JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Osteoporosis to Prevent Fractures
A Systematic Evidence Review for the US Preventive Services Task Force

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IMPORTANCE Fragility fractures result in significant morbidity.

OBJECTIVE To review evidence on osteoporosis screening to inform the US Preventive Services Task Force.

DATA SOURCES PubMed, Embase, Cochrane Library, and trial registries through January 9, 2024; references, experts, and literature surveillance through July 31, 2024.

STUDY SELECTION Randomized clinical trials (RCTs) and systematic reviews of screening; pharmacotherapy studies for primary osteoporosis; predictive and diagnostic accuracy studies.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed titles/abstracts, full-text articles, study quality, and extracted data; when at least 2 similar studies were available, meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Hip, clinical vertebral, major osteoporotic, and total fractures; mortality; harms; accuracy.

RESULTS Three RCTs and 3 systematic reviews reported benefits of screening in older, higher-risk women. Two RCTs used 2-stage screening: Fracture Risk Assessment Tool estimate with bone mineral density (BMD) testing if risk threshold exceeded. One RCT used BMD plus additional tests. Screening was associated with reduced hip (pooled relative risk [RR], 0.83 [95% CI, 0.73-0.93]; 3 RCTs; 42 009 participants) and major osteoporotic fracture (pooled RR, 0.94 [95% CI, 0.88-0.99]; 3 RCTs; 42 009 participants) compared with usual care. Corresponding absolute risk differences were 5 to 6 fewer fractures per 1000 participants screened. The discriminative accuracy of risk assessment instruments to predict fracture or identify osteoporosis varied by instrument and fracture type; most had an area under the curve between 0.60 and 0.80 to predict major osteoporotic fracture, hip fracture, or both. Calibration outcomes were limited. Compared with placebo, bisphosphonates (pooled RR, 0.67 [95% CI, 0.45-1.00]; 6 RCTs; 12 055 participants) and denosumab (RR, 0.60 [95% CI, 0.37-0.97] from the largest RCT [7808 participants]) were associated with reduced hip fractures. Compared with placebo, no statistically significant associations were observed for adverse events.

CONCLUSIONS AND RELEVANCE Screening in higher-risk women 65 years or older was associated with a small absolute risk reduction in hip and major fractures compared with usual care. No evidence evaluated screening with BMD alone or screening in men or younger women. Risk assessment instruments, BMD alone, or both have poor to modest discrimination for predicting fracture. Osteoporosis treatment with bisphosphonates or denosumab over several years was associated with fracture reductions and no meaningful increase in adverse events.

Editorial page 468

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The primary rationale for screening for osteoporosis is to identify persons who would benefit from pharmacotherapy to reduce the incidence and morbidity from fragility fractures, which are defined as fractures resulting from low-energy trauma (eg, a fall from standing height or less). In 2018, the US Preventive Services Task Force (USPSTF) recommended screening with bone measurement testing in women 65 years or older and in postmenopausal women younger than 65 years with increased risk of osteoporosis as determined by a formal clinical risk assessment tool.[1] The evidence was insufficient for the USPSTF to assess the benefits and harms of screening in men (I statement).[1] This update review evaluated the current evidence on screening to inform an updated recommendation by the USPSTF.

Methods

Scope of the Review

The review was guided by the analytic framework and key questions (KQs) shown in **Figure 1**. Additional details are provided in the full evidence report.[3]

Data Sources and Searches

PubMed, Embase, and the Cochrane Library were searched for studies published in English from April 1, 2016, through January 9, 2024. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were also searched. To supplement electronic searches (Appendix B.1 in the full report), reference lists of relevant articles and reviewer-suggested studies were reviewed. As part of ongoing surveillance, targeted journal searches were conducted to identify major studies that might affect the conclusions of the evidence and the related USPSTF recommendation. The last surveillance was on July 31, 2024.

Study Selection

Titles, abstracts, and full-text articles were reviewed by 2 independent reviewers using prespecified criteria for each KQ (Appendix B2 in the full report[3]); disagreements were resolved by discussion or a third reviewer.

For KQ1 and KQ3, randomized clinical trials (RCTs) and systematic reviews, or controlled cohort studies (for harms only) comparing screening by dual-energy x-ray absorptiometry (DXA) testing, risk assessment (eg, Fracture Risk Assessment Tool [FRAX]), or both compared with no screening among persons without known osteoporosis (ie, T-score bone mineral density [BMD] <−2.5) were eligible. For KQ4 and KQ5, RCTs or controlled cohort studies (for harms only) evaluating US Food and Drug Administration (FDA)–approved bisphosphonates or denosumab compared with placebo or no treatment were eligible if most enrolled participants did not have secondary osteoporosis or prior fragility fractures to approximate a screen-detected population. Studies of other drugs in men were also eligible. Outcomes for KQ1, KQ3, KQ4, and KQ5 included fractures, mortality, and harms.

For KQ2, primary studies or systematic reviews reporting discrimination or calibration outcomes were eligible if they evaluated risk assessment instruments (KQ2a) or BMD alone (KQ2b) for predicting future incident fracture or evaluated the accuracy of risk assessments for identifying current osteoporosis (KQ2c). Only risk assessments evaluated in at least 2 independent cohorts external to the development cohort were eligible for KQ2a and KQ2c, except if conducted in men.

Studies included in the prior 2018 review for the USPSTF[4] were reassessed against the study selection and methodological quality criteria for this update. Fair- or good-quality studies that met all study selection criteria and were conducted in countries categorized as very highly developed by the 2020 United Nations Human Development Index[5] were eligible. However, for KQ2a and KQ2b, eligibility was further limited to countries with hip fracture incidence similar to that of the United States ("moderate" category[6]), but poor-quality studies were included because of the limited pool of good- or fair-quality predictive accuracy studies.

Data Extraction and Quality Assessment

For each included study, 1 reviewer abstracted relevant characteristics (ie, population, intervention, comparator) and outcome data into a structured form and a second reviewer checked data for accuracy.

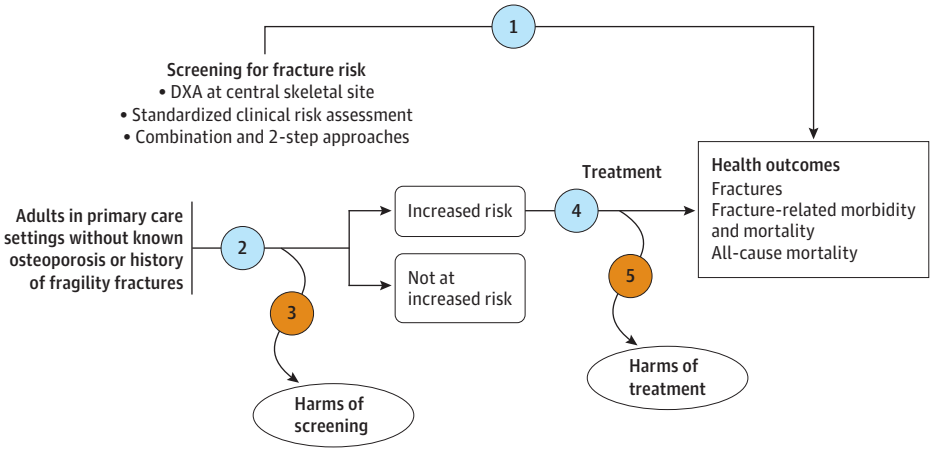
The risk of bias (ROB) for each included study was assessed by 2 independent reviewers using design-specific ROB tools (ROB 2 for RCTs,[7] ROBINS-I [Risk of Bias in Nonrandomised Studies of Interventions] for nonrandomized studies of interventions,[8] QUADAS-2 [Quality Assessment of Diagnostic Accuracy Studies 2] for diagnostic test accuracy,[9] PROBAST [Prediction Model Risk of Bias Assessment Tool] for predictive accuracy,[10-12] and ROBIS [Risk of Bias Assessment Tool for Systematic Reviews] for systematic reviews[13]). For predictive accuracy of studies evaluating risk assessment instruments, the ROB of each instrument in its development cohort(s) was evaluated using the full PROBAST instrument[10] but adapted to include health equity signaling items. The ROB for instruments evaluated in external validation cohorts was assessed using an adapted version of the PROBAST short form.[12] ROB ratings from design-specific instruments were translated to methodological quality ratings using predefined criteria developed by the USPSTF.[2] Disagreements in study quality ratings were resolved through discussion.

Data Synthesis and Analysis

Data were synthesized in narrative and tabular formats. When at least 2 similar studies were available, a quantitative synthesis was performed using random-effects models with the inverse-variance weighted method of DerSimonian and Laird[14] in Stata version 17 (StataCorp) to generate pooled estimates of the relative risk (RR), which were reexpressed as absolute risk differences (ARDs) per 1000 persons screened or treated.[15] Statistical heterogeneity was assessed by the I^2 statistic.[16,17] For KQ4 and KQ5, data were pooled across dosage groups for studies with more than 1 active intervention group. Sensitivity analyses were conducted for alternative types of vertebral fracture (clinical vs radiographic), for non–FDA-approved dosages of drugs, and with alternative methods of pooling for outcomes with rare (<1%) or 0 events in either study group.[18]

The strength of evidence (SOE) for each comparison and outcome was assessed as high, moderate, low, or insufficient using methods developed for the USPSTF and the Agency for Healthcare Research and Quality Evidence-based Practice Center program.[19,20] Two senior reviewers independently developed SOE assessments; disagreements were resolved through discussion.

Figure 1. Analytic Framework: Screening for Osteoporosis to Prevent Fractures



Key questions

1. Does screening for fracture risk or osteoporosis reduce fractures and fracture-related morbidity and mortality in adults?
2. a. What is the predictive accuracy of risk assessment tools for identifying adults who are at increased risk for hip fractures or major osteoporotic fractures?
   b. What is the predictive accuracy of bone mineral density testing with DXA at central skeletal sites for identifying adults who are at increased risk for hip or major osteoporotic fractures?
   c. What is the diagnostic accuracy of risk assessment tools for identifying adults with osteoporosis?
   d. What is the evidence to determine screening intervals, and how do these intervals vary by baseline or current individual fracture risk?
3. What are the harms of screening for fracture risk or osteoporosis?
4. What is the effectiveness of pharmacotherapy with selected FDA-approved medications on fracture incidence and fracture-related morbidity and mortality?
5. What are the harms associated with selected FDA-approved medications?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. For further details, see the USPSTF Procedure Manual.[2] DXA indicates dual-energy x-ray absorptiometry; FDA, US Food and Drug Administration.

Results

One hundred forty-five unique studies (published in 195 articles) were included in this update (**Figure 2**). A list of full-text articles that were reviewed but excluded is in Appendix C of the full report.[3]

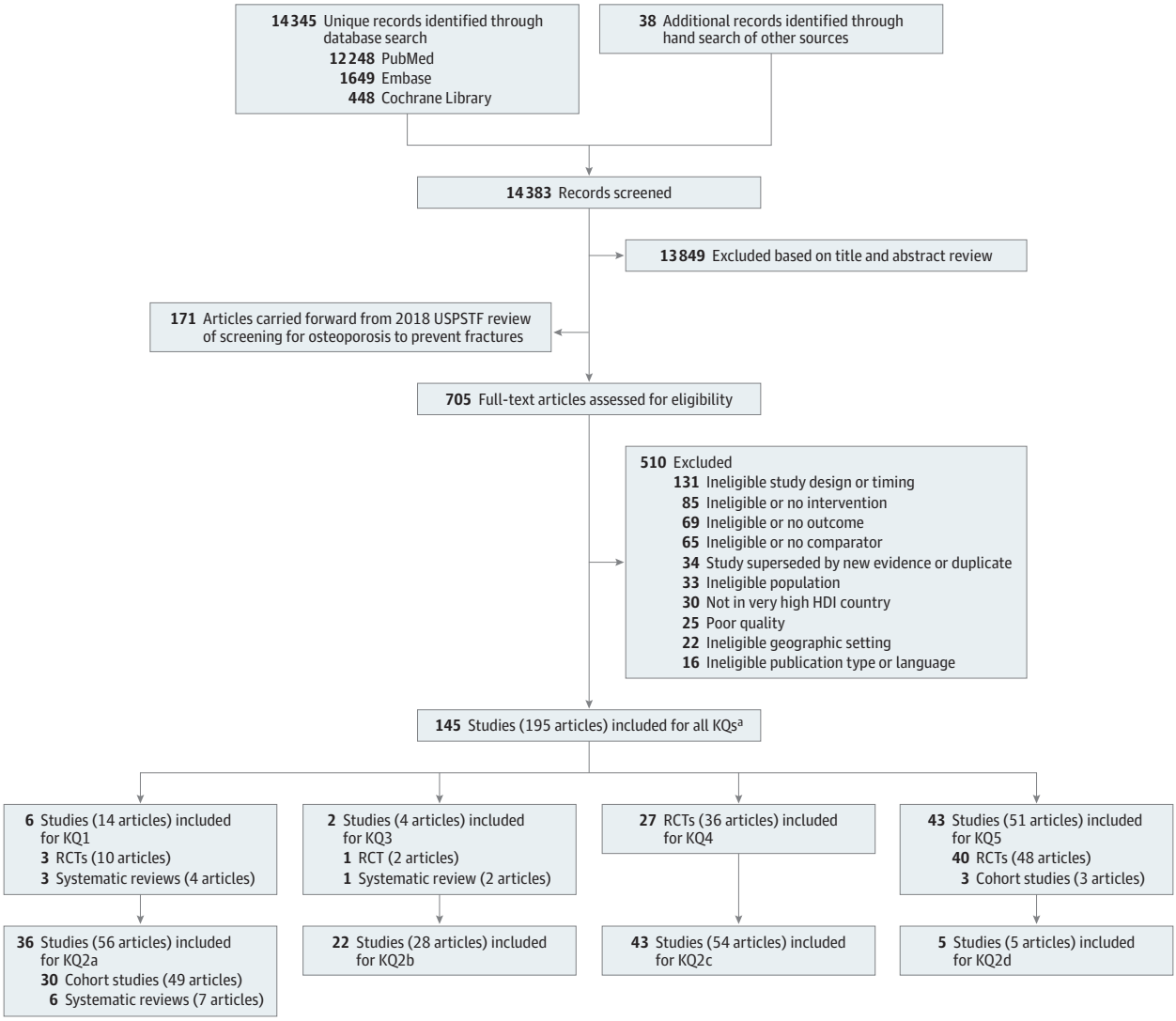
Benefits and Harms of Screening

Key Question 1. Does screening for fracture risk or osteoporosis reduce fractures or fracture-related morbidity or mortality in adults?
Key Question 3. What are the harms of screening for fracture risk or osteoporosis?

Three fair-quality, pragmatic RCTs (**Table 1**) were included: the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study (n = 34 229 randomized; n = 18 605 per-protocol 1 analysis),[21-24] the Screening in the Community to Reduce Fractures in Older Women (SCOOP) study (n = 12 483),[25-28] and the Stichting Artsen Laboratorium en Trombosedienst Osteoporosis Study (SOS) (n = 11 032).[29,30] ROSE and SOS are new to this update. All 3 RCTs randomized European women (mean or median age, 71-76 years) to screening vs usual care (ie, no systematic screening). Among those enrolled, the mean or median 10-year FRAX-estimated risk of hip fracture was 8.5% in SCOOP, 6.7% in ROSE, and 11.6% in SOS.[23,27,30] The proportion of participants with a prior fracture was 12.6% in ROSE, 22% in SCOOP, and 43% in SOS; however, there was variability in the definition and reporting of prior fractures between trials.[23,27,30] Three relevant systematic reviews were also identified that analyzed these 3 trials and reported findings similar to those of this update.[31-34]

Two RCTs (SCOOP[27] and ROSE[30]) used 2-step screening with a FRAX risk assessment (without BMD), then invited participants with a FRAX risk above a specified threshold for DXA. In contrast, SOS enrolled women known to have at least 1 clinical risk factor for osteoporosis and conducted DXA, vertebral fracture assessment, blood chemistry analyses, falls risk assessment, and FRAX without BMD.[30] In all trials, DXA results and corresponding treatment recommendations were shared with the participant and primary care clinician who together made final decisions about starting treatment. The control intervention in all 3 trials was usual care as guided by the participant's primary care clinician. The study quality was fair in all trials because of contamination in control groups, poor to modest adherence in intervention groups, and lack of blinding, which was not feasible because of the

Figure 2. Literature Search Flow Diagram: Screening for Osteoporosis to Prevent Fractures



HDI indicates human development index; KQ, key question; RCT, randomized clinical trial; USPSTF, US Preventive Services Task Force.

[a]Some studies are included in more than 1 KQ.

pragmatic nature of the trials (detailed quality assessments are reported in Appendix D of the full report[3]).

All 3 RCTs confirmed fracture outcomes through medical records or radiology reports, and the primary outcomes were any fractures (SCOOP, SOS) and MOF (ROSE); hip fractures were secondary outcomes. The relative associations between screening and fracture or mortality outcomes are shown in **Figure 3**. The pooled RR for hip fractures was 0.83 (95% CI, 0.73-0.93; 3 RCTs; 42 009 participants; I^2 = 0%); this corresponds to an ARD of 5 fewer hip fractures per 1000 people screened (95% CI, from 7 fewer to 2 fewer). The pooled RR for major osteoporotic fracture (MOF) was 0.94 (95% CI, 0.88-0.99; 3 RCTs; 42 009 participants; I^2 = 0%), corresponding to an ARD of 6 fewer per 1000 screened (95% CI, from 12 fewer to 1 fewer). The pooled estimates for all fractures or osteoporotic fractures had similar ARDs but were not statistically significant. No significant association was observed for all-cause mortality; pooled RR, 0.99 (95% CI, 0.95-1.04; 3 RCTs; 57 633 participants; I^2 = 0%), corresponding to an ARD of 1 fewer death per 1000 screened (95% CI, from 5 fewer to 4 more).

Of the 3 RCTs included for KQ1, only the SCOOP trial reported on harms of screening.[27,28] Anxiety was assessed using the Strait-Trait Anxiety Inventory–Short Form at repeated intervals over the 5-year study period.[27,28] Authors observed no difference in anxiety between screening participants (both those deemed low risk and those deemed high risk who were invited to DXA testing) and the control group participants (P = .52).[27,28] One systematic review reported on overdiagnosis.[32,33] Based on the data reported in the SCOOP and SOS RCTs, the systematic review authors estimated that the proportion of participants overdiagnosed ranged from 11.8% to 24.1%.[32,33]

Table 1. Study Characteristics of Randomized Clinical Trials of Screening to Prevent Fracture (KQ1)

Source	Recruitment setting	Age, mean (SD), y	Female, %	No. randomized	Intervention groups (No. randomized)	Study quality
ROSE Høiberg et al,[21] 2019 Rothmann et al,[22] 2017 Rubin et al,[23] 2018 Rubin et al,[24] 2015	Civic registries in southern Denmark	Median, 71 (IQR, 68-76)	100	34 229[a]	Screening: FRAX without BMD assessment, with invitation to DXA and VFA if 10-y FRAX MOF risk ≥15%; results sent to the participant and primary care clinician with treatment recommendations based on national guidelines Routine care: no contact after completion of baseline data collection, usual care guided by primary care clinician	Fair
SCOOP McCloskey et al,[25] 2018 Parsons et al,[26] 2020 Shepstone et al,[27] 2018 Shepstone et al,[28] 2012	General practice clinics in the UK	Screening: 75.5 (4.2) Routine care: 75.5 (4.1)	100	12 483	Screening: FRAX without BMD assessment; if high risk based on 10-y FRAX hip risk ≥age-specific threshold, then invitation to DXA; if below threshold, then letter sent to participants and primary care clinicians confirming low-risk status; DXA results sent to participant and primary care clinician with participant's revised FRAX risk (including BMD information), age-specific treatment thresholds, and recommendation to discuss treatment if above threshold Routine care: letter informing primary care clinician of patient's participation in the study; usual care guided by primary care clinician	Fair
SOS Elders et al,[29] 2017 Merlijn et al,[30] 2019	General practice registries in the Netherlands; only women with ≥1 clinical risks were recruited[b]	75.0 (6.7)	100	11 032	Screening: FRAX without BMD assessment, DXA, VFA, fall risk assessment, and blood chemistry analyses to exclude secondary osteoporosis; women with treatment indications based on results had referral to primary care clinician for personalized treatment advice including medication, evaluation for secondary osteoporosis, fall prevention, and calcium/vitamin D supplementation; primary care clinicians were provided group education on the study protocol and treatment options Routine care: wait-list placement for screening intervention, usual care guided by primary care clinician	Fair

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, Fracture Risk Assessment Tool; KQ, key question; MOF, major osteoporotic fracture; ROSE, Risk-stratified Osteoporosis Strategy Evaluation; SCOOP, Screening in the Community to Reduce Fractures in Older Women; SOS, Stichting Artsen Laboratorium enTrombosedienst Osteoporosis Study; VFA, vertebral fracture assessment.

[a] The intent-to-treat analysis was based on the number randomized, which occurred prior to any data collection about fracture risk. The authors also reported a per-protocol analysis for 18 605 participants. This per-protocol analysis is methodologically more similar to the designs of the SCOOP and SOS trials because only participants who completed baseline questionnaires about fracture risk were randomized to screening in those trials. Thus, the per-protocol analysis from the ROSE trial was used in the quantitative synthesis shown in Figure 3.

[b] Clinical risk factors: previous fracture after age 50 years, parental hip fracture, body mass index less than 19 (calculated as weight in kilograms divided by square of height in meters), rheumatoid arthritis, menopause before age 45 years, malabsorption syndrome, chronic liver disease, type 1 diabetes, immobility.

Accuracy of Screening Strategies

Key Question 2a. What is the predictive accuracy of risk assessment tools for identifying adults who are at increased risk for hip or major osteoporotic fractures?

Thirty cohort studies (published in 49 articles[35-83]) and 6 systematic reviews[32,84-88] reported on the accuracy (discrimination, calibration, or both) of 11 risk assessment instruments for predicting fracture (eTable 1 in the Supplement). All of the systematic reviews were good quality; however, authors of the systematic reviews generally rated the included primary studies as poor quality. All of the primary studies included for KQ2a in this update were rated as poor quality.

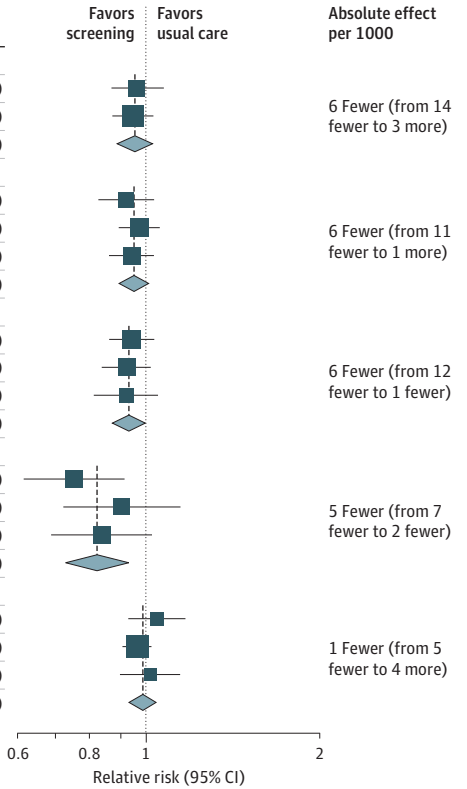
Two systematic reviews[32,87] and 25 cohort studies reported in 40 articles[35-60, 62-64, 66, 68, 69, 71, 72, 74, 76, 77, 79-83] reported on calibration outcomes for 6 risk assessment models (FRAX, Fracture Risk Evaluation Model [FREM], Fracture Risk Calculator [FRC], Garvan, Osteoporosis Self-Assessment Tool [OST], QFracture) for the prediction of MOF, hip fracture, or both. Calibration results were heterogenous, with no discernible patterns with respect to instrument, age, or sex.

Six systematic reviews[32,33,84-88] and 16 cohort studies published in 25 articles[35,45,52,53,59-63,66,67,69-73,75,77-82] reported on the discriminative accuracy of 11 risk assessment models (Escala de Predicción de fracturas Implementable en historia Clínica electronica [EPIC], FRAX, FRC, FREM, Garvan, Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], Osteoporosis Self-assessment Tool [OST], QFracture, Simple Calculated Osteoporosis Risk Estimation [SCORE], Women's Health Initiative Prediction Model) to predict MOF or hip fracture or both using primarily the area under the receiver operating characteristic curve (AUC). Findings were heterogenous (eFigures 1, 2, and 3 in the Supplement), spanning a range considered poor accuracy (AUC, 0.52) to very good accuracy (AUC, 0.93); however, most AUCs were between 0.60 and 0.80. Sources of heterogeneity in AUC estimates include age and population evaluated along with variation in outcome definitions and analytic methods used by authors. Discrimination was largely similar in men and women. For risk assessment instruments with the option to include BMD (FRAX, FRC, Garvan), the predictive accuracy was improved when BMD was included compared with the instruments alone. Further, some instruments (FRAX, FRC, Garvan, QFracture) had higher accuracy for predicting hip fracture than for predicting MOF. Few studies reported sensitivity or specificity for specific risk thresholds. In 1 cohort of US women aged 50 to 64 years, a FRAX risk threshold of 9.3% had 26% sensitivity and 83% specificity to identify MOF.[35]

Key Question 2b. What is the predictive accuracy of bone mineral density testing with dual x-ray absorptiometry at central skeletal

Figure 3. Results of Randomized Clinical Trials of Screening vs Usual Care (KQ1)

Source	Age (median or mean), y	Prior fracture, %	Mean FRAX risk, MOF/hip	Follow-up, y	No. of events/total (%)		Relative risk (95% CI)	Absolute effect per 1000
					Screened	Control		
All								
SOS[29]	75	43	24.5/11.5	3.7	626/5516 (11.3)	632/5405 (11.7)	0.97 (0.87-1.08)	6 Fewer (from 14 fewer to 3 more)
SCOOP[26]	76	22	19.3/85.0	5	951/6233 (15.3)	1002/6250 (16.0)	0.95 (0.88-1.03)	
Subgroup: I^2 = 0.0%, P = .77							0.96 (0.90-1.02)	
Osteoporotic								
SOS[29]	75	43	24.5/11.5	3.7	547/5516 (9.9)	578/5405 (10.7)	0.93 (0.83-1.04)	6 Fewer (from 11 fewer to 1 more)
ROSE[22]	70	10	20.0/6.7	5	996/9279 (10.7)	1025/9326 (11.0)	0.98 (0.90-1.06)	
SCOOP[26a]	76	22	19.3/85	5	805/6233 (12.9)	852/6250 (13.6)	0.95 (0.87-1.04)	
Subgroup: I^2 = 0.0%, P = .75							0.95 (0.91-1.01)	
MOF								
SCOOP[26a]	76	22	19.3/85.0	5	805/6233 (12.9)	852/6250 (13.6)	0.95 (0.87-1.04)	6 Fewer (from 12 fewer to 1 fewer)
ROSE[22]	70	10	20.0/6.7	5	725/9279 (7.8)	786/9326 (8.4)	0.93 (0.84-1.02)	
SOS[29]	75	43	24.5/11.5	3.7	427/5516 (7.7)	452/5405 (8.3)	0.93 (0.82-1.05)	
Subgroup: I^2 = 0.0%, P = .93							0.94 (0.88-0.99)	
Hip								
SCOOP[26]	76	22	19.3/85.0	5	164/6233 (2.6)	218/6250 (3.5)	0.75 (0.62-0.92)	5 Fewer (from 7 fewer to 2 fewer)
SOS[29]	75	43	24.5/11.5	3.7	133/5516 (2.4)	143/5405 (2.6)	0.91 (0.72-1.15)	
ROSE[22]	70	10	20.0/6.7	5	169/9279 (1.8)	202/9326 (2.2)	0.84 (0.69-1.03)	
Subgroup: I^2 = 0.0%, P = .47							0.83 (0.73-0.93)	
Mortality								
SCOOP[26]	76	22	19.3/85.0	5	550/6233 (8.8)	525/6250 (8.4)	1.05 (0.94-1.18)	1 Fewer (from 5 fewer to 4 more)
ROSE[22]	71	12	20.0/6.7	5	1968/17 072 (11.5)	2038/17 157 (11.9)	0.97 (0.92-1.03)	
SOS[29]	75	43	24.5/11.5	3.7	499/5516 (9.0)	479/5405 (8.9)	1.02 (0.91-1.15)	
Subgroup: I^2 = 0.0%, P = .42							0.99 (0.95-1.04)	



Analysis used the first per-protocol data from the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) trial for the fracture outcomes because these data reflect a similar study design as the intention-to-treat (ITT) data reported for Screening in the Community to Reduce Fractures in Older Women (SCOOP) and the Stichting Artsen Laboratorium en Trombosedienst Osteoporosis Study (SOS). See the full evidence report for a sensitivity analysis using the ITT data from the ROSE trial for the fracture outcomes. The data for mortality are the ITT population for ROSE because per-protocol data for ROSE were not reported. All estimates were calculated using the DerSimonian and Laird estimator for pooling estimates. Size of boxes indicates the weight of each study in the analysis. FRAX indicates Fracture Risk Assessment Tool; MOF, major osteoporotic fracture.

[a]SCOOP reported an outcome titled *osteoporotic fractures*, which were defined as clinical fractures excluding hand, foot, skull, or cervical vertebrae. This definition differs from the definition of MOF used by the other 2 studies (hip, clinical vertebral, distal forearm, and humerus); as such, SCOOP data were included for osteoporotic fractures and for MOF in this figure. The risk ratio estimate for MOF without SCOOP included is 0.93 (95% CI, 0.86-1.00); absolute effect: 6 fewer (from 12 fewer to 0 fewer). It also is not clear that fractures associated with trauma were excluded from SCOOP.

Table 2. Randomized, Placebo-Controlled Trials of Treatment for Osteoporosis (KQ4 and KQ5)

Source	Study quality	Total No.	Female, %	Age, mean (SD), y	Race and ethnicity, %	Percent with prior fracture[a]	T-score inclusion criteria	Dosage and duration	KQ
Alendronate									
Adachi et al,[195] 2009	Fair	438	100	65.5 (NR)	Asian: 3 Black: 1 Hispanic: 8 White: 89	6.8	<−2.0	10 mg/d; 3 mo	5
Ascott-Evans et al,[160] 2003	Fair	144	100	57.3 (6.6)	White: 91.7 Other: 8.3	0	Lumbar spine <−1.5 and >−3.5	10 mg/d;1 y	4, 5
Bell et al,[183] 2002	Fair	65	100	66 (NR)	African American[b]: 100	NR	Lumbar spine <−1.75	10 mg/d; 2 y	4, 5
Bone et al,[184] 1997	Fair	359	100	71 (NR)	White: 97	34 to 42	≤−2.0	1, 2.5, or 5 mg/d; 2 y	4, 5
Chesnut et al,[161] 1995	Fair	188	100	62.9 (6.1)	Asian: 2.1 White: 97.9	0	NR; mean T score, −1.1	Various[c]; 2 y	4, 5
Cryer et al,[196] 2005	Fair	454	100	65 (10)	Asian: 1 Black: 2 Hispanic: 5 Native American: 1 White: 91 Other: 1	NR	Any site <−2.0 and >−3.5	70 mg Weekly; 6 mo	5
FIT Cummings et al,[162] 1998 Bauer et al,[197] 2000 Quandt et al,[174] 2005 Cummings et al,[198] 2007	Good	4432[d]	100	67.6 (6.2)	White: 97	0[d]	Femoral neck <−1.6	5 mg/d for 2 y, then 10 mg/d for 1 y; 3 y	4, 5
Devogelaer et al,[199] 1996	Fair	516	100	62 (NR)	NR	NR	Lumbar spine ≤−2.5	5, 10, 20[e] mg/d; 3 y	5
Eisman et al,[200] 2004	Good	449	93-96	63.6 (NR)	Asian: 18 Hispanic: 12 White: 65.7 Other: 5	NR	NR; mean T score NR	70 mg Weekly; 3 mo	5
Greenspan et al,[201] 2002	Fair	450	92	67 (NR)	White: 96	NR	NR; mean T score NR	70 mg Weekly; 3 mo	5
Greenspan et al,[202] 2003	Good	186	100	71.5 (NR)	NR	0	NR; mean T score −1.7	10 mg/d; 3 y	5
Hosking et al,[173] 2003	Fair	549[f]	100	69 (NR)	Caucasian[b]: 99.5	48.5	Lumbar spine or total hip <−2.5 or both <−2.0	70 mg Weekly; 1 y	4, 5
Johnell et al,[203] 2002	Fair	331	100	63.6 (NR)	White: 95	NR	Femoral neck <−2.0	10 mg/d; 1 y	5
Liberman et al,[163] 1995	Fair	994	100	64 (NR)	Black: 0.4 White: 87.4 Other: 12.2	21	Lumbar spine <−2.5	5 or 10 mg/d; 3 y 20 mg/d for 2 y, followed by 5 mg/d for 1 y	4, 5
Pols et al,[166] 1999	Fair	1908	100	62.8 (7.5)	White: 94	NR	NR; mean T score	10 mg/d; 1 y	4, 5
Tucci et al,[175] 1996	Fair	478	100	64 (NR)	Asian: 8 White: 91	NR	Lumbar spine <−2.5	5, 10, or 20 mg/d for 2 y, followed by 5 mg/d; 3 y	4, 5
Ibandronate									
Chapurlat et al,[204] 2013	Fair	148	100	62.7 (5.0)	NR	NR	Lumbar spine or total hip <−1.0 and >−2.5	150 mg/mo; 2 y	5
McClung et al,[182] 2009	Fair	160	100	53 (NR)	NR	0	Lumbar spine <−1.0 and >−2.5 with total hip or femoral neck >−2.5	150 mg/mo; 1 y	4, 5
McClung et al,[205] 2004	Fair	653	100	58.2 (8.6)	NR	0	Lumbar spine <−1.0 and >−2.5	0.5, 1.0, or 2.5 mg/d; 2 y	5
Ravn et al,[170] 1996	Fair	180	100	65 (NR)	White: 100	0	NR; mean T score −1.7	0.25, 0.50, 1.0, 2.5, or 5.0 mg/d; 1 y	4, 5
Reginster et al,[172] 2005	Fair	144	100	65.7 (NR)	NR	NR	NR; mean T score −0.3 to −1.9	Various[g];3 mo	4, 5

(continued)

Table 2. Randomized, Placebo-Controlled Trials of Treatment for Osteoporosis (KQ4 and KQ5) (continued)

Source	Study quality	Total No.	Female, %	Age, mean (SD), y	Race and ethnicity, %	Percent with prior fracture[a]	T-score inclusion criteria	Dosage and duration	KQ
Riis et al,[171] 2001	Fair	240	100	66.8 (4.9)	NR	NR	Lumbar spine or femoral neck <−2.5	2.5 mg/d or intermittent cyclic dose; 2 y	4, 5
Tanko et al,[206] 2003	Fair	630	100	55 (NR)	NR	0	Lumbar spine ≥−2.5	5, 10, or 20 mg weekly; 2 y	5
Thiebaud et al,[207] 1997	Fair	126	100	64 (NR)	NR	0	Lumbar spine <−2.5	0.25, 0.5, 1.0, or 2.0 mg every 3 mo; 1 y	5
Risedronate									
Hosking et al,[173] 2003	Fair	549[e]	100	69 (NR)	Caucasian[b]: 99.5	48.5	Lumbar spine or total hip <−2.5 or both <−2.0	5 mg/d; 3 mo	4, 5
McClung et al,[164] 2001	Fair	9331	100	NR, all 70 y or older	White: 98	39 to 44	Femoral neck <−4 or <−3 with risk factor for hip fracture	2.5 or 5 mg/d; years	4, 5
Mortensen et al,[165] 1998	Fair	111	100	52.1 (3.9)	White: 100	0	*z* Score >−2.0; mean T score −1.1	5 mg cyclic or 5 mg/d; 2 y	4, 5
Shiraki et al,[208] 2003	Fair	211	99	60.3 (NR)	Japanese: 100	Mean prevalent vertebral fractures 0.3 (SD 0.8)	Lumbar spine <−2.5 without vertebral fracture; <−1.5 with vertebral fracture	1, 2.5, or 5 mg/d; 8 mo	5
Valimaki et al,[168] 2007	Fair	170	100	65.9 (6.8)	White: 100	NR	Lumbar spine >−2.5 and <−1 and proximal femur ≤−1	5 mg/d; 2 y	4, 5
Zoledronic acid									
Boonen et al,[159] 2012	Good	1199	0	Median 66	Asian: 1 Black: 1 White: 94 Other: 0.5	32	Total hip or femoral neck ≤−1.5	5 mg Every year; 2 y	4, 5
Grey et al,[185] 2009 Grey et al,[169] 2010	Fair	50	100	62 (8)	NR	42	Lumbar spine or total hip <−1 and >−2	5 mg; Single dose with 3 y follow-up	5
Grey et al,[180] 2012 Grey et al,[181] 2014 Grey et al,[178] 2017	Fair	180	100	66 (9)	NR	14 to 21	Lumbar spine or total hip <−1 and >−2.5	1, 2.5, or 5 mg; Single dose	4, 5
McClung et al,[209] 2009	Fair	581	100	59.6 to 60.5	NR	0	Lumbar spine −1.0 and −2.5 and femoral neck >−2.5	5-mg Single dose or 5 mg yearly for 2 y; 2 y	5
Reid et al,[167] 2002	Fair	351	100	65 (7)	White: 95	0	Lumbar spine <−2.0	Various[h];1 y	4, 5
Reid et al,[177] 2018 Reid et al,[176] 2019 Reid et al,[210] 2020 Reid et al,[179] 2021	Good	2000	100	71 (5.1)	East Asian: 0.02 European: 95 Indian: 0.005 Maori: 0.02 Pacific Islander: 0.01 Other: 0.002	23.7	Total hip or femoral neck −1.0 to −2.5	5 mg Every 18 mo; 6 y	4, 5
Denosumab									
Bone et al,[192] 2008	Fair	332	100	59.4 (7.5)	NR	0	Lumbar spine or total hip between −1 and −2.5	60 mg Every 6 mo; 3 y	4, 5
FREEDOM Cummings et al,[190] 2009 Watts et al,[211] 2012 Simon et al,[186] 2013 McCloskey et al,[188] 2012 Palacios et al,[193] 2015	Fair	7808	100	72.3 (5.2)	NR	50	Lumbar spine or total hip <−2.5 but >−4.0	60 mg Every 6 mo; 3 y	4, 5
Koh et al,[194] 2016	Fair	135	100	67.0 (4.9)	NR	23 to 30	Total hip or lumbar spine <−2.5 and ≥−4.0	60 mg; Single dose with 6-mo follow-up	4, 5

(continued)

Table 2. Randomized, Placebo-Controlled Trials of Treatment for Osteoporosis (KQ4 and KQ5) (continued)

Source	Study quality	Total No.	Female, %	Age, mean (SD), y	Race and ethnicity, %	Percent with prior fracture[a]	T-score inclusion criteria	Dosage and duration	KQ
Lewiecki et al,[191] 2007 McClung et al,[212] 2006	Fair	365	100	62.5 (8.1)	Black: 2.9 Hispanic: 9.5 White: 86.2 Other: 1.5	0	Lumbar spine −1.8 to −4.0 or femoral neck −1.8 to −3.5	Various[i];2 y	4, 5
Nakamura et al,[189] 2012	Fair	226	100	65.1 (6.8)	Japanese: 100	34	Lumbar spine −2.5 to −4.0 or femoral neck or total hip −2.5 to −3.5	Various[j];1 y	4, 5
ADAMO Orwoll et al,[187] 2012	Fair	242	0	65.0 (9.8)	White: 94.2	39.3	Lumbar spine or femoral neck −2.0 to −3.5[k]; or lumbar spine or femoral neck −1.0 to −3.5[k] with prior MOF	60 mg Every 6 mo; 2 y	4, 5

Abbreviations: FIT, Fracture Intervention Trial; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; KQ, key question; MOF, major osteoporotic fracture; NR, not reported.

[a] Studies define this in varying ways: any fracture, fracture after age 50 years, fragility fracture, vertebral fracture only.

[b] Study used this term.

[c] Dosages were 5 mg/d or 10 mg/d or 40 mg/d for 3 months, then 2.5 mg/d for 21 months; 20 mg/d for 1 year, then placebo for 1 year; 40 mg/d for 1 year, then placebo for 1 year.

[d] Only the portion of the enrolled population without prior vertebral fracture was used in this review.

[e] Dosage was 20 mg for first 2 years and lowered to 5 mg in the final year.

[f] Includes the alendronate, risedronate, and placebo groups.

[g] Dosages were 50 mg per month; 50 mg for the first month, then 100 mg for months 2 and 3; 100 mg per month; 150 mg per month.

[h] Dosages were 0.25 mg every 3 months, 0.5 mg every 3 months, 1 mg every 3 months, 4 mg every 1 year, 2 mg every 6 months.

[i] Dosages were 6 mg, 14 mg, or 30 mg every 3 months; 14 mg, 60 mg, 100 mg, or 210 mg every 6 months.

[j] Dosages were 14 mg, 60 mg, or 100 mg every 6 months.

[k] T scores based on male reference range.

sites for identifying adults who are at increased risk for hip or major osteoporotic fractures?

The accuracy of BMD measurement (typically at the femoral neck) for prediction of incident fractures was reported in 22 unique cohorts in 28 publications (eTable 2 and eFigure 4 in the Supplement).[41,42,46-48,54,60,62-64,68,70,71,75,89-102] One-third were poor-quality studies; most were in women, and the mean age of participants was 49 to 75 years. Four cohorts[41,63,91,100] reported at least 1 type of calibration outcome, but few authors reported detailed or consistent information. Substantial heterogeneity precluded quantitative synthesis of AUCs, which ranged from 0.60 to 0.80 for BMD (treated as a continuous variable) for prediction of MOF (13 cohorts[41,42,46-48,54,62,63,70,71,75,90,96,97,102]) and from 0.64 to 0.86 for hip fracture prediction (12 cohorts[41,42,46,48,54,62,63,71,75,90,91,93,101,102]). Few studies reported sensitivity and specificity, and thresholds varied.

Key Question 2c. What is the diagnostic accuracy of risk assessment tools for identifying adults with osteoporosis?

Forty-three unique cohorts (published in 54 articles[53,59,80,103-153]) reported on accuracy of risk assessment instruments for identifying osteoporosis (eTable 3 in the Supplement). More than one-half enrolled people with a mean age between 60 and 69 years and studies included women, men, or both. Differences in reference standards, risk assessment score thresholds, and study populations precluded quantitative synthesis. In women, AUCs ranged from 0.32 to 0.87 across 35 articles evaluating 11 instruments (eFigure 5 in the Supplement). Five articles reported results from 3 independent cohorts that retrospectively evaluated the accuracy of a FRAX MOF risk threshold of 8.4% or 9.3% in women aged 50 to 64 years, with AUCs ranging from 0.55 to 0.62; sensitivity ranged from 5% to 49% and specificity ranged from 63% to 96%.[59,103,128,129,138] In men, AUCs ranged from 0.62 to 0.94 across 18 articles evaluating 12 instruments (eFigure 6 in the Supplement). Three articles reported on accuracy among mixed populations of men and women for 3 instruments (eFigure 7 in the Supplement); findings were consistent with those reported for men and women separately.

Key Question 2d. What is the evidence to determine screening intervals, and how do these intervals vary by baseline or current individual fracture risk?

Five cohort studies,[154-158] including 3 new to this update,[156-158] evaluated the accuracy of repeat BMD measurement to predict fracture risk at an interval of 4 to 8 years after initial BMD measurement. In 4 of the 5 studies, authors reported similar accuracy for models that used initial BMD, change in BMD, or both. In the fifth study, authors reported no association between change in spine, total hip, or femoral neck BMD on repeat DXA at a mean of 4.1 years and MOF fracture (gradient of risk: hazard ratio [HR], 0.93 [95% CI, 0.81-1.06] per 1-SD increase in BMD at the femoral neck on repeat DXA).[156]

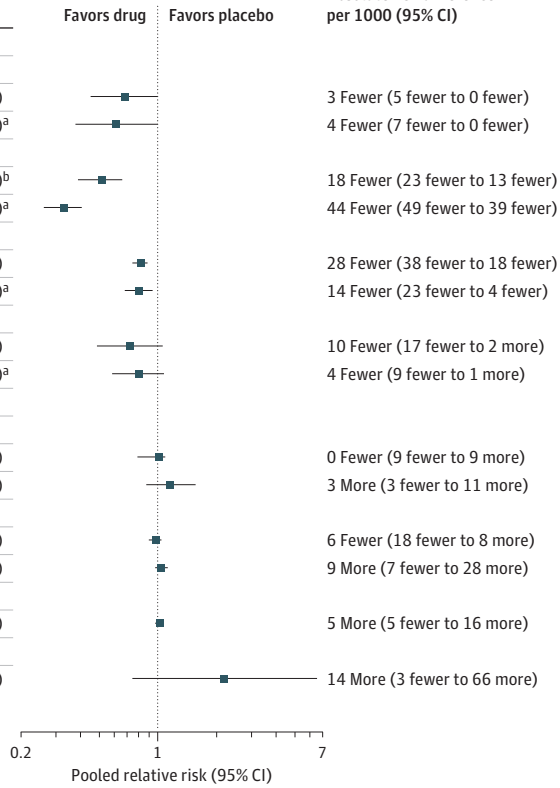
Benefits of Pharmacotherapy

Key Question 4. What is the effectiveness of pharmacotherapy with selected FDA-approved medications on fracture incidence and fracture-related morbidity and mortality?

Twenty-one RCTs (reported in 27 articles[159-185]) compared bisphosphonates (alendronate, ibandronate, risedronate, or zoledronic acid) with placebo, and 6 RCTs (reported in 9 articles[186-194]) compared denosumab with placebo. Two RCTs of alendronate,[183,184] 2 RCTs of zoledronic acid,[176-181] 1 RCT of ibandronate,[182] and 2 RCTs of denosumab[187,194] were new to this update. Three RCTs were good quality[159,162,174,176,177,179]; the rest were fair quality. A summary of trial characteristics is provided in **Table 2**. One RCT of zoledronic acid[159] and 1 study of denosumab[187] were conducted exclusively in men; 3 studies (all evaluating bisphosphonates)

Figure 4. Results of Randomized, Placebo-Controlled Trials of Treatment for Osteoporosis (KQ4 and KQ5)

Outcomes	No. of studies	No. of participants		Pooled relative risk (95% CI)	Absolute risk difference per 1000 (95% CI)
		With event	Total		
Benefits of treatment (KQ4)					
Hip					
Bisphosphonates	6	98	12055	0.67 (0.45-1.00)	3 Fewer (5 fewer to 0 fewer)
Denosumab	2	69	8050	0.61 (0.38-0.99)[a]	4 Fewer (7 fewer to 0 fewer)
Vertebral					
Bisphosphonates	10	250	9015	0.51 (0.39-0.66)[b]	18 Fewer (23 fewer to 13 fewer)
Denosumab	3	352	9179	0.33 (0.26-0.41)[a]	44 Fewer (49 fewer to 39 fewer)
Nonvertebral					
Bisphosphonates	13	1954	20929	0.81 (0.74-0.88)	28 Fewer (38 fewer to 18 fewer)
Denosumab	3	540	8382	0.80 (0.68-0.94)[a]	14 Fewer (23 fewer to 4 fewer)
Mortality					
Bisphosphonates	6	104	3714	0.71 (0.49-1.05)	10 Fewer (17 fewer to 2 more)
Denosumab	5	164	8828	0.79 (0.58-1.07)[a]	4 Fewer (9 fewer to 1 more)
Harms of treatment (KQ5)					
Discontinuations due to adverse event					
Bisphosphonates	24	2116	18617	1.00 (0.92-1.08)	0 Fewer (9 fewer to 9 more)
Denosumab	5	193	8826	1.16 (0.87-1.54)	3 More (3 fewer to 11 more)
Serious adverse event					
Bisphosphonates	21	2719	13878	0.97 (0.91-1.04)	6 Fewer (18 fewer to 8 more)
Denosumab	6	2081	8934	1.04 (0.97-1.12)	9 More (7 fewer to 28 more)
Upper GI adverse event					
Bisphosphonates	26	5873	22172	1.02 (0.98-1.06)	5 More (5 fewer to 16 more)
GI adverse event					
Denosumab	4	15	932	2.18 (0.74-6.46)	14 More (3 fewer to 66 more)



GI indicates gastrointestinal and KQ, key question.

[a]Although multiple studies reported, evidence base is dominated by 1 large (n = 7808) study.

[b]Sensitivity analysis was conducted limiting to studies reporting clinical vertebral fractures (4 studies) and the pooled relative risk was 0.44 (95% CI, 0.24-0.79; 2373 participants; I^2 = 0%).

included a small proportion of men. The remaining studies were conducted exclusively among postmenopausal women. T-score criteria for enrollment across studies varied, but only 6 required T scores in the osteoporotic range. The rest enrolled participants with T scores spanning the range considered low bone mass and osteoporosis or low bone mass only. Detailed trial characteristics, study quality assessments, and results are reported in Appendix D of the full report.[3]

Pooled results from included trials reporting vertebral fractures (clinical, radiographic, or both), nonvertebral fractures, hip fractures, and mortality are shown in **Figure 4**. Pooled RRs ranged from 0.33 to 0.81 across drugs and outcomes, with corresponding ARDs from 3 to 44 fewer events (fractures or deaths) per 1000 people treated. Findings from sensitivity analyses were consistent for each outcome when alternative pooling methods or dosages other than FDA-approved dosages were used (Appendix E.4 in the full report[3]). In the single trial conducted among men (n = 1199 with T score less than −1.5 based on device specific reference values), authors reported a reduced risk of radiographic vertebral fractures (1.5% vs 4.6%; RR, 0.33 [95% CI, 0.16-0.70]) but no significant difference in nonvertebral fractures (0.9% vs 1.3%; RR, 0.65 [95% CI, 0.21-1.97]) compared with placebo.[159]

Harms of Pharmacotherapy

Key Question 5. What are the harms associated with selected FDA-approved medications?

Forty RCTs (reported in 48 articles[159-173,175,177,178,180-185,187,189-192,194-212]) compared bisphosphonates or denosumab with placebo and reported harm outcomes. In addition, 3 controlled cohort studies evaluated bisphosphonates compared with placebo.[213-215] Five RCTs were good quality[159,162,177,197,198,200,202,210]; the rest of the RCTs and the controlled cohort studies were fair quality. A summary of RCT characteristics is provided in Table 2, and pooled findings from included trials reporting discontinuations due to adverse events, serious adverse events, or gastrointestinal adverse events are shown in Figure 4. Across these outcomes, pooled RRs ranged from 0.97 to 2.18, with corresponding ARDs from 6 fewer to 14 more per 1000 people treated and with no statistically significant associations observed. For bisphosphonates, 8 RCTs[159,162,169,177,180,202,208,209] reported 1 or more cardiovascular outcomes (eg, incidence of myocardial infarction, atrial fibrillation); generally these events were rare and estimates were imprecise (details provided in the full report[3]). For denosumab, 3 RCTs reported additional harm outcomes related to skin disease and infection; with 1 exception (incidence of eczema in 1 RCT[190]), no associations were observed.[190-192]

Table 3. Summary of Evidence on Screening for Osteoporosis to Prevent Fracture

Intervention or test/outcome	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
KQ1: Benefits of screening						
Fractures	3 RCTs[21-30] (42 009 using ROSE per-protocol-1 population) 3 Systematic reviews[31-34]	Hip fractures: Pooled RR, 0.83 (95% CI, 0.73-0.93); ARD, 5 fewer per 1000 (95% CI, from 7 fewer to 2 fewer) MOF: Pooled RR, 0.94 (95% CI, 0.88-0.99); ARD, 6 fewer per 1000 (95% CI, from 12 fewer to 1 fewer) Osteoporotic fractures: Pooled RR, 0.95 (95% CI, 0.91-1.01); ARD, 6 fewer per 1000 (95% CI, from 11 fewer to 1 more) Estimates from systematic reviews consistent	Consistent, precise for hip fractures and MOF Imprecise for osteoporotic fractures	Modest screening uptake and adherence to treatment; contamination in control groups; follow-up for only 3.7 y to 5 y	Moderate for benefit on MOF and hip fracture[a] Low for benefit on osteoporotic fractures[b]	Two-stage screening used by 2 studies; European women 60 y or older at high baseline fracture risk; extensive screening battery (imaging, laboratory values, falls assessment) used in 1 study
Mortality	3 RCTs[21-30] (57 633) 1 Systematic review[32,33]	Pooled RR, 0.99 (95% CI, 0.95-1.04); ARD, 1 fewer per 1000 (95% CI, from 5 fewer to 4 more) Estimates from systematic review consistent	Consistent, imprecise	Same as above	Low for no effect[b]	Same as above
KQ2a: Predictive accuracy of risk assessment instruments						
Calibration (MOF and hip fracture)	Two systematic reviews[32,33,87] and 25 cohorts reported in 40 articles[35-52,54-60,62-64,66,69,71,72,74,76,77,79-83] (Unable to estimate precisely due to overlap in reporting for some cohorts)	Reported for 6 instruments: FRAX, FREM, FRC, Garvan, OST, QFracture Too few studies reported calibration for instruments other than FRAX; FRAX (28 articles from 20 unique cohorts) was reasonably calibrated in some cohorts and poorly calibrated in others	Varied by instrument	All studies high risk of bias	Low for FRAX for poor to modest calibration[c] Insufficient for FRC, FREM, Garvan, OST, QFracture[d]	Studies included men and postmenopausal women
Discrimination (MOF and hip fracture)	Four systematic reviews[84-87] 16 Cohorts published in 25 articles[35,45,52,53,59-63,66,67,69-73,75,77-82] (Unable to estimate precisely due to overlap in reporting for some cohorts)	Reported for 11 instruments: EPIC, FRAX, FRC, FREM, Garvan Fracture Risk Calculator, ORAI, OSIRIS, OST, QFracture, SCORE, WHI Prediction Model AUC range: Younger women (<65 y): 0.52 to 0.71 Women: 0.63 to 0.89 Men: 0.63 to 0.93 Mixed sex: 0.61 to 0.88 FRAX, FRC, and Garvan instruments with BMD had higher AUCs compared with same instrument without BMD AUCs higher for prediction of hip fracture compared with MOF for FRAX, FRC, QFracture, and Garvan	Varied by instrument	All studies high risk of bias for development cohorts and for external validation cohorts	Low for FRAX, FRC, Garvan, QFracture for poor to modest discrimination[c] Insufficient for EPIC, FREM, OST, SCORE, WHI[d]	Studies included men and postmenopausal women, but not for all instruments
KQ2b: Predictive accuracy of BMD						
Calibration (MOF and hip fracture)	4 Articles from 4 unique cohorts[41,63,91,100] (18 145)	Inconsistent calibration measures reported across studies; calibration poor in some studies and good in others for prediction of MOF or hip fracture	Inconsistent; unable to judge precision	Not the primary aim of any study; not enough fracture events in some studies, particularly for hip fractures	Insufficient[e]	Cohorts include both men and women; persons with known osteoporosis or undergoing treatment excluded from some cohorts; BMD typically measured at femoral neck

(continued)

Table 3. Summary of Evidence on Screening for Osteoporosis to Prevent Fracture (continued)

Intervention or test/outcome	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
Discrimination (MOF and hip fracture)	18 Articles from 16 unique cohorts[41,42,46-48,54,62,63,70,71,75,90,91,93,96,97,101,102] (101 446)	AUC range: MOF: 0.60 to 0.80 (13 cohorts; 15 estimates) Hip: 0.64 to 0.86 (12 cohorts; 14 estimates) Threshold T score <−2.5 Sensitivity: MOF: 17.5% to 51.3% (5 studies) Hip: 25.0% to 66.7% (5 studies) Specificity: MOF: 70.9% to 95.4% (3 studies) Hip: 88.6% to 94.0% (4 studies)		Ten analyses were high ROB; predictive accuracy of BMD not the primary aim of any study	Low for poor to modest discrimination[c]	Same as above
KQ2c: Diagnostic accuracy (women and men)						
FRAX/ discrimination	MOF risk: 15 studies from 12 unique cohorts[59,80,103,104,108,128,129,138,141,143,144,146-148,150] (37 756 [85% women]) Hip fracture risk: 3 studies from 3 unique cohorts[104,143,148] (1710 [52% women])	MOF (9.3% or 8.4% risk threshold): Women aged 50 to 64 y (3 estimates): AUC, 0.55-0.62; sensitivity, 5%-49%; specificity, 63%-96% Men (2 estimates): AUC, 0.62-0.79; sensitivity, 39%-59%; specificity, 59%-89% MOF (>20% risk threshold): Women ≥60 y (1 estimate): AUC, 0.71 (95% CI, 0.60-0.82); sensitivity, 17%; specificity, 96% Men (1 estimate): sensitivity, 0%; specificity, 99% Mixed sex (1 estimate): AUC: 0.76 (95% CI, 0.71-0.81) MOF (various thresholds or no threshold): Women aged 50 to 64 y (2 estimates): AUC, 0.64-0.72 Men (1 estimate): AUC, 0.62 Mixed sex (1 estimate): AUC, 0.68 (95% CI, 0.63-0.72) Hip (>3% risk threshold): Women ≥60 y (1 estimate): AUC, 0.75 (95% CI, 0.65-0.86); sensitivity, 83%; specificity, 54% Men (1 estimate): AUC, 0.86 (95% CI, 0.73-0.98); sensitivity, 80%; specificity, 71% Mixed sex (1 estimate): AUC: 0.70 (95% CI, 0.64-0.75)	Inconsistent, precise	Heterogeneity in BMD sites measured; all but 1 fair quality because of unclear methods for patient selection and risk for selection bias, lack of blinding of index or reference test results, unclear BMD reference range used for T score, unclear interval between risk assessment and BMD measurement	Low for poor to modest discrimination[c]	Men and postmenopausal women from community or clinic-based populations; FRAX risk assessment without BMD input into calculation; some studies used electronic health recorddata to determine FRAX risks

(continued)

Table 3. Summary of Evidence on Screening for Osteoporosis to Prevent Fracture (continued)

Intervention or test/outcome	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
OST/discrimination	31 Studies from 29 cohorts [53,80,103,104,106-110,114,117-119,123,125-127,129,130,132,134,137-140,144-146,149,151,152] (80 592 [82% women])	AUC: Women (20 estimates): range, 0.32 to 0.89 Women aged 50 to 64 y (3 estimates): range, 0.63 to 0.75 Men (10 estimates): range, 0.63 to 0.89 Mixed sex (1 estimate): 0.76 (95% CI, 0.71 to 0.82) At a score threshold of <2: Women (11 estimates): sensitivity, 53% to 95%; specificity, 37% to 72% Women aged 50 to 64 (3 estimates): sensitivity, 56% to 79%; specificity, 56% to 70% Men (7 estimates): sensitivity, 62% to 89%; specificity, 36% to 74%	Inconsistent, precise	All but 1 fair quality; similar limitations as for FRAX above	Low for poor to modest discrimination[c]	Men and postmenopausal women from community- or clinic-based populations
KQ2c: Diagnostic accuracy (women)						
Other risk assessments/ discrimination	29 Studies from 26 cohorts[103,107,110,111,115-120,122-124,126,129,131-140,143,148,151,153] (30 621)	AUC range: 0.32 to 0.87 (25 estimates) Across various thresholds: Sensitivity range: 28% to 100% (24 estimates) Specificity range: 5% to 100% (24 estimates)	Inconsistent; precision varies by instrument	All fair quality; similar limitations as for FRAX above	Low for poor to modest discrimination (ABONE, NOF, ORAI, OSIRIS, OSTA, SCORE)[c] Insufficient (AMMEB, Garvan FRC, SOFSURF)[e]	Postmenopausal women from community and clinic-based populations
KQ2c: Diagnostic accuracy (men)						
Other risk assessments/ discrimination	21 Studies [104-106,109,112,113,121,125,127,130,141-147,149,150,152] (24 258)	AUC range 0.64 to 0.88 in the studies exclusively enrolling men and evaluating instruments developed specifically for men; AUC range 0.62 to 0.94 from the male population component of the studies with mixed populations	Inconsistent; precision varies by instrument	All but 1 study fair quality; similar limitations as for FRAX above	Low for poor to modest discrimination (FRAX, MORES, MOST, OST, OSTA)[c] Insufficient (ABONE, Garvan FRC, MSCORE, ORAI, OSIRIS, SCORE, VA-FARA)[e]	Men mostly from clinic-based populations
KQ2d: Repeat screening						
BMD at baseline and repeat BMD	5 Studies[154-158](19 957)	Predictive accuracy of repeat BMD at 4 to 8 y after initial BMD was similar to predictive accuracy of initial BMD for predicting MOF and hip fractures over follow-up of 8 to 11 y after repeat BMD	Consistent, precise	2 studies were poor quality; 3 were fair quality; indirect evidence	Moderate for no added value of repeat DXA[f]	One study exclusively in men; 1 study with 40% men; mean age, 60 to 75 y across studies
KQ3: Harms of screening						
Anxiety	1 RCT[27] (12 483)	No difference in anxiety between screening and control participants over 5 y (P = .52)	Single study, consistency unknown; precision unknown	Fair-quality pragmatic trial; modest uptake and adherence of intervention	Insufficient[d]	Two-stage screening approach in UK women aged 70 to 85 y
Overdiagnosis	1 Systematic review[32] (NA)	Based on data from 2 included RCTs, overdiagnosis estimated to range from 11.8% to 24.1%	Single review, consistency unknown; precision unknown	Good-quality systematic review; however, included RCTs are fair quality; method for estimating overdiagnosis for being labeled as "high risk" is evolving	Insufficient[g]	Two-stage screening in UK women aged 70 to 85 y in 1 study; Dutch women 60 y or older at high baseline fracture risk and extensive screening (imaging, laboratory assessment, falls assessment) in other study

(continued)

Table 3. Summary of Evidence on Screening for Osteoporosis to Prevent Fracture (continued)

Intervention or test/outcome	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
KQ4: Benefits of treatment						
Bisphosphonates						
Vertebral fracture (clinical and radiographic)	10 RCTs[159-163,165,167,168,177,184] (9015)	Pooled RR, 0.51 (95% CI, 0.39-0.66); ARD, 18 fewer per 1000 (95% CI, from 23 fewer to 13 fewer)	Consistent, precise	Most studies fair quality; evidence dominated by 3 larger studies; 5 studies had 0 events in at least 1 study group	Moderate for benefit[a]	Only 1 study in men; the rest were in mostly White postmenopausal women with low bone mass or osteoporosis
Nonvertebral fracture	13 RCTs[159,160,162-168,175,177,180,184] (20 929)	Pooled RR, 0.81 (95% CI, 0.74-0.88); ARD, 28 fewer per 1000 (95% CI, from 38 fewer to 18 fewer)	Consistent, precise	Most studies fair quality, evidence dominated by 6 larger studies; 2 studies had 0 events in at least 1 group	Moderate for benefit[a]	Only 1 study in men; the rest were in mostly White postmenopausal women with low bone mass or osteoporosis
Hip fracture	6 RCTs [162-166,177] (12 055)	Pooled RR, 0.67 (95% CI, 0.45-1.0); ARD, 3 fewer per 1000 (95% CI, from 5 fewer to 0 fewer)	Consistent, imprecise	Most studies fair quality; none were powered to evaluate hip fractures; 1 study had 0 events in at least 1 group	Low for benefit[b]	All studies in mostly White postmenopausal women with low bone mass or osteoporosis
Mortality	6 RCTs[159,170-172,177,182] (3714)	Pooled RR, 0.71 (95% CI, 0.49-1.05); ARD, 10 fewer per 1000 (95% CI, from 17 fewer to 2 more)	Consistent, imprecise	Most studies fair quality; none were powered to evaluate mortality; 3 studies with 0 events in at least 1 group	Low for benefit[b]	Only 1 study in men, the rest were in mostly White postmenopausal women with low bone mass or osteoporosis
Denosumab						
Vertebral fracture	4 RCTs[187,189,190,192] (8179)	Evidence base dominated by FREEDOM study (n = 7808 women); RR, 0.32 (95% CI, 0.26-0.41); ARD, 48 fewer per 1000 participants (95% CI, from 52 fewer to 42 fewer) All other studies with 0 to 1 events per group; pooled RR across all 4 RCTs, 0.33 (95% CI, 0.26-0.41); ARD, 44 fewer per 1000 persons (95% CI, from 49 fewer to 39 fewer)	Consistent, precise	All studies fair quality; evidence dominated by 1 study; outcome included both clinical and asymptomatic radiographic fractures	Moderate for benefit[a]	Postmenopausal women with osteoporosis or low bone mass; 1 study was only in men but had only 1 fracture event
Nonvertebral fracture	3 RCTs [187,190,192] (8382)	Evidence base dominated by FREEDOM study (n = 7808 women); 6.1% vs 7.5%; RR, 0.80 (95% CI, 0.67-0.95); ARD, 15 fewer per 1000 participants (95% CI, from 24 fewer to 4 fewer) Across all 3 RCTs, pooled RR, 0.80 (95% CI, 0.68-0.94); ARD, 14 fewer per 1000 (95% CI, from 23 fewer to 4 fewer)	Consistent, imprecise	Fair quality studies; evidence dominated by 1 large study	Low for benefit[b]	Postmenopausal women with osteoporosis or low bone mass; 1 trial was only in men but had only 3 events
Hip fracture	2 RCTs[187,190] (8050)	Evidence base dominated by FREEDOM study (n = 7808 women); 0.7% vs 1.1%; RR, 0.60 (95% CI, 0.37-0.97); ARD, 4 fewer per 1000 (95% CI, from 7 fewer to 0 fewer) No events in the other trial involving 242 men Across both studies, pooled RR, 0.61 (95% CI, 0.38-0.99); ARD, 4 fewer per 1000 from 7 fewer to 0 fewer)	Consistent, imprecise	Fair quality; large trial with uncertainties in randomization/allocation concealment, blinding, and attrition; no events in the other trial	Low for benefit[b]	Postmenopausal women with osteoporosis or low bone mass; smaller trial was only in men but had no fracture events

(continued)

Table 3. Summary of Evidence on Screening for Osteoporosis to Prevent Fracture (continued)

Intervention or test/outcome	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
Mortality	5 RCTs[187,190-192,194] (8828)	Pooled RR, 0.79 (95% CI, 0.58-1.07); ARD, 4 fewer per 1000 (95% CI, from 9 fewer to 1 more)	Consistent, imprecise	Fair quality; some uncertainties in randomization for 3 studies, allocation concealment in 4 studies, and attrition and blinding in 2 studies	Low for benefit[b]	Postmenopausal women with osteoporosis or low bone mass; 1 trial only in men but had only 2 events
KQ5: Harms of treatment						
Bisphosphonates						
Discontinuations due to adverse events	27 RCTs[160-168,170,172,173,175,180,182-184,195,196,199-201,203-207] (18 617)	Based on 24 RCTs: pooled RR, 1.00 (95% CI, 0.92-1.08); ARD, 0 fewer per 1000 (95% CI, from 9 fewer to 9 more)	Consistent, precise	Most studies fair quality, none powered for this outcome	Moderate for no effect[a]	Mostly White postmenopausal women with low bone mass or osteoporosis
Severe adverse events	22 RCTs[159,164,166-168,170,172,173,175,180,182,183,195,196,199,201,204-209] (13 878)	Based on 21 RCT comparisons: pooled RR, 0.97 (95% CI, 0.91-1.04); ARD, 6 fewer per 1000 (95% CI, from 18 fewer to 8 more)	Consistent, precise	Most studies fair quality, none powered for this outcome, not long enough to detect rare harms	Moderate for no effect[b]	Only 1 study exclusively in men, the rest were in mostly White postmenopausal women with low bone mass or osteoporosis
Upper gastrointestinal tract adverse events	26 RCTs[160,163-166,168,170,172,173,175,177,180,182,183,195-197,199-203,205-208] (22 280)	Pooled RR, 1.02 (95% CI, 0.98-1.06); ARD, 5 more per 1000 (95% CI, from 5 fewer to 16 more)	Consistent, precise	Most studies fair quality, none powered for this outcome	Moderate for no effect[a]	Mostly White postmenopausal women with low bone mass or osteoporosis
Denosumab						
Discontinuations due to adverse events	5 RCTs[187,190-192,194] (8826)	Pooled RR, 1.16 (95% CI, 0.87-1.54); ARD, 3 more per 1000 (95% CI, from 3 fewer to 11 more)	Consistent, imprecise	Fair quality; some uncertainties in randomization for 3 studies, allocation concealment in 4 studies, and attrition and blinding in 2 studies	Low for no effect[b]	Postmenopausal women with osteoporosis or low bone mass
Serious adverse events	6 RCTs[187,189-192,194] (8934)	Pooled RR, 1.04 (95% CI, 0.97-1.12); ARD, 9 more per 1000 (95% CI, from 7 fewer to 28 more)	Consistent, imprecise	Fair quality; some uncertainty for allocation concealment in all studies, randomization in 4 studies, and attrition and masking in 2 studies; not large enough or long enough to detect rare harms	Low for no effect[b]	Postmenopausal women with osteoporosis or low bone mass
Upper gastrointestinal tract adverse events	4 RCTs [189-192,194] (932)	Pooled RR, 2.18 (95% CI, 0.74-6.46); ARD, 14 more per 1000 (95% CI, from 3 fewer to 66 more)	Consistent, imprecise	Fair quality; some uncertainty for allocation concealment in all studies, randomization in 3 studies, and attrition and masking in 1 study	Low for harm[b]	Postmenopausal women with osteoporosis or low bone mass

Abbreviations: ABONE, Age, Body Size, No Estrogen instrument; AMMEB, Age, Menopause, Menarche, Body Mass Index; ARD, absolute risk difference; AUC, area under the curve; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; EPIC, Escala de Predicción de fracturas Implementable en historia Clínica electronica; FRAX, Fracture Risk Assessment Tool; FRC, Fracture Risk Calculator; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; FREM, Fracture Risk Evaluation Model; KQ, key question; MOF, major osteoporotic fracture; MORES, Male Osteoporosis Risk Estimation Score; MOST, Male Osteoporosis Screening Tool; MSCORE, Male Simple Calculated Osteoporosis Risk Estimation; NA, not applicable; NOF, National Osteoporosis Foundation instrument; ORAI, Osteoporosis Risk Assessment Instrument; OSIRIS, Osteoporosis Index of Risk; OST, Osteoporosis Self-Assessment Tool; OSTA, Osteoporosis Self-Assessment Tool for Asians; RCT, randomized clinical trial; ROB, risk of bias; ROSE, Risk-stratified Osteoporosis Strategy Evaluation; RR, relative risk; SCORE, Simple Calculated Osteoporosis Risk Estimation; SOFSURF, Study of Osteoporotic Fractures Study Utilizing Risk Factors instrument; VA-FARA, Veterans Affairs-Fracture Absolute Risk Assessment; WHI, Womens Health Initiative Prediction Model.

[a] Rated down 1 level for study limitations.

[b] Rated down 1 level for imprecision and 1 level for study limitations.

[c] Rated down 1 level for inconsistency and 1 level for study limitations.

[d] Not enough data to evaluate strength of evidence.

[e] Downgraded 1 level for study limitations, 1 level for inconsistency, and 1 level for imprecision.

[f] Downgraded 1 level for study limitations, including indirectness as these study designs did not directly compare a strategy of repeat screening with single screening.

[g] Not enough data to evaluate SOE and indirect evidence based on extrapolations.

For bisphosphonates, 5 RCTs reported 0 cases of osteonecrosis of the jaw[159,169,177,180,209] and no RCTs reported on the rare outcome of atypical femur fracture. For denosumab, 3 RCTs[187,190,194] reported 0 cases of osteonecrosis of the jaw. Two RCTs[187,194] reported on the rare outcome of atypical femur fracture and both reported 0 events. Additional information about these rare outcomes from study designs not eligible for inclusion were addressed as a Contextual Question (Appendix F.3 in the full report[3]). No studies included for KQ5 had study designs sufficient to evaluate rebound vertebral fractures after denosumab discontinuation. Findings related to rebound vertebral fractures from studies not eligible for inclusion in this update were addressed as a Contextual Question (Appendix F.4 in the full report[3]).

Three fair-quality cohort studies set in Denmark,[215] Sweden and Denmark,[214] and South Korea[213] addressed potential harms of bisphosphonate use. Two studies were limited to new users[213,215]; the third study provided sensitivity analyses for a treatment-naive cohort.[214] The studies predominantly (86%[214] and 91%[213]) or solely[215] comprised women. One study was limited to zoledronic acid,[214] a second to alendronate,[215] and the third included all bisphosphonates (which may have included non–FDA-approved bisphosphonates).[213] Detailed study characteristics, quality assessments, and results are provided in Appendix D Tables 7 and 17 of the full report.[3] In brief, 2 of the studies reported an increased risk for atypical femur fractures with bisphosphonate use compared with nonusers (adjusted HR, 2.46 [95% CI, 1.17 to 5.15], n = NR[214] and adjusted HR, 1.53 [95% CI, 1.36 to 1.73], n = 696 859[213]). However, neither study controlled for all known confounders such as smoking, body mass index (BMI), or alcohol use.

Discussion

The SOE by KQ is presented in **Table 3**. Compared with the prior review,[4] our certainty related to the direct benefits of screening has increased because of new evidence for KQ1. In contrast, the evidence remains insufficient for harms of screening (KQ3). Based on the screening strategies evaluated, the SOE was rated as moderate for a small absolute benefit on MOF and hip fractures, low for a small absolute benefit on osteoporotic fractures, and low for no effect on mortality; however, no direct evidence for BMD screening with DXA alone is available. The 3 studies included for KQ1 were pragmatic trials conducted among older European women (median age, 71 to 76 years) at relatively high risk for hip fracture (10-year estimated FRAX risks at baseline ranged from 6.7% to 11.6%). The proportion of eligible persons who participated was low (about one-third) in 1 trial[27] with evidence of selection bias toward healthy individuals, and the receipt of the screening intervention was suboptimal in the other 2 trials (55%[23] and 76%[30]). These trials were underpowered because the observed proportion of women with treatment indications and who adhered to treatment were lower than expected and because of contamination in control groups from secular trends in screening and treatment. For these reasons, the estimates of benefits probably represent the lower bounds of screening efficacy. Yet these findings may reflect the real-world effectiveness of a systematic screening program. Although these estimates represent the lower bounds of efficacy, it is not entirely clear that the findings are applicable to populations with lower fracture risk or US settings, given the use of country-specific FRAX prediction models and the thresholds for action (further DXA testing or treatment) used in these trials.

The scope of the KQ on accuracy changed between the prior report and the current update, so direct SOE comparisons are not possible. The evidence in this update was graded as low or insufficient SOE for the predictive and diagnostic accuracy of risk assessment tools and for predictive accuracy of BMD alone. Many studies were conducted using retrospectively assembled datasets of persons referred for BMD, some of whom may already have had a diagnosis of osteoporosis, been taking medication, or may have had a prior fracture. Many predictive accuracy studies focused only on discrimination outcomes and did not report sufficient information about calibration. Some used proxy data for selected risk factors or omitted those factors if data were not available, or participants were observed for fewer years than the duration used in the risk model development studies. Further, it is unclear whether data on FRAX from other countries is applicable to the US setting, given that FRAX is calibrated to each country's fracture incidence. This limitation was mitigated by restricting the KQs on predictive accuracy to countries with hip fracture incidence similar to that of the US. The diagnostic accuracy studies varied in how the DXA reference standard was measured (eg, different anatomical sites for BMD, different references to calculate T scores).

Some new evidence for treatment benefits and harms was identified for this update; however, the SOE ratings for treatment benefits (KQ4) remained largely the same as the prior review: low to moderate SOE for benefit across multiple fracture outcomes for both bisphosphonates and denosumab. For treatment harms (KQ5), the SOE was low (denosumab) and moderate (bisphosphonates) for discontinuations due to adverse events and serious adverse events and moderate for no effect on upper gastrointestinal adverse events for bisphosphonates and low for increased upper gastrointestinal adverse events for denosumab. As in the prior report, the SOE is insufficient for evaluating the effect of treatment on very rare harms such as osteonecrosis of the jaw, atypical femur fractures, rebound vertebral fractures, or harms of prolonged treatment duration. The major limitation in the treatment literature for primary prevention is that few studies included men, and all studies enrolled persons based on T scores and not based on fracture risk.

A concern across the evidence for all KQs relates to the lack of diverse populations enrolled in studies. Many studies did not report the race or ethnicity of enrolled populations, and those that did mostly enrolled exclusively or majority White populations. Given the differences in fracture incidence among persons of different races and ethnicities in the United States, studies enrolling sufficient numbers from diverse populations are needed to determine the applicability of findings in different populations.

Limitations

This review focused on 1 aspect of fracture prevention: identifying and treating osteoporosis with medication. Preventing falls is addressed by a separate USPSTF recommendation.[216] This review did not address DXA testing or treatment in persons with a history of fragility fracture or medical conditions or medications associated with secondary osteoporosis. The comparative effectiveness and harms of alternative pharmacotherapies and drug holidays was not evaluated. This review was not designed to comprehensively evaluate rare harms.

Conclusions

Screening in higher-risk women 65 years or older was associated with a small absolute risk reduction in hip and major fractures compared with usual care. No evidence evaluated screening with BMD alone or screening in men or younger women. Risk assessment instruments, BMD alone, or both have poor to modest discrimination for predicting fracture, and calibration studies were limited. Osteoporosis treatment with bisphosphonates or denosumab over several years was associated with fracture reductions and no meaningful increase in adverse events; data for longer-term or rare harms were limited, based on the evidence included in this update.

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