Cost-effectiveness of Virtual Bone Strength Testing in Osteoporosis Screening Programs for Postmenopausal Women in the United States

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Abstract: Purpose To investigate whether assessment of bone strength with quantitative computed tomography (CT) in combination with dual-energy x-ray absorptiometry (DXA) is cost-effective as a screening tool for osteoporosis in postmenopausal women. Materials and Methods A state-transition microsimulation model of osteoporosis for postmenopausal women aged 55 years or older was developed with a lifetime horizon and U.S. societal perspective. All model inputs were derived from published literature. Three strategies were compared: no screening, DXA with T score-dependent rescreening intervals, and a combination of DXA and quantitative CT with different intervals (3, 5, and 10 years) at different screening initiation ages (55-65 years). Oral bisphosphonate therapy was started if DXA hip T scores were less than or equal to -2.5, 10-year risk for hip fracture was greater than 3% (World Health Organization Fracture Risk Assessment Tool score, or FRAX), 10-year risk for major osteoporotic fracture was greater than 20% (FRAX), quantitative CT femur bone strength was less than 3000 N, or occurrence of first fracture (eg, hip, vertebral body, wrist). Outcome measures were incremental cost-effectiveness ratios (ICERs) in 2015 U.S. dollars per quality-adjusted life year (QALY) gained and number of fragility fractures. Probabilistic sensitivity analysis was also performed. Results The most cost-effective strategy was combined DXA and quantitative CT screening starting at age 55 with quantitative CT screening every 5 years (ICER, $2000 per QALY). With this strategy, 12.8% of postmenopausal women sustained hip fractures in their remaining life (no scre
year interval, was 7.5%; no screening, 11.1%; DXA screening, 9%; for wrist fractures, 14%, 17.8%, and 16.4%, respectively
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effective strategy for osteoporosis screening in postmenopausal women and has the potential to prevent a substantial number o

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Radiology

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Purpose: To investigate whether assessment of bone strength with quantitative computed tomography (CT) in combination with dual-energy x-ray absorptiometry (DXA) is cost-effective as a screening tool for osteoporosis in postmenopausal women.

Materials and Methods: A state-transition microsimulation model of osteoporosis for postmenopausal women aged 55 years or older was developed with a lifetime horizon and U.S. societal perspective. All model inputs were derived from published literature. Three strategies were compared: no screening, DXA with T score–dependent rescreening intervals, and a combination of DXA and quantitative CT with different intervals (3, 5, and 10 years) at different screening initiation ages (55–65 years). Oral bisphosphonate therapy was started if DXA hip T scores were less than or equal to −2.5, 10-year risk for hip fracture was greater than 3% (World Health Organization Fracture Risk Assessment Tool score, or FRAX), 10-year risk for major osteoporotic fracture was greater than 20% (FRAX), quantitative CT femur bone strength was less than 3000 N, or occurrence of first fracture (eg, hip, vertebral body, wrist). Outcome measures were incremental cost-effectiveness ratios (ICERs) in 2015 U.S. dollars per quality-adjusted life year (QALY) gained and number of fragility fractures. Probabilistic sensitivity analysis was also performed.

Results: The most cost-effective strategy was combined DXA and quantitative CT screening starting at age 55 with quantitative CT screening every 5 years (ICER, $2000 per QALY). With this strategy, 12.8% of postmenopausal women sustained hip fractures in their remaining life (no screening, 18.7%; DXA screening, 15.8%). The corresponding percentages of vertebral fractures for DXA and quantitative CT with a 5-year interval, was 7.5%; no screening, 11.1%; DXA screening, 9%; for wrist fractures, 14%, 17.8%, and 16.4%, respectively; for other fractures, 22.6%, 30.8%, and 27.3%, respectively. In probabilistic sensitivity analysis, DXA and quantitative CT at age 55 years with quantitative CT screening every 5 years was the best strategy in more than 90% of all 1000 simulations (for thresholds of $50000 per QALY and $100000 per QALY).

Conclusion: Combined assessment of bone strength and bone mineral density is a cost-effective strategy for osteoporosis screening in postmenopausal women and has the potential to prevent a substantial number of fragility fractures.

Online supplemental material is available for this article.

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Osteoporosis is a major public health problem that results in high societal costs and physical impairment. The main clinical outcome of osteoporosis is fracture due to low bone mass and deterioration in bone microarchitecture (1). In the United States, more than 2 million fractures each year are attributed to osteoporosis, and the direct annual costs are estimated at greater than $17 billion (2). The lifetime risk for hip fracture in a 50-year-old white woman is 16% (3), and the mortality rates in the first 3 months after hip fracture increase five- to eightfold (4). Given the aging population, the number of fractures and costs to society are only expected to rise (2). Osteoporosis is operationally defined, in the absence of fragility fracture, as low bone mineral density (BMD) at dual-energy x-ray absorptiometry (DXA) (T score ≤ -2.5).

Advances in Knowledge

- Bone strength testing with quantitative CT in addition to dual-energy x-ray absorptiometry (DXA) for determination of bone mineral density could be a cost-effective strategy for osteoporosis screening in postmenopausal women.
- The lifetime risk for hip fracture of 55-year-old postmenopausal women in our model was substantially lower (12.8%) when a combined DXA and quantitative CT bone strength screening protocol was used compared with that when women did not undergo screening (18.7%).
- The most cost-effective strategy in our model was combined DXA and quantitative CT screening starting at age 55 years, with quantitative CT rescreening every 5 years.
- Increasing the costs of the quantitative CT bone strength test had little effect on the cost-effectiveness results of bone strength screening.

The major limitation of DXA is that its use for detection of increased fracture risk is poor in the majority of individuals (5). Most patients with fragility fractures do not meet the DXA criterion for osteoporosis (ie, T score > -2.5) (6,7). DXA is a low-resolution two-dimensional technique that does not completely capture impaired bone strength in patients with osteoporosis. Modalities that allow assessment of bone strength are quantitative computed tomography (CT) and magnetic resonance (MR) imaging (8,9). A bone strength estimate is computed from bone images with a method called finite element analysis (10). The three-dimensional images of a patient's bone are transformed into a three-dimensional model consisting of multiple voxels. Each voxel is assigned a material property (cortex, trabeculae) on the basis of imaging characteristics in that voxel. This results in a three-dimensional model of the bone that simulates the material strength of the trabeculae and cortex. Virtual mechanical testing of this three-dimensional model simulates and quantifies the force (bone strength) needed to fracture the model (10). There are only a few published studies in which the ability of bone strength assessment and DXA to predict incidents of osteoporotic fracture are examined. Bone strength testing improves vertebral fracture risk assessment in elderly men when compared with DXA (11). Low bone strength also is associated with an increased risk of hip and vertebral fractures, similar to the DXA-based thresholds for BMD for osteoporosis (12). Postmenopausal women with hip fractures show lower bone strength compared with healthy women, without differences in T scores (9). Therefore, bone strength testing provides information not captured at DXA. Because executing a prospective fracture prediction study is expensive and requires extensive resources, it would be useful to know whether bone strength testing has the potential to be cost-effective, considering the higher costs of CT-based bone strength testing compared with those of DXA. We hypothesized that bone strength testing would be cost-effective as a screening tool. The purpose of our study was to investigate whether assessment of bone strength with quantitative CT in combination with DXA is cost-effective as a screening tool for osteoporosis in postmenopausal women.

Implication for Patient Care

- The combined assessment of bone strength and bone mineral density in postmenopausal women has the potential to be a cost-effective strategy for osteoporosis screening and may prevent a substantial number of fragility fractures.

Materials and Methods

We conducted a cost-utility analysis to compare different screening strategies for osteoporosis by using a societal perspective with direct and indirect costs and a lifetime horizon.

Model Structure

We developed a state transition microsimulation model of osteoporosis by

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Abbreviations:
BMD = bone mineral density
DXA = dual-energy x-ray absorptiometry
FRAX = fracture risk assessment
ICER = incremental cost-effectiveness ratio
PSA = probabilistic sensitivity analysis
QALY = quality-adjusted life year

Author contributions:
Guarantors of integrity of entire study, C.A.A., G.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, C.A.A., A.J.R., S.H., G.C.; clinical studies, S.H.; experimental studies, C.A.A., A.J.R., S.K., S.H.; statistical analysis, C.A.A., S.K., G.C.; and manuscript editing, C.A.A., A.J.R., S.K., G.C.

Conflicts of interest are listed at the end of this article.

Figure 1

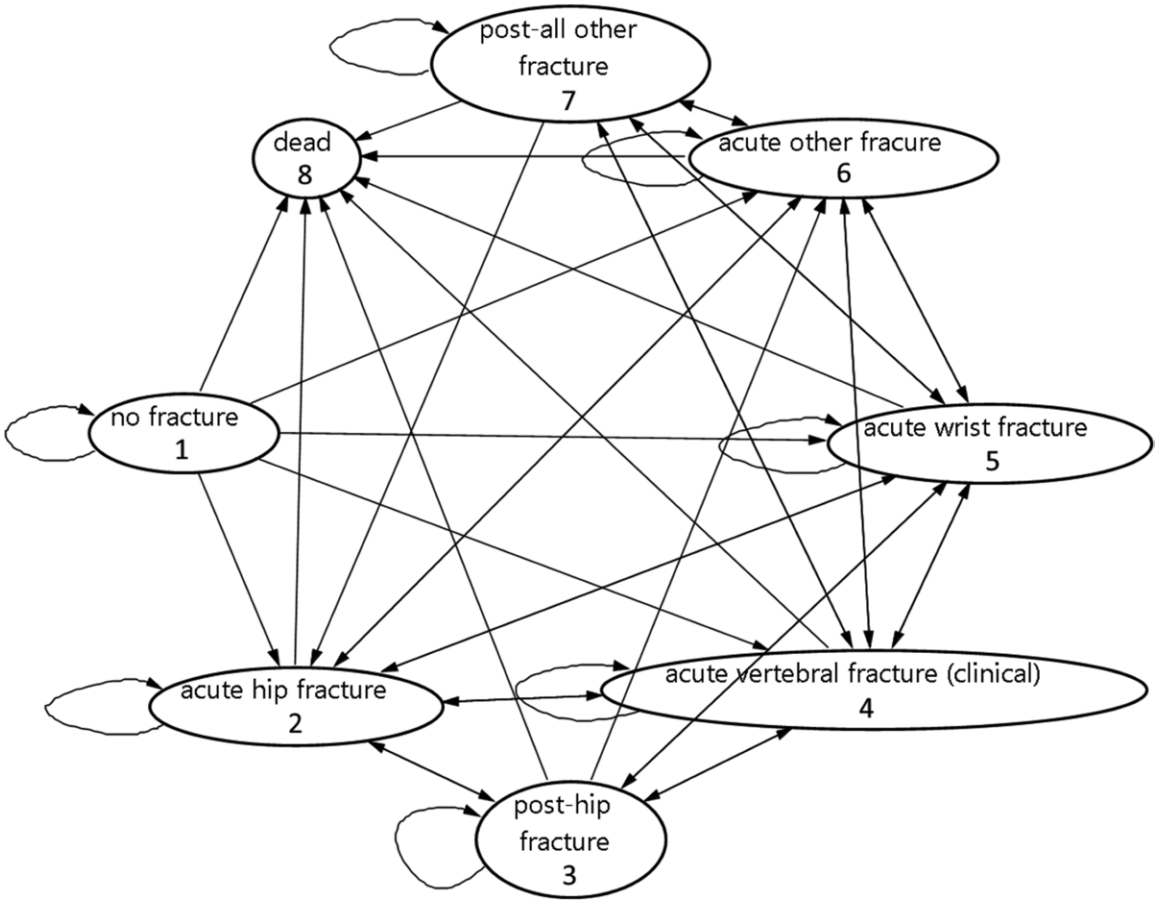

Figure 1: State transition diagram. In the first cycle all individuals started in no fracture state. In each cycle they either stayed healthy (no fracture state), sustained an acute fracture, transitioned to postfracture state after acute fracture, or died (and therefore exited the model). Acute other fractures comprised those of the humerus, ribs, distal femur, and tibia.

using modeling software (TreeAge Pro Health Care 2015; TreeAge Software, Williamstown, Mass). We simulated a hypothetical cohort of 1 million postmenopausal women. We randomly assigned six risk factors (absent or present) used in the paper chart version of the World Health Organization's fracture risk assessment tool (FRAX) (13) to each individual on the basis of reported age-dependent prevalence (previous fracture [14], fractured hip in a parent [14,15]), current smoking [16], use of glucocorticoids [15], rheumatoid arthritis [17], and consumption of three or more units of alcohol per day [15]). The model included a simulation of the U.S. Caucasian paper chart of the FRAX tool to calculate the 10-year risk for hip fracture and other major osteoporotic fracture for each individual on the basis of the number of assigned risk factors (factors, 0–6) and the BMD T score of the femoral neck (13).

The cohort transitioned through different health states in 3-month cycles for their remaining lifespan. The health states were no fracture, hip fracture, post–hip fracture, clinical vertebral fracture, wrist fracture, other fracture (humerus, ribs, distal femur, tibia), post–all nonhip fractures, and death (Fig 1). In the first cycle, all individuals started in the no fracture state. In each cycle they either stayed healthy (no fracture state), sustained a fracture, transitioned to a postfracture state after an acute fracture, or died.

We derived transition probabilities between health states from published literature (Tables 1,2). All-causes mortality of women in the general population was derived from U.S. life tables (41). The risk of dying after a hip fracture was age dependent and increased during the 1st year after the fracture (27). After the 1st year, the relative risk of dying decreased but remained higher than the background mortality (4). After a hip fracture, 20% of individuals required placement in nursing facilities for their remaining lifetime (35). We limited the maximum number of hip fractures for each individual to two (once on each side). Only

Table 1

Model Parameters

Variable*	Base Case Data	PSA	
		Distribution	Data
Prevalence of clinical risk factors (%)			
Previous fracture (14)			
Age 55–64 years	7.6	Uniform	(6.6, 8.7)
Age 65–74 years	16.3	Uniform	(14.3, 18.5)
Age ≥ 75 years	29.4	Uniform	(26.1, 32.9)
Parent hip fracture (14,15) (%)	16	Uniform	(14.5, 17.3)
Current smoking (16) (%)			
Age 55–64 years	15.2	Uniform	± 3†
Age ≥ 65 years	7.5	Uniform	± 3†
Glucocorticoids (15) (%)	3	Uniform	± 1†
Rheumatoid arthritis (17) (%)	0.98	Uniform	(0.9, 1.07)
Alcohol, three or more units per day (15) (%)	1	Uniform	(0.5, 2)†
Direct costs ($)‡			
DXA (18)	41.68	Normal	± 5
Quantitative CT plus $100 for bone strength analysis (18)	214.63	Normal	± 27
Doctor visit (18)	73.3	Normal	± 9
Alendronate (per y) (19)	76	Gamma	± 29
Hip fracture (20)	25758	Gamma	± 9659
Clinical vertebral fracture (20)	10535	Gamma	± 3951
Wrist fracture (20)	5719	Gamma	± 2145
Other fracture (20)	7014	Gamma	± 2630
Nursing home (per y) (21)	80300	Gamma	± 30113
Indirect costs ($)§			
Age younger than 65 years			
Hip fracture (22–24)	7405	Uniform	(3703–11108)
Clinical vertebral fracture (22–24)	3149	Uniform	(1575–4724)
Wrist fracture (22–24)	2041	Uniform	(1021–3062)
Other fracture (22–24)	2682	Uniform	(1341–4023)
Age 65 years or older			
Hip fracture (22–24)	1219	Uniform	(610–1829)
Clinical vertebral fracture (22–24)	518	Uniform	(259–777)
Wrist fracture (22–24)	336	Uniform	(168–504)
Other fracture (22–24)	442	Uniform	(221–663)
Relative risks			
Prior hip fracture (25)	1.56	Log-normal	(1.23, 1.98)
Prior nonhip fracture (25)	1.74	Log-normal	(1.57, 1.92)
Primary prevention			
Hip fracture (26)	0.79	Log-normal	(0.44, 1.44)
Vertebral fracture (osteoporosis) (26)	0.55	Log-normal	(0.38, 0.80)
Vertebral fracture (osteopenia) (26)‖	0.82	Log-normal	(0.33, 2.07)
Wrist fracture (26)	1.19	Log-normal	(0.87, 1.62)
Other fracture (26)	0.89	Log-normal	(0.76, 1.04)
Secondary prevention			
Hip fracture (26)	0.47	Log-normal	(0.26, 0.85)
Vertebral fracture (26)	0.55	Log-normal	(0.43, 0.69)
Wrist fracture (26)	0.5	Log-normal	(0.34, 1.73)
Other fracture (26)	0.77	Log-normal	(0.64, 0.92)
Death in 1st year after hip fracture (27)#			
Age 57 years	14.5	Gamma	± 10

Table 1 *(continues)*

35% of all occurring vertebral compression fractures were considered clinically apparent (34). Individuals could only sustain a maximum of one fracture type in each 3-month cycle.

Screening Strategies

We compared three types of screening strategies: no screening, DXA and FRAX, and combined DXA and quantitative CT (DXA/quantitative CT) and FRAX; each with screening initiation at ages 55, 60, and 65 years. FRAX risks were recalculated on the occasion of every DXA scan with all strategies. DXA rescreening intervals depended on the most current T score from the last DXA scan: every 15 years for women with normal BMD or mild osteopenia (T score > -1.5), every 5 years for those with moderate osteopenia (T score, -1.50 to -1.99), and every year for those with advanced osteopenia (T score, 2.00 to -2.49) (42). In the combined DXA/quantitative CT strategies, all individuals were first screened with DXA and FRAX. We added bone strength testing (quantitative CT) at fixed intervals (3, 5, and 10 years) in individuals with T scores greater than -2.5 who were not assigned for treatment on the basis of the FRAX tool. We defined a femoral bone strength of less than 3000 N as low bone strength on the basis of the work of Keaveny et al (10). In all strategies, individuals assigned for treatment on the basis of DXA, FRAX tool, or quantitative CT or after any fracture were exempted from further screening, because they would be treated under current osteoporosis treatment guidelines. Overall, this resulted in a total of 15 different screening strategies.

Bone Parameters

Table 2 provides the parameters we used to simulate bone quality. We assigned a BMD and a bone strength value to each individual at the start of the simulation, drawn from a normal distribution for that specific start age (36). During each cycle we simulated BMD and bone strength changes for each woman on the basis of her start value, current age, and whether the

Table 1 (continued)

Model Parameters

Variable*	Base Case Data	PSA Distribution	PSA Data
Prevalence of clinical risk factors (%)			
Age 72 years	5.2	Gamma	± 10
Age 80+ years	2.5	Gamma	± 10
Death after 1st year after hip fracture (4)	1.78	Log-normal	(1.33, 2.39)
Utilities#			
Base effectiveness in fracture-free health state (28)			
Age 55 years	0.837	Triangular	± 10
Age 65 years	0.811	Triangular	± 10
Age 75 years	0.771	Triangular	± 10
Age 85 years	0.724	Triangular	± 10
Utility modifier			
Hip fracture (29)	0.792	Triangular	± 10
Clinical vertebral fracture (29)	0.626	Triangular	± 10
Wrist fracture (29)**	0.977	Triangular	± 10
Other fracture (29)	0.867	Triangular	± 10
1st year after hip fracture (30)	0.797	Triangular	± 10
Subsequent years after hip fracture (31)	0.9	Triangular	± 10
After nonhip fracture (29,32)**	0.93	Triangular	± 10
Nursing home placement (31)	0.4	Triangular	± 10
Others‡			
Clinical vertebral fractures (33) (%)	35	Beta	± 0.13
Fracture modifier	1	Gamma	± 0.10
Probability to end up in nursing home (34) (%)	20	Beta	± 0.08
Adherence to alendronate (35) (%)	50	Beta	± 0.19

Note.—Unless otherwise indicated, data in parentheses are 95% confidence intervals. CTP code for doctor visit, 99213; DXA, 77080; for quantitative CT, 77078; for bone strength analysis, 76377. PSA = probabilistic sensitivity analysis.

* Data in parentheses are reference numbers.

† Indicates an assumption.

‡ Base case data are means and PSA data are standard deviations.

§ Data in parentheses are the range.

‖ No data for hip, others, wrist fracture for osteopenia.

Base case data are means and PSA data are standard deviation percentage of the mean.

** Capped at maximum value of 1.

individual was receiving therapy or not or was on a drug holiday. T scores for the model were calculated on the basis of each individual's current BMD.

Treatment

The model included initiation of oral bisphosphonate (alendronate) treatment in these scenarios: *(a)* DXA with T score of less than or equal to −2.5; *(b)* 10-year risk for hip fracture of greater than 3% with the FRAX tool; *(c)* 10-year risk for major osteoporotic fracture of greater than 20% with the FRAX tool, low bone strength at quantitative CT or after the first fracture was sustained. Alendronate was given in 5-year cycles (ie, 5 years of treatment and a 5-year drug holiday) (43). Individuals' BMD and bone strength slowly improved during treatment and slowly decreased during drug holidays (Table 2). We assumed an adherence to alendronate of 50% in the primary prevention scenario and complete adherence after the first fracture.

Fracture Risk

In each cycle, we calculated the risk for each fracture site on the basis of these parameters: location, age, T score, bone strength, previous fracture, and primary or secondary prevention (Tables 1, 2). We used reported fracture rates in women for each fracture site for age groups 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and greater than or equal to 85 years (base risk of the general population) (2,44). We multiplied that base risk by a T score factor derived from relative risks below certain T score thresholds for hip fractures compared with that of the general population (Table 2) (36). These relative risks were further modified on the basis of bone strength by multiplying the relative risk by a bone strength factor (Table 2). The relative risk of fracture was increased if an individual had a prior hip or nonhip fracture on the basis of data from a meta-analysis (25). We applied relative risks for primary or secondary prevention of osteoporotic fractures for each fracture site, which were derived from a Cochrane database systematic review (26).

Direct Costs

We used reported direct fracture costs for each fracture type (Table 1). These direct fracture costs accounted for surgery, hospital stay, and rehabilitation. We projected all costs in 2015 U.S. dollars, according to data from the U.S. Department of Labor and the U.S. Consumer Price Index for medical care for all urban consumers (45). We used 2015 Medicare reimbursement rates for DXA, quantitative CT, and physician office visits (18). For quantitative CT costs, we used the costs for a CT scan of the hip. For postprocessing of the images and bone strength analysis, we added $100. We assumed that there were physician office visits on the occasions of screening examinations and once each quarter in the primary prevention scenario (if the patient was adherent to the treatment) or after a first fracture. For subjects receiving treatment, we applied the costs of the generic oral form of alendronate (19). For individuals in a nursing home, we applied the median 2015 costs of nursing home care in the United States for a semiprivate room, on the basis of 365 days of care (21).

Table 2

Bone Mineral Density and Bone Strength Parameter

Variable*	Base Case Data	PSA	
		Distribution	Data
BMD			
Mean BMD at start (g/cm^2) (36)†			
Age 25 years	0.86	Normal	± 0.12
Age 55 years	0.71	Normal	± 0.12
Age 65 years	0.682	Normal	± 0.114
Age 75 years	0.618	Normal	± 0.099
BMD loss per year without treatment (37) (%)			
Age 50 years	0.109	Triangular	± 10
Age 65 years	0.368	Triangular	± 10
Age 70 years	0.471	Triangular	± 10
Age 75 years	0.559	Triangular	± 10
Age 80 years	0.647	Triangular	± 10
Age 85 years	0.824	Triangular	± 10
BMD increase per year with therapy (38) (%)	0.95	Gamma	± 0.356
BMD loss per year during drug holiday (39) (%)	0.34	Gamma	± 0.127
Relative risk for fracture based on hip T score (36) (T score factor)‡			
At age 65 years			
−3.5	3.385	Triangular	± 10
−3	2.308	Triangular	± 10
−2.5	1.462	Triangular	± 10
−2	1	Triangular	± 10
−1	0.423	Triangular	± 10
At age 75 years			
−3.5	2.186	Triangular	± 10
−3	1.465	Triangular	± 10
−2.5	0.93	Triangular	± 10
−2	0.628	Triangular	± 10
−1	0.279	Triangular	± 10
Bone strength			
Mean bone strength at start (10) (N)	(7240 – 60.7 × age)	Normal	± 600
Bone strength loss per year without therapy (10) (%)‡			
Age 45 years	1.3	Triangular	± 10
Age 55 years	1.5	Triangular	± 10
Age 65 years	1.75	Triangular	± 10
Age 75 years	2.2	Triangular	± 10
Age 85 years	2.8	Triangular	± 10
Bone strength gain per year under therapy (40) (%)	4	Gamma	± 0.375
Relative risk for fracture based on bone strength (bone strength factor)‡§			
100	2	Triangular	± 10
1000	1.6	Triangular	± 10
2000	1.4	Triangular	± 10
3000	1.2	Triangular	± 10
3800	1	Triangular	± 10
5000	0.75	Triangular	± 10
8000	0.6	Triangular	± 10

Note.—Unless otherwise indicated, base case data are means and PSA data are the standard deviations.

* Data in parentheses are reference numbers.

† Standard deviation is age dependent.

‡ Base case data are means, and the PSA data are the standard deviation as percentage of the mean.

§ Indicates an assumption.

To calculate indirect costs, we used reported estimates on days unable to work for each fracture type (hip, 127 days; vertebrae, 54 days; others, 46 days; and wrist, 35 days) (22). We used annual averages (2013) of median weekly earnings for full-time and part-time working women in the United States, adjusted for that age group's workforce participation (55–64 years and ≥ 65 years) (23,24). We applied indirect costs as onetime costs for each fracture event. We projected all indirect costs in 2015 U.S. dollars.

Utilities

We used quality-adjusted life years (QALYs) to calculate the effectiveness of our strategies. We assigned an age-dependent base effectiveness in the no fracture health state on the basis of representative U.S. values for health-related quality-of-life scores (28). Each fracture state and postfracture state comprised a utility modifier with which the base value was multiplied in that cycle (Table 1). Nursing home placement was associated with a substantial disutility as reported in a systematic review for utilities in osteoporosis-related health conditions (31).

Model Validation

We tested the external validity of our model by using a 65-year-old cohort of postmenopausal women who had not undergone screening. We compared the predicted fracture rates according to our model with reported fracture rates from independent studies not used for model inputs.

Main Analysis

We calculated incremental cost-effectiveness ratios (ICERs) for each strategy on the basis of the base case variables provided in Tables 1 and 2. We excluded strategies that were more costly but less effective than an alternative strategy (absolute dominance). We ruled out strategies if they were less costly than an alternative but had a higher ICER (weak dominance). We tracked all fracture events in the model and compared the number of fractures from the most cost-effective screening

Figure 2

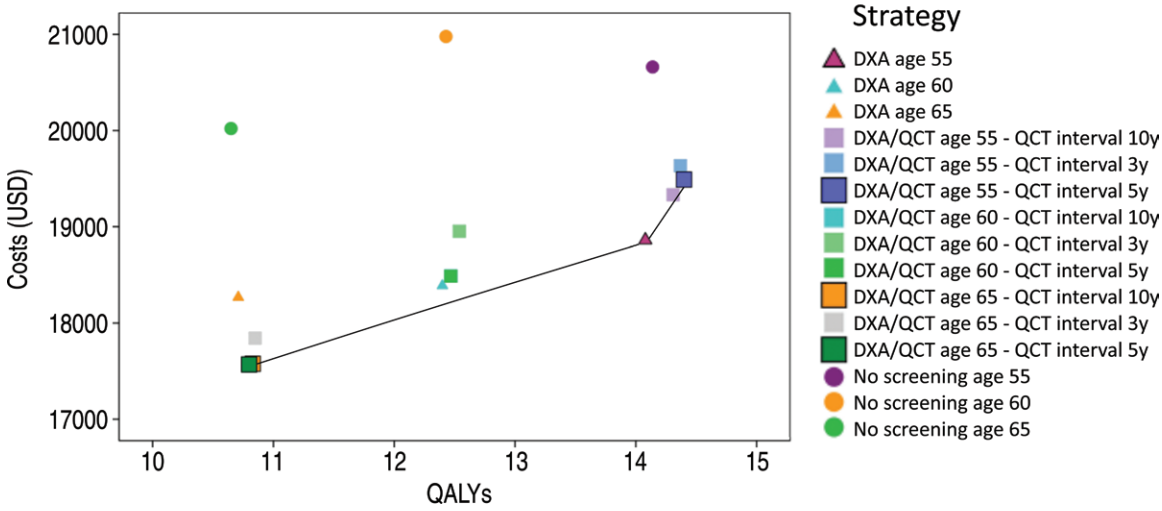

Figure 2: Graph shows costs (in U.S. dollars) and effectiveness (QALY) of each strategy for main analysis. All strategies above the connecting lines were more expensive and/or less effective and were therefore excluded and not incorporated in Table 4. DXA/quantitative CT *(QCT)* age 60–quantitative CT interval 10 years square is obscured by the DXA/quantitative CT age 60–quantitative CT interval 5 years because the squares are in the same position on the graph.

strategy with currently used scenarios (no screening and DXA screening). In our base case scenario we used 3% annual discounting of costs and effectiveness as suggested by the U.S. Panel on Cost-Effectiveness in Health and Medicine (46). Strategies with costs of $50 000 per QALY were considered very cost-effective and those of $50 000–$100 000 per QALY were considered cost-effective.

Sensitivity Analyses

We performed deterministic and PSA to address the effects of parameter uncertainty on model results. In two separate analyses, we increased and decreased the overall fracture risk for all fracture types by a factor of two (worst and best case scenario). In a third analysis, we removed the bone strength factor, neglecting the effect of bone strength on fracture risk. We used one-way sensitivity analyses to assess different levels of medication adherence (40%, 70%, 100%) and linearly increasing quantitative CT costs (including postprocessing) of $215, $340 (hip MR imaging, current procedural terminology code 73721), $460, $580, and $700. We also varied the annual discounting of costs and effectiveness from 0% (undiscounted) to 5% (46). We performed threshold analyses for major parameters to test the potential effect on our model results. The sensitivity analysis was performed by varying the following parameters for a population in which screening was initiated at age 55 years, because this was the preferred age to start any screening: adherence rate, 40%–100%; overall fracture rate, 50%–200%; costs for DXA, $1–$50; for quantitative CT, $100–$1000; and for hip fracture treatment, $10 000–$50 000; utility modifier for hip fractures, 0.6–0.9 and for vertebral fractures, 0.6–0.9. We calculated the net monetary benefits for each strategy for willingness-to-pay values of $50 000 and $100 000. Net monetary benefit was calculated by converting QALYs into U.S. dollars and then subtracting the costs for each strategy. This resulted in the net monetary benefit for that specific strategy. The threshold for each parameter that resulted in a change in the preferred strategy based on net monetary benefits was calculated.

PSA Protocol

In PSA, we ran the model 1000 times with 100 000 individuals. In each of these 1000 runs, the model was used to draw random data points for each variable according to the distributions provided in Tables 1 and 2 to address overall uncertainty of the model.

Results

Main Analysis

Model validation, as shown in Table 3, allowed us to proceed with the analyses. The most cost-effective screening strategy was combined DXA/quantitative CT with screening initiation at age 55 and a quantitative CT screening interval of 5 years (Tables 4, 5; Fig 2). The total number of fractures with that strategy was substantially lower compared with that with DXA and that with no screening (Table 5). With no screening at age 55, 18.7% of individuals in our cohort sustained a hip fracture during the remainder of their life. DXA screening starting at age 55 years reduced that percentage to 15.8%, while the most cost-effective strategy (DXA/quantitative CT at age 55 years, with a quantitative CT interval of 5 years) reduced the lifetime risk to 12.8%. The corresponding percentages of individuals starting screening at age 55

Table 3

Model Validation

Age 65, No Screening	Model Precast	Literature
Life expectancy (y)	19.6	20.5 (16)
Hip fractures		
Lifetime	19	18–20 (47,48)
By age 90 years	16.3	16.3 (49)
Wrist fractures by age 85 years	15.6	14.5 (50)*
Vertebral fractures by age 90 years	10.2	12.3 (50)†

Note.—Unless otherwise indicated, data are percentages, with the references in parentheses.

* By age 85 for women between 60–69 years.

† After 20 years for women between 60–69 years.

Table 4

Results of Main Analysis (Base Case)

Strategy	Age (y)	Interval (y)*	Cost	QALY	ICER
DXA/quantitative CT	65	5	17570	10.80	NA
DXA/quantitative CT	65	10	17580	10.83	200
DXA	55	NA	18860	14.08	400
DXA/quantitative CT	55	5	19490	14.40	2000

Note.—Screening strategies not shown were excluded because of absolute or weak dominance. The included strategies were cost-saving compared with strategies not shown. NA = not applicable.

* Interval indicates the time between quantitative CT examinations.

† ICER = Cost in U.S. dollars per QALY gained.

Table 5

Results of Base Case Analysis Fractures and Mortality

Variable	DXA/Quantitative CT at Age 55, Interval 5 years	DXA at Age 55	No Screening at Age 55
Total no. of fractures	657000 (100)	793700 (100)	935600 (100)
Hip fractures	131800 (20)	163000 (21)	196200 (21)
Vertebral fractures	80900 (12)	96500 (12)	121500 (13)
Other fractures	289000 (44)	352700 (44)	417400 (45)
Wrist fractures	155300 (24)	181500 (23)	200500 (21)
Mortality, mean age at death (y)*	84.8 ± 8.5	84.6 ± 8.4	84.6 ± 8.4

Note.—Data are number of fractures, with percentage in parentheses. Fractures for the most cost-effective screening strategy (DXA and quantitative CT at age 55, with a CT interval of 5 years) compared with current guidelines (DXA and FRAX) and no screening for the same starting age. Mortality was lower for the DXA/quantitative CT screening strategy due to a reduction in hip fractures and their associated risks of death.

* Data are means ± standard deviation.

years for vertebral fractures were 11.1% for no screening, 9% for DXA screening, and 7.5% for DXA/quantitative CT with a 5-year interval, for other fractures, 30.8%, 27.3%, and 22.6%, respectively; and for wrist fractures, 17.8%, 16.4%, and 14%, respectively.

Sensitivity Analyses

The DXA/quantitative CT strategies at age 55 years remained the most cost-effective screening strategies for assessment of those with increased or decreased overall fracture risks (Table 6). In the analysis for decreased fracture risk, the best interval for quantitative CT rescreening after DXA/quantitative CT at age 55 was every 5 years. With increased fracture risk, the 3-year interval was very cost-effective, with a cost of $440 per QALY, while the 5-year interval was not cost-effective, with a cost of $205400 per QALY. When the bone strength factor (the effect of bone strength on fracture risk) was not considered, DXA/quantitative CT at age 55 years with a 5-year interval remained the most cost-effective strategy (Table 6).

With treatment adherence of 70%, DXA/quantitative CT at age 55 years with a 3-year interval was the most cost-effective strategy (Table 6). With adherence lower than that in the base case (40% adherence), DXA/quantitative CT at age 55 with a 5-year interval was the most cost-effective strategy ($12800 per QALY, data not shown). With adherence of 100%, DXA/quantitative CT at age 55 years with a 5-year interval was very cost-effective ($2600 per QALY) and DXA/quantitative CT at age 55 with a 3-year interval was cost-effective ($75900 per QALY [data not shown]).

Increasing quantitative CT costs had little effect on the results. With quantitative CT costs of $215–$700, DXA/quantitative CT at age 55 years with a 5-year interval was the most cost-effective strategy (only data for quantitative CT costs of $700 are shown in Table 6). With 5% annual discounting, DXA/quantitative CT at age 55 years with a 5-year interval was very cost-effective (ICER, $4800 per QALY) and DXA/quantitative CT at age 55 years with a 3-year interval was cost-effective (ICER, $53400 per QALY) (Table 6). The undiscounted results are also shown in Table 6.

The cost-effectiveness of the tested strategies was most sensitive to treatment adherence (at a willingness-to-pay of $50000 and $100000) and the cost for quantitative CT (only at willingness-to-pay of $50000). Specifically, the preferred rescreening interval changed from 3 years to 10 years when the treatment adherence rate was increased to higher than 74.3% on the basis of net monetary benefits. Also, at a cost of more than $900, the quantitative CT bone strength test rescreening interval of 10 years was preferred over a 3-year interval. The model results were not sensitive to overall fracture rate, DXA costs, hip fracture costs, or utilities for hip and vertebral fractures (Appendix E1 [online]).

Table 6

Results of Sensitivity Analyses

Strategy	Start Age (y)	Interval (y)*	Cost ($)	QALYs	ICER†
50% fracture rate					
DXA	65	NA	10770	10.88	NA
DXA	55	NA	11290	14.31	150
DXA/quantitative CT	55	10	12390	14.53	5100
DXA/quantitative CT	55	5	13060	14.58	11500
200% fracture rate					
DXA/quantitative CT	65	3	29050	10.59	NA
DXA/quantitative CT	55	3	30600	14.08	440
DXA/quantitative CT	55	5	30960	14.08	205400
Bone strength factor = 1					
DXA	65	NA	14070	10.79	NA
DXA	55	NA	14350	14.22	80
DXA/quantitative CT	55	5	16320	14.51	6800
70% adherence					
DXA/quantitative CT	65	5	17150	10.82	NA
DXA	60	NA	17830	12.46	420
DXA	55	NA	18580	14.12	450
DXA/quantitative CT	55	10	19040	14.37	1900
DXA/quantitative CT	55	5	19300	14.42	5500
DXA/quantitative CT	55	3	19520	14.43	20400
Quantitative CT costs $700					
DXA	65	NA	18260	10.72	NA
DXA	60	NA	18460	12.42	120
DXA	55	NA	18720	14.09	150
DXA/quantitative CT	55	10	19930	14.33	5000
DXA/quantitative CT	55	5	20360	14.40	5800
0% discounting (undiscounted)					
DXA/quantitative CT	65	5	27500	14.68	NA
DXA/quantitative CT	60	5	30490	17.78	960
DXA/quantitative CT	55	3	34740	21.65	1100
DXA/quantitative CT	55	5	34790	21.68	1950
5% discounting					
DXA	55	NA	13290	11.31	NA
DXA/quantitative CT	55	10	13880	11.45	4400
DXA/quantitative CT	55	5	14070	11.49	4800
DXA/quantitative CT	55	3	14350	11.49	53400
PSA					
DXA/quantitative CT	65	5	21980	10.7	NA
DXA/quantitative CT	55	5	23980	13.31	560

Note.—Screening strategies not shown in this Table were ruled out because of absolute or weak dominance. Bone strength factor = 1 means that the effect of bone strength on fracture risk was neglected. Results for PSA are the average of all 1000 simulations. NA = not applicable.

* Interval indicates the time between quantitative CT examinations. DXA intervals were T score dependent.

† ICER = cost in U.S. dollars per QALY gained.

PSA Results

DXA/quantitative CT at age 55 with a 5-year interval was the most cost-effective strategy (as in our main analysis) (Table 6). DXA/quantitative CT at age 55 with a screening interval of 5 years was the most cost-effective strategy, at the $50000 per QALY threshold in 90.4% (904 of 1000) of iterations, followed by DXA at age 55 (5.4%, 54 of 1000) and DXA/quantitative CT at age 55 with a 3-year interval (4.2%, 42 of 1000). At the $100000 per QALY threshold, results were similar: The best strategy was DXA/quantitative CT at age 55 with a 5-year interval in 92% (920 of 1000) of iterations, followed by DXA (4.4%, 44 of 1000) and DXA/quantitative CT at age 55 with a 3-year interval (3.6%, 36 of 1000).

Discussion

Our model showed that the addition of bone strength testing to currently existing DXA screening recommendations for postmenopausal women would be cost-saving compared with no screening (ie, total cost of screening, prophylaxis, and treatment would be lower compared with no screening) and very cost-effective compared with DXA and use of the FRAX tool screening. The 3-year and 5-year quantitative CT rescreening intervals were cost-effective for the combined DXA/quantitative CT strategies, depending on the different parameters used in our sensitivity analysis. In general, screening initiation at age 55 years was more cost-effective compared with screening initiation at a later age. The overall most favorable screening strategy was combined DXA/quantitative CT at age 55 years with a 5-year screening interval. With this strategy, the number of fragility fractures and the associated morbidity and mortality were substantially reduced. Therefore, bone strength testing could provide a cost-effective tool to add to current osteoporosis screening programs in postmenopausal women.

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, which together cause reduced bone strength (1). DXA assessment of areal BMD does not completely capture bone strength in mechanical testing studies. Therefore, bone strength testing could provide important missing information to improve clinicians' ability to assess fracture risk (51). We acknowledge that bone strength testing is not widely available and is limited mostly to large medical centers or research groups. However, U.S. Food and Drug Administration–approved bone strength testing

is available (VirtuOst; O.N. Diagnostics, Berkeley, Calif). In our study, we did not vary the cutoff values for treatment initiation (ie, T scores, bone strength, FRAX score) in the sensitivity analyses. However, the cutoff value for low femoral bone strength (< 3000 N) was defined in the study by Keaveny et al (10) for women and men. The cutoff was derived from results of a prospective study in elderly men in which all patients with new hip fractures had a femoral bone strength of less than 2900 N (52).

Authors of previous studies have used similar state-transition model structures, assessing multiple different screening strategies at different ages (53). Although they did not find one strategy that clearly outperformed others, they also found that screening initiation at age 55 years was cost-effective. The National Osteoporosis Foundation, the American Congress of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force recommend osteoporosis screening for women age 65 years and older and in postmenopausal women with increased risk (eg, those with clinical risk factors) (54).

In other cost-effectiveness studies, DXA screening strategies consisted of fixed rescreening intervals (49). Authors of other studies looked at the time interval in which 10% of postmenopausal women with normal to mild, moderate, or advanced osteopenia developed osteoporosis by conducting competing risk analyses in 4957 postmenopausal women with no osteoporosis at baseline and follow-up of up to 15 years (43). We based the flexible DXA screening intervals on those in that study, which was a strength of our model. However, we did not investigate more aggressive DXA screening intervals and treatment strategies. Further strengths of our model were the inclusion of the FRAX tool, the patient-level simulation of bone strength, and the addition of a bone strength test. The rescreening interval of our bone strength test was fixed. Personalized screening intervals based on bone strength may result in even higher cost-effectiveness. This should be addressed in future iterations of the model.

We used quantitative CT in our model, because much more literature was available on bone strength derived with quantitative CT than that derived with MR imaging (55). However, bone strength also can be assessed with MR imaging without the use of ionizing radiation (9). Although MR imaging of the hip is more expensive than CT of the hip, we showed that increasing costs for bone strength testing had only a minor effect on cost-effectiveness. Therefore, we consider bone strength testing with MR imaging as a potential alternative to testing with quantitative CT. Although MR imaging does not provide BMD information, that information is already provided at DXA. Of note, textural analysis of the femur on pelvic radiographs is another option for assessment of fracture risk and is better for prediction of fragility fracture compared with DXA (56). In a recent cadaver study (57), investigators compared finite element–based quantitative CT (as used in our model) with DXA, radiography, and CT-based bone measurement for femur fracture prediction. That study showed that quantitative CT was the best method for prediction of failure load (57).

Our model had limitations. We assigned start values for BMD and bone strength to each individual separately. The proportion of our cohort with low BMD and low bone strength was constant due to the normal distribution of both parameters. However, because the model assigned both values independently in each simulation, the overlap between these two proportions could change. Therefore, the number of individuals identified for treatment may have changed between different analyses. However, this uncertainty was addressed in the PSA. We modeled perfect test properties for the DXA and quantitative CT tests, meaning that both tests exactly measured the simulated BMD and bone strength, respectively. Another limitation was the assumption of the bone strength factor. However, this assumption was tested in the sensitivity analyses. Also, the body of evidence in the literature regarding bone strength and fracture prediction is small compared with that for DXA. Therefore, we had to calculate fracture risk of other anatomic locations (ie, spine, wrist, others) on the basis of bone strength values measured at the hip. In a similar way, we only used hip T scores to assess fracture risk at other anatomic locations. However, hip T scores do have predictive value for fractures at other locations (58). We did not incorporate adverse effects from alendronate treatment into our model. In a randomized, double-blind trial (59), alendronate did not result in a substantially higher number of adverse effects in the upper gastrointestinal tract when compared with placebo. Our model inputs consisted mostly of data from American white women and the model is specific to U.S. health care. Finally, we did not include the potential effects of ionizing radiation on the model. However, the risks of radiation-induced cancers have been shown to be minimal in the age range for our study (60). The lifetime risk of death from radiation-induced cancer for a single abdominal CT examination (radiation of approximately 10 mSv) at age 55 years or older is estimated to be less than 0.01% (61). However, quantitative CT of the hip has a lower radiation dose (approximately 2.5–3 mSv) (62), and therefore, is presumed to have a lower risk of death from radiation-induced cancer. As stated previously, bone strength also can be computed with MR imaging as a radiation-free alternative to quantitative CT. In conclusion, the combined assessment of bone strength and BMD for osteoporosis in postmenopausal women has the potential to be a cost-effective screening strategy and to prevent a substantial number of fragility fractures.

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