

Cost-Effectiveness of Alendronate Therapy for Osteopenic Postmenopausal Women

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Background: Treatment guidelines recommend drug treatment to prevent fractures for some postmenopausal women who have low bone mass (osteopenia) but do not have osteoporosis or a history of clinical fractures.

Objective: To estimate the societal costs and health benefits of alendronate drug treatment to prevent fractures in postmenopausal women with osteopenia.

Design: Markov model with 8 health states: no fracture, post-distal forearm fracture, post-clinical vertebral fracture, post-radio-graphic (but clinically inapparent) vertebral fracture, post-hip fracture, post-hip and vertebral fractures, post-other fracture, and death.

Data Sources: Population-based studies of age-specific fracture rates and costs, prospectively measured estimates of disutility after fractures, and the Fracture Intervention Trial of alendronate versus placebo to prevent fracture.

Target Population: Postmenopausal women 55 to 75 years of age with femoral neck T-scores between -1.5 and -2.4 .

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: Five years of alendronate therapy or no drug treatment.

Outcome Measures: Costs, quality-adjusted life-years, and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: For women with no additional fracture risk factors, the cost per quality-adjusted life-year gained ranged from \$70 000 to \$332 000, depending on age and femoral neck bone density.

Results of Sensitivity Analyses: Results were sensitive to changes in fracture risk reduction attributable to alendronate and alendronate cost.

Limitations: Results apply only to postmenopausal white women residing in the United States.

Conclusion: Alendronate therapy for postmenopausal women with femoral neck T-scores better than -2.5 and no history of clinical fractures or other bone mineral density-independent risk factors for fracture is not cost-effective, assuming U.S. costs of alendronate and currently available estimates of alendronate efficacy in osteopenic women.

Ann Intern Med. 2005;142:734-741.

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Osteoporosis is associated with an increased risk for fractures, which, in turn, is associated with clinically significant morbidity. The broad consensus is that patients who present with fractures should be treated for osteoporosis (1–5). In the absence of fractures, however, the indications for antiresorptive drug therapy are controversial. Many agree that patients with osteoporosis who meet the World Health Organization criteria (bone mineral density [BMD] > 2.5 SDs less than the young healthy mean or a T-score ≤ -2.5 [6]) should be treated (1–5). However, many fractures among postmenopausal women occur in those with T-scores better than -2.5 because more women have scores in this range than in the osteoporotic range (7, 8).

While some do not recommend treating osteopenic postmenopausal women who do not have a history of clinical fracture (1, 2), guidelines published by the National Osteoporosis Foundation (3) and the American College of Obstetrics and Gynecology (4) recommend drug therapy for postmenopausal women who lack additional fracture risk factors at a T-score of -2.0 or less and for those with 1 or more additional fracture risk factors at a T-score of -1.5 or less. Miller and colleagues (9) suggested that a treatment T-score threshold of -1.8 may be reasonable for postmenopausal women even without additional fracture risk factors.

As public health policy, however, such intervention

makes sense only if the costs and risks of treatment are outweighed by a reduction in the ultimate cost and disability attributable to osteoporotic fractures. This is particularly relevant for osteopenia, since many postmenopausal women have low bone mass (10), and the societal direct medical cost of pharmacologic therapy for women with osteopenia would therefore be enormous. The cost-effectiveness of drug therapy may be particularly problematic in younger, early postmenopausal women, who, even if osteopenic, are not expected to be at high risk for fracture (11).

We aimed to estimate the lifetime health benefits and

See also:

Print

Editors' Notes	735
Editorial comment	796
Summary for Patients	I-36

Web-Only

Appendix	
Appendix Tables	
Appendix Figures	
Conversion of figures and tables into slides	

costs of alendronate therapy to prevent fracture in postmenopausal women with osteopenia. Our analysis used the societal perspective.

METHODS

We constructed a Markov cost–utility model that contained 8 health states and compared 5 years of treatment with alendronate (1 of the most commonly prescribed antiresorptive agents) with no drug therapy for women 55 to 75 years of age with varying levels of BMD T-scores (−1.5 to −2.4). The health states we used were no fracture, post-distal forearm fracture, post-clinical vertebral fracture (that is, clinically evident at onset), post-radiographic vertebral fracture (that is, not clinically evident at onset), post-hip fracture, post-other fractures (that is, fracture of the proximal forearm, humerus, scapula, clavicle, sternum, ribs, pelvis, distal femur, patella, tibia, or proximal fibula), post-hip and vertebral fracture, and death. Women in the no fracture state can develop a distal forearm, hip, clinical vertebral, radiographic vertebral, or other fracture, at which time transition to that post-fracture state occurs. We assigned the direct and indirect costs of that fracture as transition costs. We modeled the disutility associated with these fractures as a lower value of a quality-adjusted life-year (QALY) associated with that fracture state. We assigned long-term care costs beyond the first year after hip fracture as a cost per year in the post-hip and vertebral fracture or post-hip fracture state. Individuals are eligible (at risk) to move to a different state once every 6 months. We assumed a discount rate of 3% for both costs and health benefits and a drug adherence rate of 100%. For the base-case analyses, we ran the model with 9 different combinations of starting age (55, 65, and 75 years) and femoral neck T-score (−1.5, −2.0, and −2.4) until age 105 years, using Monte Carlo simulations with 40 000 trials each, by using Data Pro HealthCare software (TreeAge Software, Inc., Williamstown, Massachusetts).

Probabilities of Fractures

We developed the risks for each type of fracture as a function of age from comprehensive population-based, age-specific data for women from the Rochester Epidemiology Project (12). This database captures almost all health care utilization within Olmsted County, Minnesota (13). Since an estimated 35% of all vertebral fractures in Olmsted County were clinically evident at onset (14), we set the incidence rate of radiographic (but clinically inapparent) vertebral fracture at 1.86 times that of clinical vertebral fracture. The rates for other fractures are the sum of incidences of the specific fracture types (12). We plotted fracture rates against the midpoint of each associated age range, and we determined a best-fitting power curve for each fracture as a continuous function of age. We adjusted each fracture risk function for bone density by using the method of De Laet and colleagues (15, 16), and we pro-

Context

Many postmenopausal women have osteopenia but not osteoporosis or fracture history. Information about the cost-effectiveness of treating such women with alendronate should guide clinical recommendations.

Contribution

The investigators estimate that the costs of treating postmenopausal women with osteopenia (femoral neck T-scores > −2.5) for 5 years with alendronate range from \$70 000 to \$332 000 per quality-adjusted life-year.

Cautions

Unless the cost of alendronate decreases or new data show that alendronate reduces fracture risk more than is currently thought, treatment of osteopenia with alendronate costs more than Americans are typically willing to pay for health care interventions.

—The Editors

grammed the risk functions to change with increasing age and decreasing BMD for each stage of the Markov model.

Relative Risk for Fracture during Drug Therapy

The Fracture Intervention Trial (FIT) (17) of alendronate versus placebo enrolled many participants with osteopenia (femoral neck T-score, −1.6 to −2.5). On the basis of the clinical fracture group of FIT (women without any baseline radiographic vertebral fractures), we assumed relative risks for incident vertebral fractures of 0.54 and 0.82 for those with femoral neck T-scores of −2.0 to −2.4 and −1.5, respectively, and a relative risk for nonvertebral fractures of 1.0 for all osteopenic women receiving alendronate for the base-case analysis (17).

We further assumed a linear, gradual offset of fracture reduction benefit over the subsequent 5 years after treatment as recommended by Tosteson and colleagues (18).

Mortality

We constructed an age-specific background mortality risk function from U.S. vital statistics for 2001 to model the risk for death for each cycle of the model (19). We estimated the mortality associated with acute hip fracture to be 1.375 times the base rate (20). Since the excess mortality associated with vertebral fracture may be attributable to preexisting comorbid conditions and not the fracture (21, 22), we assumed that excess mortality was not directly attributable to vertebral fractures or other nonhip fractures.

Costs

We assumed the yearly cost of alendronate (Table 1) to be the average U.S. wholesale price for 2001 (\$842) (32) and that side effects from alendronate would generate only trivial direct medical costs. Table 1 also shows the direct medical costs associated with acute fractures (28), long-term care costs during the first and subsequent years after

Table 1. Model Parameters*

Parameter	Value	Study, Year (Reference)
QALY gained		
No fracture state	0.84	Burström et al., 2001 (23), and Macran et al., 2003 (24)
Post-distal forearm fracture	0.82 (first y), then 0.839	Kanis et al., 2004 (25)
Post-other fracture	0.753 (first y), then 0.813	Kanis et al., 2004 (25)
Post-hip fracture	0.67 (first y), then 0.68	Kanis et al., 2004 (25)
Post-clinical vertebral fracture	0.58 (first y), then 0.76	Kanis et al., 2004 (25)
Post-radiographic vertebral fracture	0.76 (first 6 y), then 0.84	Oleksik et al., 2000 (26)
Post-hip and clinical vertebral fracture	0.41 (first y), then 0.60	Tosteson et al., 2001 (27)
Direct medical costs, \$		
Acute hip fracture	25 027	
Direct medical costs	16 116	Gabriel et al., 2002 (28)
First-year long-term care	8911	Leibson et al., 2002 (29)
Acute clinical vertebral fracture	6702	Gabriel et al., 2002 (28)
Acute distal forearm fracture	3276	Gabriel et al., 2002 (28)
Acute other fracture	5561	Gabriel et al., 2002 (28)
Alendronate per y	842	
Long-term care > 1 y after hip fracture	6295	Leibson et al., 2002 (29)
Indirect fracture costs, \$		
Hip fracture	5986 (age 55 to 59 y) to 197 (age ≥ 75 y)	Meerding et al., 2004 (30)
Spine fracture	3313 (age 55 to 59 y) to 84 (age ≥ 75 y)	Meerding et al., 2004 (30)
Distal forearm fracture	1994 (age 55 to 59 y) to 53 (age ≥ 75 y)	Meerding et al., 2004 (30)
Other fracture	2708 (age 55 to 59 y) to 72 (age ≥ 75 y)	Meerding et al., 2004 (30)
Relative risk for fractures while receiving alendronate		
Nonspinal fractures	1.0	Cummings et al., 1998 (17)
Vertebral fractures	0.54 (T-score, -2.0 to -2.4), 0.82 (T-score, -1.5)	Cummings et al., 1998 (17)
Other costs, \$		
Yearly physician visit	52	CMS, 2003 (31)
Bone densitometry	139	CMS, 2003 (31)
Discount rates		
Costs	0.03	
Health benefits	0.03	

* CMS = Centers for Medicare & Medicaid Services; QALY = quality-adjusted life-year.

hip fracture (averaged for all patients with hip fracture) (29), and indirect costs of fractures (estimated in Meerding and colleagues' study [30]). The costs for 1 annual level-3 follow-up physician visit during alendronate therapy and for bone densitometry 2 years after alendronate therapy began (Table 1) are the median 2001 U.S. Medicare reimbursement rates for these services (31).

QALYs Associated with Each Health State

For 1 year in the no fracture state, we used a QALY value estimated with the EuroQoL questionnaire (EQ-5D) in representative samples of the British and Swedish populations age 60 to 69 years (23, 24, 33). We derived the QALY values for the first and subsequent years with incident hip, distal forearm, clinical vertebral, and other fractures relative to the age-matched population from direct prospective estimates of Kanis and colleagues (25) (Table 1), and we derived the QALY values for the post-hip and vertebral fracture state from Tosteson and colleagues' study (27). We assumed radiographic (clinically inapparent) vertebral fractures to have a disutility of 0.08 (26), but only for 6 years after their occurrence since such fractures oc-

curing more than 4 to 8 years ago do not seem to be associated with increased pain or limited activity (34, 35).

Sensitivity Analyses

We performed secondary analyses, assuming a gradual, linear 10-year offset of fracture reduction benefit after 5 years of drug therapy, combined with analyses modeling increased BMD-adjusted fracture risk because of additional risk factors to estimate how much additional risk is required for alendronate therapy to cost less than \$50 000 per QALY gained. We performed univariate sensitivity analyses, varying drug costs, discount rates, fracture rates, fracture costs, and the disutility from fractures and assuming preventable excess mortality for the first year after a clinical vertebral fracture. We performed 2-way sensitivity analyses, varying the relative risks for vertebral and nonvertebral fractures during alendronate therapy from 0.8 to 0.4 and from 1.0 to 0.6, respectively. Finally, we performed sensitivity analyses to model the possible effects of nonadherence to therapy, with alendronate used appropriately for only 2 years (with a 6-month offset of benefit) or used inappropriately for 2 years such that fracture reduction

Table 2. Lifetime Incremental Cost-Effectiveness Ratios of 5 Years of Drug Therapy versus No Drug Therapy*

Variable	Femoral Neck T-Score					
	-1.5		-2.0		-2.4	
	No Drug Therapy	Drug Therapy	No Drug Therapy	Drug Therapy	No Drug Therapy	Drug Therapy
Age 55 y						
Costs, \$	11 528	15 877	16 710	20 863	22 739	26 820
QALYs	14.847	14.864	14.700	14.744	14.591	14.646
ICER, \$	255 823		94 386		74 200	
Age 65 y						
Costs, \$	9142	13 401	13 502	17 568	18 261	22 222
QALYs	11.385	11.400	11.249	11.293	11.112	11.168
ICER, \$	283 933		92 409		70 732	
Age 75 y						
Costs, \$	6502	10 489	10 033	13 838	13 580	17 298
QALYs	7.826	7.838	7.811	7.846	7.673	7.716
ICER, \$	332 250		108 714		86 465	

* Costs = lifetime-accumulated costs; ICER = incremental cost-effectiveness ratio; QALYs = lifetime-accumulated quality-adjusted life-years.

benefit is reduced by one third. We also performed probabilistic sensitivity analyses by using 2-stage Monte Carlo simulations (36, 37).

The Appendix (available at www.annals.org) provides further details on the model structure, construction of fracture risk equations, direct and indirect medical costs, and the probabilistic sensitivity analyses.

Role of the Funding Source

No funding was obtained for our study.

RESULTS

For women 50 years of age, the model predicted that 17.5% and 16.0% would have hip and distal forearm fractures, respectively, during their remaining lifetimes. These results are identical to those of Melton and colleagues (38), thus supporting the external validity of our model. Our model estimated that 17.7% would have at least 1 lifetime clinical vertebral fracture, which is a modest overestimate relative to Melton and colleagues' estimate of 15.6% (38). Our model also estimated that 25.1% and 38.2% of women 50 years of age would have at least 1 lifetime radiographic clinically inapparent vertebral and other fracture, respectively.

For each analysis, we computed the incremental cost-effectiveness ratio as the difference in costs between the drug therapy and no drug therapy strategies divided by the difference in accumulated QALYs between the strategies. An incremental cost-effectiveness ratio is the cost of gaining 1 QALY. Table 2 shows the lifetime costs, QALYs, and incremental cost-effectiveness ratios for 5 years of drug therapy versus no drug therapy for 9 specified combinations of starting age and femoral neck T-score. Without additional BMD-independent fracture risk factors, all incremental cost-effectiveness ratios are greater than \$70 000 per QALY gained. For women with a T-score of -1.5, the incremental cost-effectiveness ratios are in excess of \$250 000 per QALY gained. Univariate sensitivity analyses (Table 3) show that these results are modestly sensitive to changes in fracture rates and associated disutility and discount rates and relatively insensitive to changes in fracture costs and to the inclusion of preventable excess mortality from a clinical vertebral fracture.

Figure 1 shows the effect of additional BMD-independent fracture risk factors on the incremental cost-effectiveness ratios for drug therapy versus no therapy for a 65-year-old woman with a starting T-score of -2.0. Assuming a

Table 3. Univariate Sensitivity Analyses*

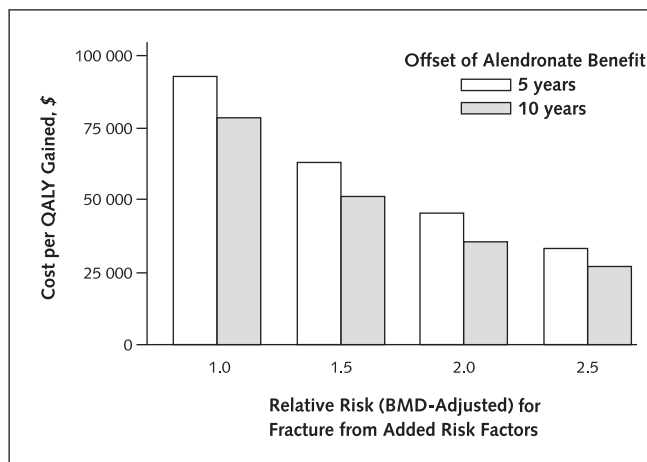
Variable	Range (Low, High)	Cost per QALY Gained, \$	
		Parameter Low	Parameter High
Discount rates	0, 0.06	71 421	117 487
Fracture costs	0.7, 1.3 times the base-case costs	96 045	89 957
Fracture rates	0.7, 1.3 times the base-case rates	144 908	67 720
Fracture disutility	0.7, 1.3 times the base-case values	133 359	73 427
Preventable vertebral fracture mortality	No, yes	92 409†	91 030‡

* Data are based on a 65-year-old woman (T-score, -2.0). QALY = quality-adjusted life-year.

† No potentially preventable excess mortality after clinical vertebral fracture.

‡ Mortality is 1.375 times the age- and sex-adjusted mortality rate for white women for first year after clinical vertebral fracture.

Figure 1. Effect of additional risk factors and offset of fracture reduction benefit on incremental cost-effectiveness ratios for drug therapy versus no drug therapy.



Data are based on 65-year-old women with T-scores of -2.0 . Cost is in 2001 U.S. dollars. BMD = bone mineral density; QALY = quality-adjusted life-year.

5-year loss of fracture reduction benefit after alendronate therapy, the cost per QALY gained with alendronate is less than \$50 000 only with additional fracture risk factors that together confer a BMD-adjusted relative fracture risk of 2.0 or higher. If fracture reduction benefit persists for 10 years after alendronate therapy, then the cost per QALY gained is less than \$50 000 if additional factors are associated with an aggregate BMD-adjusted relative risk for fracture of 1.5. For women 65 years of age with a T-score of -1.5 , under the base-case assumptions, the cost per QALY gained is \$53 730 with additional factors associated with an aggregate BMD-adjusted relative risk of 4.0.

Figure 2 shows a 2-way sensitivity analysis for a 65-year-old woman with a T-score of -2.0 and no additional

BMD-independent fracture risk factors, varying the relative risks for vertebral (both clinical and radiographic) fracture and nonvertebral fracture during alendronate therapy from 0.5 to 0.8 and from 0.6 to 1.0, respectively. If alendronate reduces the incidence of vertebral fractures by 50%, then the cost per QALY gained is less than \$50 000, only if the relative risk for nonvertebral fractures during alendronate therapy is 0.7 or less. Figure 3 shows the cost-effectiveness acceptability curves from probabilistic sensitivity analyses for women 65 years of age with a T-score of -2.0 and no additional fracture risk factors or with a T-score of -1.5 and additional BMD-adjusted relative fracture risk of 2.5 from other factors (assuming a 5-year offset of fracture reduction benefit). The probability that the cost per QALY gained is \$50 000 or less in both scenarios is 1% or less.

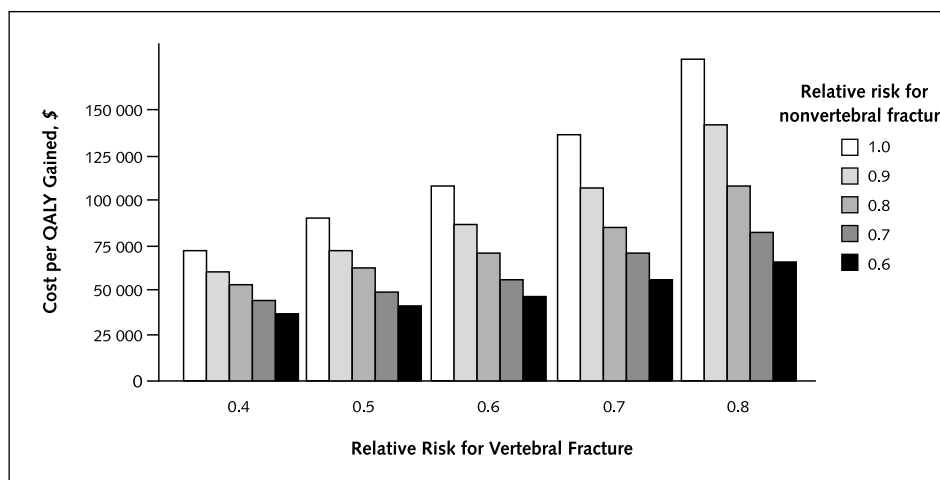
If the cost of alendronate is reduced to three quarters that of the 2001 average U.S. wholesale price (assuming a 5-year offset of drug benefit), the cost per QALY gained for a 65-year-old woman with a T-score of -2.0 is substantially less (\$73 156) compared with the base-case analysis (\$92 409). If the cost of alendronate is half that of the 2001 average U.S. wholesale price, the cost per QALY gained is \$48 750.

If alendronate therapy is used appropriately but discontinued after 1 or 2 years (assuming offset of benefit of 6 months or 1 year, respectively), the cost per QALY gained is only slightly increased to \$97 787 or \$96 337, respectively. On the other hand, if alendronate therapy is used inappropriately (such that its fracture reduction benefit is reduced by one third) and discontinued after 2 years, the cost per QALY gained is \$130 093.

DISCUSSION

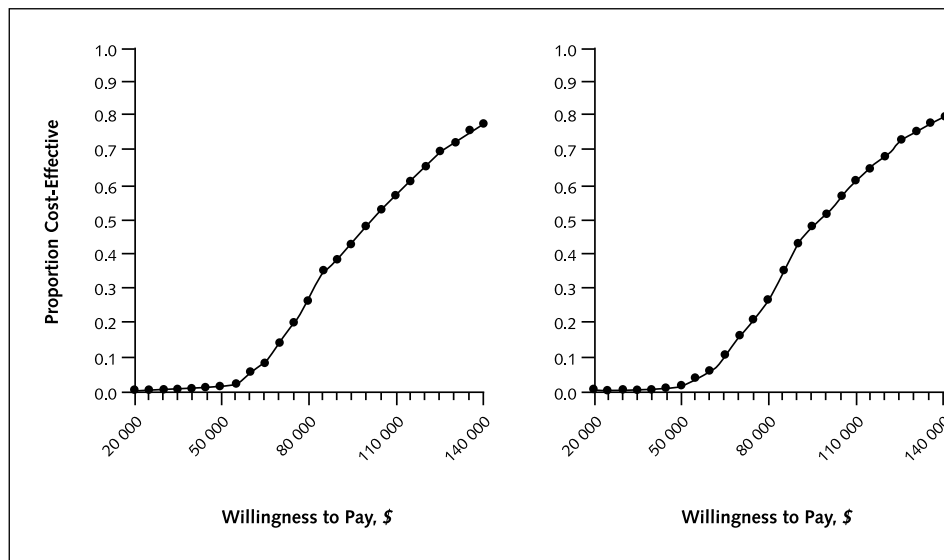
Some guidelines and recent publications have recommended extending the widely accepted indications for drug

Figure 2. Cost per quality-adjusted life-year (QALY) saved according to relative risks for vertebral and nonvertebral fractures during alendronate therapy.



Data are based on 65-year-old women with T-scores of -2.0 . Cost is in 2001 U.S. dollars.

Figure 3. Cost-effectiveness acceptability curves.



Left. Data are based on 65-year-old women with T-scores of -2.0 and no additional risk factors. **Right.** Data are based on 65-year-old women with T-scores of -1.5 and additional fracture risk factors (aggregate bone mineral density–adjusted relative risk, 2.5).

therapy to prevent osteoporotic fracture to the larger proportion of osteopenic postmenopausal women (3, 4, 9). These women are likely to be a growing segment of candidates for treatment, but they are less likely to experience fractures. If the T-score threshold for treating postmenopausal women was changed from -2.5 to -2.0 or -1.5 , then the percentages of women 65 years of age who are eligible for drug therapy would increase from 16% to 31% or 50%, respectively (10). Therefore, we must consider the societal cost of treating osteopenic women before initiating public health campaigns targeted at this group.

Assuming a societal willingness to pay of \$50 000 per QALY gained, current U.S. drug costs, and currently available estimates on the efficacy of alendronate in osteopenic women, our results indicate that alendronate is not cost-effective in osteopenic postmenopausal women who have not had any clinical fractures, unless substantial risk from additional BMD-independent fracture risk factors is present. Moreover, the cost-effectiveness may be less favorable if drug adherence decreases substantially over time, which 1 study of once-weekly alendronate therapy has documented (39). These results are probably generalizable to risedronate and raloxifene, agents of similar cost and efficacy as alendronate (40). These results are not generalizable to estrogen replacement therapy, most forms of which are less expensive than alendronate and which in combination with progestin also affect other outcomes (such as breast cancer and cardiovascular disease) (41).

Previous modeling studies have not explicitly examined the cost-effectiveness of pharmacologic therapy to prevent osteoporotic fracture in osteopenic women (42–46). Our results are nonetheless consistent with the cost-effectiveness study developed by the National Osteoporosis

Foundation (47), which estimated that alendronate would be cost-effective for a 65-year-old woman without history of fracture if her T-score was less than the threshold hip T-score (between -2.5 and -3.0).

Under certain conditions, the societal cost of antiresorptive drug therapy for osteopenic women may be less than we have estimated. First, if alendronate at full dose (10 mg daily or 70 mg once per week) reduces the risk for nonvertebral fracture among these women, then treatment may be cost-effective at least for postmenopausal women with T-scores between -2.0 and -2.4 , assuming a societal willingness to pay of \$50 000 per QALY gained. During the first 2 years of FIT, which lasted 3 years, the dosage of alendronate was only 5 mg per day, and 10 mg per day reduces bone resorption and improves bone density to a modestly greater degree (48). Second, if the cost of drug therapy is substantially reduced, then drug therapy for osteopenic women with T-scores between -2.0 and -2.4 may be cost-effective even if that therapy has no effect on the risk for nonvertebral fractures. Third, the cost per QALY gained with alendronate therapy is reduced if fracture reduction benefit persists 10 or more years after a 5-year treatment course. Although markers of bone resorption do remain lower than at pretreatment for up to 5 years after a 5-year treatment course of alendronate (49), no data suggest that reduction of fracture risk persists after discontinuation of alendronate therapy (50). Finally, alendronate therapy may be cost-effective for osteopenic women if the societal willingness to pay is substantially higher than \$50 000 per QALY gained. While many consider this to be a reasonable estimate of societal willingness to pay (44, 51), others argue that this is too conservative (52–54). Examples of medications commonly in use for which the incre-

mental cost-effectiveness ratios are around \$50 000 per QALY saved include ticlopidine versus aspirin (55) and statin use for primary prevention of coronary heart disease in those with total cholesterol levels greater than 6.475 mmol/L (>250 mg/dL) (56, 57).

Our study does have some important limitations. Our model may overestimate the true cost-effectiveness of anti-resorptive therapy in postmenopausal women because it slightly overestimates the incidence of vertebral fractures. In addition, we attributed all lifetime long-term care costs for previously community-dwelling women after hip fracture to that fracture. Without hip fracture, however, many of these individuals would accrue long-term care costs later in life because of other medical conditions. On the other hand, we did not include the indirect costs from loss of ability to do housework or care for other family members and assumed zero long-term care costs attributable to non-hip fractures. We did not model changes in BMD from alendronate therapy, but fracture reduction modeled directly from current or previous drug therapy is preferable given that BMD is an incomplete indicator of fracture risk (18, 51). Finally, we did not consider risk factors that are not measured routinely in clinical practice, such as prevalent radiographic vertebral fracture or elevated markers of bone resorption, or other risk factors, such as falls. Our results are generalizable only to the postmenopausal white female population of the United States.

Nonetheless, our study has several strengths. We have included all fractures that may be linked to osteoporosis, rather than just those of the hip, spine, and distal forearm, unlike many other published cost–utility studies of drug therapy to prevent fracture (42, 43, 46, 58). We believe that our study is the first to include estimates of indirect costs due to lost work and estimates of disutility that may occur from incident radiographic (but otherwise clinically inapparent) vertebral fractures. In addition, we have focused specifically on the cost-effectiveness of drug therapy in a postmenopausal osteopenic female population with various conditions and varying assumptions, an important focus in light of recent recommendations to broaden indications for drug therapy to include a large proportion of osteopenic postmenopausal women.

In conclusion, alendronate therapy is not cost-effective for white, early postmenopausal women who have not had a fracture and do not have additional risks strongly predictive of fracture independent of BMD, assuming current estimates of alendronate costs in the United States and efficacy in this population and a societal willingness to pay of \$50 000 per QALY gained. This conclusion should be reconsidered, however, if the cost of drug therapy is significantly lowered, if drug therapy is shown to reduce the risk for nonvertebral fractures in this population, or if fracture reduction benefit persists longer than 10 years after a 5-year treatment course.

From Park Nicollet Health Services, University of Minnesota, and Veterans Administration Medical Center, Minneapolis, Minnesota.

Potential Financial Conflicts of Interest: *Grants received:* J.T. Schousboe (Hologic, Inc.), K.E. Ensrud (Eli Lilly & Co., Pfizer, NPB Pharmaceuticals).

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APPENDIX

Model Structure

The basic model structure (Appendix Figure 1) is a Markov model with 2 strategies: treat and do not treat. Within each strategy, 7 health states are possible: no fracture, post–distal forearm fracture, post–other fracture, post–clinical vertebral fracture, post–morphometric vertebral fracture, post–hip fracture, post–hip and vertebral fracture, and death (Appendix Figure 2). In Monte Carlo simulations of this model, all individuals start in the no fracture state in both strategies.

The following features are key to this model.

1. Transitions can occur from the no fracture state to death or any other fracture state.

2. The direct medical costs of acute fracture are assigned as transition costs at the terminal nodes.

3. If an individual in the post–clinical vertebral, post–hip, or post–hip and vertebral fracture states has an additional distal forearm or other fracture, the costs of that fracture are assigned, but the person remains in the post–vertebral, post–hip, or post–hip and vertebral fracture state since the long-term disutility associated with previous vertebral and hip fractures is greater.

4. The disutility associated with these fractures is modeled as a lower value of a QALY associated with that fracture state.

5. Long-term care costs (beyond the acute fracture state) are assigned in the post–hip fracture and post–hip and vertebral fracture states.

6. Excess mortality attributable to hip fracture is assigned in the same cycle that hip fracture occurs. This represents the component of mortality after hip fracture that is in excess of the expected age-specific rate.

7. We assumed relative risks of 4.0 for a subsequent vertebral fracture after an incident vertebral fracture (59), 1.7 for a subsequent hip fracture after an incident hip fracture (60), and 2.1 for a subsequent distal forearm fracture after an incident distal forearm fracture (61). We did not model an increased risk for subsequent fractures at sites different from that of the incident fractures because we based our fracture risk equations on data for first fractures of a specific type. Since the data for other fractures include recurrent other fractures, we did not model an increased risk for a subsequent other fracture after an incident other fracture (12).

8. We modeled fracture reduction from alendronate therapy directly, by using data from the clinical fracture group of FIT (17), rather than indirectly through BMD. For this reason, we did not model changes in BMD from alendronate treatment.

Transition Probabilities

Hip, Clinical Vertebral, Radiographic (Clinically Inapparent) Vertebral, Distal Forearm, and Other Fracture Rates

We constructed age-specific first fracture rates from population-based data of residents in Rochester, Minnesota, for distal forearm, clinical vertebral, and hip fractures (12). For each of these 3 fractures, we plotted the midpoint of each age range against the fracture rate, and we fitted a power curve by using linear regression to the data to obtain a continuous function of age versus fracture rate. We aimed to estimate (with an equation

by using the actual Rochester, Minnesota, data) the age-specific fracture rate as accurately as possible rather than describe it or normalize the error of the regressions. Therefore, we determined a set of predictors that maximized the R^2 value of the regressions and yielded excellent fitting curves.

The age-specific fracture rates are for populations with a mean Z -score of 0.0. Since the relationship between fracture and BMD is exponential, the rate has to be divided by a correction factor to obtain the correct rate for an individual of that age with a Z -score of 0.0. Each power function is then adjusted for BMD according to the technique of De Laet and colleagues (15, 16). For each SD in femoral neck Z -score, we assumed a 2.6-fold change in the age-specific hip fracture rate, a 1.8-fold change in the age-specific vertebral fracture rate, and a 1.5-fold change of distal forearm fracture rate. Appendix Table 1 shows the full fracture risk equations.

For example, Appendix Figure 3 shows the plot and power curve for the relationship between age and the rate of hip fracture. From the regression output for this power curve, the age-specific fracture risk equation is therefore:

$$(8.628 \times 10^{-20}) \times \text{age}^9 - 1.022 \times 10^{-4}$$

As per De Laet and colleagues, the correction factor to adjust this for an individual with a Z -score of 0.0 is:

$$C = \int 1/(\sqrt{2\pi}) \times (e^{\lambda} - 0.5z^2) \times (a^{-Z}) \times dz$$

For hip fracture, a is 2.6 and C is 1.57854; therefore, the full hip fracture risk equation is:

$$(2.686 \times 10^{-4} + 5.702 \times 10^{-18} \times \text{age}^8) \times 2.6^{-Z} \div 1.57854$$

where Z is the Z -score for that level of BMD. The Z -score is given by:

$$(\text{BMDc} - [1.0375 - 0.00554 \times \text{age}]) \div 0.114$$

where BMDc is the current femoral neck BMD in g/cm^2 .

The expression $1.0375 - (0.00554 \times \text{age})$ is the regression equation for age-specific mean femoral neck data from the National Health and Nutrition Examination Survey (NHANES) III data (for ages 50 to 90 years), and 0.114 is the pooled SD of femoral neck BMD calculated from NHANES III data for non-Hispanic white women older than 50 years of age (10).

Current femoral neck BMD (for each stage) is:

$$\text{BMDs} - 0.00554 \times \text{age}$$

where BMDs is the starting femoral neck BMD in g/cm^2 , calculated from starting T -score by the following equation, also derived from NHANES III data:

$$\text{BMD} = 0.828 + 0.12 \times (T\text{-score})$$

where 0.828 and 0.12 are the mean and SD, respectively, of femoral neck BMD of white women 20 to 29 years of age (10).

Appendix Figure 4, Appendix Figure 5, and Appendix Figure 6 show the power curves for the clinical vertebral, distal forearm, and other fracture rates, respectively, as a function of age. The final fracture risk functions are adjusted for BMD in the

same manner as for hip fracture, assuming relative risks of 1.8 for clinical vertebral, 1.4 for distal forearm, and 1.6 for other fractures for each *Z*-score change of 1.0. These fracture risk equations allow the model at each stage to recalculate the fracture rates, since bone density and age will change with each successive stage.

An estimated 35% of vertebral fractures found in a population-based study of postmenopausal women are recognized clinically at the time of occurrence. Therefore, we assumed that the rate of radiographic vertebral fractures is 0.65/0.35 or 1.86 times the clinical vertebral fracture rate.

Relative Risks for Subsequent Fractures after Incident Fractures

The model incorporates an increased relative risk for a subsequent fracture after an incident fracture of the same type. For example, after an incident clinical vertebral fracture, we assumed relative risks of 4.0 for subsequent vertebral fractures and 1.0 for subsequent hip fractures. The reason that no increased risk is modeled for subsequent fractures at different sites than the incident fracture is that the first fracture data on which these risks are based include individuals who have had previous fractures at different sites. For example, the population at risk for hip fracture excludes individuals who have had a previous hip fracture but not those who have had a previous vertebral fracture.

Data, at least for incident hip fracture after a wrist fracture (62), suggest that the risk for subsequent fractures is highest soon after the incident fracture but wanes over time. Therefore, the model assumes an increased risk for subsequent fracture for 10 years after the incident fracture.

We assumed the relative risk for subsequent vertebral fracture after an incident vertebral fracture to be 4.0, which is the age- and BMD-adjusted estimate derived from the prospective Study of Osteoporotic Fractures (59). We assumed the relative risk for subsequent hip fracture to be 1.7 after a hip fracture, which is derived from the retrospective study of Melton and colleagues using data from the Rochester Epidemiology Project (60). This estimate was not adjusted for BMD, and estimates of these relative risks that are adjusted for BMD have not been published.

Cuddihy and colleagues (61) estimated relative risks for a subsequent distal forearm fracture after an incident distal forearm fracture of 2.79 if the initial distal forearm fracture occurred before age 70 years and 2.05 if it occurred after age 70 years. We chose the lower value to represent this relative risk in our model partly because these estimates were not adjusted for BMD.

Construction of Transition Probabilities

We multiplied the fracture risk functions, adjusted for BMD, by the appropriate relative risks of drug therapy, previous fracture within the previous 10 years, and presence of additional BMD-independent fracture risk factors. We then converted these equations into transition probabilities by using the equation: $p = 1 - \exp(\text{Rate})$.

For example, for an individual who recently had an incident clinical vertebral fracture and is receiving drug therapy, the transition probability for a subsequent clinical vertebral fracture

would be $1 - \exp(\text{RateVertFx} \times 4.0 \times 0.5)$, where the relative risks attributable to the previous vertebral fracture and drug therapy are 4.0 and 0.5, respectively.

Direct Medical Costs of Fractures

We derived the cost of fractures from Gabriel and colleagues' study (28), which tracked all direct medical costs (excluding outpatient medications, long-term care costs, durable medical equipment, and ambulance utilization) for those with almost any type of fracture from 1989 to 1991. Gabriel and colleagues used unit cost estimates from the Mayo Cost Data Warehouse rather than charges.

Median costs (along with 25th and 75th percentiles) are reported for cases compared with their utilization the year before the fracture or with age- and sex-matched concurrent controls. Mean costs of fractures are not directly reported, but they can be derived by comparison with age- and sex-matched controls as the total number of individuals reporting fractures. The total cost differentials compared with controls are reported. For distal forearm, clinical vertebral, and hip fractures, we assumed that the assigned direct medical cost of fracture was the total difference in direct medical costs between the population with that specific fracture and the control group divided by the number of people with that fracture (Appendix Table 2) (24).

Gabriel and colleagues (28) grouped other fractures into 3 categories: "like a spine fracture," "like a hip fracture," and "like a wrist fracture." From the proportional incidence of each of these 3 groups, we also derived a mean cost of another fracture (Appendix Table 2).

We assumed that a physician visit for possible osteoporosis and bone densitometry would be done after an acute fracture, and Appendix Table 2 includes those costs (\$52 and \$139 [in 2001 U.S. dollars], respectively) to give the direct medical costs for acute hip, clinical vertebral, distal forearm, and other fractures of \$16 116, \$6721, \$3745, and \$5580, respectively.

Long-Term Care Costs

Liebson and colleagues (29) compared the nursing home utilization of 312 elderly individuals after hip fracture with an age- and sex-matched control group. Among those not residing in a nursing home before fracture, 128 were admitted to a nursing home within 3 months of hip fracture compared with 7 controls and had a mean length of stay of 161 days. Since the mean daily cost of long-term care estimated by the Centers for Medicare & Medicaid Services (63) is \$118 per day (in 1995 U.S. dollars), the total cost of long-term care attributable to hip fracture for the first year after that fracture is \$2 298 578 or \$7368 per hip fracture. After adjustment for inflation for long-term care (63), this cost in 2001 U.S. dollars is \$8911.

Of the 121 excess patients admitted to a nursing home within 3 months of hip fracture, 38 (12.2% of the original cohort of 312) were still in the nursing home after 1 year. For these 38 individuals, again assuming a cost of \$118 per day, total permanent long-term care costs would be \$1 636 660 or \$5246 (in 1995 U.S. dollars) per patient with hip fracture (or \$6295 [in 2001 U.S. dollars] per year for all patients with hip fracture).

Indirect Costs of Fractures from Lost Work

Meerding and colleagues (30) have recently published estimates of lost days of work after various injuries, including hip, clinical vertebral, upper-extremity, and lower-extremity fractures. They based their data on a postal questionnaire of patients in the Dutch Injury Surveillance System, a population-based registry of individuals presenting to emergency departments with injuries throughout the Netherlands. **Appendix Table 3** shows the odds ratios of lost work for fractures relative to superficial wounds, as well as the absolute number of workdays lost due to each fracture type (Dr. Meerding. Personal communication.).

We multiplied the estimated mean workdays lost by 7/5 and then divided the result by 365 to estimate the mean proportion of a year lost from work due to each fracture type. We used the data for upper-extremity fractures as a surrogate for distal forearm fracture and those for lower-extremity fractures as the surrogate for other fractures. We multiplied these proportions by the mean age-specific salary for U.S. women (64) and workforce participation rate (65) to derive age-specific indirect costs for each fracture type (**Appendix Table 4**).

For hip fracture, since we assume permanent nursing home placement for 12% of patients, a permanent loss of income of 0.12 times the age-specific loss of earnings for the first year after hip fracture is assumed for all subsequent years until death.

Disutility from Acute Fracture

Appendix Table 5 summarizes the assumed disutility of fractures and the sources from which they were derived. Kanis and colleagues (25) have recently reported prospectively measured estimates of disutility of women presenting to emergency departments with various acute fractures. They showed a much greater disutility associated with clinical vertebral fractures than other studies have estimated. Kanis and colleagues (25) recommended that the mean QALY value for the first year after a clinical vertebral, hip, or distal forearm fracture should be the age-specific QALY value for those without a fracture multiplied by 0.626, 0.792, or 0.977, respectively.

Assuming a QALY value of 0.84 for those without fracture, the utility loss for the first year after clinical vertebral, hip, and distal forearm fractures would be 0.31, 0.17, and 0.02, respectively.

However, only 22% of all vertebral fractures in women were clinical vertebral fractures requiring emergency department care (25). Clinical vertebral fractures in Melton and colleagues' study (14) (on which we based the clinical fracture rate function used in our study) included those not sufficiently symptomatic to require emergency department care, and 20% of these were found to be asymptomatic on radiography performed for other clinical reasons. Therefore, we assumed a loss of 0.26 for the first year after clinical vertebral fracture.

Since morphometric vertebral fractures are otherwise not detected clinically at the time they occur but do seem to be associated with some loss of quality of life, estimating their loss is difficult. We have estimated a utility loss of morphometric vertebral fracture of 0.08 per year. We estimated this with measurements by using the EQ-5D of participants in the Multiple Out-

comes of Raloxifene (MORE) trial (26) with at least 1 prevalent radiographic vertebral fracture compared with those with no prevalent radiographic vertebral fractures. Longitudinal data from the Study of Osteoporotic Fractures (35) and from the Hawaii Osteoporosis Study (66, 67) do indicate, however, that morphometric fractures more than 4 or 8 years old, respectively, do not cause lower quality of life. Therefore, we assumed a QALY loss of 0.08 for only 6 years after an incident morphometric fracture that would otherwise not be clinically detected.

Kanis and colleagues (25) also directly measured the utility loss for the first year after a humerus fracture (0.206) multiplied by the QALY value of those with no fracture. They also estimated the utility loss of pelvic and tibial fractures to be the same as that of humerus fractures; the utility loss of distal femur fractures to be the same as that of hip fractures; and the utility loss due to rib, clavicle, scapula, or sternal fractures to be the same as that of distal forearm fractures. We also assumed that the utility loss for the first year after other forearm or patellar fractures was the same as that of distal forearm fractures.

We then estimated the aggregate utility loss of other fracture from the utility loss assumed for each fracture, adjusted for the proportion of all other fractures among women 50 to 60 years of age that each fracture represents. Therefore, we calculated the utility loss for the first year after other fracture to be 0.104 times the QALY value of someone without a fracture. Assuming a baseline QALY value of 0.84 for women 50 to 60 years of age, we assumed a utility loss of 0.087 for the first year after other fracture and 0.027 for subsequent years after other fracture.

Ranges for Probabilistic Sensitivity Analyses

Direct Fracture Costs

We assumed that direct fracture costs would follow a log-normal distribution (**Appendix Table 6**). We derived the mean and 75th percentile costs for each fracture type from the data of Gabriel and colleagues (28). We modeled the log (75th percentile of cost) minus log (mean cost) to represent 0.675 of an SD of the distribution of the log (fracture costs).

Long-Term Care Costs

We estimated the proportion of individuals requiring long-term care beyond the first year after hip fracture to be 12% (38 of 312 individuals), and we assumed that this followed a binomial distribution (**Appendix Table 6**). A normal approximation to this yields an SD of \$951, with the point estimate of \$6295 (2001 U.S. dollars) per year.

Fracture Rates

Because these rates vary by age and BMD as continuous functions, modeling distributions for these is much more difficult than for costs. The proportions of individuals at risk who have a first distal forearm fracture, clinical vertebral, or hip fracture within each specified age range (12) can be considered to follow a binomial distribution (**Appendix Table 6**). The 95% CIs can be calculated by using an exact method appropriate for proportions close to 0 (68). If a normal approximation to these distributions is then assumed, the SD for these proportions is 15% or

less of the point estimate for those 65 years of age and older for hip fractures and is 15% or less of the point estimate for those 60 years of age and older for nonhip fractures.

For the probabilistic sensitivity analysis, we created an additional normally distributed variable with a mean value of 1.0 and SD of 0.15. We then multiplied this by the fracture rates, so that fracture rates vary together over a normal distribution with the means equal to the point estimates rendered by the fracture risk equations.

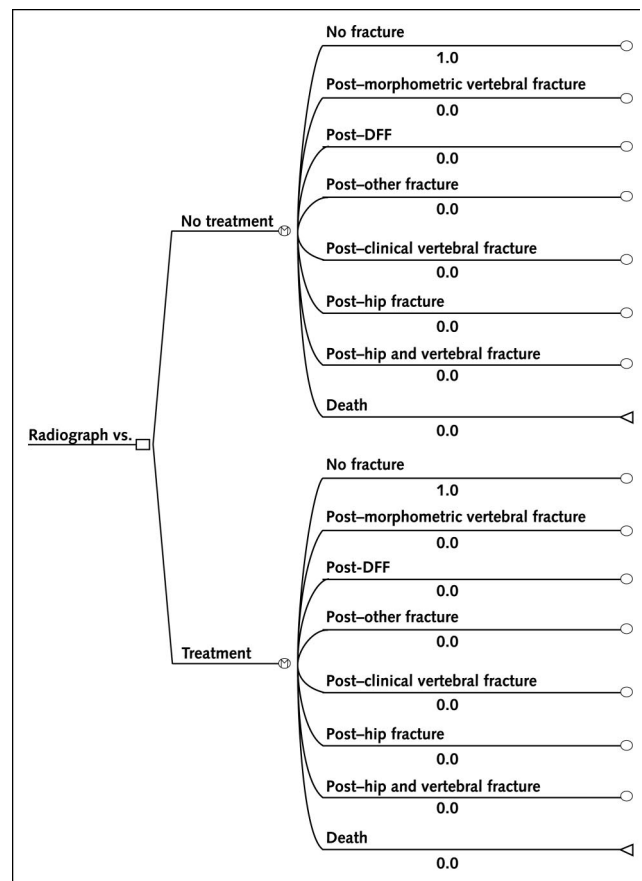
Indirect Costs Due to Lost Productivity and QALY Loss Attributable to Fractures

Because of uncertainty about these estimates, we have assumed a uniform distribution for these costs and loss of QALYs. To achieve this, we created 2 separate variables with means of 1.0. Each variable was uniformly distributed from 0.5 to 1.5 (Appendix Table 6). All indirect costs are multiplied by 1 of these variables, and all disutility estimates were multiplied by the other variable.

Performance of Probabilistic Sensitivity Analyses

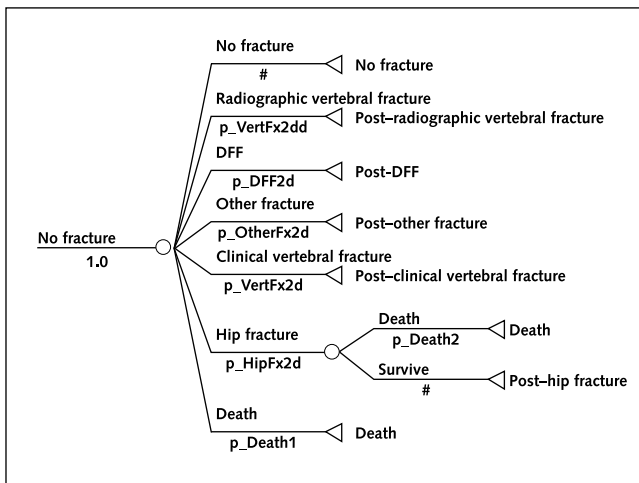
We performed the analyses with 400 simulations with 2000 trials per simulation. For each simulation, we randomly selected the variable values from the distributions described earlier. We then plotted the distribution of the resulting 400 incremental cost-effectiveness ratios as a cost-effectiveness acceptability curve, where cost-effectiveness thresholds are on the x-axis (from \$20 000 to \$140 000 per QALY gained) and the y-axis represents the proportion of simulations with incremental cost-effectiveness ratios less than the cost-effectiveness threshold.

Appendix Figure 1. Overall Markov model structure.



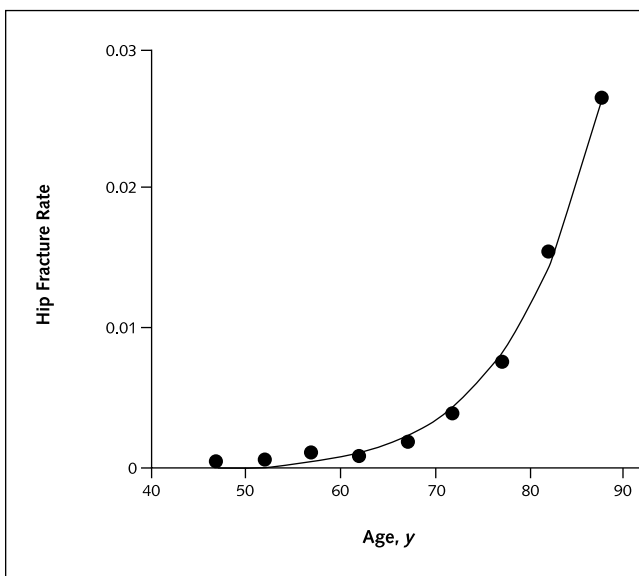
DFF = distal forearm fracture.

Appendix Figure 2. Expanded subtree for the no fracture state—no drug therapy strategy.

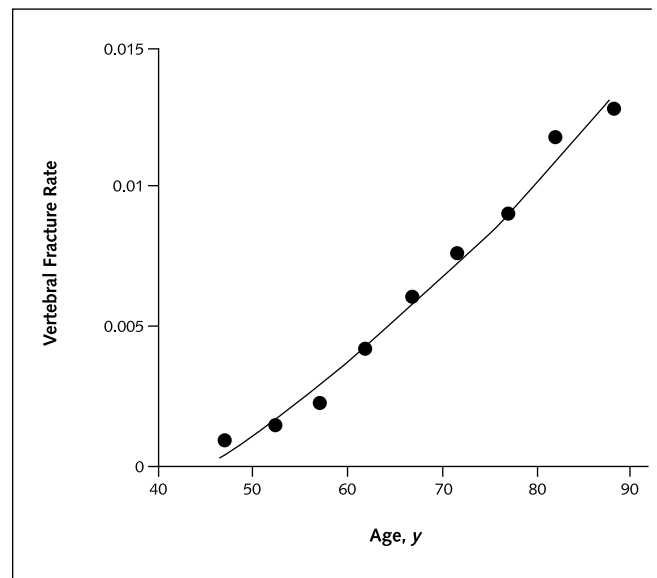


p_HipFx2d, p_VertFx2d, p_OtherFx2d, p_DFF2d, p_VertFx2dd, and p_Death1 are the transition probabilities of incident hip fracture, clinical vertebral fracture, other fracture, distal forearm fracture, radiographic (but clinically unapparent) vertebral fracture, or death, respectively, from the no fracture state without alendronate therapy. p_Death2 is the transition probability of death from the hip fracture state in excess of the age- and sex-specific death rate. DFF = distal forearm fracture.

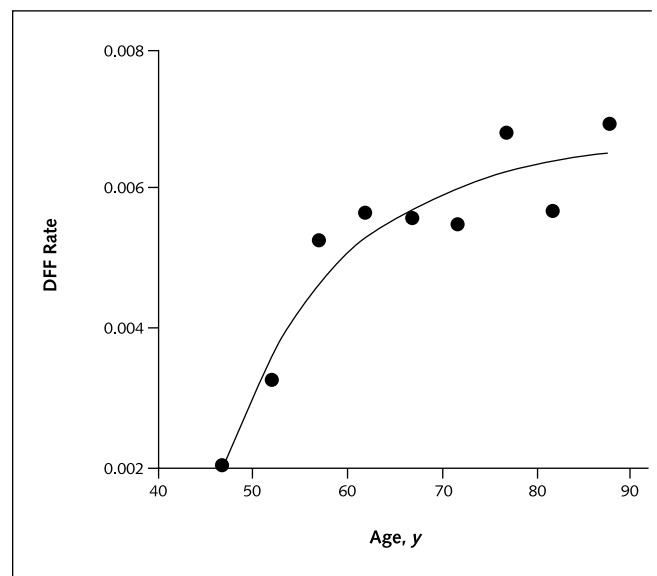
Appendix Figure 3. Hip fracture rate power curve.



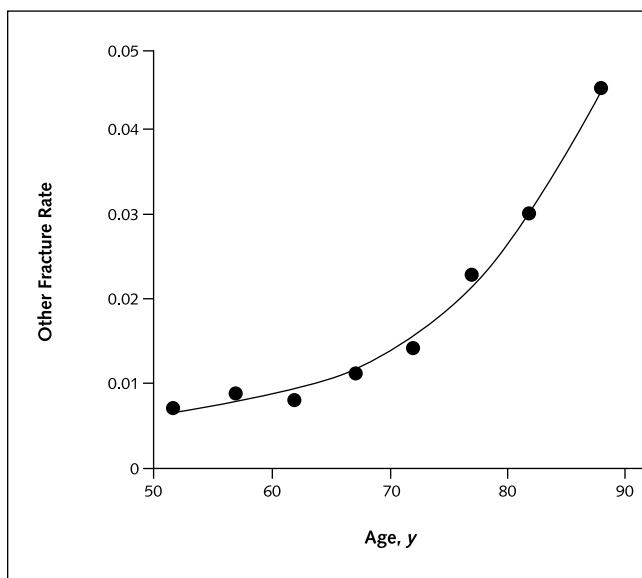
Appendix Figure 4. Clinical vertebral fracture rate power curve.



Appendix Figure 5. Distal forearm fracture (DFF) rate power curve.



Appendix Figure 6. Other fracture rate power curve.



Appendix Table 1. Fracture Risk Equations for Each Fracture Type

Fracture Type	Fracture Risk Equation*
Hip fracture	$(2.686 \times 10^4 + 5.702 \times 10^{18} \times \text{Age}^8) \times 2.6^{-z} \div 1.57854$
Clinical vertebral fracture	$(2.3325 \times 10^6 \times \text{Age}^2 - 0.00465282) \times 1.8^{-z} \div 1.18856$
Radiographic (not clinically apparent) vertebral fracture	$1.86 \times (2.3325 \times 10^6 \times \text{Age}^2 - 0.00465282) \times 1.8^{-z} \div 1.18856$
Distal forearm fracture	$(0.006904 - 23812.1 \times \text{Age}^4) \times 1.4^{-z} \div 1.05824$
Other fracture	$(0.00578 + 9.723 \times 10^{16} \times \text{Age}^7) \times 1.6^{-z} \div 1.11678$

* As function of age and bone mineral density.

Appendix Table 2. Mean Direct Fracture Costs

Fracture Type	Total Medical Cost, \$	Patients with Fracture, <i>n</i>	Mean Cost (in 1995 U.S. Dollars), \$	Mean Cost (in 2001 U.S. Dollars), \$
Hip	2 410 366	187	12 890	15 925
Spine	1 491 929	283	5272	6511
Distal forearm	538 000	188	2862	3554
Other	2 042 461	493	4348	5389

Appendix Table 3. Workdays Lost because of Acute Fracture

Fracture Type	Duration of Lost Work Odds Ratio*	Mean Workdays Lost, <i>d</i>
Hip	26.2	90.7
Spine	13.6	38.8
Upper extremity	13.0	24.7
Lower extremity other than hip	9.5	33.1

* Relative to superficial open wounds.

Appendix Table 4. Indirect Costs of Incident Fractures*

Age	Proportion in Workforce	Vertebral Fracture, \$	Hip Fracture, \$	Distal Forearm Fracture, \$	Other Fracture, \$
45–54 y	0.74	3313	7382	1994	2708
55–59 y	0.60	2540	5986	1616	2195
60–61 y	0.48	2032	4788	1293	1756
62–64 y	0.34	1440	3392	916	1244
65–69 y	0.20	418	984	266	361
70–74 y	0.11	230	541	146	198
≥75 y	0.04	84	197	53	72

* Values are in 2001 U.S. dollars. Mean wage for women 45 to 64 years of age and ≥65 years of age in workforce full- or part-time estimated to be \$28 453 per year and \$14 031 per year, respectively.

Appendix Table 5. Disutility Due to Incident Fractures

Fracture State	Disutility in First Year	Disutility in Subsequent Years	Study, Year (Reference)
Post-hip fracture	0.17	0.16	Kanis et al., 2004 (25)
Post-clinical vertebral fracture	0.26	0.08	Kanis et al., 2004 (25)
Post-radiographic vertebral fracture	0.08	0.08*	Oleksik et al., 2000 (26)
Post-vertebral and hip fracture	0.43	0.24	Tosteson et al., 2001 (27)
Post-distal forearm fracture	0.02	0.001	Kanis et al., 2004 (25)
Post-other fractures	0.087	0.027	Kanis et al., 2004 (25)

* For 5 subsequent years only.

Appendix Table 6. Variable Distributions for Probabilistic Sensitivity Analyses*

Variable	Distribution
Fracture costs	Log-normal
Hip fracture	Mean (±SD), 10.1285 ± 0.2377
Clinical vertebral fracture	Mean (±SD), 8.8130 ± 0.7142
Distal forearm fracture	Mean (±SD), 8.2282 ± 0.9850
Other fracture	Mean (±SD), 8.6269 ± 0.7225
Long-term care costs	Normal: mean (±SD), 6295 ± 951
Fracture rates	Normal: mean (±SD), fracture risk equation value ± (0.15 × mean)
Indirect costs	Uniform: range, 0.5 × (base value) to 1.5 × (base value)
QALY	Uniform
Post-hip fracture	Range, 0.585 to 0.755 (first year), 0.60 to 0.76 (subsequent years)
Post-clinical vertebral fracture	Range, 0.45 to 0.71 (first year), 0.72 to 0.80 (subsequent years)
Post-radiographic (clinically unapparent) vertebral fracture	Range, 0.72 to 0.80 (first 8 years), then to 0.84
Post-distal forearm fracture	Range, 0.81 to 0.83 (first year), then to 0.839 (subsequent years)
Post-other fracture	Range, 0.713 to 0.793 (first year), 0.803 to 0.823 (subsequent years)

* QALY = quality-adjusted life-year.