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Screening for Osteoporosis: An Update for the U.S. Preventive Services Task Force

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Background: This review updates evidence since the 2002 U.S. Preventive Services Task Force recommendation on osteoporosis screening.

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

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

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

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

Data Synthesis: Risk-assessment instruments are modest predictors of low bone density (area under the curve, 0.13 to 0.87; 14 instruments) and fractures (area under the curve, 0.48 to 0.89; 11 instruments); simple and complex instruments perform similarly. Dual-energy x-ray absorptiometry predicts fractures similarly for men and women; calcaneal quantitative ultrasonography also predicts fractures, but correlation with dual-energy x-ray absorptiometry is low. For postmenopausal women, bisphosphonates, parathyroid hormone, raloxifene, and estrogen reduce primary vertebral fractures. Trials are lacking for men. Bisphosphonates are not consistently associated with serious adverse events; raloxifene and estrogen increase thromboembolic events; and estrogen causes additional adverse events.

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

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

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For author affiliations, see end of text.
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Editor's Note: As part of the U.S. Preventive Services Task Force's (USPSTF) ongoing commitment to clarity about its work and methods, it has begun to invite public comment on all draft recommendation statements before publication of the final statements. Because of this new initiative, the recommendation on screening for osteoporosis does not appear with this accompanying background review. The USPSTF's draft recommendation statement on screening for osteoporosis is now available for public comment at www.ahrq.gov/clinic/tfcomment.htm. Comments will be accepted. The USPSTF will consider submitted comments when it finalizes the recommendation for subsequent publication in Annals *and posting on the USPSTF Web site at www.ahrq.gov/clinic/prevenix.htm.*

This systematic evidence review is an update for the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for osteoporosis. In 2002, on the basis of results of a previous review (1, 2), the USPSTF recommended bone density screening for women 65 years or older and for women aged 60 to 64 years at increased risk for osteoporotic fractures (3, 4). They made no recommendations for or against screening postmenopausal women younger than 60 years or women aged 60 to 64 years without increased risk. Men were not considered in the previous recommendation.

Osteoporosis is a systemic skeletal condition characterized by low bone mass and microarchitectural deterioration of bone tissue that increases bone fragility and risk for fractures (5). Osteoporosis may occur without a known cause or secondary to another condition. Osteoporosis is diagnosed in persons on the basis of presence of a fragility fracture or by bone mass measurement criteria. These criteria were developed by the World Health Organization from epidemiologic data that describe the normal distribution of bone mineral density (BMD) in a young healthy

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Context

In 2002, the U.S. Preventive Services Task Force recommended bone density testing for women 65 years or older and women 60 to 64 years with increased fracture risk and made no recommendation for or against screening other women or men.

Contribution

This review of studies related to osteoporosis screening that were published from January 2001 to December 2009 found no trials of screening. Evidence showed that risk-assessment instruments predict low bone density and fractures, dual-energy x-ray absorptiometry predicts fractures similarly in both sexes, and calcaneal ultrasonography predicts fracture but correlates poorly with dual-energy x-ray absorptiometry. Trials show that bisphosphonates, parathyroid hormone, raloxifene, and estrogen prevent primary vertebral fractures in women. Prevention trials are lacking in men.

Implication

Recommendations for osteoporosis screening must be based on indirect evidence that is largely from studies of women.

—The Editors

reference population (6). Osteoporosis is diagnosed when the BMD at the spine, hip, or wrist is 2.5 or more SDs below the reference mean (T-score of −2.5 or less), and low bone density or mass is diagnosed when BMD is from 1.0 to 2.5 SDs below the reference mean. Other important components of the condition, such as rate of bone loss and quality of bone, are not well characterized clinically.

Estimates indicate that as many as 50% of Americans older than 50 years will be at risk for osteoporotic fractures during their lifetimes (5). This translates to 12 million persons with osteoporosis by 2012 (5). Specific prevalence rates depend on how bone density is measured and characteristics of the population. Rates for women are higher than those for men; rates vary by race, with the highest rates in white persons; and rates for all demographic groups increase with age (7–9). Older persons have much higher fracture rates than younger persons with the same bone density because of increasing risks from other factors, such as bone quality and tendency to fall (10).

All types of fractures are associated with higher mortality rates (11–14). Men are more likely than women to die in the year after a hip fracture, with mortality rates for men estimated at up to 37.5% (15). Fractures adversely affect function and quality of life, resulting in chronic pain, disability, and high costs (5). Despite increased awareness of the magnitude and consequences of osteoporosis and recommendations for screening and treatment from several groups, osteoporosis is underdetected and inadequately treated in the United States (16, 17). Reasons for this are unclear, although the differing recommendations for identifying candidates for testing and treatment, confusion in interpreting results of testing, and fragmentation of health care may contribute (18).

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

Methods

The USPSTF and the Agency for Healthcare Research and Quality (AHRQ) developed key questions for this review. Investigators created an analytic framework, incorporating the key questions and outlining the patient populations, interventions, outcomes, and harms of the screening process (**Appendix Figure 1**, available at www.annals.org). The target populations include postmenopausal women and men older than 50 years without known previous osteoporosis-related fragility fractures or secondary causes of osteoporosis. Harms of screening include consequences of false-positive and false-negative tests, patient anxiety and other psychosocial responses, unnecessary treatment, as well as adverse outcomes from medications.

Data Sources and Searches

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the fourth quarter of 2009) and MEDLINE (January 2001 to December 2009) for relevant studies and systematic reviews. A technical report (19) describes search strategies and additional details. We also conducted secondary referencing by manually reviewing reference lists of key papers and searching citations by using Web of Science (20). **Appendix Figure 2** (available at www.annals.org) shows the results of our literature search.

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each key question (19). We included randomized, controlled trials (RCTs) with fracture or fracture-related morbidity and mortality outcomes to determine the effectiveness of osteoporosis screening and studies of any design to determine harms from screening.

To determine the accuracy and clinical applicability of risk-assessment instruments, we included studies of externally validated instruments that reported performance characteristics. Instruments were included if they were derived from an initial population and then tested in a separate population; derived from computer modeling, consen-

sus, or another study and then tested in a novel population; or derived from any source and tested against T-scores or actual fracture rates in a population. We did not include internally validated measures (imputation methods or cross-validation). To determine the performance of bone measurement tests in predicting fractures, we limited studies to existing systematic reviews and technology assessments of procedures currently used in U.S. practice and large population-based studies relevant to primary care settings. We included any studies providing data about screening intervals.

To evaluate the efficacy and harms of medications to reduce fractures in a screening-detected population, we included RCTs and meta-analyses of RCTs that reported fracture and fracture-related outcomes and adverse effects for medications used in the United States. Outcomes included specific types of fractures; fracture-related morbidity, including loss of function, pain, quality of life, and other reported health outcomes; and fracture-related mortality. We excluded nondrug therapies because they are addressed in other reviews for the USPSTF (for example, calcium, vitamin D, exercise, and fall prevention) and combination therapies. We focused on trials that enrolled patients without known previous osteoporosis-related fragility fractures, such as vertebral compression or hip fractures, and without known secondary causes of osteoporosis because this population is most relevant to screening. We included trials that met 1 of the following 3 criteria. First, the trial excluded persons with previous vertebral or other presumably osteoporotic fractures. Second, the trial permitted persons with previous osteoporotic fractures, but the overall proportion of participants with fractures was less than 20%, or the trial reported results separately for participants with and without previous fractures. We considered trials meeting this criterion to be applicable to primary prevention based on epidemiologic data (21). Third, the trial did not report the proportion of participants with previous osteoporotic fractures, but inclusion criteria did not select persons on the basis of presence of a previous fracture, and mean BMD T-scores were −3.0 or more. This threshold was selected because placebo-controlled trials that enrolled more than 20% of women with previous fractures reported mean baseline BMD T-scores less than −3.0 (22–25).

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

Data Abstraction and Quality Assessment

Details about the patient population, study design, analysis, follow-up, and results were abstracted. By using predefined criteria developed by the USPSTF (26), 2 investigators rated the quality of studies (good, fair, or poor) and resolved discrepancies by consensus. We assessed the overall strength of the body of evidence for each key question (good, fair, or poor) by using methods developed by the USPSTF on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence (26).

Data Synthesis and Analysis

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

Several trials included in the meta-analyses reported few, rare, or 0 fracture events. The primary analyses excluded trials with 0 events in both groups, resulting in loss of data, and applied a constant continuity correction of 0.5 for trials with 0 events in 1 group, potentially biasing inferences (27, 28). In addition, the random-effects Mantel–Haenszel method we used may be unsuitable when events are rare (27). We therefore conducted sensitivity analyses to determine the effects of alternate pooling methods on estimates by using the Peto odds ratio (OR), fixed-effects Mantel–Haenszel method with an alternative continuity correction, and the pooled arcsine difference (27–29). The **Appendix** (available at www.annals.org) provides details about the methods and results of these analyses, as well as other sensitivity analyses.

Role of the Funding Source

The AHRQ funded this work, developed key questions in conjunction with USPSTF members, and assisted with internal and external review of the draft, but had no additional role in the design, conduct, or reporting of the review. External experts not affiliated with the USPSTF reviewed the draft manuscript.

Results

Effectiveness and Harms of Osteoporosis Screening in Reducing Fractures, Morbidity, and Mortality (Key Questions 1 and 4)

We identified no trials of the effectiveness of screening and no studies evaluating potential harms from screening. Adverse outcomes from medications are addressed by key question 6.

Performance of Risk-Assessment Instruments to Stratify Individuals Into Risk Categories (Key Question 2)

Thirty-three studies evaluated 21 externally validated clinical risk-assessment instruments and reported performance estimates of the area under the curve (AUC) for the receiver-operating characteristic curve predicting either bone density or fractures (30–62). Eight instruments were tested with men (30, 36, 45–47, 57, 60, 61). Instruments include from 1 (33, 34, 37, 38, 48) to more than 15 (32, 45) variables, although most include age, weight or body mass index, and previous fracture. Family history of fractures, smoking status, and estrogen use are also commonly included. Important methodological limitations of studies include nonrepresentative samples, cross-sectional rather than prospective data collection, inconsistent performance of the reference standard, and differences in performance measures across studies. The technical report (19) describes additional studies of instruments that were internally validated or not validated or did not report AUC estimates, along with studies that combined clinical risk factors with peripheral dual-energy x-ray absorptiometry (DEXA) or quantitative ultrasonography (QUS) measures.

Twenty-three studies of 14 instruments to predict low BMD (T-score of −2.5 or less) reported AUC estimates ranging from 0.13 to 0.87, with most between 0.60 and 0.8 (30, 32–35, 37, 38, 42–44, 47–53, 55, 56, 58–61) (**Table 1**). Although some instruments had high AUC estimates in selected studies, none demonstrated high estimates in several studies. Instruments with fewer risk factors often did as well or better than those with more. For example, the Osteoporosis Self-assessment Screening Tool (OST) includes only age and weight, has similar AUC estimates as other more complicated instruments, and has been validated in both men (30, 47, 61) and women (37, 43, 44, 48, 53, 55). Eleven studies of 11 instruments to predict fractures reported AUC estimates from 0.48 to 0.89 (31, 36, 39–41, 45, 46, 52, 54, 57, 62) (**Table 1**). Four studies included both men and women (36, 45, 46, 57); all others included only women.

The World Health Organization and National Osteoporosis Foundation recently developed the FRAX instrument to predict individual fracture risks (46, 63). FRAX estimates adjust for nationality and include femoral neck BMD if available and age, sex, height, body mass index, previous fracture, family history of fracture, glucocorticoid use, current smoking status, daily alcohol use of 3 units or more, rheumatoid arthritis, and other secondary causes of osteoporosis. FRAX was derived from combined data from 46 340 persons from 9 different cohorts and subsequently tested in 230 486 persons from 11 validation cohorts (46). Seven derivation cohorts and 1 validation cohort included men. Although the risk calculator is available on a Web site (www.shef.ac.uk/FRAX/), the source code is not accessible. The AUC estimates for FRAX ranged from 0.54 to 0.78 for osteoporotic fractures (40, 46, 57) and 0.65 to 0.81 for hip fractures (46) (**Table 1**). Three studies compared FRAX with simple models, such as age and BMD or age and fracture history, and found that simple models did as well as FRAX in predicting hip and other clinical fractures (40, 64) and vertebral fractures (39). We did not identify studies that prospectively tested FRAX in clinic populations or determined its effectiveness in selecting patients for therapy.

Performance of DEXA in Predicting Fractures in Men (Key Question 3a)

Two good-quality, prospective cohort studies evaluated the performance of DEXA in predicting fractures in men and compared results of men with those of women (65–67). The Rotterdam Study compared 4731 women and 3075 men 55 years or older from the same community at the same time (65, 66). Nonvertebral fractures were determined 6 to 7 years after baseline BMD from fracture reports, and vertebral fractures were determined from follow-up radiography by using morphometric criteria. For each sex-specific SD decrease in femoral neck BMD, the hazard ratio for all nonvertebral fractures was 1.4 (95% CI, 1.2 to 1.6) for men and 1.5 (CI, 1.4 to 1.6) for women and were similar for several site-specific fractures (65, 66). The hazard ratio for vertebral fractures was 1.8 (CI, 1.3 to 2.4) for men and 1.9 (CI, 1.6 to 2.4) for women.

A study of BMD and risk for hip and nonvertebral fractures compared men enrolled in MrOS (Osteoporotic Fractures in Men Study) with women in SOF (Study of Osteoporotic Fractures) and reported similar results (67). However, in this study, DEXA of the femoral neck was associated with a higher relative risk for hip fracture in men (3.68 [CI, 2.68 to 5.05]) than in women (2.48 [CI, 2.09 to 2.95]). Additional studies are consistent with findings from the Rotterdam Study and MrOS (68–70). Variations in estimates may be due to the different patient populations, study designs, and other factors.

Performance of Peripheral Bone Measurement Tests in Predicting Fractures (Key Question 3b)

Several peripheral bone measurement tests have been developed, although clinical practice and recent research focus on QUS of the calcaneous. For postmenopausal women, 7 studies of DEXA and QUS report similar AUC estimates and risk ratios for fracture outcomes in general, although results vary across studies (71–77) (**Appendix Table 1**, available at www.annals.org). For all fractures combined, AUC estimates range from 0.59 to 0.66, and risk ratios range from 1.81 to 2.16 for DEXA of the femoral neck. For QUS, AUC estimates are approximately 0.60, and risk ratios range from 1.26 to 2.25. Similar results were found in 5 studies of men (68–70, 73, 78) (**Appendix Table 1**). For hip fractures specifically, DEXA of the femoral neck is associated with higher risk ratios than QUS for men and women in most studies (70, 72).

Screening Intervals (Key Question 3c)

In a large, good-quality, prospective cohort study (SOF) of 4124 women 65 years or older, repeated BMD measurement up to 8 years after an initial measurement

Table 1. **Performance of Externally Validated Risk-Assessment Instruments***

Instrument or Study (Reference)	Studies, *n*	Participants, *n*	Components	Range of AUC (95% CI)†
Instruments that predict low bone density‡				
ABONE (34)	1	2365	Age, weight, estrogen use	0.72 (SD, 0.01)
Body weight (33, 34, 37, 38, 47, 48)	6	9065	Weight <70 kg	0.13–0.79
DOEScore (52)	1	1256§	Age, weight, previous fracture	0.75
Gnudi and Sitta (42)	1	1187§	Weight, age at menarche, years since menopause, uses arms to rise from seated position, previous fracture, mother had fracture	0.74
Masoni et al (49)	1	195§	BMI, >10 y since menopause, calcium intake <1200 mg/d, previous fracture, kyphosis	0.83 (0.76–0.91)
MORES (60)	1	2995§	Age, weight, history of COPD	0.84 (0.81–0.87)
NOF guideline (34, 38, 50)	3	3092	Age; weight; previous fracture at age >40 y; current smoker; parent had hip, wrist, or spine fracture age at ≥50 y	0.60–0.70
OPERA (56)	1	1522	Age, weight, previous fracture, early menopause, systemic glucocorticoid use	Femoral neck, 0.81 (0.79–0.83); lumbar spine, 0.87 (0.85–0.88)
ORAI (33–35, 37, 38, 43, 44, 48, 50, 55)	10	11 093	Age, weight, current estrogen use	0.32–0.84
OSIRIS (37, 44, 48, 51, 58)	5	2657	Age, weight, current estrogen use, previous fracture	0.63–0.80
OST (30, 37, 38, 43, 44, 47, 48, 53, 55, 61)	10	13 825§	Age, weight	0.33–0.89
SCORE (32, 34, 35, 37, 43, 44, 50, 55, 59)	9	13 710	Age, weight, race, rheumatoid arthritis, estrogen use, fracture at age >46 y	0.66–0.87
SOF (32)	1	416	Age, current weight less than weight at age 25 y, 13 additional variables‖	0.54 (0.48–0.60)
SOFSURF (37)	1	208	Age, weight, smoking status, previous postmenopausal fracture	0.72 (0.77–0.67)
Instruments that predict fracture				
ABONE (62)	1	469	Age, weight, estrogen use	Any fracture, 0.63 (0.54–0.71)
Body weight <70 kg (154 lb) (62)	1	469	Weight	Any fracture, 0.60 (0.52–0.68)
DOEScore (52)	1	1256§	Age, weight, previous fracture	0.48
EPESE (36)	1	7654§	Age >75 y; BMI; female; white; previous stroke; cognitive, ADL, or vision impairments; antiepileptic drug use	Any fracture, 0.64–0.69; hip fracture, 0.76–0.79
Fracture index (SOF) (31)	1	14 461§	Age, weight, fracture at age >50 y, mother had hip fracture at age >50 y, weight ≤57 kg (125 lb), current smoker, uses arms to rise from seated position, total hip BMD T-score	Hip fracture, 0.71 with BMD and 0.77 without BMD
FRAX (39, 40, 46, 57)	4	286 499§	Age, BMI, previous fracture, family history of fracture, glucocorticoid use, current smoker, alcohol use of 3 units/d or more, rheumatoid arthritis, hip BMD T-score if available	Osteoporotic fracture, 0.54–0.78; hip fracture, 0.65–0.81
Garvan nomogram (57)	1	200	Age, sex, femoral neck BMD, body weight, history of fractures at age >50 y, history of falls within the previous 12 mo	0.76–0.84
Minimum data set (41)	1	1427§	Age, weight, height, locomotion, recent fall, ADL score, cognition score, urinary incontinence	Any fracture, 0.63 (0.55–0.71)
ORAI (62)	1	469	Age, weight, current estrogen use	Any fracture, 0.65 (0.57–0.73)
QFracture (45)	1	3 633 812§	Age, BMI, estrogen use, smoking status, daily alcohol use, parental history of osteoporosis¶, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants, corticosteroids, history of falls, menopausal symptoms¶, chronic liver disease, gastrointestinal malabsorption¶	Any fracture, 0.86–0.89
WHI (54)	1	161 808§	Age, weight, self-reported health, height, fracture at age ≥55 y, race, physical activity, smoking status, parent had hip fracture, corticosteroid or hypoglycemic agent use	Hip fracture, 0.80 (0.75–0.85) with BMD; 0.71 (0.66–0.76) without BMD

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

* Includes studies of externally validated instruments reporting performance measures with AUC estimates.

† Where provided or calculated for individual study results.

‡ BMD T-score of −2.5 or less.

§ Includes both derivation and validation cohorts.

‖ Additional variables include first-degree relative who had a hip fracture; previous fracture at age >50 y; no walking for exercise; uses arms to rise from seated position; current use of benzodiazepines, anticonvulsants, or corticosteroids; resting pulse >80 beats/min; on feet <4 h/d; dementia diagnosis; not using menopausal hormone therapy; height ≥5 ft, 7 in, at age 25 y; and race other than black.

¶ Variables used for calculating QFracture score for women but not for men.

Table 2. **Fracture Outcomes of Placebo-Controlled Primary Prevention Trials, by Type of Fracture***

Medication	Vertebral		Nonvertebral	
	RR (95% CI)	Trials, *n* (Reference)	RR (95% CI)	Trials, *n* (Reference)
Bisphosphonates				
Alendronate	0.60 (0.44–0.83)	3 (82, 83, 87)	0.88 (0.55–1.40)	3 (82, 86, 90)
Combined bisphosphonates	0.66 (0.50–0.89)	7 (82, 83, 85, 87–89, 91)	0.83 (0.64–1.08)	9 (82, 85, 86, 88–93)
Parathyroid hormone	Women: 0.32 (0.14–0.75); men: 0.49 (0.22–1.09)	Women: 1 (94); men: 1 (95)	Women: 0.97 (0.71–1.33); men: 0.51 (0.10–2.48)	Women: 1 (94); men: 1 (95)
Raloxifene	0.61 (0.54–0.69)	2 (96, 97)	0.97 (0.87–1.09)	2 (97, 98)
Estrogen				
Estrogen with progestin†	0.66 (0.46–0.92)‡	1 (99)	No evidence	–
Estrogen alone§	0.62 (0.42–0.93)‡	1 (100)	No evidence	–

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

did not result in statistically significant differences in AUC and risk ratio estimates for nonvertebral, hip, or vertebral fractures (79). No studies of screening intervals have been conducted in men or other groups of women.

Efficacy of Medications for Reducing Osteoporosis-Related Fractures (Key Question 5)

Primary Prevention Trials in Postmenopausal Women

Bisphosphonates. Fifteen placebo-controlled RCTs of bisphosphonates met inclusion criteria (25, 80–93) (**Appendix Table 2**, available at www.annals.org). The FIT (Fracture Intervention Trial) met criteria for good quality (82). Of 13 trials rated as fair quality, 8 lacked information on randomization, allocation concealment, or outcomes blinding (25, 84, 86, 89–93); 5 trials did not report intention-to-treat analysis or blinding of providers (80, 81, 85, 87, 88). One poor-quality trial did not report blinding, intention-to-treat analysis, or attrition (83).

In 11 trials, mean baseline femoral neck BMD T-scores were −1.0 to −2.5 (80–84, 87–90, 92, 93); 1 trial enrolled women with T-scores less than −2.5 (25); and 3 trials enrolled women with T-scores greater than −1.0 (85, 86, 91). Five trials excluded or did not enroll women with previous vertebral fractures (80–82, 84, 92); 2 trials enrolled more than 20% of participants with previous vertebral fractures but reported results in the subgroup of women without previous fractures (25, 87); and the remainder did not report the proportion of women with previous fractures. Only FIT—the large, 4-year trial of alendronate—was designed to evaluate fractures as primary outcomes (82).

Bisphosphonates reduced vertebral fractures compared with placebo (relative risk [RR], 0.66 [CI, 0.50 to 0.89]; 7 trials) (82, 83, 85, 87–89, 91) (**Table 2**). Results based on alternative methods for pooling were nearly identical (**Appendix Table 3**, available at www.annals.org). Including all trials, the absolute risk for vertebral fracture was 1.9% for bisphosphonates versus 3.1% for placebo. Subgroup analyses of individual bisphosphonates were limited by few fractures (range, 0 to 20 events) for drugs other than alendronate. Results were similar in a sensitivity analysis based on a broader definition for primary prevention that added 6 trials (≤40% of participants with previous vertebral fractures or baseline T-scores less than −3.0) (22, 24, 87, 101–103).

For total nonvertebral fractures, a pooled analysis of trials indicated no statistically significant effects for bisphosphonates compared with placebo (RR, 0.83 [CI, 0.64 to 1.08]; 9 trials) (82, 85, 86, 88–93) (**Table 2**). Differences were also not significant for alendronate. Subgroup analyses of other bisphosphonates were limited by few fractures (range, 5 to 18 events). Results for bisphosphonates were statistically significant when estimated using alternative pooling methods (Peto OR, 0.84 [CI, 0.72 to 0.98]; fixed-effects Mantel–Haenszel with inverse sample size continuity correction RR, 0.86 [CI, 0.74 to 0.99]) (**Appendix Table 3**). A sensitivity analysis based on a broader definition for primary prevention described earlier was also statistically significant (RR, 0.82 [CI, 0.69 to 0.96]; 14 trials) (22, 24, 82, 85–89, 91–93, 101–103). Results for hip, wrist, or ankle fractures were not statistically significant (**Table 2**) but were limited by few fractures. For all analyses, estimates that included or excluded trials with 0 events were nearly identical, suggesting that including these trials would have little effect on results.

We could not adequately assess whether estimates of efficacy varied in women according to their mean baseline BMD because only FIT stratified results (82). In FIT, for women with baseline femoral neck T-scores less than −2.5, alendronate reduced all types of fractures combined (RR, 0.64 [CI, 0.50 to 0.82]) and vertebral (RR, 0.50 [CI,

Table 2—Continued

Hip		Wrist		Ankle	
RR (95% CI)	Trials, *n* (Reference)	RR (95% CI)	Trials, *n* (Reference)	RR (95% CI)	Trials, *n* (Reference)
0.78 (0.44–1.38)	2 (82, 90)	0.76 (0.27–2.16)	2 (82, 90)	0.40 (0.08–2.07)	1 (90)
0.70 (0.44–1.11)	3 (25, 82, 90)	0.67 (0.25–1.82)	3 (82, 90, 93)	0.33 (0.08–1.44)	2 (90, 93)
No evidence	–	No evidence	–	No evidence	–
0.97 (0.62–1.52)	1 (96)	0.83 (0.66–1.05)	1 (96)	0.94 (0.60–1.47)	1 (96)
0.67 (0.47–0.96)	1 (99)	0.71 (0.69–0.85)	1 (99)	0.71 (0.69–0.85)	1 (99)
0.61 (0.41–0.91)	1 (100)	No evidence	–	No evidence	–

0.31 to 0.82]) and hip (0.44 [CI, 0.18 to 0.97]) fractures specifically. For women with T-scores from −1.6 to −2.0 or −2.0 to −2.5, we found nonstatistically significant trends toward reduced vertebral fractures but no effects on all types of fractures combined.

Parathyroid Hormone. A trial of parathyroid hormone evaluated fracture outcomes after 18 months in postmenopausal women with a BMD T-score less than −3.0 and no prevalent vertebral fractures (81% of enrollees) or a T-score less than −2.5 and 1 to 4 prevalent fractures (19%) (94). The trial was considered fair quality because it did not describe blinding of outcomes. In women without previous fractures, parathyroid hormone reduced new vertebral fractures from 2.1% to 0.7% (RR, 0.32 [CI, 0.14 to 0.75]). Among all women, no difference in nonvertebral fractures was found (**Table 2**).

Raloxifene. The MORE (Multiple Outcomes of Raloxifene) trial included women with BMD T-scores less than −2.5 with or without previous vertebral fractures (96, 98, 104). The RUTH (Raloxifene Use for the Heart) trial was designed primarily to determine the effects of raloxifene on coronary events and invasive breast cancer, and fractures were secondary outcomes (97). In a pooled analysis of both trials, raloxifene reduced vertebral (RR, 0.61 [CI, 0.54 to 0.69]) but not nonvertebral (RR, 0.97 [CI, 0.87 to 1.09]) fractures (105) (**Table 2**). In MORE, risk for vertebral fractures was reduced for women with or without previous vertebral fractures (96, 104).

Estrogen. The WHI (Women's Health Initiative) is the largest prevention trial of estrogen (conjugated equine estrogen) with and without progestin (medroxyprogesterone acetate) that reports fracture outcomes in postmenopausal women. Both trials reported reduced clinical vertebral, hip, and all fractures combined compared with placebo (99, 100) (**Table 2**). However, results of both trials were not statistically significant for selective sites, such as the hip, when CIs were adjusted.

Primary Prevention Trials in Men

The only primary prevention trial for men evaluated the effects of parathyroid hormone in men with osteoporosis (baseline BMD lumbar spine T-scores, −2.0 to −2.4) and met criteria for good quality (95). Results indicated a trend toward reduced vertebral (RR, 0.49 [CI, 0.22 to 1.09]) and nonvertebral (RR, 0.51 [CI, 0.10 to 2.48]) fractures with parathyroid hormone, but fractures were few and results did not reach statistical significance (95, 106).

Harms Associated With Medications for Osteoporosis and Low Bone Density (Key Question 6)

Bisphosphonates

Although case reports of serious upper gastrointestinal adverse events have been reported with all bisphosphonates, systematic reviews and individual trials found no differences with placebo in rates of serious gastrointestinal adverse events (107, 108) or withdrawals (109–116) (**Appendix Table 4**, available at www.annals.org). The FDA recently issued a report that summarized 54 cases of esophageal adenocarcinoma associated with bisphosphonates (117).

Evidence on the risk for atrial fibrillation with bisphosphonates is mixed (112, 113, 118–121). The FDA issued an interim report of an ongoing review based on data from nearly 20 000 patients treated with bisphosphonates in placebo-controlled trials (122). Results indicated no clear association between bisphosphonate exposure and the rate of serious or nonserious atrial fibrillation.

Case reports of severe musculoskeletal pain that may be reversible after discontinuing the medication have been reported with all bisphosphonates. Zoledronic acid was associated with increased musculoskeletal events in a systematic review of trials (123). Case reports of osteonecrosis of the jaw are primarily from patients with cancer who receive intravenous doses of bisphosphonates that are higher than doses used for osteoporosis treatment or prevention (124). Case reports of atypical, low-energy fractures of the femo-

ral diaphysis in long-term users of alendronate have also been reported, but the incidence is unknown (125–127).

Calcitonin and Parathyroid Hormone

Evidence of harms is limited by few trials and inconsistent reporting of adverse events. Calcitonin does not increase risk for the acute coronary syndrome; and calcitonin and parathyroid hormone do not increase risk for cancer or increase mild gastrointestinal events (123).

Raloxifene

Raloxifene increases risk for thromboembolic events but not for coronary heart disease, stroke, or endometrial cancer (97, 128, 105). It can cause hot flashes, leg cramps, and peripheral edema (96, 97, 104). Raloxifene also reduces risk for invasive breast cancer in women without preexisting breast cancer (97, 105).

Estrogen

Both estrogen with progestin and estrogen alone increase thromboembolic events (129, 130) and strokes (100, 131). Estrogen with progestin increases risk for coronary heart disease events (132) and breast cancer (133), does not increase risk for endometrial cancer (134), and reduces risk for colon cancer (135). Estrogen alone did not affect these outcomes in the WHI (100, 136, 137).

Discussion

Table 3 summarizes the evidence reviewed for this update, and an outcomes table providing an illustration of the clinical application of the evidence is described in the **Appendix** and **Appendix Table 5** (see also **Appendix Figures 3** and **4**, available at www.annals.org). No RCTs evaluated the overarching questions of the effectiveness and harms of screening for osteoporosis in reducing fractures and fracture-related outcomes for postmenopausal women and men. Therefore, no direct evidence that screening improves outcomes is available. Support for population screening would be based on evidence that individual risk for fracture can be estimated and fractures can be significantly reduced for persons at risk.

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

Data from large population-based cohorts indicate that the predictive performance of DEXA is similar for men and women. Calcaneal QUS using various types of devices can predict fractures of the femoral neck, hip, or spine in men and women, although variation exists across studies. Quantitative ultrasonography has low correlation with DEXA, and it is not clear how QUS can be used to select persons for medications that were proven efficacious on the basis of DEXA criteria. Data are lacking to determine how frequently to obtain bone measurements, although 1 study indicated no advantage to repeated measures that were 8 years apart (79).

No trials of medications report effects on fracture-related morbidity and mortality. For postmenopausal women, bisphosphonates, parathyroid hormone, raloxifene, and estrogen reduce primary vertebral fractures. Bisphosphonates significantly reduce nonvertebral fractures in sensitivity analyses that used alternative pooling methods or broadened our definition of primary prevention—consistent with meta-analyses of secondary prevention trials of alendronate and risedronate (109, 111). Estrogen also reduces nonvertebral fractures in trials when using unadjusted estimates, but results are not statistically significant when estimates are adjusted. In the only primary prevention trial that stratified results according to baseline BMD, benefits were observed only in patients with T-scores of −2.5 or less (82). For men, no primary prevention trials of bisphosphonates exist, and results from a single trial of parathyroid hormone did not reach statistical significance.

Trials and safety reviews have not supported consistent associations with serious upper gastrointestinal adverse events, atrial fibrillation, or osteonecrosis of the jaw in otherwise healthy patients taking bisphosphonates for fracture prevention. The FDA has recently highlighted case reports of esophageal cancer and severe musculoskeletal pain. An analysis of data from 3 trials published after our searches found no association between bisphosphonate use and atypical fractures of the subtrochanteric or diaphyseal femur, with an event rate of 2.3 per 10 000 patient-years (138). Evidence on harms associated with calcitonin and parathyroid hormone for treatment of osteoporosis is limited. Raloxifene and estrogen with and without progestin increase thromboembolic events; estrogen with and without progestin increases stroke; and estrogen with progestin increases coronary heart disease among older users and breast cancer.

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

Available evidence is also limited. Trials of medications vary in size, duration, quality, and applicability and have few fracture outcomes. Primary prevention trials and trials that enroll men or persons with low BMD (that is, baseline BMD T-scores from −1.0 to −2.5) are lacking. Applying the results of clinical trials to patient care is especially difficult when selection criteria are rigid and study participants do not represent the community population. This is particularly true in older populations, in which

Table 3. **Summary of Evidence**

Studies	Design	Limitations	Consistency	Applicability	Overall Quality
Effectiveness and harms of osteoporosis screening in reducing fractures, morbidity, and mortality (KQs 1 and 4)					
No trials	–	–	–	–	–
Performance of risk-assessment instruments to stratify individuals into risk categories (KQ 2)					
21 risk-assessment instruments with BMD or fracture outcomes that have external validation and reported AUC estimates	Cohort, cross-sectional	Most studies are cross-sectional and instruments have not been applied to a prospective clinical population	Not consistent	Difficult to apply population-determined results to individuals in a clinical setting	Fair
Findings: Several risk-assessment instruments have been developed and validated; they are modest predictors of low bone density or fracture; simple models predict as well as complex ones, and none demonstrates superiority over the others.					
Performance of DEXA in predicting fractures in men (KQ 3a)					
5 studies	Prospective cohort	Few large studies include men	Consistent	Population estimates may not apply to individuals	Fair to good
Findings: DEXA is not a perfect predictor of fractures, but for each SD reduction in femoral neck BMD, the hazard ratio for various fracture outcomes increases to similar levels for men and women.					
Performance of peripheral bone measurement tests in predicting fractures (KQ 3b)					
5 studies in men; 7 studies in postmenopausal women	Prospective cohort, retrospective cohort, cross-sectional	Variability in how measures were used; focus on QUS	Consistent	Population estimates may not apply to individuals	Fair to good
Findings: Calcaneal QUS predicts fractures of the femoral neck, hip, or spine, although variation exists across studies and correlation with DEXA is low.					
Screening intervals (KQ 3c)					
1 study	Prospective cohort	Only 1 relevant study in postmenopausal women	Not applicable	Population estimates may not apply to individuals, particularly those different from the study cohort	Fair
Findings: Repeating a BMD measurement up to 8 y after an initial measurement does not significantly improve predictive performance for nonvertebral, hip, or vertebral fractures.					
Efficacy of medications for reducing osteoporosis-related fractures (KQ 5)					
Women: 15 trials of bisphosphonates, 1 trial of PTH, 2 trials and 1 meta-analysis of raloxifene, 2 trials of estrogen; men: 1 trial of PTH	RCTs	Strength of evidence varies by medication	Consistent	Primary prevention trials are most applicable to a screening-detected population	Poor to good
Findings: For women, bisphosphonates, PTH, raloxifene, and estrogen reduce vertebral fractures; bisphosphonates reduce nonvertebral fractures in sensitivity analyses; medications are effective for BMD T-scores of −2.5 or less. For men, 1 trial of PTH showed nonsignificant trends for reduced fractures.					
Harms associated with medications for osteoporosis and low bone density (KQ 6)					
21 studies of bisphosphonates; 1 systematic review of calcitonin and PTH; 5 studies of raloxifene; 8 studies of estrogen	RCTs, observational studies, case reports and series	Strength of evidence varies by medication	Consistent	Applicable	Poor to good
Findings: Serious GI events, atrial fibrillation, osteonecrosis of the jaw, severe musculoskeletal pain, and esophageal cancer have been reported for bisphosphonates, but the incidence and degree of risk are difficult to estimate for those using them for prevention; raloxifene and estrogen increase thromboembolic events; estrogen increases stroke; and estrogen with progestin increases CHD and breast cancer.					

AUC = area under the curve; BMD = bone mineral density; CHD = coronary heart disease; DEXA = dual-energy x-ray absorptiometry; GI = gastrointestinal; KQ = key question; PTH = parathyroid hormone; QUS = quantitative ultrasonography; RCT = randomized, controlled trial.

comorbid conditions and use of several medications are common and would disqualify patients from enrolling in most trials.

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

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Appendix: Additional Details of Analysis

Adjustment for Rare or 0 Events in the Meta-analysis

To evaluate potential effects of including 0 event trials, we compared the pooled arcsine difference (a measure of risk difference) with and without 0 event trials (29). To evaluate the influence of alternative methods for pooling trials with uncommon outcomes or 0 events in 1 group on the combined results, we compared results from the primary analyses with the Peto ORs and the fixed-effects Mantel–Haenszel RRs with an alternative continuity correction (inverse of the sample size of the opposite treatment group [28]).

Additional Sensitivity Analysis

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

To determine whether baseline BMD affected results, we conducted an analysis that stratified trials according to the mean baseline BMD (T-score less than vs. greater than −2.0). For trials that did not report mean baseline T-scores, we calculated them from mean baseline BMD at the femoral neck by using the FRAX Patch program, version 1.4 (Oregon Osteoporosis Center, Portland, Oregon). We verified that in trials that reported mean baseline T-scores and BMD, reported T-scores were similar to results by using FRAX Patch. If femoral neck BMD was not reported, we used baseline total hip BMD. The FRAX Patch program includes adjustments according to densitometer manufacturer. If the manufacturer was not reported, we calculated T-scores for all 3 manufacturers included in the FRAX Patch and averaged the scores.

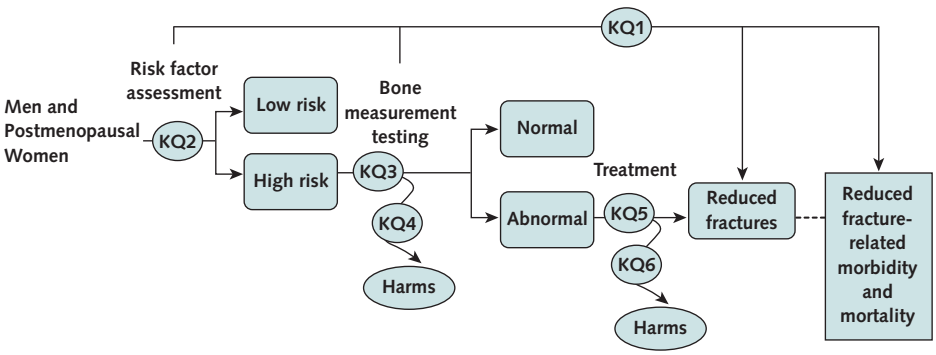
To determine whether our criteria for selecting primary prevention trials affected results, we conducted sensitivity analyses on fracture estimates that included trials that enrolled up to 40% of participants with previous vertebral fractures or did not report baseline vertebral fracture rates and reported a baseline BMD T-score less than −3.0 (22, 24, 87, 101–103).

Screening Strategies and Yield

To estimate the effect of screening 10 000 postmenopausal women with DEXA for primary fracture prevention, we created an outcomes table on the basis of assumptions from the reviewed studies (**Appendix Table 5**). Although these calculations have important limitations and underestimate the uncertainty in the evidence, they provide an illustration of the clinical application of the evidence and may be useful to clinicians and the USPSTF. Data include age-specific prevalence rates expressed in 5-year intervals (139), and treatment effects based on results of the FIT for women without previous vertebral fractures with T-scores of −2.5 or less (82). Results indicate numbers needed to screen to reduce fractures that decline with successive ages consistent with previous estimates (1, 2) (**Appendix Figure 3**).

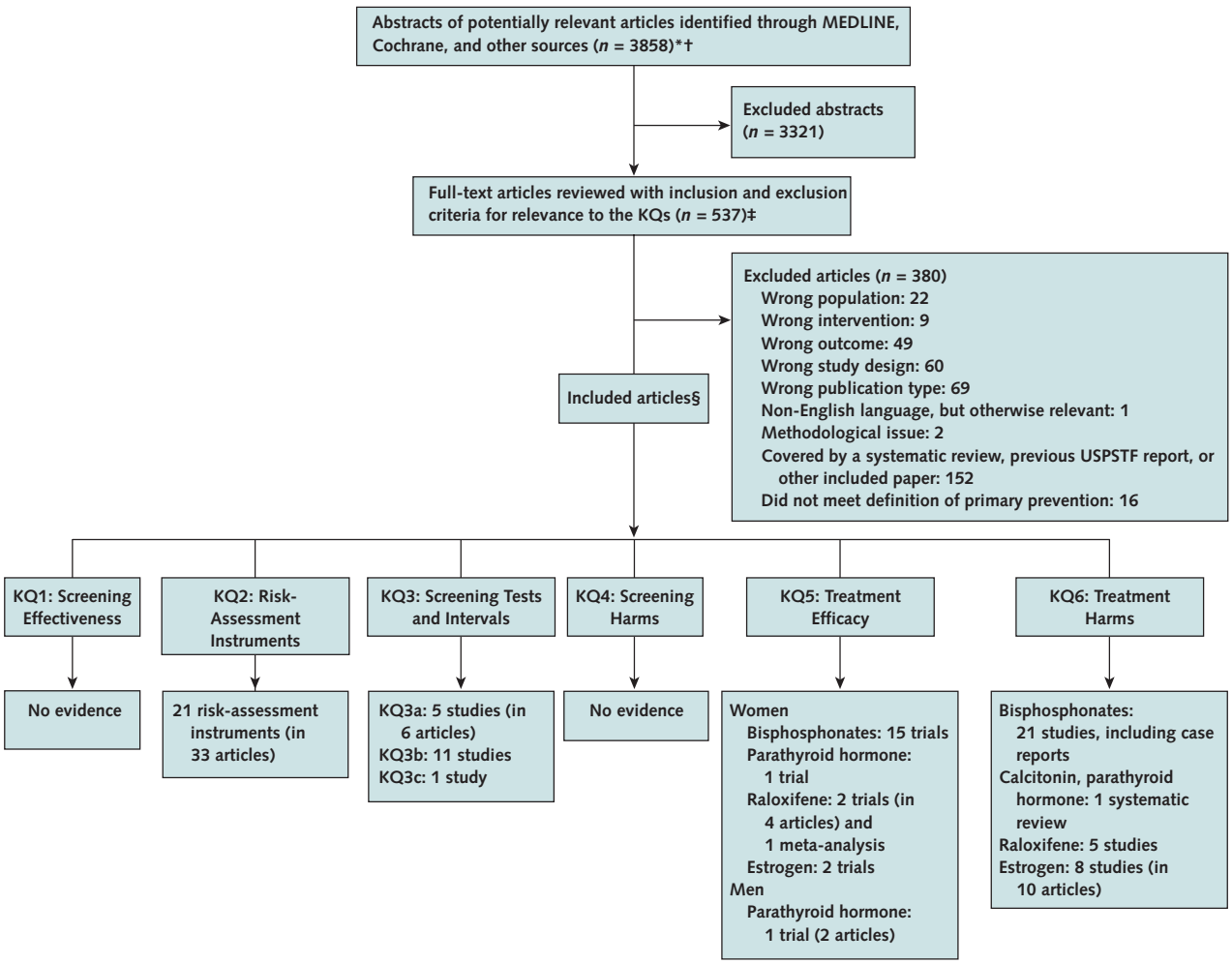
To determine the influence of risk factors in selecting women for densitometry screening, we estimated 10-year risks for major osteoporotic and hip fractures for U.S. white women by using the online FRAX calculator (www.shef.ac.uk/FRAX/). By using risk estimates for women aged 65 years with no additional risk factors as the reference case (9.3% risk for osteoporotic and 1.2% risk for hip fractures), we identified age-specific and risk factor–specific categories of women with similar or higher-risk estimates (**Appendix Figure 4**). Some women younger than 65 years with risk factors exceed the risk equivalents of the reference case. These estimates may be useful in selecting candidates for densitometry screening. Results of densitometry further characterize fracture risk and are useful in determining the appropriateness of medication. Trials support the efficacy of medications to prevent primary fractures only for women with BMD T-scores of −2.5 or less.

Appendix Figure 1. **Analytic framework and KQs.**



KQ = key question.

Appendix Figure 2. **Literature search and selection.**



KQ = key question; USPSTF = U.S. Preventive Services Task Force.
* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Identified from reference lists and suggested by experts.
‡ Some abstracts and articles were considered for more than 1 KQ.
§ Additional articles are described in the technical report (19).

Appendix Table 1. Recent Studies Comparing Performance of Bone Measurement Tests in Predicting Fractures

Study, Year (Reference)	Participants, *n*	Type of Fracture	Bone Measurement Test	AUC (95% CI or SE)	RR for Fracture (95% CI)*	
Women†						
Hans et al, 1996 (71)	5662	Hip	DEXA femoral neck; QUS BUA; QUS SOS	Not reported	1.9 (1.6–2.4)‡; 2.0 (1.6–2.4); 1.7 (1.4–2.1)	
Bauer et al, 1997 (72)	6189	Nonvertebral; hip	DEXA femoral neck; SXA calcaneus; QUS BUA	Not reported	1.3 (1.1–1.5)§; 1.4 (1.2–1.6); 1.3 (1.2–1.5)	2.6 (1.9–3.8)§; 2.2 (1.9–3.0); 2.0 (1.5–2.7)
Khaw et al, 2004 (73)	8328	All	QUS BUA; QUS SOS	Not reported	1.90 (1.36–2.66); 1.62 (1.26–2.08)	
Alexandersen et al, 2005 (74)	1034	All	DEXA spine; DEXA femoral neck; DEXA distal radius; QUS SOS; QUS UBPI	0.60 (0.56–0.65); 0.66 (0.62–0.71); 0.64 (0.59–0.68); 0.60 (0.56–0.65); 0.60 (0.55–0.64)	1.35 (1.19–1.54); 1.81 (1.51–2.16); 1.47 (1.28–1.68); 1.26 (1.12–1.42); 1.55 (1.26–1.90)	
Glüer et al, 2005 (75)	87	Vertebral	DEXA spine; QUS SOS; QUS BUA; QUS stiffness	Not reported	2.13 (1.08–4.16); 2.58 (1.17–5.68); 2.13 (1.04–4.34); 2.83 (1.26–6.34)	
Stewart et al, 2006 (76)	775	All	DEXA lumbar spine; DEXA femoral neck; QUS BUA	0.63 (0.60–0.67); 0.59 (0.56–0.63); 0.62 (0.59–0.66)	1.80 (1.17–2.77); 2.16 (1.35–3.47); 2.25 (1.51–3.34)	
Frediani et al, 2006 (77)	1534	Vertebral	DEXA spine; DEXA femoral neck; QUS stiffness; QUS stiffness plus DEXA spine; QUS stiffness plus DEXA femoral neck	0.95 (0.3); 0.89 (0.3); 0.93 (0.4); 0.97 (0.2); 0.95 (0.3)	4.18 (3.05–6.82)‖; 3.13 (2.76–6.90); 4.18 (3.35–7.13)	
Men						
Mulleman et al, 2002 (68)	102	All	DEXA lumbar spine; DEXA femoral neck; DEXA hip; QUS BUA; QUS SOS; QUS stiffness	0.80 (0.71–0.88); 0.73 (0.64–0.82); 0.81 (0.71–0.88); 0.69 (0.60–0.78); 0.75 (0.66–0.83); 0.74 (0.65–0.83)	2.8 (1.6–5.0)¶; 1.9 (1.1–3.2); 3.4 (1.6–7.0); 1.6 (1.0–2.4); 2.3 (1.4–3.6); 2.1 (1.3–3.3)	
Khaw et al, 2004 (73)	6471	All	QUS BUA; QUS SOS	Not reported	1.87 (1.23–2.86)**; 1.65 (1.17–2.33)	
Gonnelli et al, 2005 (69)	407	All	DEXA hip; QUS stiffness; combined	Not reported	3.4 (2.5–4.8); 3.2 (2.3–4.5); 6.1 (2.6–14.3)	
Varenna et al, 2005 (78)	4832	Nonvertebral; hip	QUS BUA; QUS SOS; QUS stiffness	Not reported	1.38 (1.22–1.59)††; 1.27 (1.17–1.38); 1.14 (0.96–1.40)	2.24 (1.61–3.08)††; 2.19 (1.56–3.11); 1.71 (1.18–3.24)
Bauer et al, 2007 (70)	5608	Nonvertebral; hip	DEXA femoral neck; DEXA hip; QUS BUA; QUS SOS; QUS QUI	Not reported	1.6 (1.4–1.9)§; 1.6 (1.4–1.9); 1.6 (1.4–1.8); 1.6 (1.4–1.9); 1.6 (1.4–1.9)	3.5 (2.5–4.9)§; 2.9 (2.2–4.0); 2.0 (1.5–2.8); 2.2 (1.6–3.1); 2.2 (1.6–3.1)

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

* For studies reporting more than 1 type of fracture, results for the first type are provided first, then results for the second type.

† Adapted from the Canadian Agency for Drugs and Technologies in Health Technology Report (140). Data from references 71 and 72 included for completeness.

‡ Per SD reduction in BMD or QUS measure, adjusted for age, weight, and clinic center.

§ Per SD reduction in BMD or QUS measure, adjusted for age and clinic.

‖ Adjusted for years of menopause, weight, height, and body mass index.

¶ Per SD reduction in BMD or QUS measure.

** Per SD reduction in QUS measure, adjusted for age, previous fracture, smoking status, weight, and height.

†† Per SD reduction in QUS measure, adjusted for age, weight, calcium intake, current smoking status, regular walking outside, bedridden periods >2 mo.

Appendix Table 2. Placebo-Controlled Primary Prevention Trials of Medications

Study, Year (Reference)	Participant Characteristics	Intervention; Duration	Fracture Rates (Drug and Placebo); RR (95% CI)			Quality Rating
			Vertebral	Nonvertebral	Hip	
Bisphosphonates*						
Alendronate						
Ascott-Evans et al, 2003 (80)†	Postmenopausal women aged <80 y with 85% of enrollees aged <65 y; mean T-score, −2.3; no previous fractures	10 mg/d; 1 y	0/95 and 0/47; RR not estimable	0/95 and 0/47; RR not estimable	NR	Fair
Chesnut et al, 1995 (81)‡	Women at least 5 y postmenopausal; aged 43–75 y; mean age, 63 y; mean hip T-score, −1.1; no previous fractures	10 mg/d; 2 y	0/30 and 0/31; RR not estimable	Unclear	NR	Fair
FIT, 1998 (82)‡	Women at least 2 y postmenopausal; mean age, 67.7 y; mean T-score, −2.2; no previous fractures	5 mg/d; 2 y (then 10 mg/d; 2 y)	43/2214 and 78/2218; 0.55 (0.38–0.80)	261/2214 and 294/2218; 0.89 (0.76–1.04)	19/2214 and 24/2218; 0.79 (0.44–1.44)	Good
Dursun et al, 2001 (83)‡	Postmenopausal women mean age, 61.2 y; mean T-score, −1.5; previous fracture unknown	10 mg/d; 1 y	12/51 and 14/50; 0.84 (0.43–1.63)	NR	NR	Poor
Hosking et al, 1998 (86)	Women ≥6 mo postmenopausal; mean age, 53.3 y; mean T-score, −0.1; previous fracture unknown	5 mg/d; 2 y	0/498 and 0/502§; RR not estimable	22/498 and 14/502§; 1.58 (0.82–3.06)	NR	Fair
Liberman et al, 1995 (87)‡	≥5 y postmenopausal; mean age, 64 y; mean T-score, −2.2; 21% with previous vertebral fracture	10 mg/d; 3 y	4/384 and 5/253§; 0.53 (0.14–1.94)	NR	NR	Fair
Pols et al, 1999 (90)	Women ≥3 y postmenopausal; mean age, 63.0 y; mean T-score, −2.0; unknown previous fracture	10 mg/d; 1 y	Not assessed	19/950 and 37/958; 0.52 (0.30–0.89)	2/950 and 3/958; 0.67 (0.11–4.01)	Fair
Etidronate						
Herd et al, 1997 (84)‡	Women 1–10 y postmenopausal; mean age, 54.8 y; mean T-score, −1.3; no previous fracture	Cyclical 400 mg/d; 2 y	0/75 and 0/77; RR not estimable	NR	NR	Fair
Meunier, 1997 (88)‡	Women 6–60 mo postmenopausal; mean age, 52.7 y; mean T-score, −1.1; unknown previous fracture	Cyclical 400 mg/d; 2 y	1/27 and 0/27; 3.00 (0.13–70.53)	2/27 and 3/27; 0.67 (0.12–3.68)	NR	Fair
Pouilles et al, 1997 (91)†	Women 6–60 mo postmenopausal; mean age, 53.8 y; mean T-score, −0.8; unknown previous fracture	Cyclical 400 mg/d; 2 y	1/54 and 0/55; 3.05 (0.13–73.37)	1/54 and 6/55; 0.51 (0.13–1.93)	NR	Fair
Risedronate						
Hooper et al, 2005 (85)‡	Women 6–36 mo postmenopausal; mean age, 53 y; mean T-score, −0.7; unknown previous fracture	5 mg/d; 2 y	10/129 and 10/125; 0.97 (0.42–2.25)	5/129 and 6/125; 0.81 (0.25–2.58)	NR	Fair
McClung et al, 2001 (25)	Mean age, 74 y; mean T-score, −3.7; some women with previous fracture, results reported for women with no baseline fracture (43% of enrollees)	2.5 or 5 mg/d; 3 y	NR	NR	14/1773 and 12/875; 0.58 (0.27–1.24)	Fair
Mortensen et al, 1998 (89)‡	Women 6–60 mo postmenopausal; mean age, 51.5 y; mean T-score, −1.1; unknown previous fracture	5 mg/d; 2 y (follow-up 3 y)	1/37 and 0/36; 0.97 (CI 0.90–1.05)	0/37 and 3/36; 0.14 (0.01–2.60)	0/37 and 0/36; RR not estimable	Fair
Välimäki et al, 2007 (93)†	Women ≥5 y postmenopausal; osteoporosis risk factors or low hip BMD; mean age, 65.9 y; mean T-score, −1.2; unknown previous fracture	5 mg/d; 2 y	0/114 and 0/56; RR not estimable	2/114 and 2/56; 0.49 (0.07–3.40)	0/114 and 0/56; RR not estimable	Fair
Zoledronic acid						
Reid et al, 2002 (92)†‡	Women ≥5 y postmenopausal; mean age, 64.2 y; mean T-score, −1.2; no previous vertebral fracture	4 mg over 1 y in 1–4 infusions; 3 y	0/174 and 0/56; RR not estimable	4/174 and 1/59; 1.36 (0.15–11.89)	NR	Fair

Continued on following page

Appendix Table 2—**Continued**

Study, Year (Reference)	Participant Characteristics	Intervention; Duration	Fracture Rates (Drug and Placebo); RR (95% CI)			Quality Rating
			Vertebral	Nonvertebral	Hip	
PTH						
Greenspan et al, 2007 (94)‡	Postmenopausal women; mean age, 64.4 y; T-score ≤−3.0 and no prevalent vertebral fractures or T-score, −2.5 with 1 to 4 vertebral fractures; mean T-score, −2.2; 19% with previous vertebral fracture	PTH, 100 μg daily injection; 18 mo	7/1050 and 21/1011; 0.32 (0.14–0.75); for those without baseline fracture	72/1286 and 72/1246; 0.97 (0.71–1.33); for all participants	NR	Fair
Orwoll et al, 2003 (95)‡	Men; mean age, 59 y; mean T-score,−2.7; unknown previous fracture	Teriparatide, 20 or 40 μg daily injection; 11 mo	NR	2/151 (20 μg), 1/139 (40 μg), and 3/147 (placebo)	NR	Good
Selective estrogen receptor modulators						
MORE, 2002, 2005, 1999 (96, 98, 104)‡	Postmenopausal women; median age, 66.9 y; mean femoral neck or lumbar spine T-score, −2.57; 37% with previous vertebral fractures	Raloxifene, 60 or 120 mg/d; 4 y	169/2259 (60 mg), 159/2277 (120 mg), and 287/2292 (placebo); 0.64 (0.63–0.76) (60 mg) and 0.57 (0.48–0.69) (120 mg)	548/4536 (both doses combined) and 296/2292; 0.93 (0.81–1.06)	56/4536 (both doses combined) and 29/2292; 0.97 (0.62–1.52)	Good
RUTH, 2006, 2008 (97, 141)†‡	Postmenopausal women with heart disease or risk factors; median age, 67.5 y; unknown previous fracture	Raloxifene, 60 mg/d; 5.6 y	6/5044 and 97/5057; 0.65 (0.47–0.89)	428/5044 and 438/5057; 0.96 (0.84–1.09)	NR	Good
Estrogen						
WHI, 2003 (99)†‡	Postmenopausal women; mean age, 63.3 y; mean lumbar spine T-score, −1.28 in subset; 14% with previous fractures after age 55 y	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d; 5.6 y	41/8506 and 60/8102; 0.65 (nCI, 0.46–0.92)	Wrist fracture, 189/8506 and 245/8102; 0.71 (nCI, 0.59–0.85)	52/8506 and 73/8102; 0.67 (nCI, 0.47–0.96; aCI, 0.41–1.10)	Fair
WHI, 2004 (100)†‡	Postmenopausal women; mean age, 63.6 y; unknown BMD; 12% with previous fracture	CEE, 0.625 mg/d; 6.8 y	39/5310 and 64/5429; 0.62 (nCI, 0.63–0.79; aCI, 0.34–1.13)	NR	38/5310 and 64/5429; 0.61 (nCI, 0.41–0.91; aCI, 0.33–1.11)	Fair

aCI = adjusted CI; BMD = bone mineral density; CEE = conjugated equine estrogen; FIT = Fracture Intervention Trial; MORE = Multiple Outcomes of Raloxifene Evaluation; MPA = medroxyprogesterone acetate; nCI = nominal CI; NR = not reported; PTH = parathyroid hormone; RR = relative risk; RUTH = Raloxifene Use for the Heart; WHI = Women's Health Initiative.

* BMD T-scores for bisphosphonate trials are based on femoral neck measurements and calculated by using the FRAX patch instrument, unless stated otherwise.

† Clinical vertebral fractures only.

‡ Radiologically confirmed fracture incidence.

§ Subgroup of women with no previous vertebral compression fractures.

Appendix Table 3. **Sensitivity Analysis for Trials With Few, Rare, or 0 Fracture Events**

Alternative Method	Fracture Outcome (95% CI)				
	Vertebral	Nonvertebral	Hip	Wrist	Ankle
Arcsine difference, 0 event trials included	−0.03 (−0.05 to 0.00)	−0.03 (−0.05 to 0.00)	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.03)	−0.03 (−0.09 to 0.02)
Arcsine difference, 0 event trials excluded	−0.03 (−0.06 to −0.01)	−0.03 (−0.05 to 0.00)	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.03)	−0.03 (−0.09 to 0.02)
0 event trials excluded					
Mantel–Haenszel relative risk, random-effects model, constant continuity correction (added 0.5 to each group)	0.66 (0.49 to 0.89)	0.83 (0.64 to 1.08)	0.78 (0.44 to 1.38)	0.67 (0.25 to 1.82)	0.33 (0.08 to 1.44)
Peto odds ratio	0.63 (0.47 to 0.84)	0.84 (0.72 to 0.98)	0.78 (0.44 to 1.38)	1.05 (0.78 to 1.41)	0.33 (0.08 to 1.35)
Mantel–Haenszel relative risk, fixed-effects model, variable continuity correction (added inverse of the sample size in the opposite treatment group)	0.65 (0.49 to 0.85)	0.86 (0.74 to 0.99)	0.78 (0.44 to 1.38)	1.03 (0.77 to 1.38)	0.32 (0.07 to 1.49)

Appendix Table 4. Adverse Health Outcomes from Studies, by Medication

Adverse Outcome	Evidence
Bisphosphonates	
Withdrawals	No differences with placebo for alendronate (111), etidronate (110), risedronate (109), zoledronic acid (112, 113), and ibandronate (114–116).
Gastrointestinal events	Mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn) were associated with etidronate and pamidronate in meta-analyses of trials (123); however, several trials were conducted before current preventive dosing measures were widely practiced and may not be relevant. No associations were with alendronate, ibandronate, risedronate, or zoledronic acid. Serious events, including esophageal ulcerations, have been reported for all bisphosphonates, although some trials predate preventive measures (107) and another uses a noncomparable control group (108). Esophageal adenocarcinoma was reported by the FDA in 54 cases of bisphosphonate users (117).
Atrial fibrillation	Data from the HORIZON trial of zoledronic acid (112), FIT of alendronate (118), and a meta-analysis of risedronate trials (119) suggest associations with severe atrial fibrillation. Observational studies of alendronate and etidronate reported conflicting results (120, 121). A report from the FDA based on data from nearly 20 000 patients treated with bisphosphonates in placebo-controlled trials found no associations with atrial fibrillation (122).
Musculoskeletal symptoms	Zoledronic acid was associated with increased muscular and joint pain, arthritis, and muscle cramps (RR, 4.52 [95% CI, 3.48–5.43]; 3 trials) (123). Severe reversible musculoskeletal pain has been reported for all bisphosphonates.
Osteonecrosis of the jaw	A report from the FDA described 151 case reports of osteonecrosis of the jaw through 2003 (124). Of these, 139 occurred in patients with cancer who used high-dose intravenous pamidronate or zoledronic acid and in 12 patients who used alendronate.
Parathyroid hormone	
Cancer	No association (RR, 0.49 [CI, 0.27–0.90]; 3 trials) (123).
Mild gastrointestinal events	No association (RR, 1.39 [CI, 0.98–2.00]; 2 trials) (123).
Calcitonin	
Acute coronary syndrome	No association (RR, 0.98 [CI, 0.07–13.7]; 3 trials) (123).
Cancer	No association (123).
Mild gastrointestinal events	No association (RR, 0.96 [CI, 0.63–1.48]; 15 trials) (123).
Raloxifene	
Thromboembolic events	Increased (RR, 1.60 [CI, 1.15–2.23]; 2 trials) (105).
Coronary heart disease	No association (RR, 0.95 [CI, 0.84–1.06]; 2 trials) (105).
Stroke	No association (RR, 0.96 [CI, 0.67–1.38]; 2 trials) (105).
Breast cancer	Reduced risk for invasive breast cancer in older women without preexisting cancer (RR, 0.44 [CI, 0.27–0.71]; 2 trials) (105).
Endometrial cancer	No association (RR, 1.14 [CI, 0.65–1.98]; 2 trials) (129).
Others	Increased vasomotor symptoms and leg cramps (105).
Estrogen	
Thromboembolic events	Increased with E + P (RR, 2.06 [CI, 1.57–2.70]) (129); results for E-alone were not statistically significant when all events were combined (RR, 1.32 [CI, 0.99–1.75]) (130) but were increased for DVT (RR, 1.47 [CI, 1.06–2.06]) and PE (RR, 1.37 [CI, 1.12–4.40]) when evaluated separately in the WHI (130).
Coronary heart disease	Increased with E + P (RR, 1.24 [CI, 1.00–1.54]) (132)† but not with E-alone (RR, 0.95 [CI, 0.79–1.16]) (136) in the WHI. Women starting E + P within 10 y from the onset of menopause had reduced risk compared with those starting later (142).
Stroke	Increased with E + P (RR, 1.31 [CI, 1.02–1.68]) (131) and E-alone (RR, 1.39 [CI, 1.10–1.77])‡ (100) in the WHI.
Breast cancer	Increased with E + P (RR, 1.24 [CI, 1.01–1.54]) (133) but not with E-alone (RR, 0.80 [CI, 0.62–1.04]) (137) in the WHI.
Endometrial cancer	No association with E + P (RR, 0.81 [CI, 0.48–1.36]) (134) in the WHI.
Others	Decreased colon cancer with E + P (RR, 0.54 [CI, 0.36–0.82]) (135), but not E-alone (RR, 1.08 [CI, 0.75–1.55]) (100) in the WHI. Increased vaginal bleeding.

DVT= deep venous thrombosis; E-alone = estrogen without concomitant use of progestin; E + P = estrogen and concomitant use of progestin; FDA = U.S. Food and Drug Administration; FIT = Fracture Intervention Trial; HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial; PE = pulmonary embolism; RR = risk ratio; WHI = Women's Health Initiative.

* If meta-analysis.

† Adjusted CI, 0.97–1.60.

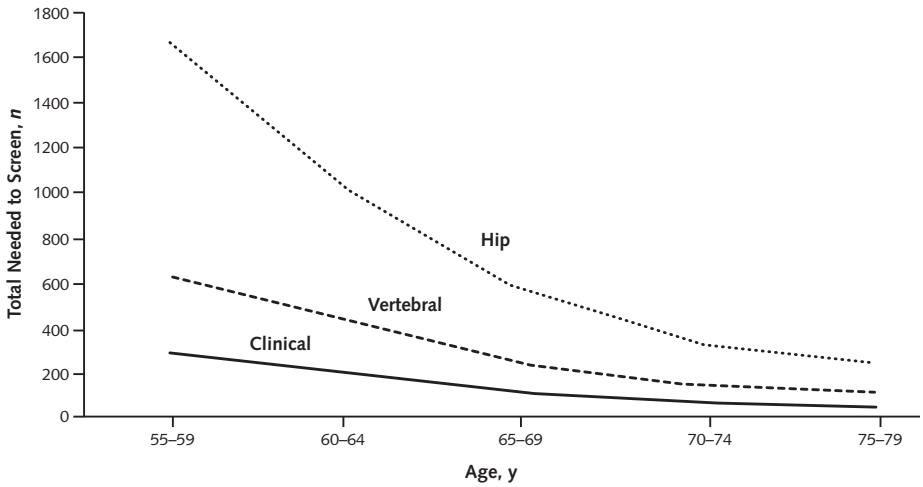
‡ Adjusted CI, 0.97–1.99.

Appendix Table 5. Screening Outcomes for Women Without Previous Vertebral Fractures*

Variable	Age				
	55–59 y	60–64 y	65–69 y	70–74 y	75–79 y
Assumptions					
Number undergoing screening	10 000	10 000	10 000	10 000	10 000
Prevalence of osteoporosis (T-score of −2.5 or less)†	0.0445	0.0650	0.1200	0.2025	0.2850
RR for clinical fracture with alendronate (CI, 0.50–0.82)‡	0.64	0.64	0.64	0.64	0.64
RR for vertebral fracture with alendronate (CI, 0.31–0.82)‡	0.50	0.50	0.50	0.50	0.50
RR for hip fracture with alendronate (CI, 0.18–0.97)‡	0.44	0.44	0.44	0.44	0.44
Outcomes, *n*					
Cases of osteoporosis identified (10 000 × prevalence)	445	650	1200	2025	2850
Clinical fractures expected with no therapy (24.50%)‡	109	159	294	496	698
Clinical fractures expected with therapy (16.38%)‡	73	106	197	332	467
Clinical fractures prevented	36	53	97	164	231
Vertebral fractures expected with no therapy (7.25%)‡	32	47	87	147	207
Vertebral fractures expected with therapy (3.63%)‡	16	24	44	74	103
Vertebral fractures prevented	16	23	43	73	104
Hip fractures expected with no therapy (2.75%)‡	12	18	33	56	78
Hip fractures expected with therapy (1.25%)‡	6	8	15	25	36
Hip fractures prevented	6	10	18	31	42
Number needed to screen to prevent 1 fracture over 5 y					
Clinical fracture	278	187	103	61	43
Vertebral fracture	625	435	233	137	96
Hip fracture	1667	1000	556	323	238

RR = risk ratio.
* Assumptions based on population estimates and results of the Fracture Intervention Trial for women with T-score of −2.5 or less.
† From reference (139).
‡ From results of the Fracture Intervention Trail for women with a BMD T-score of the femoral neck of −2.5 or less (82). Event rates have been recalculated for 5 y.

Appendix Figure 3. **Number of women needed to screen to prevent 1 fracture in 5 years.**



Estimates are based on age-specific prevalence rates of osteoporosis (139) and effects on fracture reduction with bisphosphonates from the Fracture Intervention Trial (82).

Appendix Figure 4. **Ten-year risks for major osteoporotic and hip fractures for U.S. white women estimated from the online FRAX calculator.**

Risk Factor	Age								
	50 y	55 y	60 y	65 y	70 y	75 y	80 y	85 y	90 y
Osteoporotic fracture (none or 1 factor)									
None	3.7	5.7	7.6	9.3	12.0	15.0	20.0	23.0	20.0
Low BMI*	3.8	5.9	7.9	9.8	12.0	16.0	22.0	24.0	21.0
Parent had hip fracture	7.3	11.0	15.0	18.0	18.0	25.0	34.0	39.0	35.0
Current smoker	3.9	6.0	8.1	10.0	13.0	16.0	22.0	25.0	21.0
Daily alcohol use†	4.4	6.9	9.1	11.0	14.0	19.0	25.0	28.0	25.0
Hip fracture (none or 1 factor)									
None	0.2	0.4	0.7	1.2	2.4	4.6	7.6	9.4	8.7
Low BMI	0.3	0.6	1.0	1.9	3.6	6.8	11.0	13.0	12.0
Parent had hip fracture	0.3	0.5	0.9	1.6	5.0	15.0	24.0	29.0	26.0
Current smoker	0.3	0.5	1.0	1.8	3.5	6.5	11.0	13.0	11.0
Daily alcohol use	0.3	0.5	1.0	1.9	3.6	6.9	11.0	14.0	13.0
Osteoporotic or hip fracture (>1 factor)									
Low BMI and parent had hip fracture	7.4/0.4	11.0/0.7	15.0/1.4						
Low BMI and current smoker	4.0/0.5	6.2/0.8	8.5/1.5						
Low BMI and daily alcohol use	4.5/0.5	7.1/0.8	9.6/1.6						
Parent had hip fracture and current smoker	7.6/0.4	12.0/0.7	15.0/1.3						
Parent had hip fracture and daily alcohol use	8.7/0.4	13.0/0.7	17.0/1.3						
Current smoker and daily alcohol use	4.6/0.4	7.2/0.8	9.8/1.5						
Low BMI, parent had hip fracture, and current smoker	7.8/0.6	12.0/1.1	16.0/2.0						
Low BMI, parent had hip fracture, and daily alcohol use	8.8/0.6	14.0/1.1	18.0/2.1						
Low BMI, current smoker, and daily alcohol use	4.9/0.7	7.6/1.3	10.0/2.3						
Parent had hip fracture, current smoker, and daily alcohol use	9.1/0.6	14.0/1.1	18.0/2.0						
All 4 risk factors	9.3/0.9	14.0/1.7	19.0/3.1						

Major osteoporotic fractures include hip, clinical vertebral, proximal humerus, and distal forearm. Highlighted risks equal or exceed the reference case (woman aged 65 years with no risk factors: 9.3% for osteoporotic fracture; 1.2% for hip fracture). BMI = body mass index.

* Normal BMI = 25.0 kg/m^2 based on average height of 163 cm (64.17 in) and weight of 66.5 kg (146.61 lb). Low BMI = 21.2 kg/m^2 based on average height of 163 cm (64.17 in) and weight of 56.7 kg (125 lb).

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