Screening for Postmenopausal Osteoporosis: A Review of the Evidence for the U.S. Preventive Services Task Force

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Background: **Although osteoporotic fractures present an enormous health burden, it is not clear whether screening to identify high-risk persons is appropriate.**

Purpose: **To examine evidence on the benefits and harms of screening postmenopausal women for osteoporosis.**

Data Sources: **MEDLINE (1966 to May 2001), HealthSTAR (1975 to May 2001), and Cochrane databases; reference lists; and experts.**

Study Selection: **English-language abstracts that included original data about postmenopausal women and osteoporosis and addressed the effectiveness of risk factor assessment, bone density tests, or treatment were included.**

Data Extraction: **Selected information about patient population, interventions, clinical end points, and study design were extracted, and a set of criteria was applied to evaluate study quality.**

Data Synthesis: **No trials of the effectiveness of screening have been published. Instruments developed to assess clinical risk factors for low bone density or fractures have moderate to high sensitivity and low specificity. Among different bone density tests measured at various sites, bone density measured at the femoral neck by dual-energy x-ray absorptiometry is the best predictor of hip fracture. Women with low bone density have approximately a 40% to 50% reduction in fracture risk when treated with bisphosphonates.**

Conclusions: **Population screening would be based on evidence that the risk for osteoporosis and fractures increases with age, that the short-term risk for fracture can be estimated by bone density tests and risk factors, and that fracture risk can be reduced with treatment. The role of risk factor assessment and different bone density techniques, frequency of screening, and identification of subgroups for which screening is most effective remain unclear.**

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Half of all postmenopausal women will have an osteoporosis-related fracture during their lives, including one quarter who will develop a vertebral deformity (1) and 15% who will suffer a hip fracture (2). Hip fractures are associated with high mortality rates and loss of independence (3, 4). Although many vertebral fractures are detected only incidentally on radiography, some cause severe pain, leading to 150 000 hospital admissions per year in persons older than 65 years of age, 161 000 physician office visits, and more than 5 million days of restricted activity in those 45 years of age or older (5).

Low bone density has been used to predict risk for fractures as well as to diagnose osteoporosis. Osteoporosis has been defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (6, 7). This definition emphasizes that, in addition to bone mass, the structure of bone is an important factor in the pathogenesis of fractures.

A World Health Organization working group (8) proposed that osteoporosis should be diagnosed in epidemiologic studies when bone mineral density is 2.5 SDs or more below the mean for healthy young adult women at the spine, hip, or wrist (corresponding to a T-score ≤ -2.5) or when patients have a history of atraumatic fracture (9). By the World Health Organization definition, up to 70% of women older than 80 years of age have osteoporosis (10). Age is also an important factor in the relationship between bone density and the absolute risk for fracture. Older women have a much higher fracture rate than younger women with the same bone density because of increasing risk from other factors, such as bone quality and tendency to fall (11).

Despite the high prevalence of osteoporosis and the effect of fractures on mortality, independence, and quality of life, it is not clear whether it is appropriate to screen asymptomatic postmenopausal women. Recent systematic reviews and guidelines disagree about which women should be screened and when (12–20). This disagreement reflects, in part, gaps in the evidence. For example, most guidelines recommend using risk factors to select patients for bone density testing, but because of inadequate data there is no consensus on which risk factors to use. As part of the U.S. Preventive Services Task Force update of its 1996 recommendation (21), we examined evidence on the benefits and harms of screening postmenopausal women for osteoporosis. Specifically, we addressed the role of risk factors in identifying high-risk women, techniques of bone density testing to identify fracture risks, effectiveness of treatment in reducing fracture risk, and harms of screening and treatment.

Methods

Additional methods used for this review, including determination of the quality of studies (22), are detailed in **Appendix Tables 1, 2,** and **3** (available at www.annals.org) and in a separate report (23). The analytic framework and key questions are detailed in the **Appendix Figure** (available at www.annals.org). Relevant studies were identified from multiple searches of MEDLINE (1966 to May

2001), HealthSTAR (1975 to May 2001), and Cochrane databases; reference lists of systematic reviews; and experts. We also sent letters to manufacturers of bone density devices requesting additional information about the performance of their instruments, but we received no new data.

Two reviewers read each abstract to determine its eligibility. We included English-language abstracts that contained original data about postmenopausal women and osteoporosis and addressed screening or the effectiveness of risk factor assessment, bone density testing, or treatment. We considered screening to be the process of assessing postmenopausal women without known osteoporosis for risk of osteoporotic fractures by identification of risk factors, including low bone density. Postmenopausal women were those who had experienced surgical or natural menopause, regardless of age. Women with preexisting atraumatic fractures were not considered in the screening population because they had confirmed osteoporosis according to the World Health Organization definition.

For studies of prediction, we selected articles that reported the relationship between risk factor assessment methods or bone density tests and bone density, bone loss, or fractures. We reviewed studies of medications used for treatment and present results for bisphosphonates. We focused on randomized, controlled trials of therapies reporting radiographically verified, nontraumatic fracture outcomes because fractures are a stronger measure of effectiveness than bone density. We excluded studies of primary prevention of osteoporosis, such as the role of nutrition, calcium consumption, and physical activity. We also excluded secondary causes of osteoporosis, such as corticosteroid use and certain chronic diseases, and studies that did not provide sufficient information to allow determination of the method for selecting patients and for analyzing data. Investigators read the full-text versions of the retrieved papers and reapplied the initial eligibility criteria. To assess the internal validity of individual studies, we applied a set of criteria developed by the third U.S. Preventive Services Task Force (**Appendix Table 1**, available at www.annals.org) (22).

In this paper, we highlight studies that are applicable to current practice standards, have high-quality internal validity ratings, and are most generalizable to the U.S. population of postmenopausal women under consideration for screening. We created an outcomes table to summarize the number of hip and vertebral fractures prevented based on age-specific prevalence rates and treatment effects obtained from results of the reviewed studies. We conducted a sensitivity analysis to determine the influence of risk factors on the number needed to screen.

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RESULTS

Studies of Screening

We identified no studies about the effectiveness of screening in reducing osteoporotic fractures. Without direct evidence from screening studies, recommendations about screening need to rely on evidence that risk factor assessment or bone density testing can adequately identify women who could ultimately benefit from treatment.

Risk Factor Assessment

Hundreds of studies report associations between risk factors and low bone density and fractures in postmenopausal women (24). The most comprehensive study of risk factors in a U.S. population is the Study of Osteoporotic Fractures, a good-quality prospective study of 9516 women 65 years of age and older (25). In this study, 14 clinical risk factors were identified as significant predictors of hip fracture in multivariable models (age; maternal hip fracture; no weight gain; height; poor self-rated health; hyperthyroidism; current use of benzodiazepines, anticonvulsants, or caffeine; not walking for exercise; lack of ambulation; inability to rise from a chair; poor scores on two measures of vision; high resting pulse; and any fracture since 50 years of age). The relative risk for hip fracture per decrease of 1 SD in calcaneal bone density was 1.6 (95% CI, 1.3 to 1.9). This was comparable to the magnitude of the relative risks of most of the other significant predictors in the model, which ranged from 1.2 to 2.0. Women with at least 5 of the 14 risk factors had increased rates of hip fractures compared with those who had 0 to 2 risk factors at all levels of calcaneal bone density.

To determine which risk factors could be important in women younger than 65 years of age, we reviewed eight observational studies of risk factors and fractures of various types conducted in populations in which at least 50% of participants were younger than 65 years of age. **Table 1** lists risk factors that were statistically significant predictors for fractures in multivariable models (26–33). These results could not be quantitatively combined because risk factors were defined differently in each study.

Results of risk factor studies have been used to assess risk in individuals. We identified 10 cross-sectional studies that described methods of determining risk for low bone density for individual women based on selected clinical risk factors (**Table 2**) (34–43). The most common methodologic limitations of these studies are lack of validation and lack of generalizability because of small numbers of patients or nonrepresentative patients. We also identified 8 studies of clinical risk factors to determine fracture risk (**Table 2**) (44–51). None of these studies received a good rating for internal validity. Four studies evaluated hip frac-

Table 1. **Risk Factors for Fractures in Women 50–65 Years of Age**

Risk Factor	Relative Risk for Fracture (95% CI)	Reference
Age		
Per 2 y	1.11 (1.01–1.21)	26
Per 5 y	1.94 (1.55–2.42)	27
Body mass index		
Per increase of 10 kg/m^2	0.58 (0.36–0.92)	27
≥25.6 kg/m^2	wrist, 0.7 (0.5–0.9); ankle, 1.6 (1.0–2.4)	26
≥28.6 kg/m^2	wrist, 0.5 (0.4–0.7); ankle, 2.0 (1.3–3.1)	26
Low	1.1 (1.0–1.2)	29
Height (per 0.1 m)	1.58 (1.18–2.12)	27
Mother with fracture	1.27 (1.16–1.40)	30
Grandmother with hip fracture	3.70 (1.55–8.85)	31
Hormone replacement therapy		
Current use	0.82 (0.74–0.91)	30
Per 5 y of use	0.5 (0.2–0.9)	28
>2 y of use	0.44 (0.22–0.89)	32
Long history of use	0.70 (0.50–0.96)	33
African American ethnicity	0.54 (0.41–0.72)	30
Diabetes mellitus	9.17 (3.38–24.92)	27
Chronic conditions	1.3 (1.1–1.5)	26
Disability pension	3.79 (2.15–6.68)	27
Long-term work disability	1.3 (1.1–1.6)	26
Self-rated health (fair or poor)	1.79 (1.52–2.11)	30
Moderate daily physical activity	0.61 (0.37–0.99)	32
Alcohol		
≥100 g/wk	1.70 (1.08–2.67)	33
Regular use	1.4 (1.3–4.4)	29
1 to 6 drinks/wk	0.85 (0.75–0.96)	30
Smoking		
Current	1.5 (1.3–1.5); 1.14 (1.00–1.30)	26, 30
Former	1.09 (1.00–1.19)	30
≥11 cigarettes/d	3.0 (1.9–4.6)	26
Unmarried	2.16 (1.28–3.64)	27
College education or higher	1.26 (1.16–1.38)	30
Age at menopause	0.94 (0.88–0.99)	32
Time since menopause		30
10–19 y	1.18 (1.01–1.38)	
20–29 y	1.31 (1.12–1.54)	
30 y	1.51 (1.26–1.81)	
Oophorectomy before age 45	3.64 (1.01–13.04)	33
≥5 children	2.5 (1.1–6.7)	29

ture outcomes, two evaluated vertebral fractures, and two evaluated all types of fractures. These studies described the association of risk factors with fractures known to have occurred already (four case–control studies) or how well they would predict fractures in the future (four prospective cohort studies).

A recent study compared the performance of five clinical decision rules for bone density testing among 2365 postmenopausal women 45 years of age or older who were enrolled in a community-based study of osteoporosis in Canada (52). These rules included guidelines from the National Osteoporosis Foundation (53); the Simple Calculated Osteoporosis Risk Estimation (SCORE) rule (age, weight, ethnicity, estrogen use, presence of rheumatoid arthritis, history of fractures) (41); the Osteoporosis Risk Assessment Instrument (ORAI) (age, weight, current use of hormone replacement therapy) (43); the Age, Body Size, No Estrogen rule (54); and body weight criterion (weight < 70 kg) (38). None of the decision rules had good discriminant performance. In this study, SCORE and ORAI had the highest area under the receiver-operating characteristic curves (0.80 and 0.79, respectively [sensitivity, 99.6% and 97.5%; specificity, 17.9% and 27.8%, respectively]). Details of how to use SCORE and ORAI are given in **Table 2**.

Bone Density Tests

Several technologies are available to measure bone density (55–58), although correlations among different bone density devices are low (0.35 to 0.60) (59–79). Dual-energy x-ray absorptiometry is considered the gold standard because it is the most extensively validated test against fracture outcomes. When used in the same patients, dual-energy x-ray absorptiometry machines from different manufacturers differ in the proportion of patients diagnosed as having osteoporosis by 6% to 15% (80–85). Published studies consistently show that the probability of receiving a diagnosis of osteoporosis depends on the choice of test and site (86–90). One analytic study, for example, found that 6% of women older than 60 years of age would receive a diagnosis of osteoporosis if dual-energy x-ray absorptiometry of the total hip were used as the only test, compared

Table 2. **Studies of Risk Factor Assessment***

Study, Year (Reference)	Design	Participants, *n*	Validated	Risk Factors Included	Outcome
Bone density outcomes					
Slemenda et al., 1990 (34)	Cross-sectional	124	No	Age, height, weight, calcium intake, caffeine intake, alcohol and tobacco use, urinary markers of bone turnover	Correct classification of high or low BMD (lowest third of participants)
Falch et al., 1992 (35)	Cross-sectional	73	Yes	Low body weight, reduced renal phosphate reabsorption, smoking	Bone loss
Ribot et al., 1992 (36)	Cross-sectional	1565	No	Weight, menopause, duration of menopause	Vertebral BMD < -2 SD
Elliot et al., 1993 (37)	Cross-sectional	320	Yes	Spine BMD: age, weight, smoking status, age at menarche; femoral neck BMD: age, weight, family history, activity, smoking status	Low lumbar spine and femoral neck BMD (lowest third of age-matched normal range)
Michaëlsson et al., 1996 (38)	Cross-sectional	175	No	Weight $>$ 70 kg	Femoral neck BMD < -2.5 SD
Verhaar et al., 1998 (39)	Cross-sectional	61	No	Arm span–height difference of ≥3 cm; arm span–height difference, age $<$ or $>$ 70 y, and whether arm span was $<$ or $>$160 cm	BMD ≤ -2.5 SD and vertebral fracture
Ballard et al., 1998 (40)	Cross-sectional	1158	No	Age, age at menopause, height, weight, gravidity, parity, current use of steroids, current use of HRT	Osteoporosis of femoral neck, spine, or both
Lydick et al., 1998 (41)	Cross-sectional	1279	Yes	SCORE = age (3 × first digit of age in years), weight (−1 × weight in pounds/10 and truncated to integer), ethnicity (5 if not black), estrogen use (1 if never used), rheumatoid arthritis (4 if present), history of fractures (4 for each fracture after age 45 y of wrist, hip, or rib, to a maximum of 12)	Femoral neck BMD ≤ -2 SD
Goemaere et al., 1999 (42)	Cross-sectional	300	No	18-item questionnaire of risk factors for osteoporosis (ethnicity; height loss; age; weight; smoking, coffee, alcohol, dairy product use; activity; family history; existence of comorbid conditions; history of wrist fracture; menopause before age 45 y; corticosteroid use)	Lumbar spine, femoral neck, and hip BMD
Cadarette et al., 2000 (43)	Cross-sectional	926	Yes	ORAI = age (15 points if ≥75 y, 9 if 65–74 y, 5 if 55–64 y), weight (9 if <60 kg, 3 if 60–69.9 kg), current use of HRT (2 if not currently using)	Hip or lumbar spine BMD ≤ -2.5 SD
Fracture outcomes					
Kleerekoper et al., 1989 (44)	Case–control	663	No	Model 1: total months of lactation, family history of osteoporosis, years postmenopause, weight Model 2: breastfed, surgical menopause, age at menarche, age, smoking status	Vertebral fractures
van Hemert et al., 1990 (45)	Cohort	1014	No	Age, metacarpal cortical area, relative cortical area, BMI, height, diameter of forearm, diameter of knee, age at menarche, age at menopause, smoking, number of children, period of lactation	Osteoporotic fractures
Cooper et al., 1991 (46)	Case–control	1012	No	Age, height, vertebral fracture after age 45 y, age at last menstrual period, number of children, ever use of oral corticosteroids	Vertebral fractures
Wolinsky and Fitzgerald, 1994 (47)	Cohort	368	No	White ethnicity, female sex, living in southern United States, age, hospitalization in the previous year, previous fall, body mass	Hip fractures
Johnell et al., 1995 (48)	Case–control	5618	No	Late menarche, poor mental score, low BMI, low level of physical activity, little exposure to sunlight, and low consumption of calcium and tea	Hip fractures
Ranstam et al., 1996 (49)	Case–control	7474	No	Mental–functional risk score: knowledge of the day of week, knowledge of age, ability to wash, ability to dress	Hip fractures
Tromp et al., 1998 (50)	Cohort	1469	No	Female sex, living alone, past fractures, inactivity, height, use of analgesics	Probability of fractures
Burger et al., 1999 (51)	Cohort	5208	No	Model with BMD: age, sex, height, use of a walking aid, current smoking, BMD of femoral neck Model without BMD: age, sex, height, use of a walking aid, current smoking, weight	Hip fractures

* BMD = bone mineral density; BMI = body mass index; HRT = hormone replacement therapy; NPV = negative predictive value; PPV = positive predictive value; ORAI = Osteoporosis Risk Assessment Instrument; ROC = receiver-operating characteristic (≥0.80 usually indicates effectiveness); SCORE = Simple Calculated Osteoporosis Risk Estimation.
† Based on criteria developed by the U.S. Preventive Services Task Force (22).

with 14% with dual-energy x-ray absorptiometry of the lumbar spine, 3% with quantitative ultrasonography, and 50% with quantitative computed tomography (87).

The likelihood of receiving a diagnosis of osteoporosis also depends on the number of sites tested. Testing in the forearm, hip, spine, or heel generally identifies different

Table 2—**Continued**

Performance	Quality Rating†
Midshaft radius: 68% low, 77% high Lumbar spine: 61% low, 45% high Femoral neck: 66% low, 53% high	Poor
Sensitivity, 36%; specificity, 89%; PPV, 74%	Poor
Sensitivity, 73%; specificity, 66%	Fair
Lumbar spine: sensitivity, 86%; specificity, 32% Femoral neck: sensitivity, 89%; specificity, 25%	Fair
Sensitivity, 94%; specificity, 36%; PPV, 21%; NPV, 97%	Fair
Arm span only: sensitivity, 58%; specificity, 56% Arm span, age, arm span length: sensitivity, 81%; specificity, 64%	Poor
ROC area, 0.73	Fair
Sensitivity, 89%; specificity, 50%; ROC area, 0.81 using a score of ≥6	Good
Lumbar spine: ROC area, 0.66 Femoral neck: ROC area, 0.69 Hip: ROC area, 0.76	Fair
Sensitivity, 95%; specificity, 41%, using a score of ≥9	Good
Model 1: mean ROC area ± SE, 0.55 ± 0.07; sensitivity, 56%; specificity, 54% Model 2: mean ROC area ± SE, 0.51 ± 0.042; sensitivity, 63% specificity, 39%	Fair
Sensitivity, 48%; specificity, 82%	Fair
Sensitivity, 51%; specificity, 69%	Fair
ROC area, 0.71; sensitivity, 64.7%; specificity, 65.7%	Fair
Sensitivity, 55%; specificity, 65%	Fair
A less than perfect score had a sensitivity of 46% and a specificity of 79%	Fair
No predictors, 0%; 4 predictors, 12.9%	Fair
Model with BMD: ROC area, 0.88; sensitivity, 70%; specificity, 84% Model without BMD: ROC area, 0.83; sensitivity, 70%; specificity, 83%	Fair

groups of patients. For example, a physician cannot definitively say that a patient does not have osteoporosis on the basis of a forearm test alone. Conversely, although test results at any site are associated to some degree with fractures at other sites, a physician may not be able to assess whether a patient with a low T-score on a hand or forearm test has substantial bone loss at other sites.

A meta-analysis assessed 23 publications from 11 separate prospective cohort studies published before 1996 (91). Nearly all of the data were from women in their late 60s or older. No studies of ultrasonography were included. The meta-analysis indicated that dual-energy x-ray absorptiometry at the femoral neck predicted hip fracture better than measurements at other sites and was comparable to forearm measurements for predicting fractures at other sites (92–94). For bone density measurements at the femoral neck, the pooled relative risk per decrease of 1 SD in bone density was 2.6 (CI, 2.0 to 3.5). In direct comparisons, heel ultrasonography was slightly worse than but comparable to dual-energy x-ray absorptiometry of the hip in women older than 65 years of age (**Table 3**) (92, 94–100). For both tests, a result in the osteoporotic range is associated with an increased short-term probability of hip fracture. No data compare dual-energy x-ray absorptiometry and ultrasonography for prediction of fracture in women younger than 65 years of age.

The National Osteoporosis Risk Assessment study (30) recently evaluated the performance of peripheral densitometry in predicting fractures. This prospective study of ambulatory postmenopausal women 50 years of age or older with no previous osteoporosis diagnoses recruited 200 160 participants from 4236 primary care practices in 34 U.S. states. Women received baseline T-scores by measuring bone density at the heel (single-energy x-ray absorptiometry or quantitative ultrasonography), forearm (peripheral dual-energy x-ray absorptiometry), or finger (peripheral dual-energy x-ray absorptiometry). After 12 months of follow-up, women with T-scores less than or equal to −2.5 had an adjusted risk for all types of fractures that was 2.74 (CI, 2.40 to 3.13) times higher than women with normal baseline bone density. Results varied by type of test and site; those identified as osteoporotic by dual-energy x-ray absorptiometry had higher fracture rates. Tests were not compared with dual-energy x-ray absorptiometry of the femoral neck, and the study did not describe how tests performed by age group or risk category.

Treatment

The U.S. Food and Drug Administration has approved hormone replacement therapy, bisphosphonates, raloxifene, and calcitonin for osteoporosis prevention or treatment, or both. Our review of estrogen and selective estrogen receptor modulators is presented elsewhere (101).

A recent meta-analysis (102) of 11 randomized trials (103–113) enrolling 12 855 women found that at least 5 mg of alendronate per day reduced vertebral fractures in 8 trials (relative risk, 0.52 [CI, 0.43 to 0.65]). Alendronate also reduced forearm fractures in 6 trials involving 3723 participants (dosage, ≥10 mg/d; weighted relative risk,

Table 3. **Prospective Studies of Dual-Energy X-Ray Absorptiometry and Ultrasonography That Reported Hip Fractures***

Cohort (Reference)	Sample	Age (Range)	Follow-up	Participants	Probability of Hip Fracture†				
						DEXA of the Hip		QUS of the Heel	
						Low Risk	High Risk	Low Risk	High Risk
		y		*n*					
Study of Osteoporotic Fractures (92, 94–96)	Community-dwelling white women from 4 areas in the United States who were recruited from lists	≥65	1.8–2.9	5236	0.009	0.005	0.023	0.006	0.018
		65–79	2.9					0.006	0.23
		≥80	2.9						
		65–69	1.8	2371	0.003	0.0028	0.005		
		70–74	1.8	3013	0.0076	0.005	0.016		
		75–79	1.8	1728	0.007	0.003	0.019		
		80–84	1.8	731	0.018	0.007	0.049		
		≥85	1.8	291	0.024	0.014	0.028		
Epidemiologie de L'Osteoporose (97–100)	Women from 5 cities in France who were recruited from voting lists and health insurance companies	≥75	2	5656	0.02	0.033	0.008	0.012	0.029
		<80	2	3982	0.013	0.002	0.025		
		≥80	2	3616	0.028	0.006	0.04		

* DEXA = dual-energy x-ray absorptiometry; QUS = quantitative ultrasonography.
† Probability of hip fracture if bone density was classified as high or low risk.

0.48 [CI, 0.29 to 0.78]), hip fractures in 11 trials involving 11 808 participants (dosage, ≥5 mg/d; weighted relative risk, 0.63 [CI, 0.43 to 0.92]), and other nonvertebral fractures in 6 trials involving 3723 participants (dosage, 10 to 40 mg/d; weighted relative risk, 0.51 [CI, 0.38 to 0.69]). These trials included follow-up data ranging from 1 to 4 years; effect sizes for longer periods of use are not known. We evaluated data from these trials to determine whether women who have a similar overall risk for fracture but different bone densities derive similar benefit from treatment. This question is clinically important because accepted criteria for initiating treatment are lacking.

The Fracture Intervention Trial (FIT) of alendronate was conducted with two groups of participants and provides some information about levels of risk. One group (FIT-I) included a higher-risk sample of 2027 women who had T-scores of −1.6 or lower and preexisting vertebral fractures (104). The 3-year risk for hip fracture was 2.2% in the placebo group and 1.1% in the alendronate group (relative hazard, 0.49 [CI, 0.23 to 0.99]), and the 3-year risk for any clinical fracture was 18.2% in the placebo group and 13.6% in the alendronate group (relative hazard, 0.72 [CI, 0.58 to 0.90]). A second study from FIT (FIT-II) included a lower-risk sample of 4432 women who also had T-scores of −1.6 or lower but did not have preexisting vertebral fractures (114). The 4-year incidences of hip fracture (1.1%) and any clinical fractures (14.1%) in the placebo group were lower than those observed in the FIT-1 placebo group. In FIT-II, only the subgroup of treated patients who had T-scores lower than −2.5 (n = 1627) had a significant risk reduction for all clinical fractures, from 19.6% to 13.1% (relative risk, 0.64 [CI, 0.50 to 0.82]). No reduction in risk for fractures was seen in patients who had T-scores between −1.6 and −2.5.

The results from FIT suggest that women with more risk factors for fracture relating to bone structure and integrity, such as age, very low bone density, or preexisting vertebral fractures, derive the greatest absolute benefit from treatment. However, FIT did not examine other nonskeletal risk factors, such as psychomotor impairment, poor gait, and other factors that increase the risk for falling. The effect of some of these risk factors on the benefit of treatment was examined in a randomized trial of another bisphosphonate, risedronate (115). Risedronate had no effect on hip fracture rates among women 80 years of age or older who had one or more risk factors for falls but who did not necessarily have low bone density. In the same report, in women 70 to 79 years of age with severe osteoporosis (T-score < −3), risedronate reduced hip fractures by 40% (relative risk, 0.6 [CI, 0.4 to 0.9]; number needed to treat for benefit, 77).

Trial results are not applicable to a screening program unless the trials included patients who would be identified by screening the general population. We examined recruitment and eligibility characteristics of the 10 published randomized trials of alendronate to assess whether selection biases or other biases might have affected their generalizability (**Table 4**) (103–112). Overall, the trials included relatively healthy women with low bone density who were not using estrogen. Except for participants in two trials involving women who had recently gone through menopause and were not osteoporotic, most participants were older than 65 years of age.

The FIT-II is the largest study and provided the most detailed description of recruitment and results (107). In FIT-II, researchers recruited the sample of 4432 women by mailing a query to more than 1 million women selected from the general population in 11 cities. Women who had medical problems (for example, dyspepsia) or who used estrogen were excluded. Fifty-four thousand women (approximately 5.4%) responded by telephone; of these, 26 137 (52%) had a screening visit. A higher than expected proportion of these (65%) had sufficiently low bone density to enroll in the study. Of this 65%, 57% were classified as "ineligible, did not wish to continue, or screened after recruitment to this arm." It is not clear from this description how many patients did not meet the eligibility criteria. In addition, an unspecified number of patients (up to 28 000) were found to be ineligible at the initial stage of recruitment. The demographic characteristics of eligible and screened but excluded participants were not reported. None of the other randomized trials disclosed any details of how their samples were recruited or how many respondents were found to be ineligible before randomization.

In other clinical areas, the results of industry-sponsored trials were significantly more favorable to newer therapies than trials funded by nonprofit organizations (116, 117). Because all 11 trials of alendronate were funded wholly or in part by the manufacturer, we were unable to assess the influence of sponsorship on effect size. If effectiveness of treatments is less than estimated in these trials, the efficiency of screening to identify candidates for treatment will be reduced and the number needed to screen for benefit will increase.

Harms

Several potential harms are associated with screening and treatment. A test result indicating osteoporosis could produce anxiety and perceived vulnerability (118) that may be unwarranted. On a quality-of-life questionnaire, women with osteoporosis voiced significantly more fears than women who had normal bone density (119). Some women may be falsely reassured if abnormal results from last year's dual-energy x-ray absorptiometry of the hip appear "improved" on this year's normal calcaneal ultrasonogram. The potential time, effort, expense, and radiation exposure of repeated scans over a lifetime have not yet been determined.

Potential harms may also arise from inaccuracies and misinterpretations of bone density tests. The variation among techniques, along with the lack of methods to integrate bone density results with clinical predictors, makes it difficult for clinicians to provide accurate information to patients about test results. In one study, physicians found densitometry reports confusing and were not confident that their interpretations of T-scores were accurate (120). False-positive results could lead to inappropriate treatment, and false-negative results could lead to missed treatment opportunities.

Harms of treatment depend on the medication used. Overall, gastrointestinal side effects occur in approximately 25% of patients taking alendronate, but in controlled trials these rates were usually not significantly higher than those for placebo. High rates of serious gastrointestinal side effects have been observed among Medicare enrollees taking

Table 4. **Randomized, Controlled Trials of Alendronate with Fracture Outcomes***

Study, Year (Reference)	Duration	Age	Sample	Exclusion Criteria†	Participants Lost to Follow-up	Quality Rating‡
	y				*n/n (%)*	
Adami et al., 1995 (103)	2	48–76	9 Italian centers; T-score < −2 (0.67 g/cm²); 5% vertebral fractures	Narrow	32/211 (15.2)	Fair to good
Black et al., 1996 (104)	3	55–81	11 U.S. cities; BMD <0.68 g/cm²; no previous vertebral fractures	Broad (medical illness, dyspepsia)	81/2027 (4)	Good
Bone et al., 1997 (105)	2	>60	15 U.S. sites; BMD <0.84 g/cm²; average of 20 y since menopause; 30.7% vertebral fractures	Broad (medical illness, NSAIDs, GI drugs)	19/359 (5.3)	Fair to good
Chesnut et al., 1995 (106)	2	42–75 (avg. 63)	7 centers; spine BMD <0.88 g/cm²; average hip BMD, 0.7 g/cm²; ≥5 y since menopause	Broad	26/157 (16.6)	Fair
Cummings et al., 1998 (107)	4	55–81	11 U.S. cities; BMD <0.68 g/cm² (average, 0.59 g/cm²); no previous vertebral fractures	Broad (medical illness, dyspepsia)	179/4432 (4)	Good
Greenspan et al., 1998 (108)	2.5	>65	1 Boston center; no BMD entry criteria	Narrow ("good health")	33/120 (27.5)	Fair
Hosking et al., 1998 (109)	4	45–59	4 centers; BMD >0.8 g/cm²; <10% prevalent vertebral fractures	Narrow ("good health")	287/1499 (19.1)	Fair
Liberman et al., 1995 (110)	3	45–80	2 multicenter trials; T-score <−2.5; 21% prevalent vertebral fractures	Narrow ("good health")	170/994 (17.1)	Good
McClung et al., 1998 (111)	3	40–59	15 centers; T-score <−2; 6–36 mo since menopause; no previous vertebral fractures	Narrow ("good health," estrogen use)	(31 at 3 y)	Fair
Pols et al., 1999 (112)	1	40–82 (mean 63)	153 centers; T-score <−2.8	Narrow ("good health")	211/1908 (11.1)	Fair

* BMD = bone mineral density; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.
† In general, "narrow" criteria excluded estrogen users and patients with illnesses affecting bone metabolism.
‡ Based on criteria developed by the U.S. Preventive Services Task Force (22).

Table 5. **Screening for Osteoporosis in 10 000 Postmenopausal Women: Hip and Vertebral Fracture Outcomes by 5-Year Age Intervals***

Variable	Age Group					
	50–54 y	55–59 y	60–64 y	65–69 y	70–74 y	75–79 y
Base-case assumptions†						
Prevalence of osteoporosis	0.0305	0.0445	0.065	0.120	0.2025	0.285
Relative risk for hip fracture with treatment	0.63	0.63	0.63	0.63	0.63	0.63
Relative risk for vertebral fracture with treatment	0.52	0.52	0.52	0.52	0.52	0.52
Adherence to treatment	0.7	0.7	0.7	0.7	0.7	0.7
Results, *n*						
Identified as high risk (osteoporotic)	305	445	650	1200	2025	2850
Hip fractures prevented	1	2	5	14	39	70
NNS to prevent 1 hip fracture	7446	4338	1856	731	254	143
NNT to prevent 1 hip fracture	227	193	121	88	51	41
Vertebral fractures prevented	5	7	22	40	95	134
NNS to prevent 1 vertebral fracture	1952	1338	458	248	105	75
NNT to prevent 1 vertebral fracture	60	60	30	30	21	21

* NNS = number needed to screen for benefit; NNT = number needed to treat.
† Estimates for assumptions include age-specific prevalence rates for osteoporosis and probabilities of fractures; relative risk of 0.63 for hip fractures and 0.52 for vertebral fractures with treatment; treatment adherence of 0.7 (see text). Formulas for calculations are described in Appendix Table 2.

alendronate (121). The long-term adverse effects of alendronate are unknown.

Costs of screening vary with technique, and average 2000 Medicare reimbursement rates were $133 for dual-energy x-ray absorptiometry and $34 for ultrasonography (122). Abnormal results on ultrasonography may require confirmatory dual-energy x-ray absorptiometry before treatment because clinical trials are based on entry criteria using dual-energy x-ray absorptiometry. Most women would require repeated tests over several years before receiving a diagnosis of osteoporosis and leaving the screening pool. Treatment costs also vary; alendronate currently costs approximately $3 per daily dose.

Screening Strategies

To estimate the effect of screening 10 000 postmenopausal women for osteoporosis on reducing hip and vertebral fractures, we created an outcomes table based on assumptions from the reviewed studies (**Table 5**). These estimates include age-specific prevalence rates expressed in 5-year age intervals (123) and treatment effects based on trial results (risk reduction, 37% for hip fracture and 50% for vertebral fracture) (102, 104, 115, 124). We estimated an adherence rate of 70% based on reports of adherence and side effects from treatment trials, assuming less optimal adherence in the general population.

When the assumptions in **Table 5** are used, if 10 000 women 65 to 69 years of age underwent bone densitometry (dual-energy x-ray absorptiometry of the femoral neck), 1200 would be identified as high risk (T-score ≤ -2.5). If these women were offered treatment that resulted in a 37% reduction in hip fracture risk and a 50% reduction in vertebral fracture risk and 70% adhered to therapy, then 14 hip fractures and 40 vertebral fractures would be prevented over a 5-year period. The number of women in this age group needed to screen to prevent one hip fracture in 5 years would be 731, and the number of women with low bone density needed to treat for benefit would be 88. The number needed to screen to prevent one vertebral fracture would be 248, and the number needed to treat for benefit would be 30. Treatment has significant costs and potential harms; when the number needed to screen for benefit is high, the balance of benefits and harms may become unfavorable. These numbers become more favorable in older persons because the prevalence of osteoporosis increases steadily with age.

There is interest in whether risk assessment can be used to select patients for bone densitometry, which is costly. Our literature review indicated that the prevalence of osteoporosis, the predictability of densitometry, and the effectiveness of treatment might be lower for younger than for older postmenopausal women. To determine whether it is useful to consider clinical risk factors when screening younger postmenopausal women, we also included risk estimates for clinical risk factors in a sensitivity analysis. Our review of observational studies with younger postmenopausal women indicated that three consistent predictors of fracture are increasing age, low weight or body mass index, and nonuse of hormone replacement therapy (defined by current use, ever use, or certain durations of use*).* These three variables are also used in ORAI to identify women with low bone density (43) and were the variables most strongly associated with low bone density in a study enrolling mostly younger postmenopausal women in the United States (125). On the basis of these studies, we estimated that one of these risk factors increases the probability of having osteoporosis by up to 100% and increases the risk for fracture by 70% (relative risk, 1.7).

For younger age groups, the presence of clinical risk factors influences outcomes. For example, only five hip fractures are prevented over 5 years when all women 60 to 64 years of age are screened; however, nine hip fractures are prevented if women have a factor that increases fracture risk by 70%. For women 60 to 64 years of age who have such a risk factor, the number needed to screen is 1092 and the number needed to treat for benefit is 72 to prevent 1 hip fracture. These numbers approach those of women 65 to 69 years of age (**Figure**).

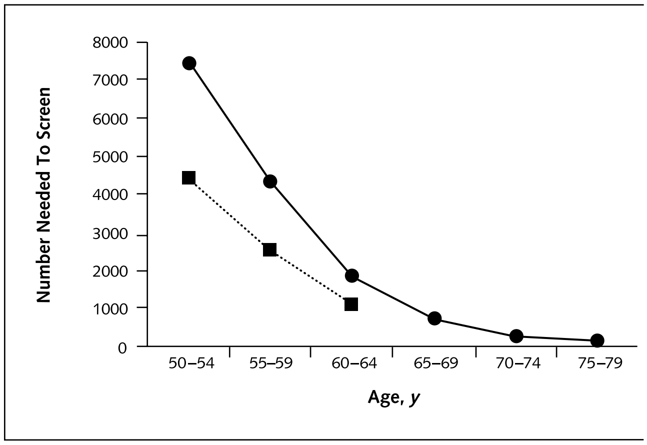
Discussion

Although many studies have been published about osteoporosis in postmenopausal women, no trials have evaluated the effectiveness of screening; therefore, no direct evidence that screening improves outcomes is available. Instruments developed to assess clinical risk factors for low bone density or fractures generally have moderate to high sensitivity and low specificity. Many have not been validated, and none have been widely tested in a practice setting. Among different bone density tests measured at various sites, bone density measured by dual-energy x-ray absorptiometry at the femoral neck is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Heel ultrasonography and other peripheral bone density tests, however, can also predict short-term fracture risk. Bisphosphonates decrease fracture risk by approximately 40% to 50% in women with low bone density.

Support for population screening would be based on evidence that the prevalences of osteoporosis and fractures increase with age, that the short-term risk for fracture can be estimated by bone density tests and risk factors, and that the fracture risk among women with low bone density can be significantly reduced with treatment. We applied these data to generate an outcomes table of screening strategies that provides estimates of the numbers of women needed to screen and treat to prevent fractures. Age-based screening is supported by prevalence data, that is, the number needed to screen to prevent fractures decreases sharply as age and prevalence increase. Use of risk factors, particularly increasing age, low weight, and nonuse of estrogen replacement, to screen younger women may identify additional high-risk women and provide absolute benefit similar to that yielded by screening older women without risk factors. These findings relate to screening asymptomatic women only and do not apply to women considered for testing because of preexisting or new fractures or the presence of secondary causes of osteoporosis.

Our approach has several limitations, however, and results from a well-designed trial of screening strategies should supersede our estimations, which are based on indirect evidence. The estimates in the outcomes table are limited by assumptions that are arguable or highly variable by patient and setting. Our assumptions of treatment effect and adherence are especially optimistic and reflect results of clinical trials, not clinical practice. We chose a 5-year time horizon based on the short-term predictability of bone density tests as well as on results of short-term treatment trials. Long-term outcomes may provide a more accurate estimate of benefits. Also, we cannot exclude the possibility that harms outweigh benefits, particularly since the long-term effects of bisphosphonates are not yet known.

Figure. **Number needed to screen to prevent one hip fracture in 5 years.**



The dotted line indicates women with at least one risk factor; the solid line indicates women without risk factors.

The evidence on which we based our conclusions is also limited. Overall, evidence is stronger for women older than 65 years of age than for younger women because more research has been done in older age groups. Bone loss in the perimenopausal and early postmenopausal years is important to long-term bone health, but few published studies address screening and treatment for younger postmenopausal women. Fracture risk is determined not only by bone density but also by bone characteristics that are difficult to measure in a clinical setting, such as bone structure and morphologic characteristics. No bone density studies or treatment trials include large numbers of nonwhite women, and it may be difficult to provide ethnicity-specific screening recommendations in the absence of more evidence.

The role of clinical risk factors is still unclear. Although many risk factors are associated with osteoporosis and fractures, how to use them to select women to test or treat is uncertain. The risk factors identified by our literature review and used in the outcomes table are only best estimates. Other risk factors may prove to be equally predictive when used for screening purposes. Further validation of existing risk assessment instruments or development of new ones would be useful. Few studies have evaluated the effect of altering modifiable risk factors, such as smoking cessation, strength and balance training, and visual correction. These interventions may prove to be as effective as drug therapy in preventing fractures and may also be important effect modifiers that would alter the effectiveness of treatments.

Peripheral bone density tests have not been extensively studied for screening. Results from the National Osteoporosis Risk Assessment Study (30) indicate that peripheral tests can predict short-term fracture rates in a primary care population that would be targeted for screening. Most treatment trials use dual-energy x-ray absorptiometry of the hip as an entry criterion, and results may not apply to women whose diagnosis is determined by other tests. A sequential approach, in which women with low values on a peripheral test are subsequently tested by dual-energy x-ray absorptiometry of the hip to determine treatment needs, may be useful, although this approach has not been evaluated. Further research is needed to define the appropriate use of these technologies.

How frequently to screen has also not been specifically studied, but data are needed to determine optimal screening intervals. Estimations can be made based on the age-specific prevalence of osteoporosis and the precision of bone density tests. Less frequent testing for younger postmenopausal women when prevalence is lower (for example, 5-year intervals) and more frequent testing for older women (for example, 2-year intervals) might be reasonable, but further research is needed. Screening intervals of less than 2 years seem unwarranted because the precision error of densitometry would likely exceed the estimated bone loss in such a brief period (126). After a woman is screened and determined to have osteoporosis, future screening with bone density testing would be unnecessary.

Osteoporotic fractures present an enormous health burden on an expanding elderly population. Further research to more accurately determine the benefits and harms of screening is of paramount importance.

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Current author addresses, the Appendix Tables, and the Appendix Figure are available at www.annals.org.

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Appendix Table 1. **Summary of Evidence Quality**

Key Questions	Evidence Code*	Quality of Evidence†	
		Internal Validity	External Validity
Does screening using risk factor assessment or bone density testing reduce fractures?	None		
Does risk factor assessment accurately identify women who may benefit from bone density testing?	II-2	Poor to good: small studies, risk assessment instruments often not validated	Poor to fair: no instruments used widely for screening purposes, although some were developed from community-based studies
Do bone density measurements accurately identify women who may benefit from treatment?	II-2	Fair to good: studies indicate the short-term predictability for fracture	Fair: not known how well results of studies translate to practice
What are the harms of screening?	II-2, III	Poor to fair: small studies, descriptive	Poor: small studies, selected participants
Does treatment reduce the risk of fractures in women identified by screening?	I	Good: bisphosphonate trials indicate fracture prevention	Poor to fair: may be differences between trial participants and primary care patients
What are the harms of treatment?	I, II-2	Poor to good: long-term effects of newer agents not known	Poor to fair: difficult to know how risks affect individual patients

* Evidence codes are based on study design categories (22): I = randomized, controlled trials; II-1 = controlled trials without randomization; II-2 = cohort or case–control analytic studies; II-3 = multiple time series, dramatic uncontrolled experiments; III = opinions of respected authorities, descriptive studies.
† Based on criteria developed by the U.S. Preventive Services Task Force (22).

Appendix Table 2. **Formulas for Calculations in Outcomes Table**

Number of hip fractures in untreated women with osteoporosis
- No risk factors: (5-year probability of hip fracture in women with osteoporosis) × (prevalence of osteoporosis) × N
- At least one risk factor: 1.7 × (5-year probability of hip fracture in women with osteoporosis) × (prevalence of osteoporosis) × N

Number of hip fractures in treated women with osteoporosis
- No risk factors: (RR for hip fracture from treatment trials) × (0.7 adherence) × (number of hip fractures in untreated women with osteoporosis) + (1 − 0.7 adherence) × (number of hip fractures in untreated women with osteoporosis)
- At least one risk factor: (relative risk for hip fracture from treatment trials) × (0.7 adherence) × (number of hip fractures in untreated women with osteoporosis with ≥1 risk factor) + (1 − 0.7 compliance) × (number of hip fractures in untreated women with osteoporosis with ≥1 risk factor)

Number needed to screen for benefit
- N/(number of hip fractures without treatment − number with treatment)

Number needed to treat
- Number of women with osteoporosis/(number of hip fractures without treatment − number with treatment)

Appendix Table 3. **Criteria for Grading the Internal Validity of Individual Studies***

Randomized, controlled trials
- Adequate randomization, including concealment and equal distribution of potential confounders among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Equal, reliable, and valid measurements (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Intention-to-treat analysis

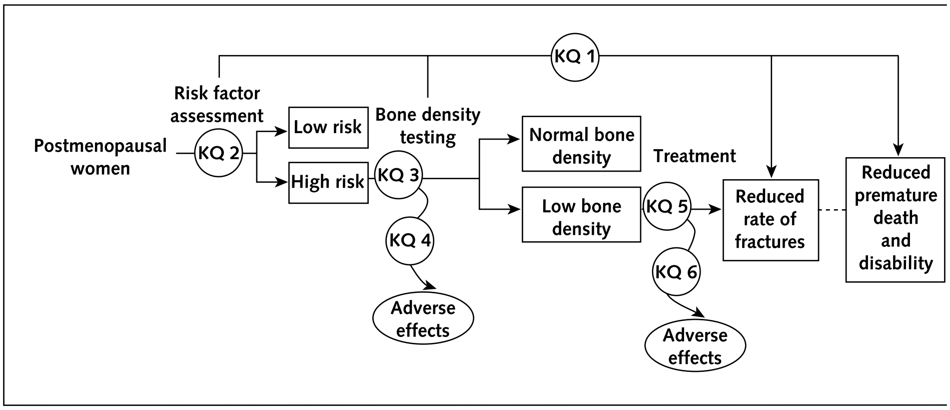
Case–control studies
- Accurate ascertainment of cases
- Nonbiased selection of case-patients and controls with exclusion criteria applied equally to both
- High response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Cohort studies
- Consideration of potential confounders with restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Equal, reliable, and valid measurements (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Adjustment for potential confounders in analysis

Diagnostic accuracy studies
- Screening test relevant, available for primary care, adequately described
- Uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Adequate sample size
- Administration of reliable screening test

* The Methods Work Group for the U.S. Preventive Services Task Force developed a set of criteria to determine how well individual studies were conducted (internal validity) (22). The Task Force defined a three-category rating of "good," "fair," and "poor," based on these criteria. In general, a good study is one that meets all criteria well. A fair study is one that does not meet, or it is not clear that it meets, at least one criterion but has no known important limitation that could invalidate its results. A poor study has important limitations. These specifications are not meant to be rigid rules but rather are intended to be general guidelines; individual exceptions, when explicitly explained and justified, can be made.

Appendix Figure. **Analytic framework.**



The analytic framework is a schematic outline used to define the population, preventive service, diagnostic or therapeutic interventions, and intermediate and health outcomes considered in the review. The arrows represent key questions that the evidence must answer, and demonstrate the chain of logic that evidence must support, to link the preventive service to improved health outcomes. KQ = key question. KQ 1: Does screening using risk factor assessment or bone density testing reduce fractures? KQ 2: Does risk factor assessment accurately identify women who may benefit from bone density testing? KQ 3: Do bone density measurements accurately identify women who may benefit from treatment? KQ 4: What are the harms of screening? KQ 5: Does treatment reduce the risk of fractures in women identified by screening? KQ 6: What are the harms of treatment?