.17)[a]	7/112;13/125 RR, 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 7. Fracture outcomes of placebo-controlled primary prevention trials of etidronate

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)	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 RR, 3.00 (0.13-70.53)	2/27; 3/27 RR, 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 8. Fracture outcomes of placebo-controlled primary prevention trials of raloxifene

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)	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) RR, 0.7 (0.5-0.8) 4 years 169/2259 (60 mg); 287/2292 (placebo)[a] RR, 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) RR, 0.63 (0.52-0.77)	3 years 437/4536 (both doses combined[b]); 240/2292 (placebo) RR, 0.9 (0.8-1.9) 4 years 548/4536 (both doses combined[b]); 296/2292 (placebo) RR, 0.93 (0.81-1.06)	3 years 40/4536 (both doses combined[b]); 18/2292 (placebo) RR, 1.1 (0.6-1.9) 4 years 56/4536 (both doses combined[b]); 29/2292 RR, 0.97 (0.62-1.52)	3 years Wrist fracture 151/4536 (both doses combined[b]); 86/2292 (placebo) RR, 0.9 (0.6-1.1) Ankle fracture 34/4536 (both doses combined[b]); 28/2292 (placebo) RR, 0.6 (0.4-1.0) 4 years Wrist fracture 180/4536 (both doses combined[b]); 109/2292 RR, 0.83 (0.66-1.05) Ankle fracture 54/4536 (both doses combined[b]); 29/2292 RR, 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 9. 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 Fracture 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 <-2.5: n=120 (29.1%) Total hip T-score of <-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 RR, 3.73 (0.22 to 61.96] Clinical fractures 21/314; 1/46 RR, 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 RR, 0.29 (0.06 to 1.36)	Fair
Cummings et al, 2009[238]	Women ages 60-90 years with BMD T-score of <-2.5 but not <-4.0 at the lumbar spine or total hip	Denosumab 60 mg every 6 months for 36 months subcutaneously	86/3702;264/3691 RR, 0.32 (0.26 to 0.41)[b]	238/3902; 293/3906 RR, 0.80 (0.67 to 0.95)[c]	26/3902; 43/3906 RR, 0.60 (0.37 to 0.97)[c]	New clinical vertebral fracture 29/3902; 92/3906 RR, 0.31 (0.20 to 0.47)[c] Multiple (≥2) new vertebral fractures 23/3702; 59/3691 RR, 0.39 (0.24 to 0.63)[b]	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 10. 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 Fracture Risk in Treatment Group; Risk in Control Group RR (95% CI)	Quality Rating
Greenspan et al, 2007 [36]	Postmenopausal women with mean age 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[239]	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 11. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
Cummings et al, 1998[200]	Women at least 2 years postmenopausal, ages 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 ages 60-90 years with osteoporosis defined by lumbar spine or total hip BMD T-score <-2.5 or both <-2.0; mean age 69 years; 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 GI 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 11. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
Johnell et al, 2002[244]	Postmenopausal women, age <75 years; >2 years since 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[245]	Cases of women with atrial fibrillation and flutter compared with 5 controls matched on age, sex, and county from Danish registry[a] Osteoporosis rates: 1209 (8.9%) of case participants 5328 (7.8%) of control participants	Any bisphosphonates	NR	NR	NR	435/13,586 cases (3.2%) and 1958/68,054 population controls (2.9%) RR for new users: 0.75 (0.49-1.16)	Good
Cummings et al, 2008[246]	Women at least 2 years postmenopausal, ages 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
Ascott-Evans et al, 1995 (#8399)	Postmenopausal women age <80 years with 85% of enrollees age <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 AE 60/95; 30/49 RR, 0.99 (0.76-1.29)	Fair
Chesnut et al, 1995[203]	Women≥ 5 years post-menopausal; ages 43-75 years 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

Appendix F Table 11. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
Hosking et al, 1998[215]	Women ≥6 months postmenopausal; mean age 53.3 years; mean T-score -0.1; prior fracture unknown	Alendronate 5 mg/day or placebo; 2 years	67/997; 27/503 RR, 1.25 (0.81-1.93)	NR	Upper GI AE, any type: 300/997; 148/502 RR, 1.02 (0.87-1.21)	CV AE: 99/997; 47/502 RR, 0.11 (0.05-0.22)	Fair
Greenspan et al, 2003[247]	Women ages 65-90 years; mean age 71.5; baseline femoral neck T-score -1.7; baseline fracture rate NR	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[248]	Postmenopausal women, ≥6 months after last menses, age ≥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 AE: 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 Nonserious upper GI bleed: 1/291; 0/147	Any AE: 166/291; 76/147; RR, 1.10 (0.92-1.33) Death: 0/291; 0/147	Fair
Greenspan et al, 2003[252]	Postmenopausal women or men with osteoporosis determined by BMD or clinical diagnosis; mean age 67; 92% female; baseline antiresorptive use 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 AE: 104/224; 97/226; RR, 1.08 (0.88-1.33)	Fair

Appendix F Table 11. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
Bauer et al, 2000[249]	Women at least 2 years postmenopausal, ages 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; RR, 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 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
Cryer et al, 2005[250]	Postmenopausal women, ≥6 months after last menses, age ≥40 years (or 25 years if surgical menopause) with low BMD defined as T-score <-2.0 below young mean bone mass at 1 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 to 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

Appendix F Table 11. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
Tucci, et al, 1996[251]	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 NR	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
Eisman et al, 2004[253]	Postmenopausal women and men with osteoporosis (as determined by investigators); mean age 63.6 years; 93%-96% female; baseline fracture rate NR	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 12. Harms 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[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 AE: 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 ages 50 to 85 years; 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 5 mg of zoledronic acid at baseline and 12 months; 24 months	NR	149/588; 154/611 RR, 1.01 (0.83-1.22)	NR	Any AE: 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 (1.01-21.55) 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[272]	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 12. Harms 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR (95% CI)	Other Adverse Events	Quality Rating
McClung et al, 2009[273]	Postmenopausal women age ≥45 years who had low bone mass, defined as BMD T-score <-1.0 and >-2.5 at the lumbar spine and BMD T-score >-2.5 at 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 AE: 186/189; 173/181; 186/202; RR (G1/G3), 0.98 (0.94-1.03); RR (G2/G3), 1.038 (0.99-1.09) Myalgia: 38/189; 41/181; 14/202; RR (G1/G3), 2.77 (1.55-4.95); RR (G2/G3), 3.27 (1.84-5.79) Arthralgia: 54/189; 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: 0/189; 0/181; 0/202 Atrial fibrillation: 0/189; 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 13. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[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
Hooper et al, 2005[227]	Women 6-36 months postmenopausal; mean age 53 years; mean lumbar T-score -0.7; unknown prior fracture	Risedronate 5 mg/day; 2 years	7/129; 6/125 RR,1.13 (0.39 to 3.27)	12/129; 22/125 RR, 0.53 (0.27 to 1.02)	Upper GI event: 25/129; 20/125; RR, 1.21 (0.71 to 2.06)	NR	Fair
McClung et al, 2001[223]	Women age ≥70 years; results only reported 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 followup 2.3 years)	550/3104; 564/3134 RR, 0.98 (0.89 to 1.10)	943/3104; 973/3134 RR, 0.98 (0.91 to 1.05)	Upper GI event: 657/3104; 684/3134 RR, 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 (followup 3 years)	3/37;2/36 RR, 1.46 (0.26 to 8.23)	NR	Dyspepsia: 6/37;10/36 RR, 0.59 (0.24 to 1.44) Abdominal pain: 3/37;4/36; RR, 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 RR, 0.53 (0.23 to 1.23)	12/114 ; 3/56 RR, 1.97 (0.58 to 6.68)	Upper GI event: 21/115; 14/55; RR, 0.72 (0.40 to 1.30)	NR	Fair
Fogelman et al, 2000[b226]	Postmenopausal women age <80 years, mean lumbar T-score <-2.0; mean age 65 years; 31% with vertebral fractures	Risedronate 5 mg/day; 2 years	19/175; 14/173 RR, 1.34 (0.70 to 2.59)	26/173; 27/180 RR, 1.00 (0.61 to 1.65)	Upper GI event: 40/174; 47/180; 0.88 (0.61 to 1.27)	NR	Fair

Appendix F Table 13. 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 AE Risk in Treatment Group; Risk in Control Group RR (95% CI)	Gastrointestinal AE[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
Shiraki et al, 2003[281]	Mostly women ages 40-75 years with senility and postmenopausal osteoporosis; mean age 60.3 years; mean # 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
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 RR, 1.26 (0.67 to 2.35)	15/222; 12/108 RR, 0.61 (0.30-1.25)	Upper GI event: 1/222; 29/108; RR, 1.02 (0.70-1.49)	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 14. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[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 RR, 11.23 (0.64 to 200.68)	8/75; 7/77 RR, 1.17 (0.44 to 3.07)	GI AE events: 9/75; 17/77 RR, 0.54 (0.26 to 1.14)	Infection: 18/74; 22/76 RR, 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 RR, 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); RR, 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 15. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other Adverse Events	Quality Rating
Chapurlat et al, 2013[282]	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 AE (including fractures): 4/71; 6/76 RR, 0.71 (0.21 to 2.42)	15/71; 13/76 RR, 1.23 (0.63 to 2.41)	NR	NR	Fair
McClung et al, 2004[283]	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 due to AE: 5/161; 5/165; 7/163; 9/159 RR, 0.55 (0.19 to 1.60) RR, 0.54 (0.18 to 1.56) RR, 0.76 (0.29 to 1.99) Percentage of all subjects who withdrew from study medication because of 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 AE: 6/161; 13/165; 5/163; 8/159 RR, 0.74 (0.26 to 2.09) RR, 1.57 (0.67 to 3.68) RR, 0.61 (0.20 to 1.82) Any drug-related serious AE: 0/161; 0/165; 0/163; 0/159 RR, not calculable	Dyspepsia: 16/161; 14/165; 15/163; 14/159 RR, 1.13 (0.57 to 2.23) RR, 0.96 (0.47 to 1.96) RR, 1.05 (0.52 to 2.09) Gastroenteritis: 9/161; 4/165; 5/163; 6/159 RR, 1.48 (0.54 to 4.07) RR, 0.64 (0.18 to 2.23 RR, 0.81 (0.25 to 2.61) Nausea: 6/161;1/165; 4/163; 3/159 RR, 1.98 (0.50 to 7.76) RR, 0.32 (0.03 to 3.06) RR, 1.30 (0.30 to 5.72) GI pain: 2/161; 0/165; 4/163; 4/159 RR, 0.49 (0.09 to 2.66) RR, 0.11 (0.01 to 1.98) RR, 0.98 (0.25 to 3.83) GI disorder: 1/161; 2/165; 0/163; 3/159 RR, 0.33 (0.03 to 3.13) RR, 0.64 (0.11 to 3.79) RR, 0.14 (0.01 to 2.68) Eructation: 1/161; 1/165; 1/163; 1/159 RR, 0.99 (0.06 to 15.65)	NR	Fair

Appendix F Table 15. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other Adverse Events	Quality Rating
					RR, 0.96 (0.06 to 15.28) RR, 0.98 (0.06 to 15.47) Gastritis: 0/161; 1/165; 2/163; 1/159 RR, 0.33 (0.01 to 8.02) RR, 0.96 (0.06 to 15.28) RR, 1.95 (0.18 to 21.30) Dysphagia: 2/161; 1/165; 1/163; 0/159 RR, 4.94 (0.24 to 102.06) RR, 2.89 (0.12 to 70.46) RR, 2.91 (0.12 to 71.32) Vomiting: 2/161; 0/165; 1/163; 0/159; RR, 4.94 (0.24 to 102.06) 1 mg vs. placebo: RR not calculable [2.92 (0.12 to 71.32)] Esophagitis: 1/161; 0/165; 1/163; 1/159 RR, 0.99 (0.06 to 15.65) RR, 0.32 (0.01 to 7.83) RR, 0.98 (0.06 to 15.46) GI carcinoma: 0/161; 0/165; 1/163; 0/159 0.5 mg vs. placebo: RR not calculable 1 mg vs. placebo: RR not calculable [0.98 (0.02 to 49.17)] GI hemorrhage: 0/161; 0/165; 0/163; 1/159 RR, 0.33 (0.01 to 8.02)		

Appendix F Table 15. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other Adverse Events	Quality Rating
					RR, 0.32 (0.01 to 7.83) RR, 0.33 (0.01 to 7.92) Hemorrhage gastritis: 1/161; 0/165; 0/163; 0/159 RR, 2.96 (0.12 to 72.20) 1 mg vs. placebo: RR not calculable 2.5 mg vs. placebo: RR not calculable RR, 0.96 (0.02 to 48.29) RR, 0.98 (0.02 to 48.87)		
Ravn et al, 1996[284]	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 RR, 0.50 (0.05 to 5.22) RR, 2.00 (0.40 to 10.11) RR, 1.00 (0.15 to 6.64) RR, 0.20 (0.01 to 4.00) RR, 3.00 (0.66 to 13.69)	1/30; 1/30; 0/30; 2/30; 1/30; 3/30 RR, 0.33 (0.04 to 3.03) RR, 0.33 (0.04 to 3.03) RR, 0.14 (0.01 to 2.65) RR, 0.67 (0.12 to 3.71) RR, 0.33 (0.04 to 3.03)	GI AE: 12/30; 17/30; 8/30; 5/30; 17/30; 11/30 RR, 1.09 (0.57 to 2.07) RR, 1.55 (0.88 to 2.72) RR, 0.73 (0.34 to 1.55) RR, 0.45 (0.18 to 1.15) RR, 1.55 (0.88 to 2.72) Diarrhea: 6/30; 5/30; 2/30; 2/30; 9/30; 2/30 RR, 3.00 (0.66 to 13.69) RR, 2.50 (0.53 to 11.89) RR, 1.00 (0.15 to 6.64) RR, 1.00 (0.15 to 6.64) RR, 4.50 (1.06 to 19.11)	Infection: 1/26; 0/22; 0/26; 0/24; 0/18; 0/25 RR, 2.89 (0.12-67.76) RR, 1.13 (0.02-54.72) RR, 0.96 (0.02-46.76) RR, 1.04 (0.02-50.43) RR, 1.37 (0.03-65.94) Death: 0/26; 0/22; 0/26;1/24; 0/18; 1/25 RR, 0.32 (0.01-7.53)	Fair

Appendix F Table 15. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other Adverse Events	Quality Rating
Reginster, et al, 2005[285]	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 RR, 0.39 (0.02 to 7.71) RR., 0.39 (0.02 to 7.71) RR, 0.20 (0.01 to 4.03) RR, 0.50 (0.05 to 5.27) Any drug-related AE leading to withdrawal: 0/18; 0/18; 0/36; 1/36; 2/36 RR, 0.39 (0.02 to 7.71) RR, 0.39 (0.02 to 7.71) RR, 0.20 (0.01 to 4.03) RR, 0.50 (0.05 to 5.27)	0/18; 0/18; 0/36; 0/36; 0/36 RR not calculable	Upper GI AE within 3 days of treatment: 0/18; 4/18; 8/36; 9/36; 6/36 RR, 0.15 (0.01 to 2.52) RR, 1.33 (0.43 to 4.13) RR, 1.33 (0.51 to 3.46) RR, 1.50 (0.60 to 3.78) Upper GI AE any time during treatment: 3/18; 11/18; 15/36; 15/36; 12/36 RR, 0.50 (0.16 to 1.55) RR, 1.83 (1.02 to 3.31) RR, 1.25 (0.68 to 2.28) RR, 1.25 (0.68 to 2.28)	Death: 0/18; 0/18; 0/36; 0/36; 0/36 RR, 1.95 (0.04 to 94.37) RR, 1.94 (0.04 to 94.37) RR, 1.00 (0.02 to 49.08) RR, 1.00 (0.02 to 49.08)	Fair
Riis et al, 2001[286]	Women at least 5 years postmenopausal; mean age 67 years; average spinal T-score <-3.2; unknown prior fracture	Continuous therapy with 2.5 mg ibandronate daily or intermittent cyclical therapy with 20 mg ibandronate every other day for first 24 days 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 first 12 months, ibandronate-treated groups showed a numerically higher incidence of diarrhea vs. placebo groups. Incidence of diarrhea was lower during the second year	Death: 1/81; 0/78; 1/81 RR, 1.00 (0.06 to 15.72) RR, 0.35 (0.01 to 8.37)	Fair

Appendix F Table 15. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other Adverse Events	Quality Rating
Tanko et al, 2003[287]	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 AE 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 AE: 6%; 5%; 3%; 3%	NR	Fair
Thiebaud et al, 1997[288]	Women at least 5 years postmenopausal; mean age 64 years; mean T-score 0.71 at 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 nondrug related serious AEs	6/24; 6/27; 7/26; 3/23; 4/26 No differences between groups RR, 1.63 (0.52 to 5.07) RR, 1.44 (0.46 to 4.54) RR, 1.75 (0.58 to 5.27) RR, 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 16. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Quality Rating
Johnell et al, 2002[244]	Postmenopausal women; mean age 63.6 years (≤75); T-score ≤-2.0	Raloxifene, 60 mg/day; 1 year	7/82; 4/82 RR, 1.75 (0.53-5.75)	None reported	Hot flashes: 4/82; 4/82: RR, 1.00 (0.26-3.86) Sweating: 1/82; 2/82; RR, 0.50 (0.05-5.41) Abdominal pain: 6/82; 5/82; RR, 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[308], Barrett-Connor et al, 2004[307], Keech et al, 2005[309], Cauley et al, 2001[310], Sontag et al, 2010[241]	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 and 4 years	3 years: 527/5129 (both doses combined[a]); 227/2576 (placebo); RR, 1.17 (1.01-1.35) 4 years: 327/2557 (60 mg); 285/2576 (placebo); RR, 1.16 (1.00-1.34)	3 years VTE events: 25/2557 (60 mg); 8/2576 (placebo); RR, 3.15 (1.42-6.97) 4 years VTE events All participants: 33/2557 (60 mg); 17/2576 (placebo); RR, 1.78 (0.99-3.19) Participants without baseline vertebral fracture: 17/1574 (60 mg); 13/1629 (placebo); RR, 1.35 (0.66-2.78) DVT All participants: 20/2557 (60 mg); 8/2576 (placebo); RR, 2.52 (1.11-5.71) Participants without baseline vertebral fracture: 12/1574 (60 mg); 6/1629 (placebo); RR, 21.07 (0.78-5.50) CHD: 50/5127 (both doses combined[a]); 28/2576 (placebo); HR, 0.88 (0.56-1.40) Stroke: 22/2557 (60 mg); 32/2576 (placebo); RR, 0.69	3 years Flu syndrome: 346/2557 (60 mg); 293/2576 (placebo); RR, 1.19 (1.03-1.38) Hot flashes: 249/2557 (60 mg); 165/2576 (placebo); RR, 1.52 (1.26-1.84) Leg cramps: 178/2557 (60 mg); 96/2576 (placebo); RR, 1.87 (1.47-2.38) Peripheral edema: 134/2557 (60 mg); 114/2576 (placebo); RR, 1.18 (0.93-1.51) Endometrial cavity fluid: 60/2557 (60 mg); 43/2576 (placebo); RR, 1.41 (0.95-2.07) 4 years Flu syndrome: 415/2557 (60 mg); 360/2576 (placebo); RR, 1.16 (1.02-1.32) Hot flashes All participants: 272/2557 (60 mg); 183/2576 (placebo); RR, 1.50 (1.25-1.79) Participants without baseline	Good

Appendix F Table 16. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Quality Rating
				(0.40-1.18) Pulmonary embolism All participants: 11/2557 (60 mg); 4/2576 (placebo); RR, 2.77 (0.88-8.69) Participants without baseline vertebral fracture: 6/1574 (60 mg); 3/1629 (placebo); RR, 2.07 (0.52-8.26) Retinal vein thrombosis: 2/2557 (60 mg); 5/2576 (placebo); RR, 0.40 (0.08-2.08) Any coronary event: 45/2557 (60 mg); 55/2576; RR, 0.82 (0.56-1.22) Any cerebrovascular event: 37/2557 (60 mg); 41/2576 (placebo); RR, 0.91 (0.58-1.41) Any cardiovascular event: 82/2557 (60 mg); 96/2576 (placebo); RR, 0.86 (0.63-1.18) Any cardiovascular event (in women at increased risk): 28/359 (60 mg); 41/317 (placebo); RR, 0.60 (0.38-0.95) Endometrial cancer: 5/2557 (60 mg); 5/2576 (placebo); RR, 1.01 (0.29-3.48)	vertebral fracture: 158/1574 (60 mg); 103/1629 (placebo); RR, 1.59 (1.25-2.01) Leg cramps: 234/2557 (60 mg); 154/2576 (placebo); RR, 1.53 (1.26-1.86) Peripheral edema All participants: 182/2557 (60 mg); 158/2576 (placebo); RR, 1.16 (0.94-1.43) Participants without baseline vertebral fracture: 104/1574 (60 mg); 80/1629 (placebo); RR, 1.34 (1.01-1.79) Endometrial cavity fluid: 99/2557 (60 mg); 76/2576 (placebo); RR, 1.31 (0.98-1.76) Diabetes: 38/2557 (60 mg); 17/2576 (placebo); RR, 2.25 (1.27-3.98)	

Appendix F Table 16. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Quality Rating
McClung et al, 2006[303]	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 RR, 0.98 (0.51-1.86)	Any serious AE: 14/163; 4/83 RR, 1.78 (0.61-5.24)	Hot flashes: 39/163; 17/83; RR, 1.30 (0.68-2.47) Leg cramps: 28/163; 11/83; RR, 1.17 (0.70-1.93) Vaginal bleeding: 3/163; 3/83; RR, 0.51 (0.10-2.47)	Fair
Meunier et al, 1999[304]	Postmenopausal women, mean age 60.2 years (range, 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 RR, 0.67 (0.16-2.80)	DVT: 0/45; 0/40 RR not calculable	Hot flashes: 4/45; 4/40; RR, 0.89 (0.24-3.32) Change in endometrial thickness (mm): mean, 0.49±1.45; mean, 0.44±1.47 (p=NS)	Good
Miller et al, 2008[305]	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 RR, 0.89 (0.61-1.31)	Any serious AE: 29/311; 28/310; RR, 1.03 (0.63-1.69) Myocardial infarction: 0/311; 1/310; RR, 0.33 (0.01-8.12) DVT: 0/311; 1/310; RR, 0.33 (0.01-8.12) Retinal vein thrombosis: 1/311; 0/310; RR, 2.99 (0.12-73.13)	Hot flashes: 58/311; 44/310 RR, 1.31 (0.92-1.88) Leg cramps: 37/311; 36/310 RR, 1.02 (0.67-1.58)	Fair
Morii et al, 2003[306]	Postmenopausal women; mean age raloxifene group 65.2 years, mean age placebo group 64.3 years (≤80 years); lumbar T-score ≤2.5; 26% prior vertebral fracture	Raloxifene 60 mg/day; 1 year	7/92; 3/97 RR, 2.36 (0.63-8.85)	Any serious AE: 5/92; 7/97 RR, 0.75 (0.25-2.29) VTE: 0/92; 0/97; RR not calculable Colitis ischaemic: 1/92; 1/97 RR, 1.05 (0.07-16.61) Gastrointestinal disorder NOS: 0/92; 0/97; RR not calculable	No events of interest reported	Fair

Appendix F Table 16. 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 AE Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Other AE[a] Risk in Treatment Group; Risk in Control Group RR, (95% CI)	Quality Rating
				Oesophageal carcinoma NOS: 0/92; 1/97; RR, 0.35 (0.01-8.51) Dissecting aortic aneurysm: 1/92; 0/97; RR, 3.16 (0.13-76.63) Hypertension NOS: 0/92; 1/97; RR, 0.35 (0.01-8.51)		

[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 17. 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 AE Risk in Treatment Group; Risk in Control Group RR [95% CI]	Gastrointestinal AE[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	42/314; 4/46 RR, 1.54 [0.58 to 4.09]	11/314; 1/46 RR, 1.61 [0.21 to 12.19]	1/314; 0/46	Death: 1/314; 0/46 Cardiac disorder: 6/314; 2/46; RR, 0.45 [0.02 to 10.83] Serious infection: 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 RR, 0.50 [0.05 to 5.49]	18/164; 9/165 RR, 2.01 [0.93 to 4.35]	2/164; 0/165	Death: 0/164; 0/165 RR not calculable Rash: 14/164; 5/165 RR, 2.82 [1.04 to 7.64] Serious infection: 8/164; 1/165	Fair
Cummings et al, 2009[238] Watts et al, 2012[311]	Women ages 60 to 90 years with a BMD T-score <-2.5 at the lumbar spine or total hip	Denosumab 60 mg every 6 months for 36 months subcutaneously	93/3886; 81/3876 RR, 1.15 [0.85 to 1.54]	1004/3886; 972/3876 RR, 1.03 [0.95 to 1.11]	NR	Death: 70/3886; 90/3876; RR, 0.78 [0.57 to 1.06] Osteonecrosis of the jaw: 0/3886; 0/3876; RR not calculable Cardiovascular events 186/3886; 178/3876; RR, 1.04 [0.85 to 1.27] Eczema: 118/3886; 65/3876; RR, 1.81 [1.34 to 2.44] Serious infection: 159/3886;133/3876; RR, 1.19 [0.95 to 1.49]	Fair

Appendix F Table 17. 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 AE Risk in Treatment Group; Risk in Control Group RR [95% CI]	Gastrointestinal AE[a] Risk in Treatment Group; Risk in Control Group RR [95% CI]	Other Adverse Events	Quality Rating
						Serious skin infection (cellulitis and erysipelas): 15/3886; 1/3876; RR, 14.96 [1.98 to 113.21]	

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[239]	Men with mean age 59 years; mean T-score -2.7; unknown prior fracture	Teriparatide 20 or 40 µg daily injection; mean treatment duration: 11 months	14/151 (20 µg); 18/139 (40 µg); 7/147 (placebo) RR, 1.94 (0.81-4.69) RR, 2.72 (1.17-6.3)	Cancer: 3/151 (20 µg); 0/139 (40 µg); 3/147 (placebo) RR, 0.97 (0.20-4.74) RR, 0.15 (0.008-2.900)	Nausea: 0/151(20 µg); 5/139 (40 µg); 0/147 (placebo)	Fair

Abbreviations: RR= risk ratio; ug= micrograms

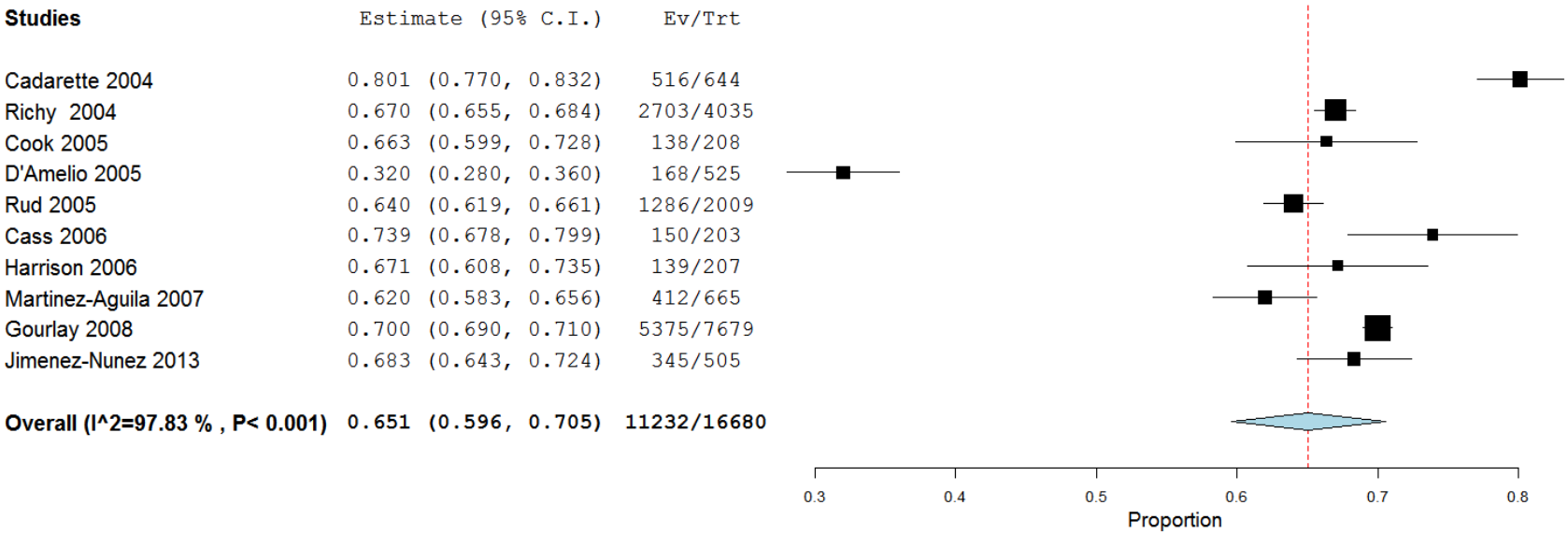
Appendix G Table 1. Completed trials

Principal Investigators	Location	Population	Approximate Size	Investigations	Outcomes	Status as of 2017
Hyoung-Moo Park	Seoul, Republic of Korea	Women, postmenopausal	150	Risedronate combined, Risedronate, 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, age <80 years, postmenopausal with osteoporosis		Raloxifene HCL 60 mg, Raloxifene 120 mg, 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	Females ages 45 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 2 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	Females ages 45 to 70 years with osteoporosis	50	Teriparatide, Placebo	Bone mineral density will be measured at 6 and 12 months	Completed, not published

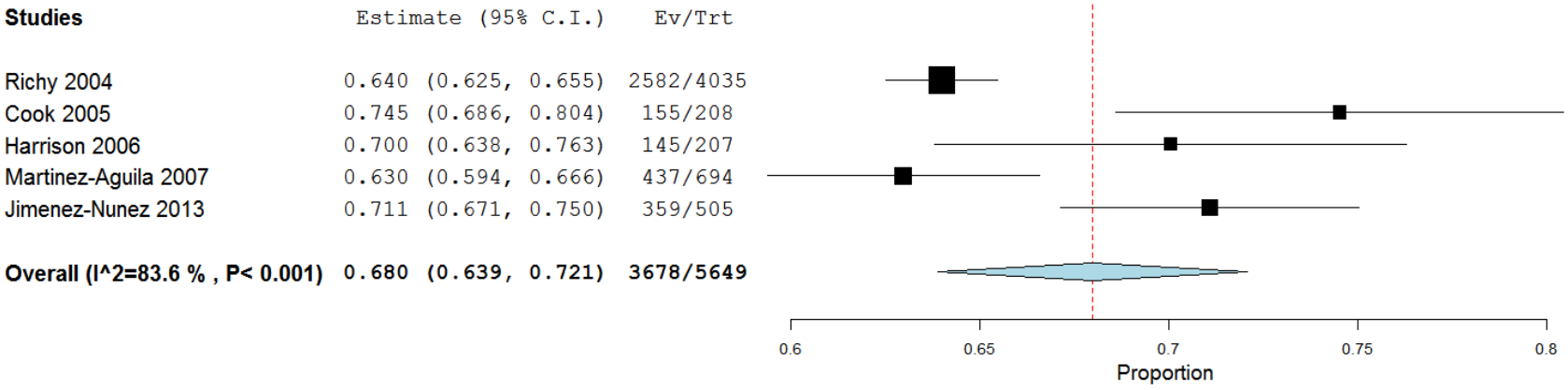
Appendix G Table 2. Ongoing trials

Principal Investigators	Location	Population	Approximate Size	Investigations	Outcomes	Status as of 2017
Sudhaker D Rao, MD, Henry Ford Health System	United States	Women age 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 age 65 years and older	1000	(Zoledronic Acid) Zoledronic acid for osteoporotic fracture prevention (ZEST II)	Total nontraumatic 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 [Time Frame: Baseline and 12 months] [Designated as safety issue: Yes]	Recruiting
Susan L. Greenspan, University of Pittsburgh	United States	Men and women age 65 years and older	212	Preventing osteoporosis using denosumab (PROUD)	Increased bone density of the total hip/spine	Recruiting

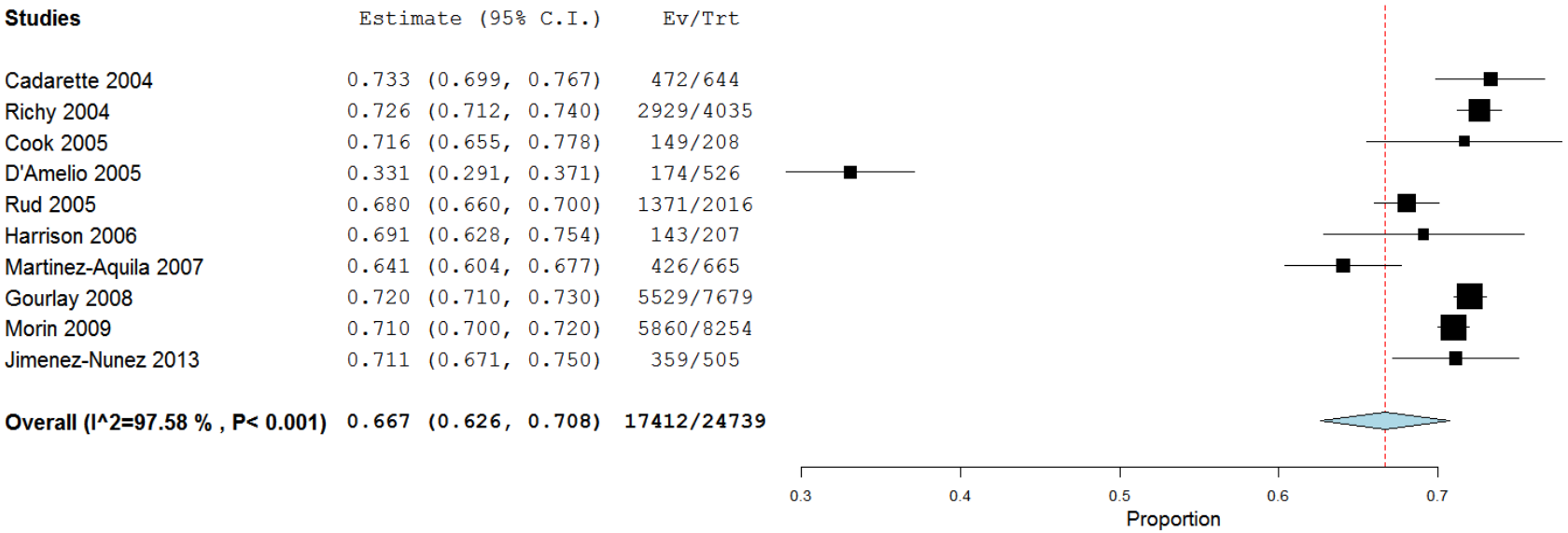
Appendix H Figure 1. Osteoporosis Risk Assessment Instrument (ORAI) in women



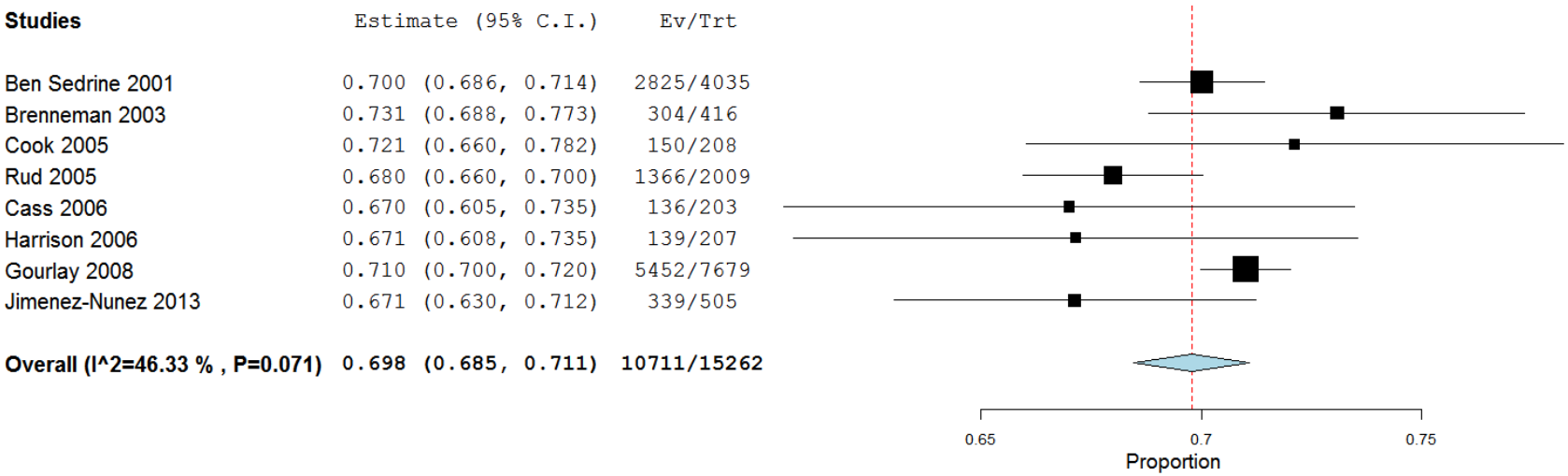
Appendix H Figure 2. Osteoporosis Index of Risk (OSIRIS) in women



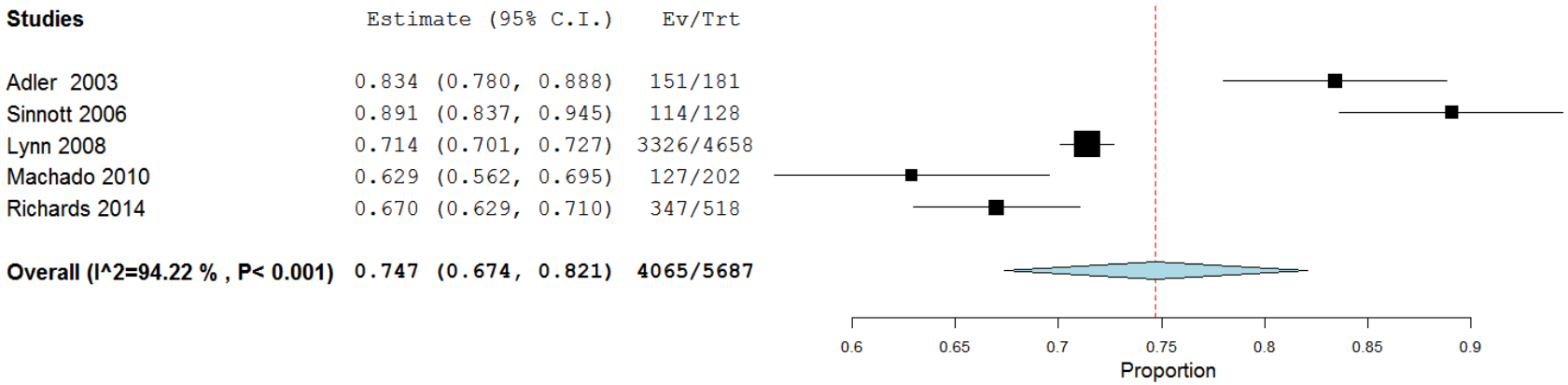
Appendix H Figure 3. Osteoporosis Self-Assessment Tool (OST) in women



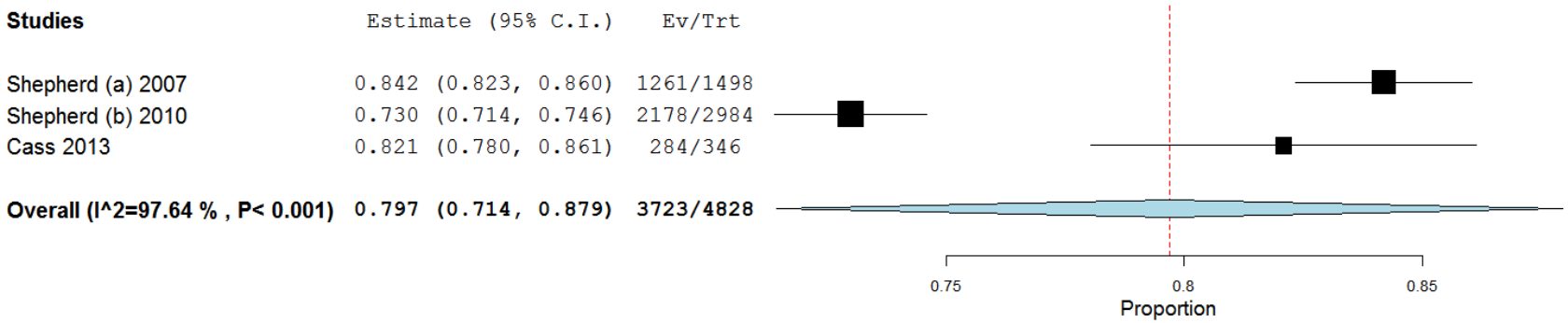
Appendix H Figure 4. Simple Calculated Osteoporosis Risk Estimation (SCORE) in women



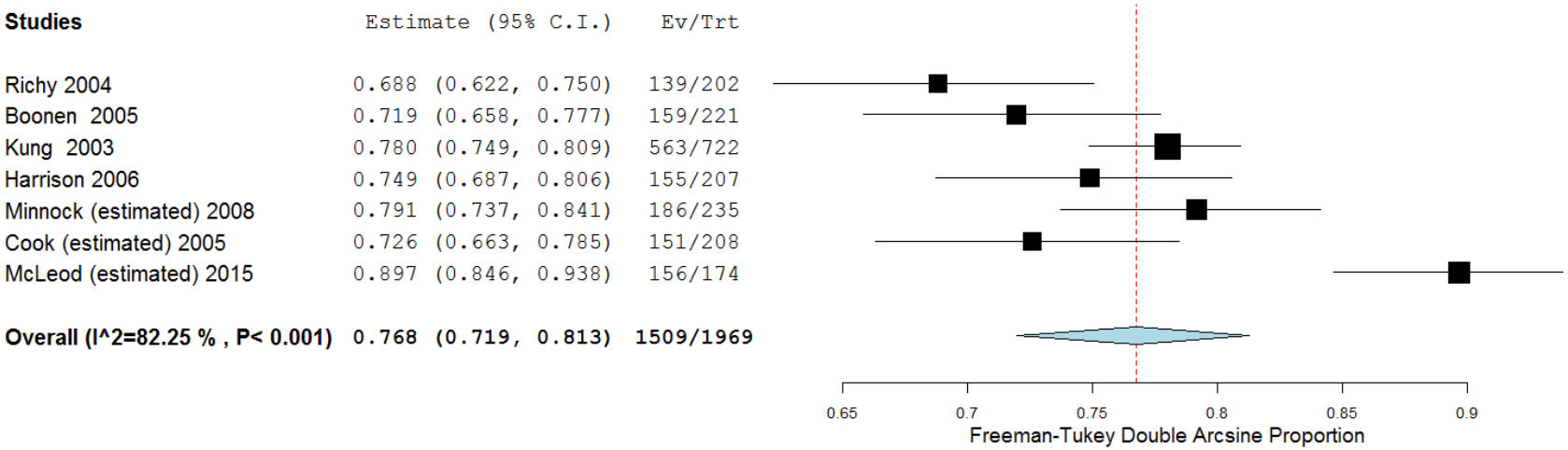
Appendix H Figure 5. OST in men



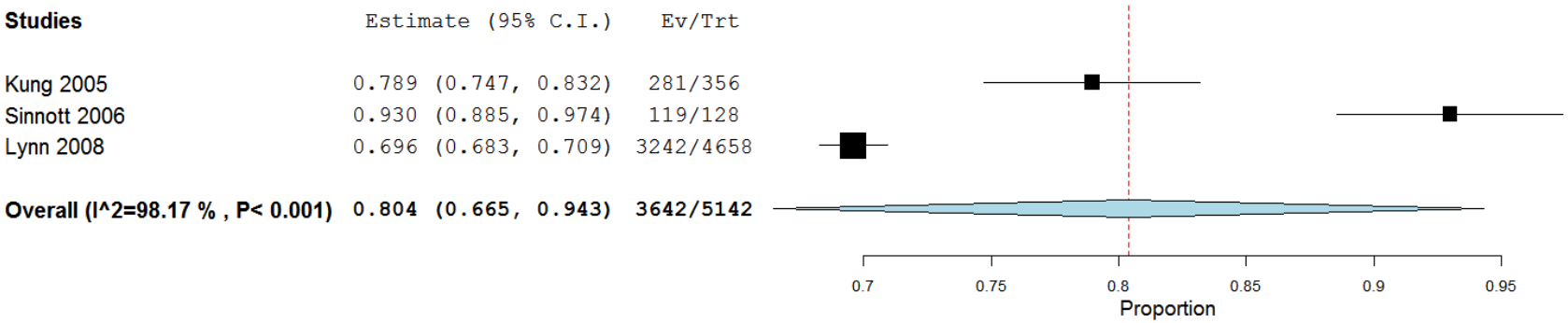
Appendix H Figure 6. Male Osteoporosis Risk Estimation Score (MORES) in men



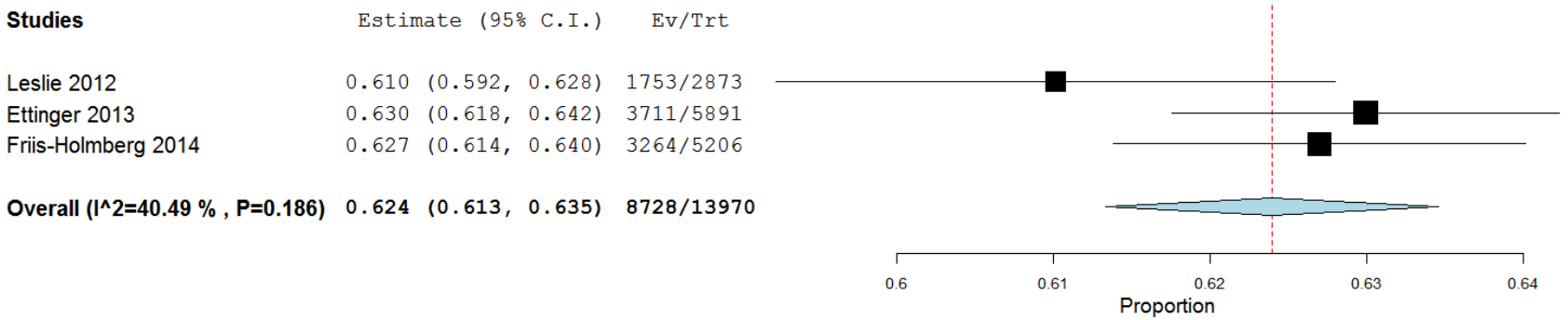
Appendix H Figure 7. Quantitative ultrasound for screening osteoporosis for women



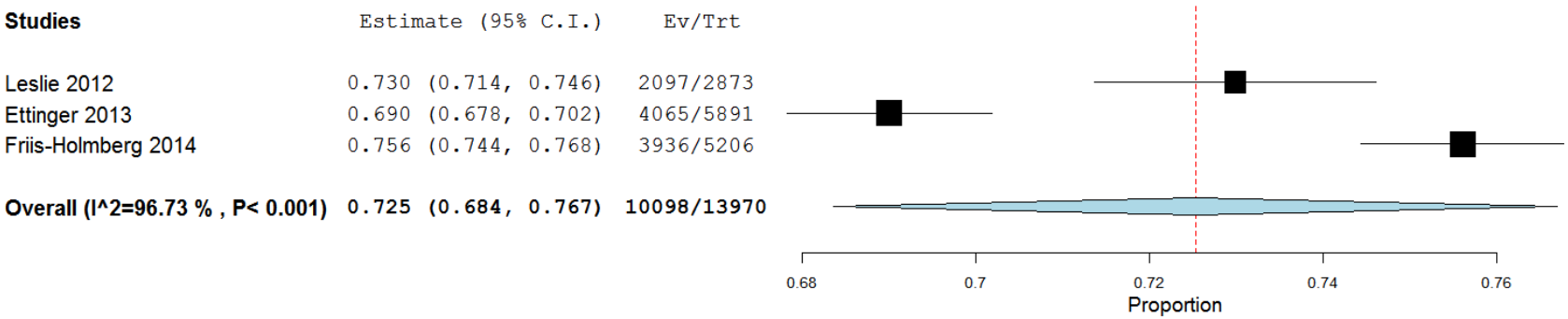
Appendix H Figure 8. Quantitative ultrasound for screening osteoporosis for men



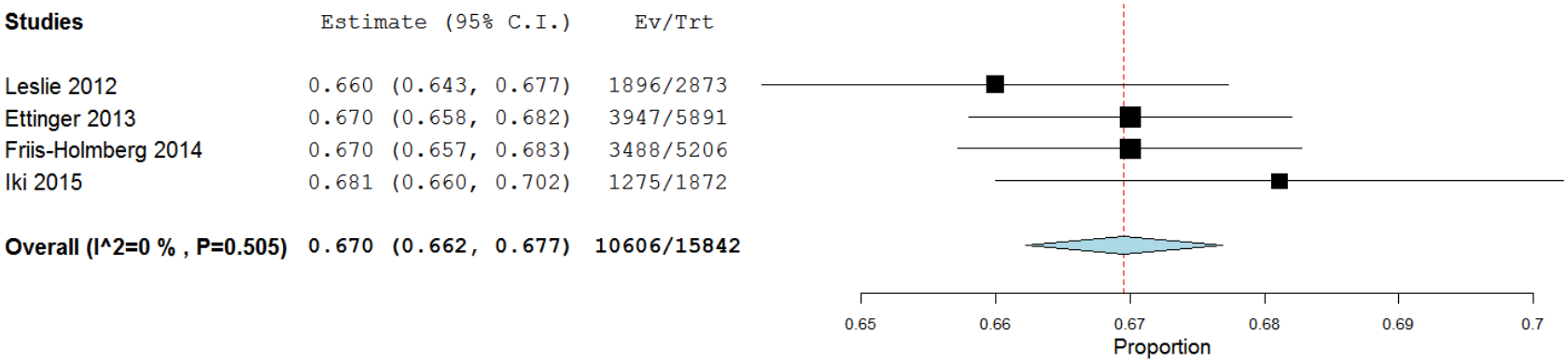
Appendix H Figure 9. FRAX without bone mineral density testing for predicting major osteoporotic fractures in men



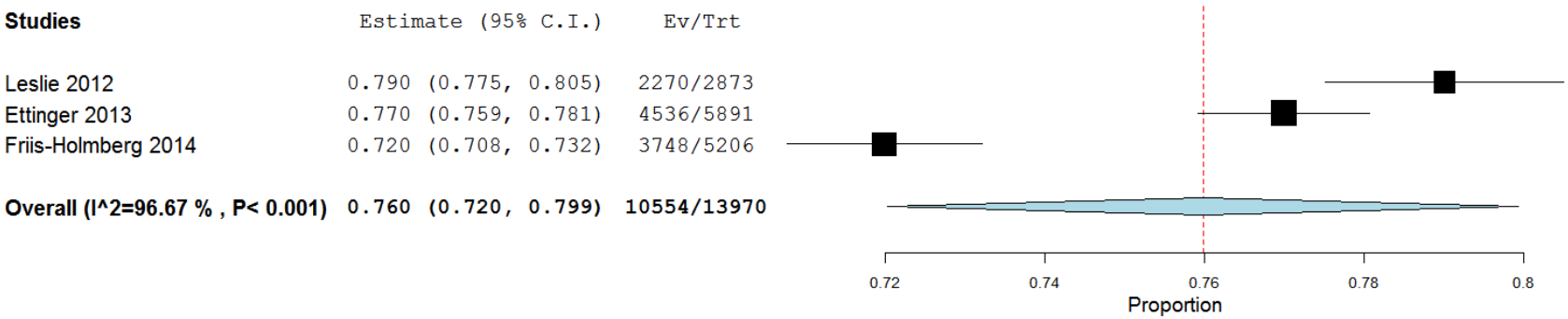
Appendix H Figure 10. FRAX without bone mineral density testing for predicting hip fractures in men



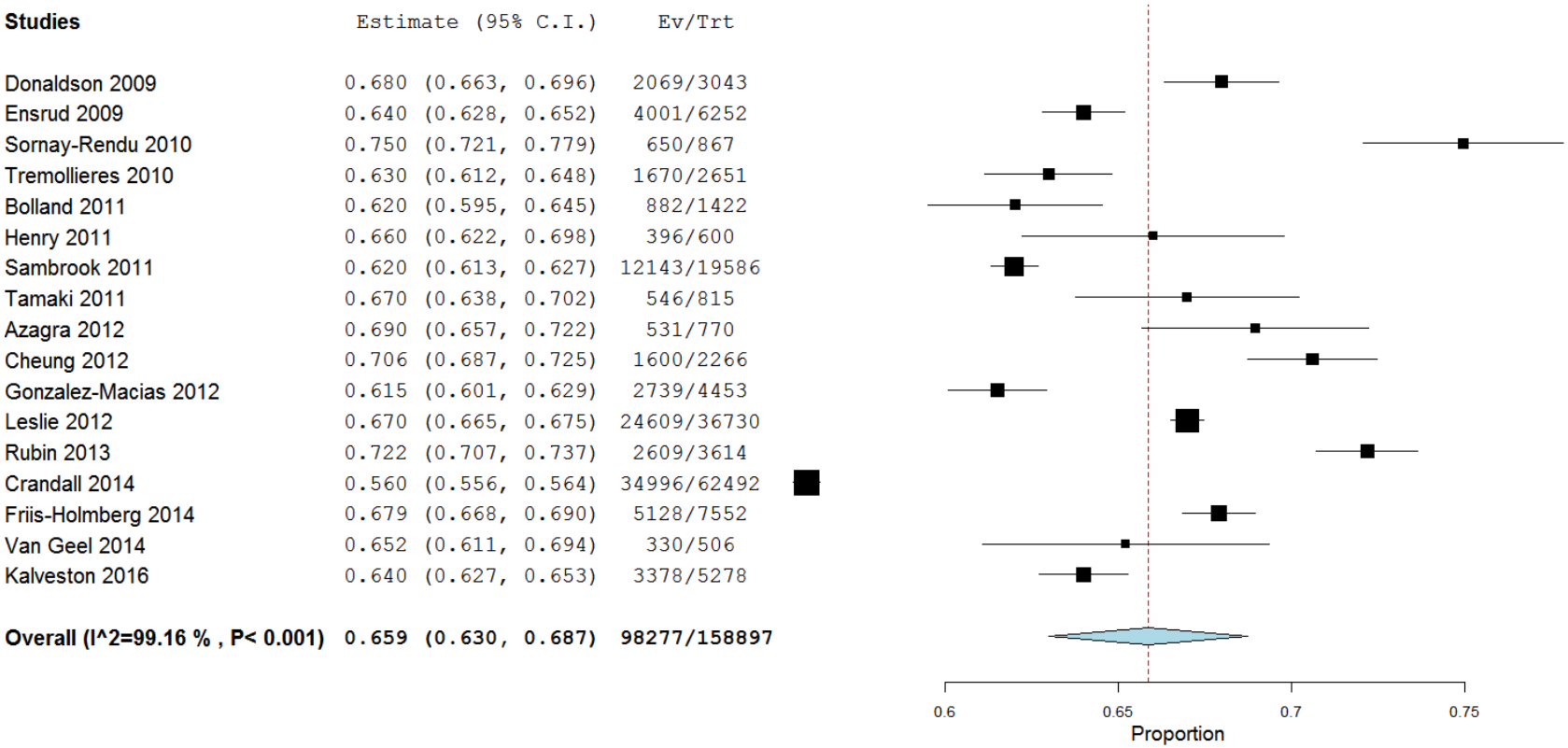
Appendix H Figure 11. FRAX with bone mineral density testing for predicting major osteoporotic fractures in men



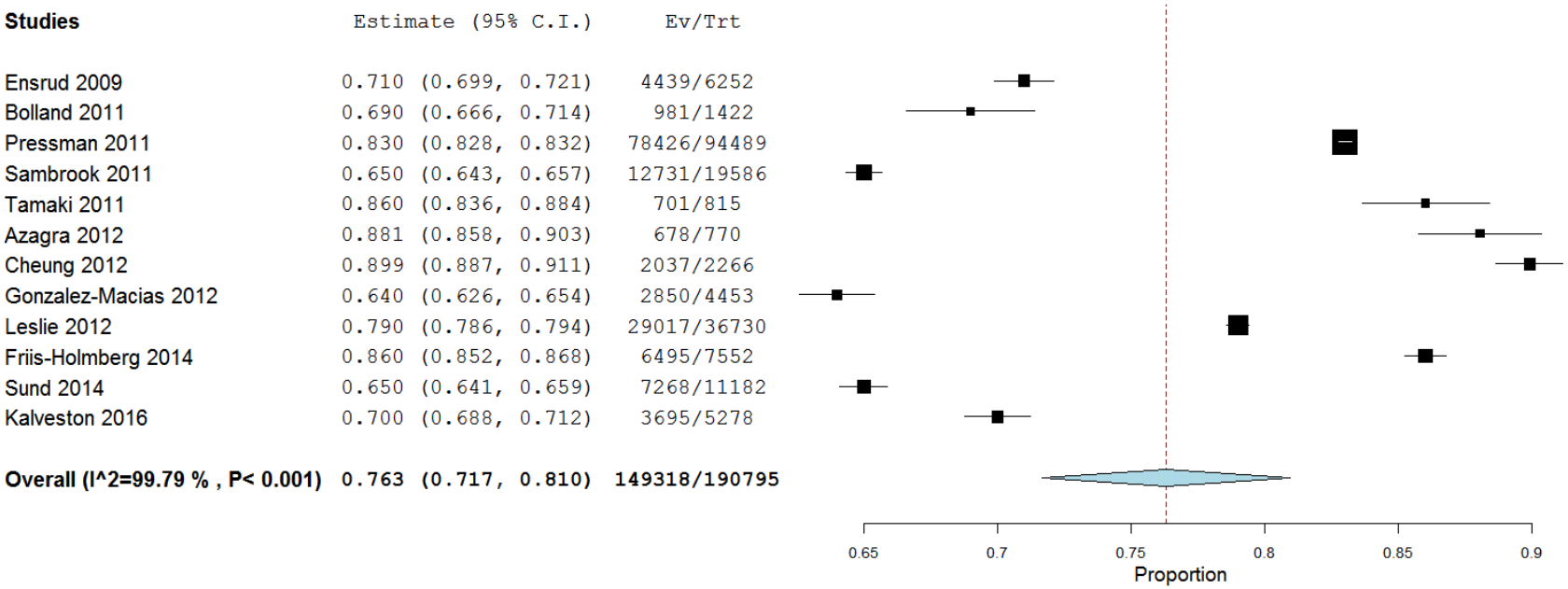
Appendix H Figure 12. FRAX with bone mineral density for predicting hip fractures in men



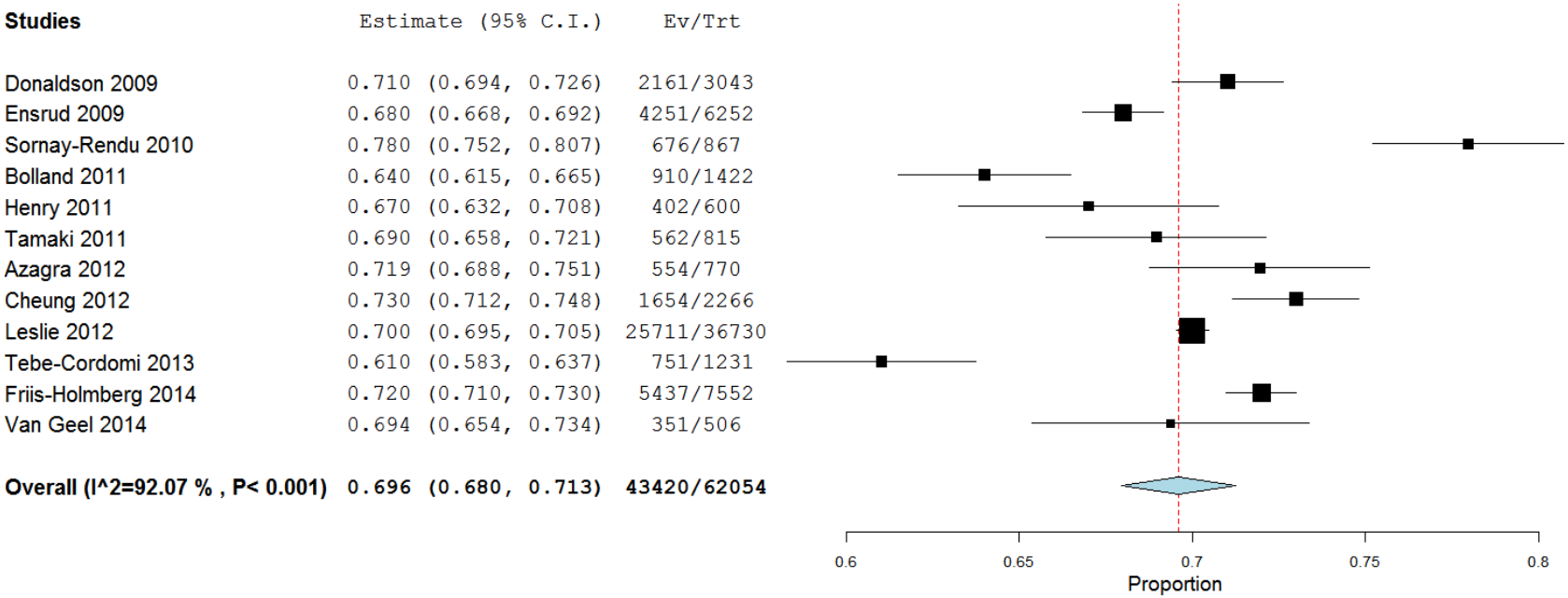
Appendix H Figure 13. FRAX without bone mineral density testing for predicting major osteoporotic fractures in women



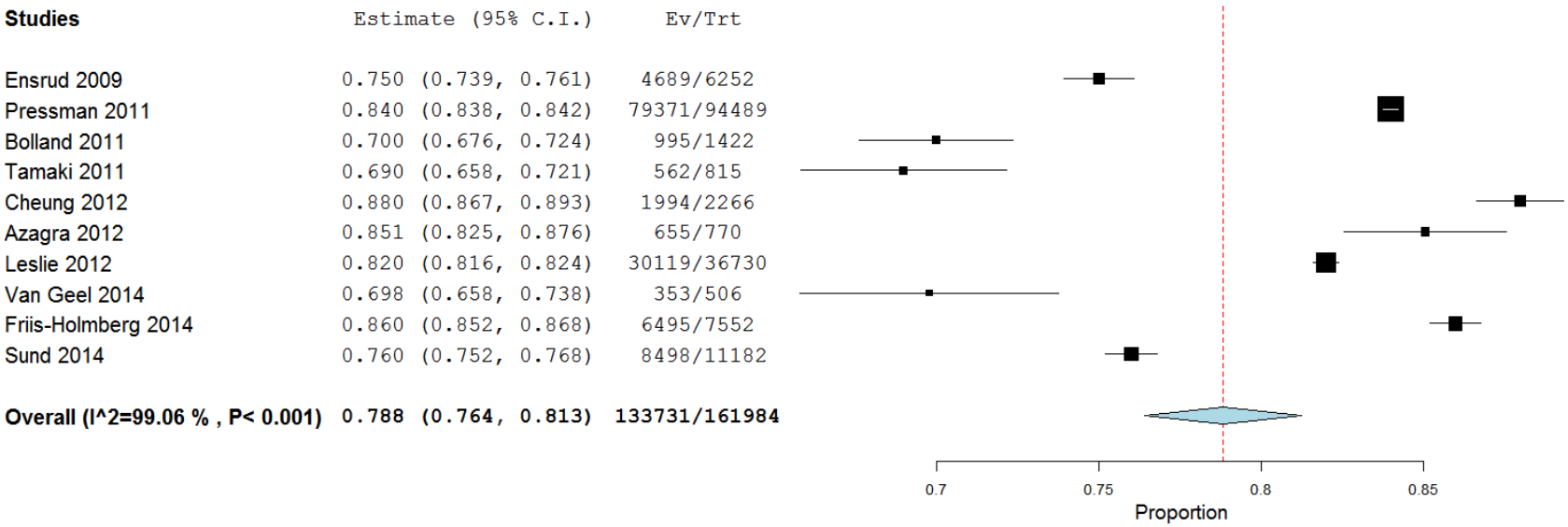
Appendix H Figure 14. FRAX without bone mineral density testing for predicting hip fractures in women



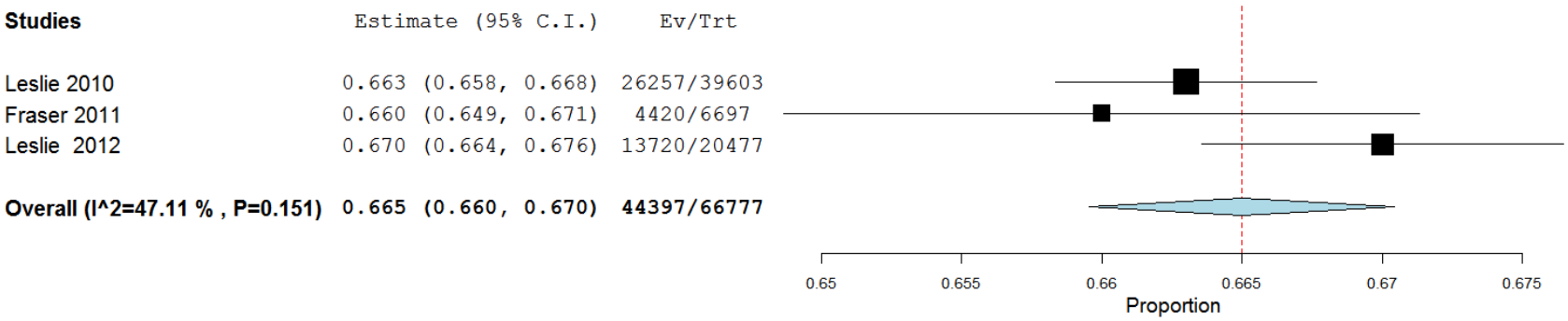
Appendix H Figure 15. FRAX with bone mineral density testing for predicting major osteoporotic fractures in women



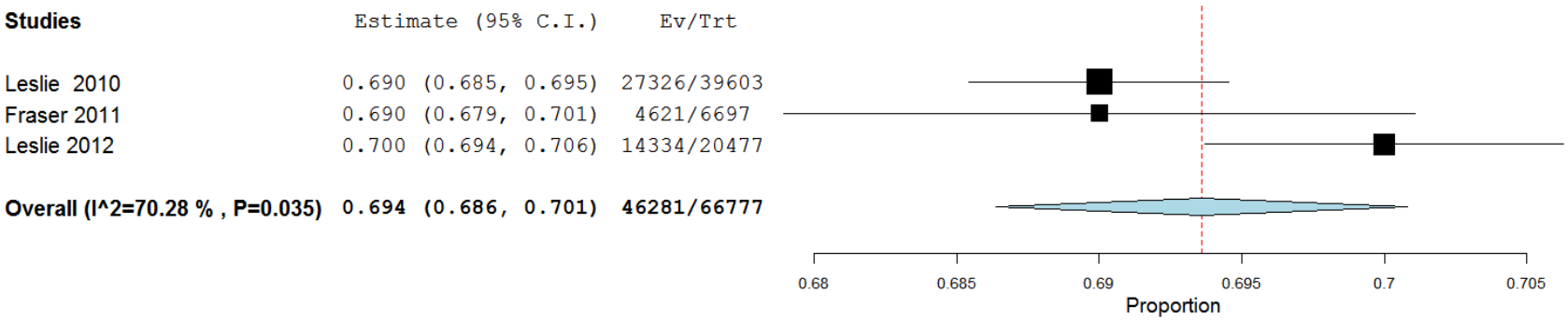
Appendix H Figure 16. FRAX with bone mineral density testing for predicting hip fractures in women



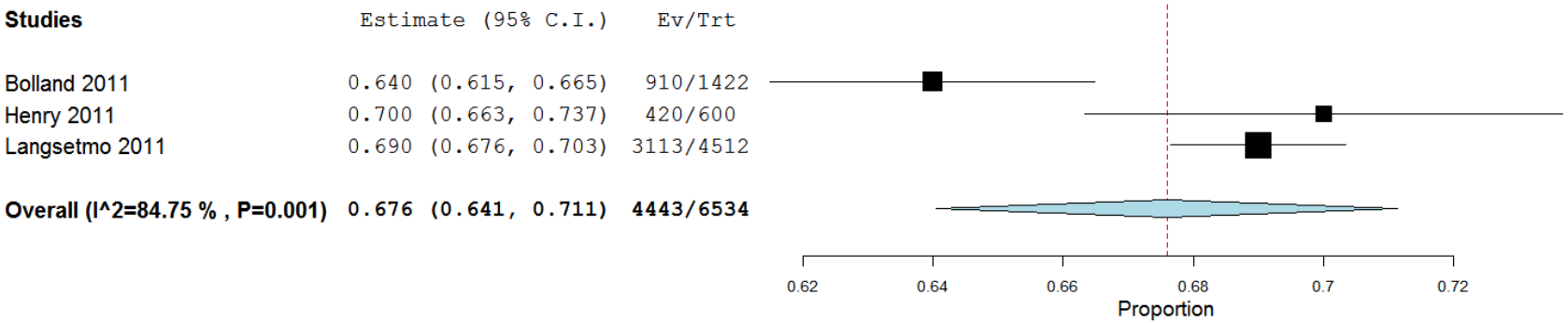
Appendix H Figure 17. FRAX without bone mineral density testing for predicting major osteoporotic fractures in both sexes



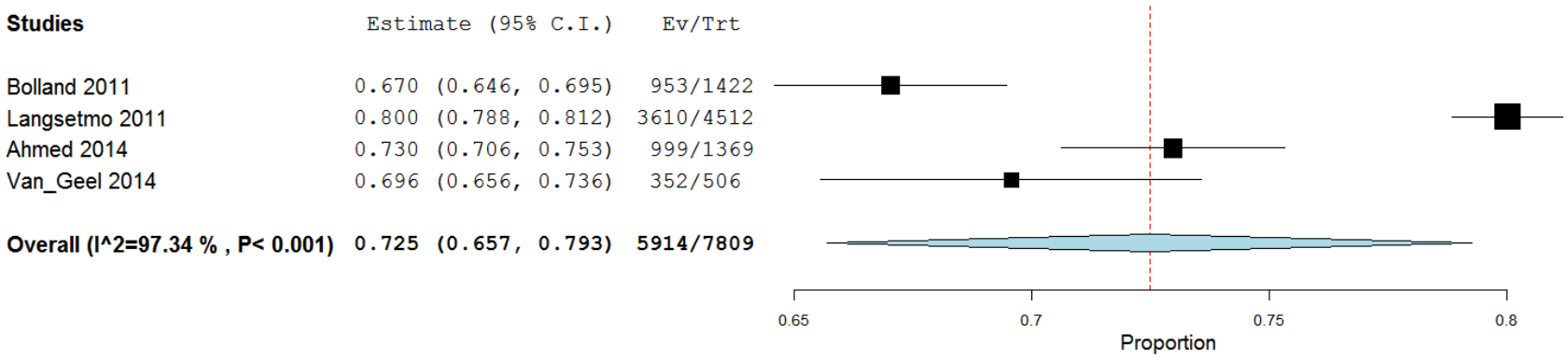
Appendix H Figure 18. FRAX with bone mineral density testing for predicting major osteoporotic fractures in both sexes



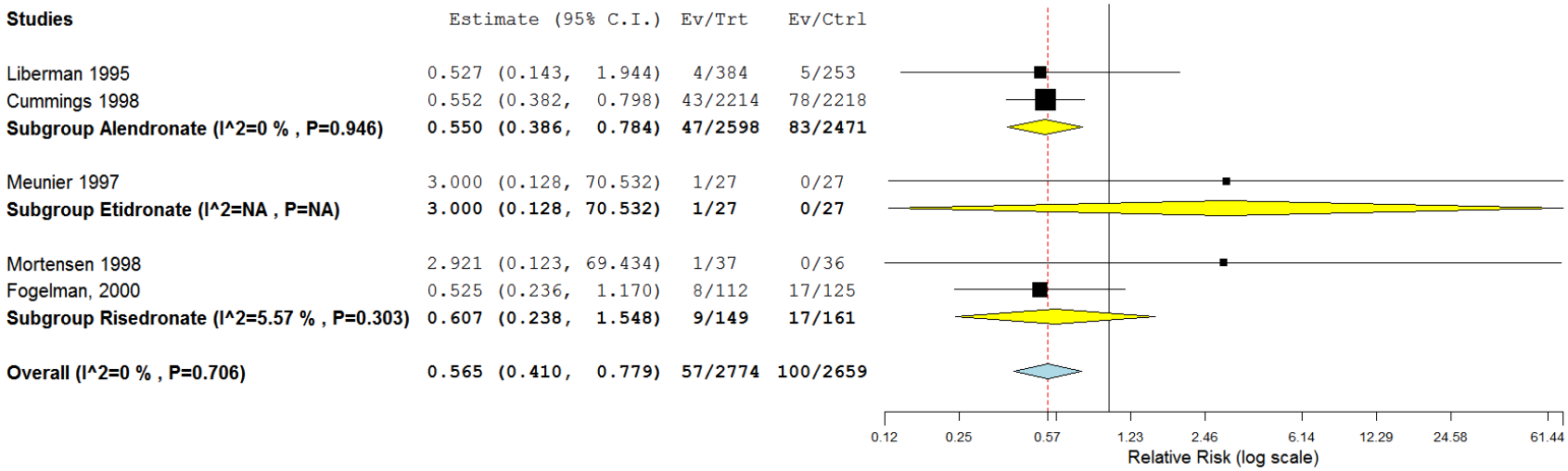
Appendix H Figure 19. Garvan Fracture Risk Calculator with bone mineral density testing for predicting major osteoporotic fractures in women



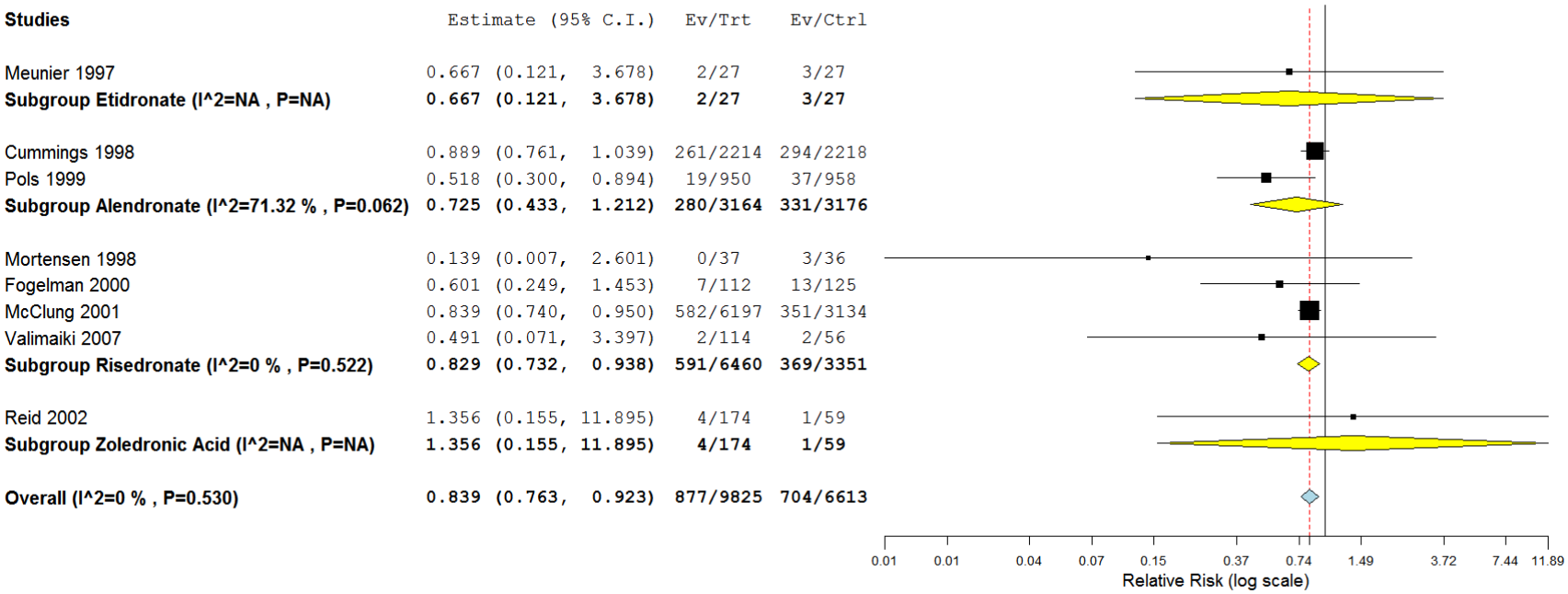
Appendix H Figure 20. Garvan Fracture Risk Calculator with bone mineral density testing for predicting hip fractures in women



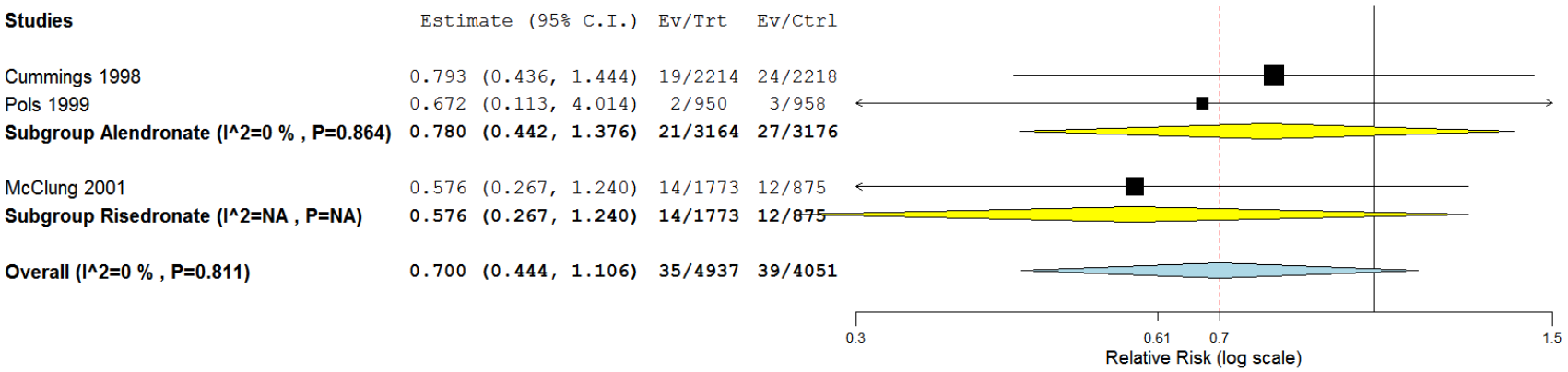
Appendix H Figure 21. Vertebral fracture outcomes for bisphosphonates



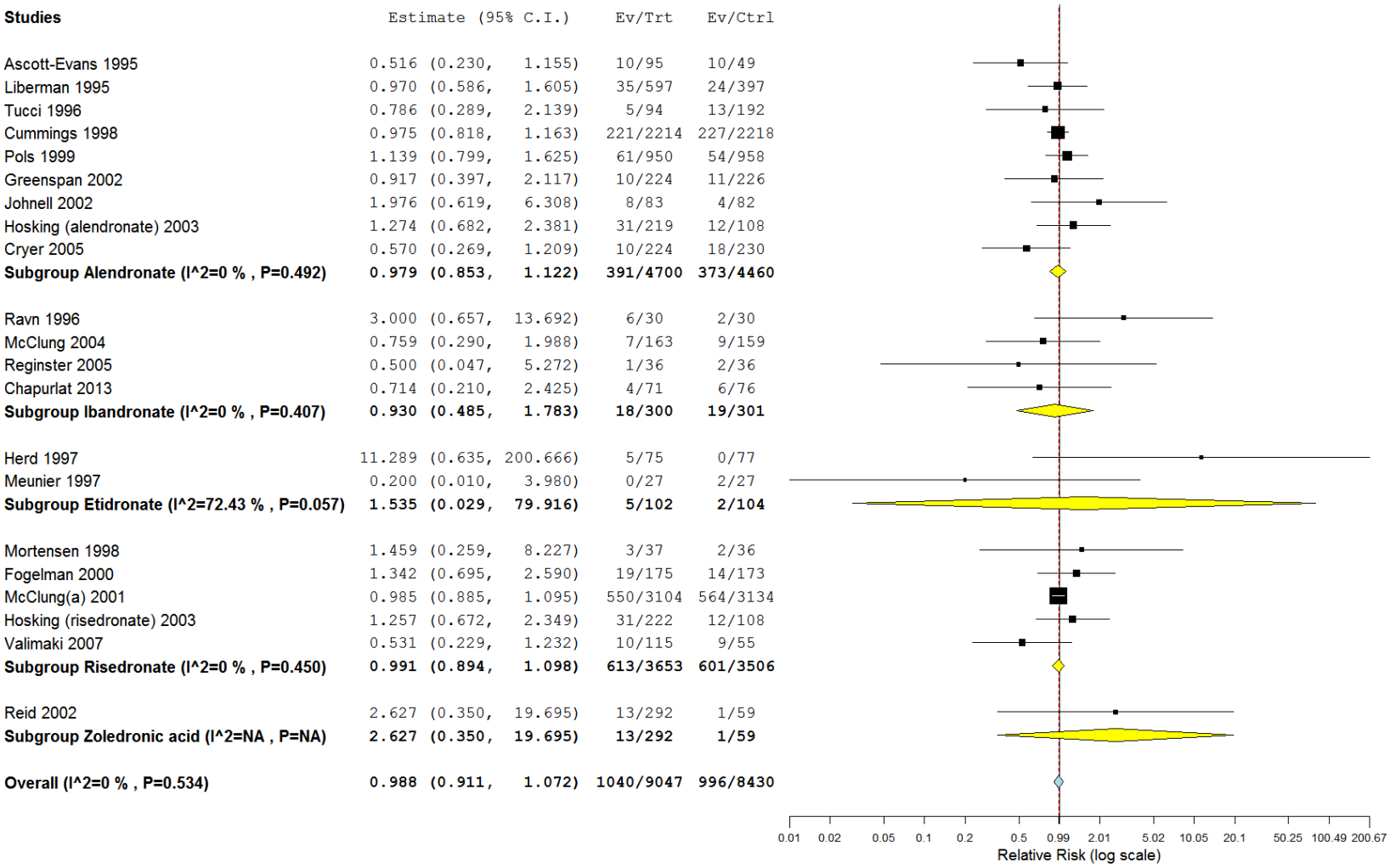
Appendix H Figure 22. Nonvertebral fracture outcomes for bisphosphonates



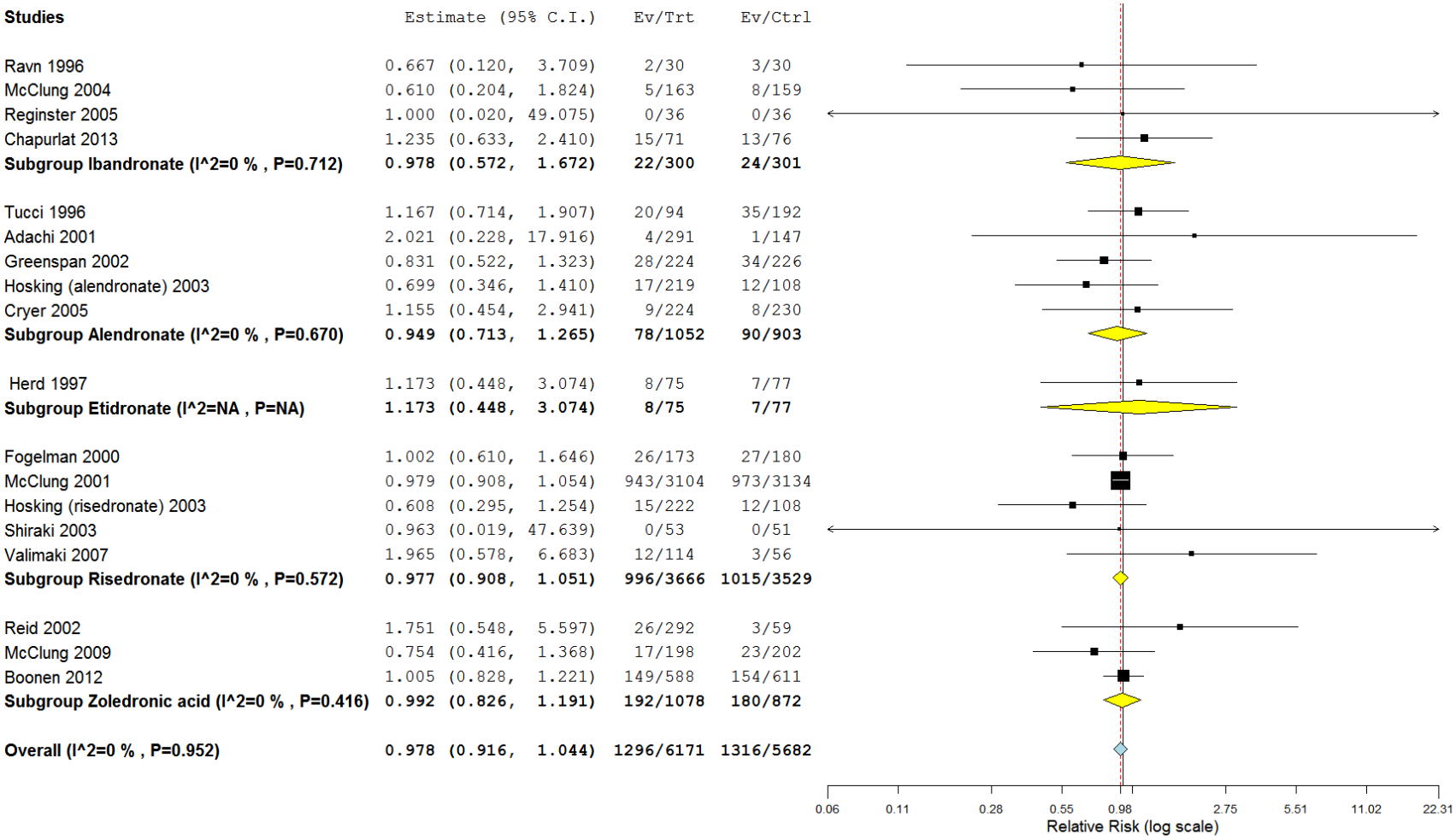
Appendix H Figure 23. Hip fracture outcomes for bisphosphonates



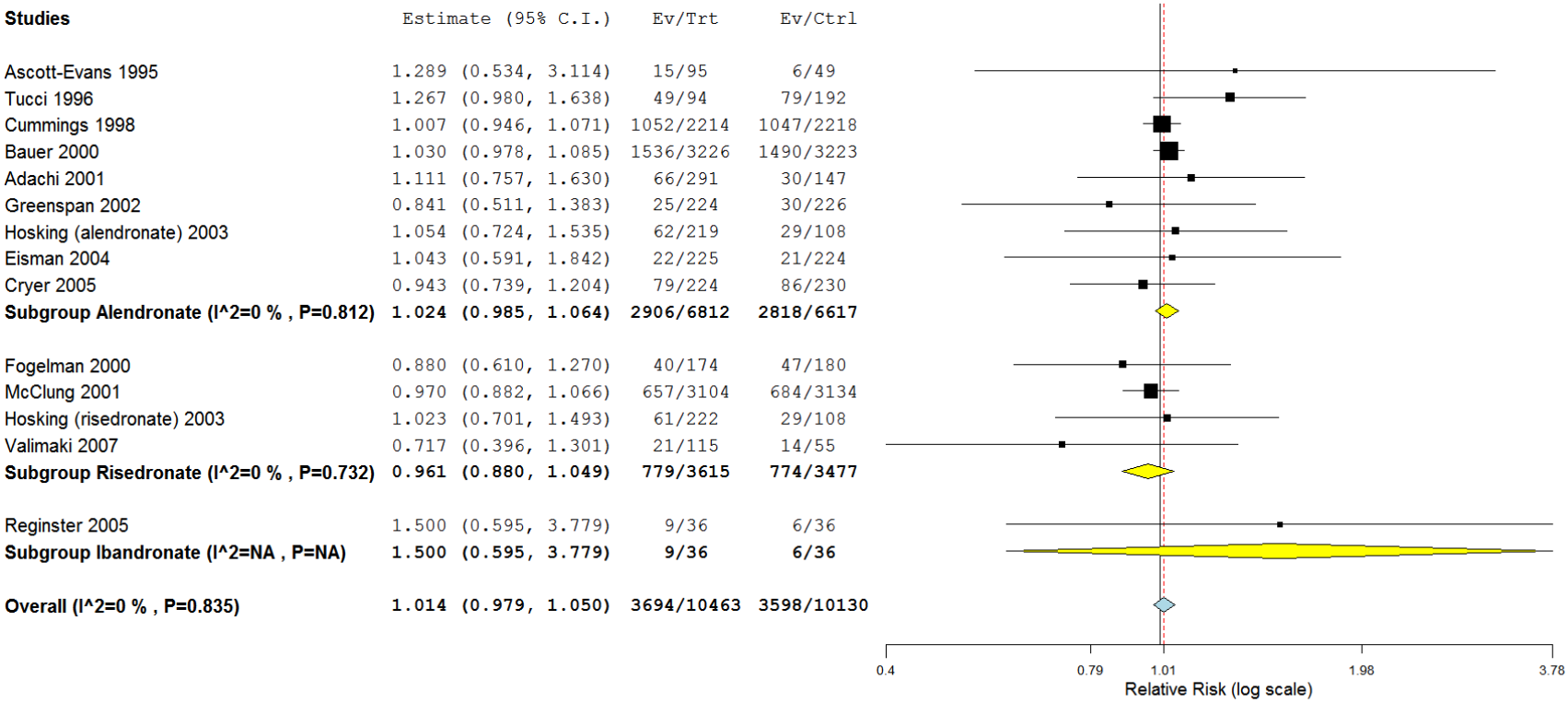
Appendix H Figure 24. Discontinuation due to adverse events for bisphosphonates versus placebo



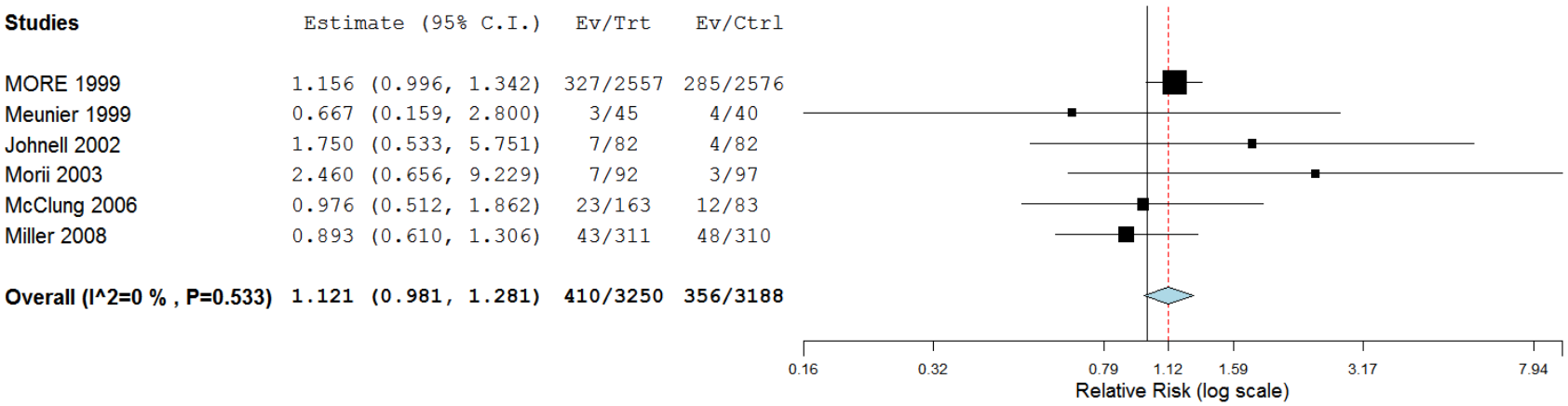
Appendix H Figure 25. Serious adverse events for bisphosphonates versus placebo



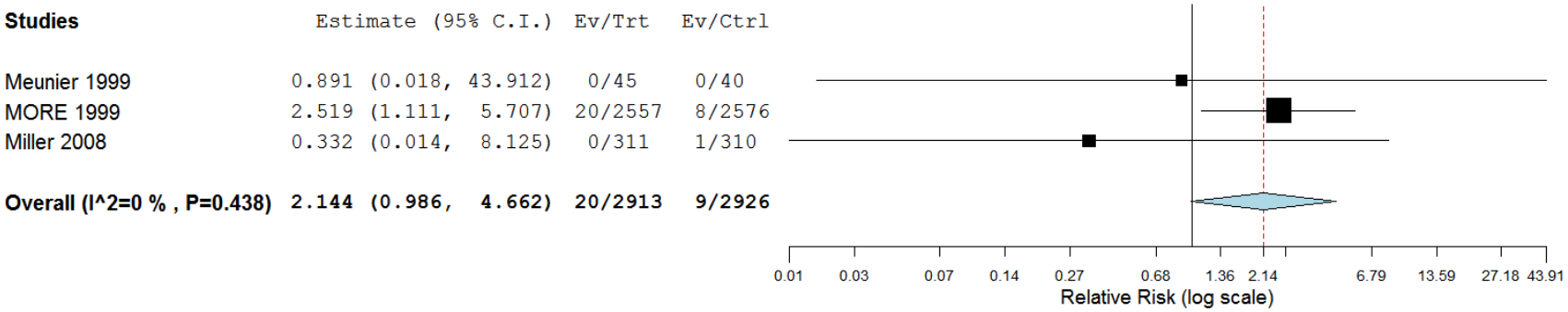
Appendix H Figure 26. Upper gastrointestinal events for bisphosphonates versus placebo



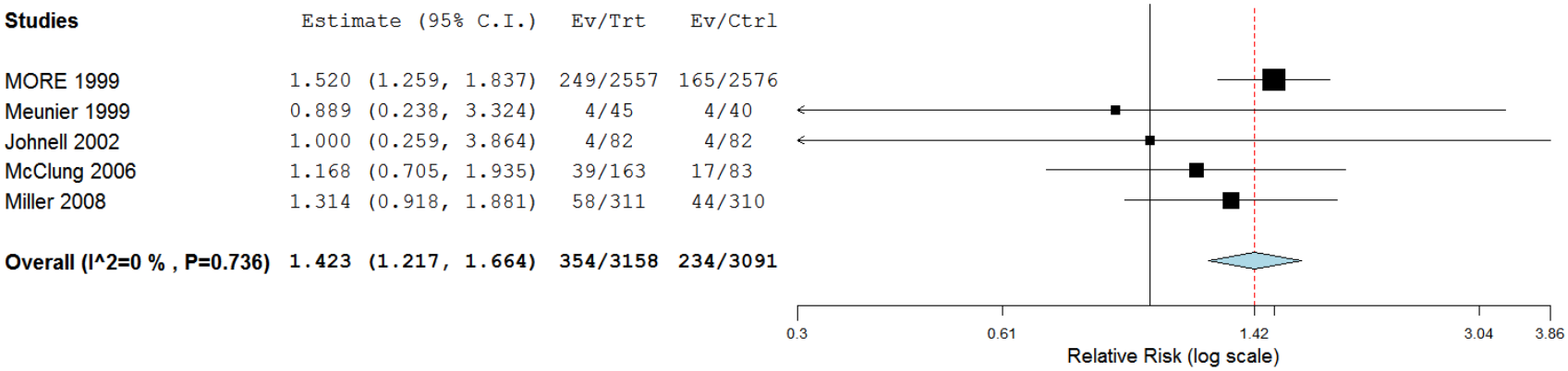
Appendix H Figure 27. Discontinuations due to adverse events for raloxifene versus placebo



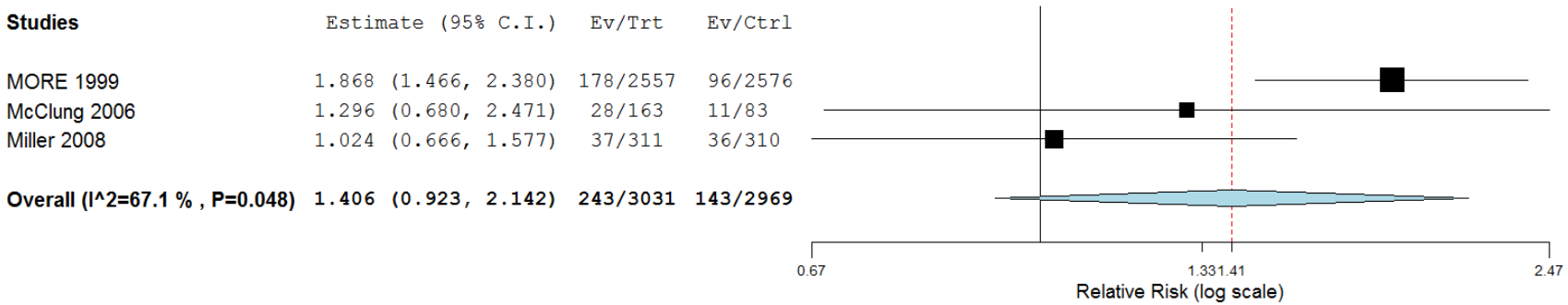
Appendix H Figure 28. Deep vein thrombosis for raloxifene versus placebo



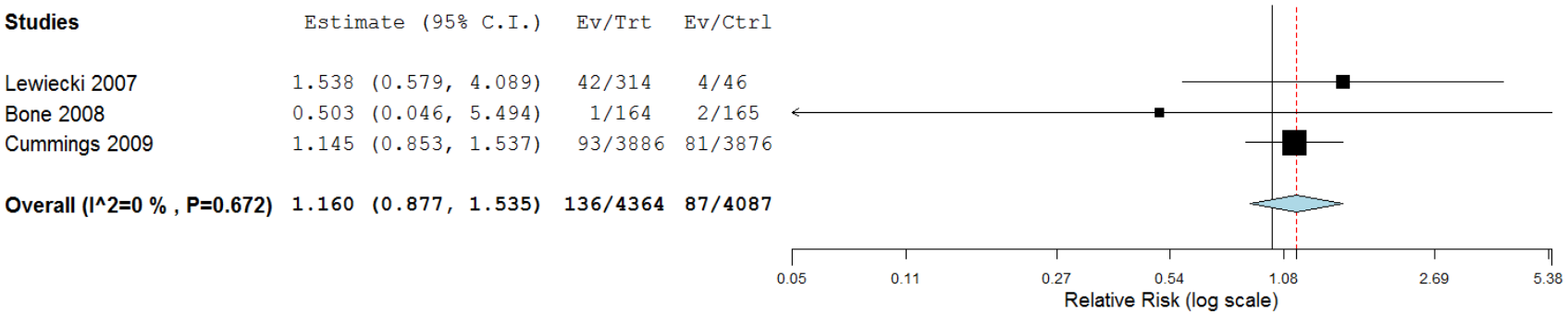
Appendix H Figure 29. Hot flashes for raloxifene versus placebo



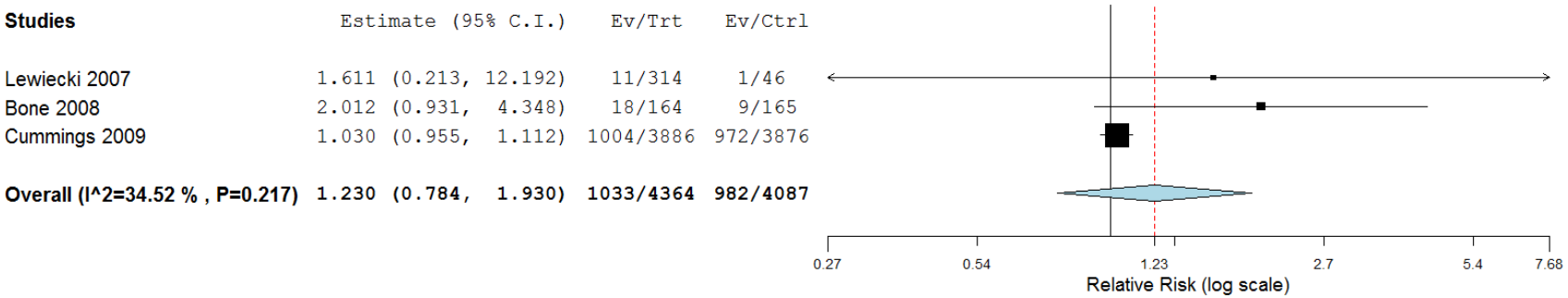
Appendix H Figure 30. Leg cramps for raloxifene versus placebo



Appendix H Figure 31. Discontinuations due to adverse events for denosumab versus placebo



Appendix H Figure 32. Serious adverse events for denosumab versus placebo



Appendix H Figure 33. Serious infections for denosumab versus placebo