

Therapies for Treatment of Osteoporosis in US Women: Cost-effectiveness and Budget Impact Considerations

Anna N. A. Tosteson, ScD; Russel T. Burge, PhD;
Deborah A. Marshall, PhD; and Robert Lindsay, MD

Osteoporosis has been defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.¹ The National Health and Nutrition Examination Survey (NHANES) III estimated that 13% to 18% of women in the United States have osteoporosis.² The prevalence of postmenopausal osteoporosis (PMO) increases with age from approximately 6% at age 50 years to more than 50% above age 80 years.² The high osteoporosis prevalence coupled with its significant health consequences makes effective prevention and treatment leading public health concerns.^{3,4}

Current treatment options include bisphosphonates (eg, alendronate, risedronate, ibandronate), calcitonins, parathyroid hormone (PTH), and selective estrogen receptor modulators.

Cost-effectiveness analysis provides important information about the value of alternative therapies that may assist decision makers who seek to equitably allocate constrained resources to achieve maximum healthcare benefits on a population level. Although several articles have addressed the economic value of specific agents,⁵⁻⁷ the cost-effectiveness of all currently available bone-specific agents approved for treatment of PMO in the United States has not been reported. Another point of differentiation is that our study includes a population-based budget impact analysis to evaluate a policy to extend treatment to all eligible patients within defined risk groups. Budget impact analysis estimates the cost of treatment on an annual basis for budgeting purposes.

The objective of this study was to evaluate (from the healthcare system perspective) the cost-effectiveness of risedronate therapy compared with alendronate, ibandronate, and PTH for the treatment of women with PMO at high fracture risk. A secondary objective was to estimate the population-level impact of a decision to provide bisphosphonate treatment to all eligible US women not currently treated.

Objective: To evaluate the cost-effectiveness of osteoporosis treatments for women at high fracture risk and estimate the population-level impact of providing bisphosphonate therapy to all eligible high-risk US women.

Study Design: Fractures, healthcare costs, and quality-adjusted life-years (QALYs) were estimated over 10 years using a Markov model.

Methods: No therapy, risedronate, alendronate, ibandronate, and teriperatide (PTH) were compared among 4 risk groups. Sensitivity analyses examined the robustness of model results for 65-year-old women with low bone density and previous vertebral fracture.

Results: Women treated with a bisphosphonate experienced fewer fractures and more QALYs compared with no therapy or PTH. Total costs were lowest for the untreated cohort, followed by risedronate, alendronate, ibandronate, and PTH in all risk groups except women aged 75 years with previous fracture. The incremental cost-effectiveness of risedronate compared with no therapy ranged from cost saving for the base case to \$66,722 per QALY for women aged 65 years with no previous fracture. Ibandronate and PTH were dominated in all risk groups. (A dominated treatment has a higher cost and poorer outcome.)

Treating all eligible women with a bisphosphonate would cost an estimated additional \$5563 million (21% total increase) and would result in 390,049 fewer fractures (35% decrease). In the highest risk group, the additional cost of therapy was offset by other healthcare cost savings.

Conclusions: Osteoporosis treatment of high-risk women is cost-effective, with bisphosphonates providing the most benefit at lowest cost. For highest risk women, costs are offset by savings from fracture prevention.

(*Am J Manag Care.* 2008;14(9):605-615)

STUDY DESIGN

Model Overview

A validated fracture incidence-based Markov model of osteoporosis was used to compare the economic value of the alternative strategies.

A modeling approach was chosen primarily because of the lack of head-to-head clinical trials comparing current bone-specific therapies across multiple populations. The model was devel-

In this issue
Take-away Points / p614
www.ajmc.com
Full text and PDF

For author information and disclosures,
see end of text.

oped in consultation with a committee of academic advisors who retained control over design and methodologic decisions. In accordance with US Panel on Cost Effectiveness in Health and Medicine guidelines,⁸ the model underwent extensive validation to ensure it accurately predicted long-term fracture and mortality rates. Details of the model design, structure, assumptions, and validation have been presented previously.^{5,9}

In brief, the model is a Markov state-transition model in which a hypothetical cohort of patients moves between several short-term and long-term health states over time. The model uses annual, state-dependent transition probabilities to estimate the expected number of fractures, healthcare costs, and quality-adjusted life-years (QALYs) for each strategy. The model included 1 entry state (Healthy), 3 long-term postfracture states (Healthy Post-Vertebral Fracture, Healthy Post-Hip Fracture, and Healthy Post-2nd Hip Fracture), and death. Short-term states (Hip Fracture, 2nd Hip Fracture, Vertebral Fracture), where patients enter and leave within a year, also were included to capture the acute care costs and decrements in quality of life that are associated with fracture.

METHODS

Patient Population

Among women with low bone mineral density (BMD) (≤ 2.5 standard deviations below the young adult mean), 4 risk groups were evaluated based on age and history of vertebral fracture as follows: women aged 65 years with and without a prevalent vertebral fracture, and women aged 75 years with and without a previous vertebral fracture. The main subgroup of interest, used as the base case, was women aged 65 years with low BMD and a prior vertebral fracture.

Data and Assumptions

For all model parameters, published data sources were used wherever possible and consisted primarily of clinical trials, economic studies, observational studies, and epidemiologic databases. Details are provided below and summarized in **Table 1**. With respect to treatment, the base-case estimates for therapy duration, offset, and discontinuation were derived from advice from clinical experts.

Fracture Incidence

Our analysis focuses on treatment of postmenopausal women at high risk for fractures; therefore, fracture rates in the age-matched general population were adjusted to reflect the increased risk of new fractures in patients with low BMD and a previous vertebral fracture using the relative risk values noted in Table 1.¹⁷ This adjustment has been described fully elsewhere.⁵

Age-specific hip fracture incidence rates for the total US female population aged 65 to 100 years (all races) were obtained from a retrospective study on the Nationwide Inpatient Sample 2001 hospital discharge database. The analysis included only closed fractures that did not result from severe trauma, and were defined as inpatient hospital cases with 1 of the following *International Classification of Diseases, Ninth Revision* codes as the primary diagnosis: 820.0x (transcervical), 820.2x (pertrochanteric), 820.8x (neck of femur).¹⁰

Age-specific incidence rates for clinically ascertained vertebral fracture were taken from an analysis of the Rochester Epidemiological Project database, which captured patients treated on both an inpatient and outpatient basis (only 24% of fracture patients are hospitalized).

Mortality in the year after hip fracture was modeled based on analysis of Medicare claims data from 1999 to 2000 with age-specific mortality rates per 10,000 estimated at 130.29 for age 65 to 69 years, 138.07 for age 70 to 74 years, 166.80 for age 75 to 79 years, 203.38 for age 80 to 84 years, 298.74 for age 85 to 89 years, and 298.74 for age 90 years and older. No excess mortality was modeled following vertebral fracture.

Treatment Efficacy

The bone-specific osteoporosis treatments evaluated in the model include risedronate, alendronate, ibandronate, and PTH. These reflect current practice patterns, capturing those treatments that are used most frequently. The model did not consider possible concomitant calcium or vitamin D treatment with these therapies, as the efficacy estimates for the comparator therapies were derived from comparisons with placebo patients who received clinically appropriate calcium and/or vitamin D supplementation. To estimate fracture rates in the treated cohort, therapy-specific efficacy rates were multiplied by adjusted age-specific fracture incidence. Therapy-specific efficacy values (percent risk reduction for hip and vertebral fracture) were obtained from randomized controlled trials with a patient population similar to the base-case risk group.¹²⁻¹⁶ For PTH and ibandronate, where there was no evidence (statistically significant data from a randomized controlled trial) to support the effect of a treatment on the incidence of hip fracture, only the effect on the incidence of vertebral fracture was modeled. Although we modeled clinical vertebral fracture incidence, treatment effectiveness was estimated based on clinical trial data, which relies on radiographically evident vertebral fracture.

Direct Medical Costs

All costs are given in 2005 US dollars. Annual therapy costs were based on First Data Bank February 2005 values of

Table 1. Data and Assumptions Pertaining to Hip and Vertebral Fracture

Epidemiologic Data	Value	
	Hip Fracture ¹⁰	Clinical Vertebral Fracture ¹¹
General population fracture rates per 10,000 by age group		
65-69 y	18.1	68.2
70-74 y	37.1	116.7
75-79 y	79.0	156.6
80-84 y	157.7	257.9
85-89 y	263.4	313.2
90-94 y	345.8	313.2
95-100 y	306.2	313.2
Treatment efficacy (reduction in fracture risk), mean (CI)		
Risedronate	60 (20, 80) ¹²	41 (18, 57) ¹³
Alendronate	51 (1, 77) ¹⁴	47 (32, 59) ¹⁴
PTH	0	65 (45,78) ¹⁵
Ibandronate	0	49 (14, 69) ¹⁶
Relative risk in target population¹⁷		
65 y, previous fracture	6.41	5.65
65 y, no previous fracture	4.18	2.05
75 y, previous fracture	3.91	3.73
75 y, no previous fracture	2.73	1.65
Fracture costs		
First year (65-74 y)	\$39,555.24 ¹⁸⁻²²	\$3237.88 ^{18-21,23,24,a}
First year (75-84 y)	\$40,600.10 ¹⁸⁻²²	\$3090.74 ^{18-21,23,24,a}
Subsequent years	\$4706.23 ²⁰⁻²¹	\$218 ^{21,a}
Fracture disability^b		
First year (65-74 y)	0.18 ²⁵	0.16 ¹⁷ /0.55 ^{25,c}
First year (75-84 y)	0.12 ²⁵	0.11 ¹⁷ /0.47 ^{25,c}
Subsequent years (65-74 y)	0.09 ²⁶	0.08 ²⁷ /0.275 ^{26,c}
Subsequent years (75-84 y)	0.06 ²⁶	0.055 ²⁷ /0.235 ^{26,c}
<p>CI indicates confidence interval; PTH, parathyroid hormone. ^aUnit cost was adjusted downward to reflect the proportion of patients seeking medical care and the proportion of clinical cases admitted to acute care hospitals. ^bValues shown are decrements on a quality-adjusted life-year scale. ^cValues represent no prior hip fracture/prior hip fracture.</p>		

\$799.76 for risedronate, \$771.36 for ibandronate, \$835.64 for alendronate, and \$6291.72 for PTH. Age-specific costs in the year after a hip or vertebral fracture included hospitalization (acute inpatient, rehabilitation/short-stay, and readmission),^{17,18} physician visits,²⁰ emergency department visits, home healthcare, disability/dependence, nonmedical home care, and outpatient, nursing home, and other long-term care costs (Table 1).¹⁹⁻²⁴ All unit costs were updated

to year 2005 using the medical care component of the consumer price index.²⁷

Utility

To calculate the QALYs, utility weights were applied to each health state. Utilities reflect how quality of life in a health state is valued on a scale from 0 (death) to 1 (perfect health). This analysis assumed an age-specific utility weight

of 0.833 for women aged 65 to 69 years and 0.792 for women aged 75 to 79 years in the general population.²⁸ Age-specific utilities were reduced following fracture based on published evidence (Table 1).^{25,26}

Cost-effectiveness Analysis

The cost-effectiveness of alternative therapies for PMO was assessed as the incremental cost per hip fracture averted and the incremental cost per QALY gained. The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total expected discounted costs between the treatment groups by the difference in expected health effects (either fractures or QALYs) when treatments were ranked by increasing cost.

Base-case estimates for therapy duration, offset, and discontinuation were derived from advice from clinical experts. In the base-case analysis, women who received a bisphosphonate were assumed to be treated for 3 years and women who received PTH were assumed to be treated for 18 months. Once treatment was terminated, it was assumed to have no residual efficacy (ie, immediate therapy offset). Cost and health outcomes were tracked over a 10-year time horizon, with both costs and outcomes discounted at a rate of 3% per year. Costs included therapy cost over the treatment period and all fracture-related costs both in the year of fracture and all subsequent years.

Sensitivity Analysis

To test the robustness of model results, model parameters were varied in multiple 1-way sensitivity analyses for women aged 65 years with low BMD and a previous vertebral fracture. To characterize the impact of uncertainty on treatment efficacy in the cost-effectiveness analyses, analyses that utilized either upper or lower bounds of the 95% confidence intervals for treatment efficacy for each agent were undertaken. Analyses that varied the analytic time horizon from 3 years to lifetime (base case = 10 years) and modified the therapy offset to 5 years (base case = immediate offset) also were undertaken. Therapy offset, or percentage of maximum effect after cessation of therapy, was assumed to decline linearly over time at 90%, 70%, 50%, 30%, and 10% for years 1, 2, 3, 4, and 5, respectively.⁵ For alendronate, however, based on data from the Fracture Intervention Trial Long-term Extension (FLEX) study,^{17,29} a 50% slower rate of efficacy decline was used (ie, 90%, 80%, 70%, 60%, 50%). The impact of health utilities on the base-case estimates was evaluated first by varying the utilities by $\pm 25\%$, and then by limiting utility decrements due to fracture only to the year of the fracture.²⁵ Additional analyses that addressed therapy discontinuation and fracture costs also were completed based on results from

the Persistence Study of Ibandronate versus Alendronate (PERSIST) trial.³⁰ We used a cumulative therapy discontinuation rate of 76%,⁵ except for ibandronate, for which persistence was assumed to be 50% better than it was for weekly bisphosphonate dosing.³⁰

Given that treatment efficacy is a key factor driving the results of the cost-effectiveness analysis, we explored a broad range of comparisons for this parameter value. The trials were not able to show any statistically significant difference in effects because they may have been underpowered for hip fractures; therefore, we explored a 1-way sensitivity analysis scenario where a 90% hip fracture efficacy rate was applied to PTH. We also undertook a probabilistic sensitivity analysis, applying triangular distributions to the efficacy variables and using upper and lower 95% confidence intervals as minimum and maximum values.

Budget Impact Analysis

The budget impact of bisphosphonate treatment for all eligible high-risk women not currently receiving active therapy was assessed for 3- and 10-year time horizons and compared with current treatment practice. Therapy assignment for women on a bisphosphonate was based on current market shares.^{31,32} The relevant population size for each risk group was based on US population statistics.³³ Unpublished estimates were used to estimate the proportion of women with low BMD² and a previous vertebral fracture.¹¹

RESULTS

Over the 10-year period, women aged 65 years with a previous vertebral fracture who were treated with a bisphosphonate (risedronate, alendronate, or ibandronate) experienced fewer hip and vertebral fractures (a total of 441-464 fractures) compared with those receiving no therapy (550 fractures) or treatment with PTH (501 fractures) (Table 2). Likewise, those treated with a bisphosphonate (risedronate, alendronate, or ibandronate) had more QALYs (6.646, 6.647, and 6.624 QALYs, respectively) compared with those receiving no therapy (6.580 QALYs) or treatment with PTH (6.608 QALYs). The most hip fractures (n = 137) and vertebral fractures (n = 413) were experienced by those who received no therapy. Women treated with risidronate experienced the fewest hip fractures (n = 105), whereas patients treated with ibandronate experienced the fewest vertebral fractures (n = 327). Except for those who received no therapy, women treated with PTH experienced the most vertebral fractures (n = 364), whereas those treated with ibandronate or PTH experienced the most hip fractures (n = 137). A similar pattern was observed among treatments across each risk group.

■ **Table 2.** Costs, Outcomes, and Incremental Cost-effectiveness Estimates by Risk Group^a

Risk Group and Therapy	Cost per Patient, \$	QALYs per Patient	No. of Fractures per 1000 Patients		Incremental Cost	
			Vertebral	Hip	Per QALY Gained	Per Hip Fracture Averted
Base case (age 65 y, low BMD, previous fracture)						
No therapy	8696	6.580	413	137	—	—
Risedronate	10,136	6.646	341	105	\$22,068	\$45,865
Alendronate	10,548	6.647	331	110	\$362,845	Dominated
Ibandronate	11,879	6.624	327	137	Dominated	Dominated
PTH	20,800	6.608	364	137	Dominated	Dominated
Age 65 y, low BMD, no previous fracture						
No therapy	5311	6.708	150	89	—	—
Risedronate	7569	6.741	124	69	\$66,722	\$109,576
Alendronate	7912	6.741	120	72	Dominated	Dominated
Ibandronate	8713	6.725	119	89	Dominated	Dominated
PTH	17,548	6.719	132	89	Dominated	Dominated
Age 75 y, low BMD, previous fracture						
Risedronate	16,564	5.662	436	234	—	—
Alendronate	17,348	5.659	420	246	Dominated	Dominated
No therapy	17,903	5.578	539	311	Dominated	Dominated
Ibandronate	20,849	5.615	413	311	Dominated	Dominated
PTH	29,815	5.602	466	311	Dominated	Dominated
Age 75 y, low BMD, no previous fracture						
No therapy	12,390	5.694	239	220	—	—
Risedronate	12,442	5.747	193	165	\$991	\$946
Alendronate	13,072	5.743	186	173	Dominated	Dominated
Ibandronate	15,572	5.713	184	220	Dominated	Dominated
PTH	24,456	5.706	207	220	Dominated	Dominated

BMD indicates bone mineral density; PTH, parathyroid hormone; QALYs, quality-adjusted life-years.

^aIbandronate and PTH were assumed to have no clinical benefit for the reduction of hip fractures. Because these treatments are more expensive than no therapy and there was no reduction in hip fractures, these treatments were dominated. (A dominated treatment is one with a higher cost and poorer outcome. Alendronate is also dominated for many risk groups.)

Total cost was lowest for the untreated cohort, followed by risedronate, alendronate, ibandronate, and PTH in all risk groups except patients aged 75 years with previous fracture. In that group the total costs were lowest for the risedronate cohort, followed by alendronate, no therapy, ibandronate, and PTH.

Cost-effectiveness Analysis

The incremental cost-effectiveness of risedronate in the women aged 65 years who had no previous fracture was \$22,068 per QALY gained and \$45,865 per hip fracture averted compared to no therapy (Table 2). Compared with rise-

dronate, the cost-effectiveness of alendronate was \$362,845 per QALY gained. Other therapies resulted in higher costs and poorer health outcomes, and therefore were dominated. (A dominated treatment is one with a higher cost and a poorer outcome.)

The cost-effectiveness of risedronate was the most favorable compared with all other therapeutic alternatives for all patient risk groups, ranging from cost saving compared with no therapy for patients aged 75 years with a previous fracture to \$66,722 per QALY gained compared with no therapy for patients aged 65 years with no previous fracture. Both ibandronate and PTH were dominated in all patient risk groups.

■ **Table 3.** Sensitivity Analyses^a

Analysis	Incremental Cost	
	Per QALY Gained	Per Hip Fracture Averted
Base case (age 65 years, low BMD, previous fractures)		
Risedronate	\$22,068	\$45,865
Alendronate	\$362,845	Dominated
Lower treatment efficacy^b		
Risedronate	\$114,694	\$277,208
Alendronate	\$196,140	Dominated
Higher treatment efficacy^b		
Risedronate	\$7474	\$16,030
Alendronate	\$621,513	Dominated
Lifetime time horizon		
Risedronate	\$14,031	\$49,664
Alendronate	Dominated	Dominated
Three-year time horizon		
Risedronate	\$85,391	\$74,326
Alendronate	\$258,803	Dominated
Five-year therapy offset^c		
Risedronate	\$1773	\$2974
Alendronate	\$9437	\$67,027
Utility decrements reduced 25%		
Risedronate	\$28,169	\$45,865 ^d
Alendronate	\$786,181	Dominated
Utility decrements increased 25%		
Risedronate	\$18,137	\$45,865 ^d
Alendronate	\$236,008	Dominated
No ongoing fracture utility decrement		
Risedronate	\$48,543	\$45,865 ^d
Alendronate	Dominated	Dominated
Three-year therapy duration		
Risedronate	\$21,704	\$52,120
Alendronate	\$269,312	Dominated
Therapy discontinuation^e		
Risedronate	\$38,062	\$86,405
Alendronate	\$289,919	Dominated
Ibandronate	\$458,313	Dominated
Fracture costs reduced 25%		
Risedronate	\$30,606	\$63,606
Alendronate	\$308,317	Dominated
Fracture costs increased 25%		
Risedronate	\$13,531	\$28,121
Alendronate	\$417,373	Dominated

BMD indicates bone mineral density; QALY, quality-adjusted life-year.

^aFor each scenario, no therapy was the least expensive option and so was the choice against which active therapies were compared. In each scenario, risedronate was the next more costly option and was compared with no therapy, and alendronate was compared with risedronate. Ibandronate and parathyroid hormone were dominated in all scenarios, except for the therapy discontinuation scenario where ibandronate was not dominated for incremental cost per QALY gained. (A dominated treatment is one with a higher cost and poorer outcome.) Except where noted, only the risedronate and alendronate comparison is shown in the table for simplification.

^bBased on bounds of 95% confidence intervals for treatment efficacy reported in clinical trials.

^cTherapy offset (percentage of maximum efficacy) was assumed at 90%, 70%, 50%, 30%, and 10% for years 1, 2, 3, 4, and 5, respectively. Based on FLEX study data¹⁷⁻²⁹ alendronate's efficacy decline was assumed to be 50% slower versus other therapies, or 90%, 80%, 70%, 60%, and 50% for years 1-5.

^dChanges in utility values affect only the QALY measures and do not have any impact on the cost per hip fracture averted.

^eDiscontinuation rates were 25% within 3 months, 23% for remainder of year 1; 18% within year 2; 10% within year 3; 0% over years 4 and 5.⁵ For ibandronate, discontinuation rates were reduced by 50% based on data from the PERSIST trial.³⁰

Sensitivity Analysis

The cost-effectiveness results changed qualitatively with changes in the assumptions about treatment efficacy and analytical time horizon (Table 3). That is, from the decision makers' point of view, when \$50,000 per QALY was considered to be a decision threshold, the decision to adopt a treatment strategy changed. When the low estimates for efficacy were modeled, the cost-effectiveness for risedronate compared with no therapy changed from \$22,068 per QALY gained to \$114,694 per QALY gained. When a 3-year time horizon was assumed, the cost-effectiveness estimates for risedronate compared with no therapy changed from \$22,068 per QALY gained to \$85,391 per QALY gained, and the cost-effectiveness estimates for alendronate compared with risedronate changed from \$362,845 to \$258,803 per QALY gained. Although the cost-effectiveness estimates for alendronate compared with risedronate changed substantially in the sensitivity analyses, all the values were much greater than \$50,000 (ie, dominated), with the only exception being the 5-year therapy offset scenario, where alendronate's cost per QALY gained was similar to risedronate's, so this would not likely impact the adoption decision. A comparable pattern emerged for the results reported as cost per hip fracture averted. Both ibandronate and PTH were dominated in all of the sensitivity analyses measured as both cost per

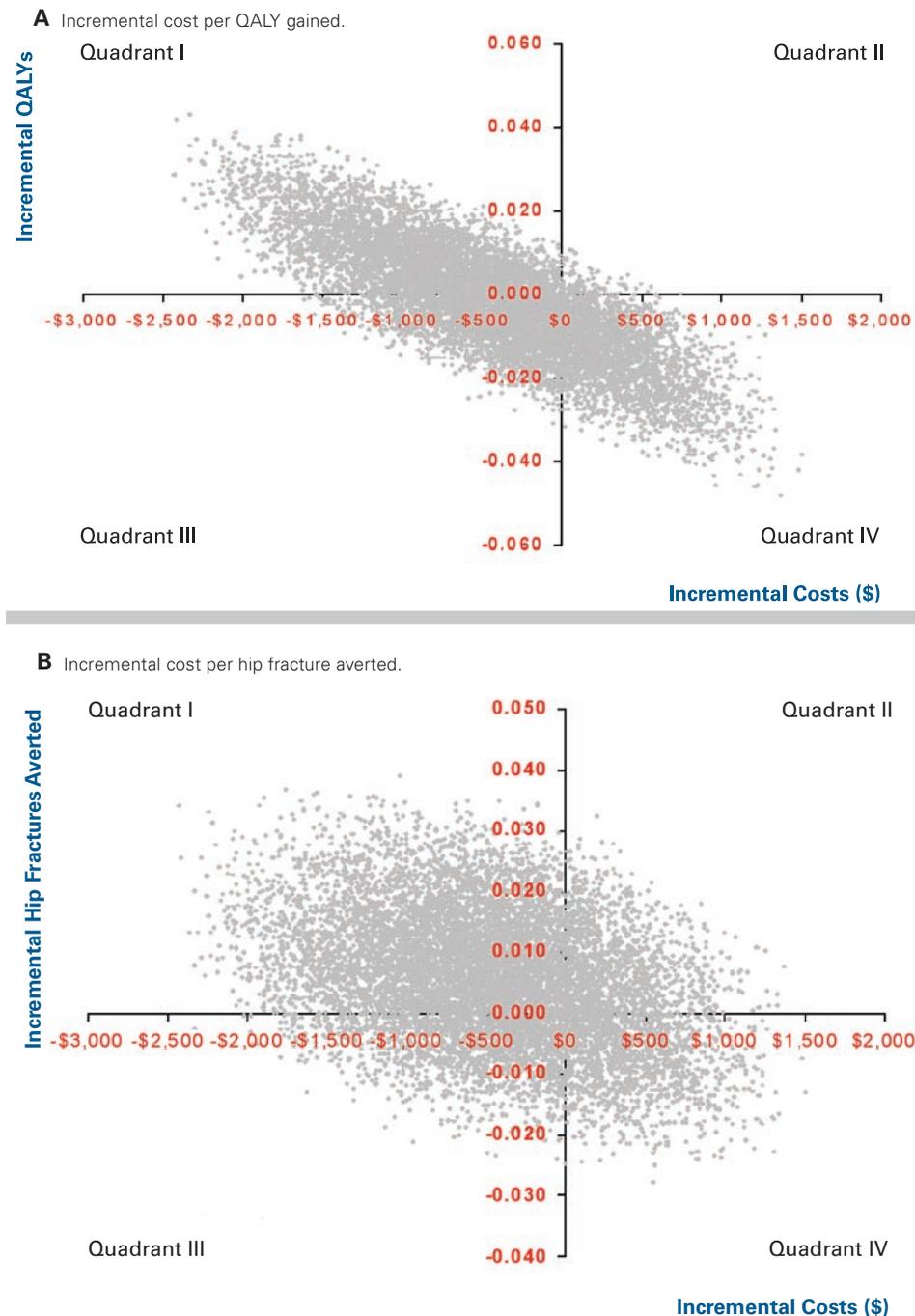
QALY gained and cost per hip fracture averted, except for the therapy discontinuation analysis, where ibandronate was on the cost-effectiveness frontier for cost per QALY gained.

Results from a probabilistic sensitivity analysis of the impact of efficacy variability on the base-case results are shown in the **Figure**. Almost 44% of 10,000 simulations showed risedronate dominating alendronate for cost per QALY estimates (Figure A), whereas nearly 25% of the trials showed the converse result. Incremental costs per hip fracture averted (Figure B) indicated dominance for risedronate in 56.4% of the simulations, whereas the reverse held in 13.4% of the simulations. (Similar cost per QALY analyses for risedronate vs ibandronate and PTH revealed dominance for risedronate in 93.1% and 99.8% of the simulations, respectively; there was 0% shown for dominance over risedronate.) In the simulations for incremental cost per hip fracture averted, risedronate dominated ibandronate and PTH in 100% of the simulations (results not shown).

Budget Impact Analysis

Aggregating the 4 risk groups yielded an estimated 8.23 million women in the United States aged 65 to 84 years with low BMD. Currently, 27% of these women receive bisphosphonates and a further 2.9% receive PTH or calcitonin. The rest remain untreated. Based on our estimates of cost-effectiveness of the individual therapies over a 3-year time horizon, a decision to treat the approximately 5.7 million women not receiving active therapy with bisphosphonates would cost an additional \$5563 million

Figure. Incremental Cost: Risedronate vs Alendronate



(21% increase in total cost) and would result in an additional 83,159 QALYs (0.45% increase) and 390,049 fewer fractures (35% decrease) (Table 4).

In the highest risk group (women aged 75 years with previous fracture), the additional cost of therapy was offset by the savings in inpatient, outpatient, and long-term care for

■ **Table 4.** Budget Impact Over 3-year Time Horizon^a

Characteristic	Current Practice			Total
	Bisphosphonates ^b	Other Osteoporosis Treatments ^c	Untreated	
Aggregate age 65-84 y, with low BMD				
Number of QALYs	5,082,432	527,272	12,862,998	18,472,703
Total societal cost	9165	793	15,999	25,957
Inpatient care	2131	427	8577	11,134
Outpatient care	261	52	1005	1318
Long-term care	1580	315	6417	8312
Therapy	5193	—	—	5193
Total number of fractures	234,560	45,752	838,359	1,118,670
Age 75 y, with previous fracture				
Number of QALYs	1,798,540	185,556	1,673,646	3,657,742
Total societal cost	3978	417	3,760	8154
Inpatient care	1111	222	2,001	3334
Outpatient care	135	27	241	403
Long-term care	850	168	1,518	2537
Therapy	1881	—	—	1881
Total number of fractures	118,694	23,110	208,441	350,245

BMD indicates bone mineral density; QALYs, quality-adjusted life-years.

^aCosts are displayed in millions of dollars. The totals for the risk group composed of women age 75 years with previous fracture are subsets of the aggregate totals.

^bFor this analysis, bisphosphonates included risedronate, alendronate, and ibandronate.

^cFor this analysis, other osteoporosis treatments include parathyroid hormone, selective estrogen-receptor modulators, and calcitonin. In the scenario where those who were untreated in current practice were treated with bisphosphonates, the group being treated with parathyroid hormone, selective estrogen-receptor modulators, and calcitonin was assumed to remain the same.

a net savings of \$18 million (0.2% decrease in total cost), accompanied by an additional 18,232 QALYs (0.5% increase) and 96,786 fewer fractures (28% decrease).

Currently 48.5% of women with previous fracture (aged 65-84 years with low BMD) are treated with bisphosphonates and an additional 5.1% receive PTH or calcitonin. A policy decision to treat with bisphosphonates the approximately 1.5 million untreated women in this group would result over a 3-year period in 32,558 QALYs gained (0.46% increase) and 155,038 fractures avoided (28% decrease), at an additional societal cost of \$783 million (6.2% increase) (data not shown).

DISCUSSION

This analysis focused on bone-specific osteoporosis treatments that are available in the United States and are used most frequently in current practice. Our evaluation of the cost-effectiveness of these osteoporosis treatments over a 10-year time horizon in 4 cohorts of postmenopausal women highlights where intervention is most economical. As anticipated, ICERs were smallest in those at highest risk. Indeed, among

women aged 75 years with prior fracture, treatment with risedronate was estimated to be cost saving compared with no intervention. Although osteoporosis treatment was not cost saving for other risk groups, the ICERs for risedronate were within commonly acceptable ranges and smaller than those for the other treatment alternatives considered in this analysis (ratios ranging from \$991 to \$67,000 per QALY gained). Although alendronate provided a small additional increment in QALYs compared with risedronate, this came at a cost of \$362,845 per QALY gained. Ibandronate and PTH were both more costly and less effective than alternative treatments.

Because of differences in study design, patient risk profiles, and model structures, direct comparisons with other US studies are difficult to make.^{6,34-37} However, our cost-effectiveness findings are comparable to those reported for the United Kingdom⁷ and for Sweden, Finland, Spain, and Belgium³⁸: risedronate appeared to be reasonably cost-effective compared with commonly discussed policy thresholds for intervention. In spite of differences in base-case assumptions, both our US-focused analysis and the UK analysis suggest that risedronate treatment may be cost saving relative to no intervention for

Treatment of Osteoporosis in US Women

All Those Untreated Receive Bisphosphonates				
Bisphosphonates ^b	Other Osteoporosis Treatments ^c	Total	Difference (Impact)	Percent Change
18,028,590	527,272	18,555,862	83,159	0.45
30,727	793	31,520	5563	21
6609	427	7035	(4099)	-37
790	52	842	(476)	-36
4945	315	5259	(3052)	-37
18,383	—	18,383	13,190	254
682,869	45,752	728,621	(390,049)	-35
3,490,417	185,556	3,675,974	18,232	0.5
7719	417	8136	(18)	-0.2
2157	222	2379	(955)	-28.6
262	27	289	(114)	-28.3
1650	168	1818	(718)	-28.3
3650	—	3650	1769	94.1
230,349	23,110	253,459	(96,786)	-28

women aged ≥ 75 years old who have sustained a prior fracture. Furthermore, because our analysis focused on vertebral and hip fractures, the cost-effectiveness estimates are conservative; the inclusion of other fractures would improve (lower) estimates of cost-effectiveness. Thus, our analysis provides further evidence that selectively targeting high-risk populations is economically attractive, which is consistent with summary conclusions from a recent, comprehensive review of the cost-effectiveness literature in which bisphosphonates were found to be the most cost-effective therapies, especially in women aged 70 years and older with previous fractures.³⁹

An important distinction between earlier reports on the cost-effectiveness of risedronate and ours is the inclusion of alternative bisphosphonates (alendronate and ibandronate) and PTH as comparators. Although some argue that only head-to-head comparisons of pharmaceutical agents in clinical trials provide a valid basis for economic evaluation, an important role for model-based analyses is integration and comparison of data from multiple sources.⁹ To that end, we included alendronate, ibandronate, and PTH as comparators. Because of differences in acquisition costs between

these agents and differing efficacy profiles, neither ibandronate nor PTH was identified as a cost-effective alternative to risedronate or alendronate.

Another way in which this study differs from previous cost-effectiveness studies on osteoporosis is our population-based budget impact analysis, which we used to evaluate a policy to extend treatment to all eligible patients within defined risk groups. After conducting a cost-effectiveness analysis on 4 risk populations to estimate the marginal cost effects from therapy alternatives, we conducted a budget impact analysis to predict the overall total cost impact to payers from such a policy if it were to be implemented in the United States. Although the cost-effectiveness analyses compared equivalent-sized cohorts, the budget impact analysis compared unequal numbers of patients in defined populations before and after the policy change. The budget impact analysis used estimates of current treatment patterns (no treatment, distribution by treatment type) to project the costs and benefits over a 3-year period. These results further support treatment of high-risk PMO populations because of the gain in QALYs and, in the case of the subgroup of women aged 75 years with previ-

Take-away Points

This study evaluated the population-level impact of providing osteoporosis therapy to all eligible high-risk US women not currently treated and estimated the cost-effectiveness of alternative osteoporosis treatments.

- Bisphosphonate treatment would increase costs by 21%, but fractures would decrease 35%.
- If only the highest risk group were treated, the additional cost of therapy would be offset by other cost savings. Treatment also would be cost-effective when targeted to appropriate at-risk populations.
- These findings have important implications for the management of women at high risk for osteoporosis, who are largely undertreated in current practice.

aged ≥ 65 years, any age-specific population-based estimates of utility are likely to already include the effect of fractures. Thus, a more conservative estimate would only include fracture disutility for a limited period following fracture.

In summary, treatment of osteoporosis among women in the United States can be cost-effective when targeted to appropriate at-risk populations. Recent US analyses indicate

that it is cost-effective to treat individuals with 10-year hip fracture risk of 3% or more.⁴⁶ Among available osteoporosis therapy alternatives, risedronate appears to have the most favorable cost-effectiveness profile. From a health policy perspective, scarce resources are best allocated to therapies with evidence of cost-effectiveness.

ous fracture, overall cost savings because of the reduction in healthcare services. One challenge in integrating clinical trial data in an economic-modeling framework is translating trial-reported treatment efficacy measures into clinically meaningful events. To do this, we assumed that treatment efficacy in reducing vertebral fracture risk did not depend on whether fractures were clinically ascertained, which is supported by a study of Chesnut et al,⁴⁰ who reported similar relative risk reductions for radiographic and clinical vertebral fractures.

A limitation of the modeling framework we utilized was its focus on fracture incidence and mortality from fracture and other causes. Thus, we were not able to assess the economic value of any of the bone-targeted agents studied compared with raloxifene, which has favorable extraskelatal effects on breast cancer incidence.⁴¹⁻⁴⁴ We also did not consider the impact of drug side effects on the cost-effectiveness of treatment. Although concerns have been raised regarding bisphosphonate treatment and osteonecrosis of the jaw, the vast majority of such cases were found among cancer patients receiving frequent intravenous bisphosphonates, and the risk among osteoporosis patients using oral bisphosphonates is very low.⁴⁵

In addition, we did not model treatment strategies, where switching between treatments would be expected. Nonetheless, our budget impact analysis highlights the potential for bone-targeted agents to improve health at a reasonable cost.

Several of the sensitivity analyses deserve comment. First, the analysis using a lifetime time horizon, which is important because it is consistent both with cost-effectiveness evaluation guidelines⁸ and previous analyses of osteoporosis,³¹ resulted in an ICER that was nearly 50% lower than that of the base case. Second, although uniformly lowering or raising the utility decrements associated with fractures by 25% changed the ICER only by approximately \$10,000, eliminating the ongoing decrement in utility associated with fracture more than doubled the ICER for risedronate. To the extent that vertebral fractures are highly prevalent in the population

that it is cost-effective to treat individuals with 10-year hip fracture risk of 3% or more.⁴⁶ Among available osteoporosis therapy alternatives, risedronate appears to have the most favorable cost-effectiveness profile. From a health policy perspective, scarce resources are best allocated to therapies with evidence of cost-effectiveness.

Acknowledgments

We would like to thank Michael Maschio, MSc, Marg Hux, MSc, Nicole Brazier, MSc, Nicole Ferko, MSc, Melissa Thompson, MBA, and Roberta Irvine from i3 Innovus for contributions to the completion of this manuscript.

Author Affiliations: From the Department of Medicine, Dartmouth Medical School, and The Dartmouth Institute of Health Policy and Clinical Practice (ANAT), Lebanon, NH; Global Health Economics & Outcomes Research, Abbott Laboratories (RTB), Abbott Park, IL; the College of Pharmacy (RTB), University of Cincinnati, Cincinnati, OH; Global Health Economics & Outcomes Research (DAM), i3 Innovus, Burlington, Ontario; and the Division of Clinical Research (RL), Helen Hays Hospital, West Haverstraw, NY.

Funding Source: This study was funded by The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals, Cincinnati, OH, and sanofi-aventis, Bridgewater, NJ).

Author Disclosure: Dr Burge is an employee of Abbott Laboratories. Dr Marshall is an employee of i3 Innovus and reports receiving payment for the preparation of the manuscript. Dr Lindsay reports having served as a paid consultant for Procter & Gamble, GlaxoSmithKline, and Wyeth Pharmaceuticals, and reports receiving lecture fees from Eli Lilly & Company, sanofi-aventis, and GlaxoSmithKline. Dr Tosteson reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (ANAT, RTB, RL); acquisition of data (RTB, DAM); analysis and interpretation of data (ANAT, RTB, DAM); drafting of the manuscript (ANAT, DAM, RL); critical revision of the manuscript for important intellectual content (ANAT, RTB, DAM, RL); statistical analysis (RTB, DAM); provision of study materials or patients (ANAT); obtaining funding (RTB, DAM); administrative, technical, or logistic support (RTB, DAM); and supervision (ANAT, DAM, RL).

Address correspondence to: Anna N. A. Tosteson, ScD, HB 7505 Clinical Research, Dartmouth Medical School, One Medical Ctr Dr, Lebanon, NH 03756. E-mail: anna.tosteson@dartmouth.edu.

REFERENCES

1. National Institutes of Health. *Osteoporosis Prevention, Diagnosis and Therapy*. Consensus Development Conference Statement. March 27-29, 2000. <http://consensus.nih.gov/2000/2000Osteoporosis111html.htm>. Accessed July 9, 2008.
2. Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res*. 1997;12(11):1761-1768.

3. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada, 1: introduction. *CMAJ*. 1996;155(7):921-923.
4. **Bone Health and Osteoporosis: A Report of the Surgeon General.** Rockville, MD: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General; 2004. <http://www.surgeongeneral.gov/library/bonehealth/content.html>. Accessed July 9, 2008.
5. Grima DT, Burge RT, Becker DL, Tosteson AN. Short-term cost effectiveness of bisphosphonate therapies for postmenopausal osteoporotic women at high risk of fracture. *P&T*. 2002;27(9):448-455.
6. Pfister AK, Welch CA, Lester MD, Emmett MK, Saville PD, Duerring SA. Cost-effectiveness strategies to treat osteoporosis in elderly women. *South Med J*. 2006;99(2):123-131.
7. Kanis JA, Borgstrom F, Johnell O, Jonsson B. Cost-effectiveness of risedronate for the treatment of osteoporosis and prevention of fractures in postmenopausal women. *Osteoporos Int*. 2004;15(11):862-871.
8. Gold MR, Siegal JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
9. Tosteson AN, Jönsson B, Grima DT, O'Brien BJ, Black DM, Adachi JD. Challenges for model-based economic evaluations of postmenopausal osteoporosis interventions. *Osteoporos Int*. 2001;12(10):849-857.
10. **Nationwide Inpatient Sample.** Hip fracture rates (820XX codes, closed only). 2001. The Healthcare Cost and Utilization Project. Sponsored by the Agency for Healthcare Research and Quality. http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2001.jsp. Accessed July 9, 2008.
11. Melton LJ 3rd, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. *Osteoporos Int*. 1999;9(1):29-37.
12. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*. 2001;344(5):333-340.
13. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282(14):1344-1352.
14. Black DM, Cummings SR, Karf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348(9041):1535-1541.
15. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434-1441.
16. **Roche Pharmaceuticals.** Boniva product monograph. Nutley, NJ: Roche Laboratories Inc; 2003.
17. Black DM, Palermo L, Grima DT. Developing better economic models of osteoporosis: considerations for the calculation of the relative risk of fracture. *Value Health*. 2006;9(1):54-58.
18. **Agency for Healthcare Research and Quality.** Nationwide Inpatient Sample, Release 10. Healthcare Cost and Utilization Project. 2001. http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2001.jsp. Accessed July 9, 2008.
19. Hoerger TJ, Downs KE, Lakshmanan MC, et al. Healthcare use among U.S. women aged 45 and older: total costs and costs for selected postmenopausal health risks. *J Womens Health Gend Based Med*. 1999;8(8):1077-1089.
20. **US Congress, Office of Technology Assessment.** *Cost-Effectiveness Analysis and Evidence on Benefits, Risks and Costs*. Washington, DC: US Government Printing Office; August 1995. OTA-BP-H-160. *Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy*; vols 1 and 2.
21. **National Osteoporosis Foundation.** Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost effectiveness analysis. *Osteoporos Int*. 1998;8(10):S03-S82.
22. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res*. 1997;12(1):24-35.
23. Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. *Bone*. 1994;15(4):377-386.
24. Phillips S, Fox N, Jacobs J, Wright WE. The direct medical costs of osteoporosis for American women aged 45 and older, 1986. *Bone*. 1988;9(5):271-279.
25. Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ III. Impact of hip and vertebral fractures on quality-adjusted life years. *Osteoporos Int*. 2001;12(12):1042-1049.
26. Jonsson B. Targeting high-risk populations. *Osteoporos Int*. 1998;8(suppl 1):S13-S16.
27. **US Department of Labor, Bureau of Labor Statistics.** Consumer Price Index, U.S. City Average—Medical Care. 2006.
28. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making*. 1993;13(2):89-102.
29. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927-2938.
30. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract*. 2006;60(8):896-905.
31. **IMS Health.** National Prescription Audit. Plymouth Meeting, PA: IMS Health; 2005.
32. **Thompson Medstat.** Database (2002-2003). 2006.
33. **US Census Bureau.** 2000 Census. <http://www.census.gov/main/www/cen2000.html>. Accessed July 9, 2008.
34. Buckley LM, Hillner BE. A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *J Rheumatol*. 2003;30(1):132-138.
35. Eamshaw SR, Graham CN, Ettinger B, Amonkar MM, Lynch NO, Middelhoven H. Cost-effectiveness of bisphosphonate therapies for women with postmenopausal osteoporosis: implications of improved persistence with less frequently administered oral bisphosphonates. *Curr Med Res Opin*. 2007;23(10):2517-2529.
36. Schousboe JT, Ensrud KE, Nyman JA, Kane RL, Melton LJ III. Potential cost-effective use of spine radiographs to detect vertebral deformity and select osteopenic post-menopausal women for amino-bisphosphonate therapy. *Osteoporos Int*. 2005;16(12):1883-1893.
37. Schousboe JT, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med*. 2005;142(9):734-741.
38. Borgstrom F, Carlsson A, Sintonen H, et al. The cost-effectiveness of risedronate in the treatment of osteoporosis: an international perspective. *Osteoporos Int*. 2006;17(7):996-1007.
39. Florence RL, Iglesias CP, Johnson JM. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. *Pharmacoeconomics*. 2007;25(11):913-933.
40. Chesnut CH III, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*. 2004;19(8):1241-1249.
41. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab*. 2002;87(8):3609-3617.
42. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA*. 2002;287(7):847-857.
43. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355(2):125-137.
44. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat*. 2001;65(2):125-134.
45. Woo SB, Hellstein JW, Kaimar JR. Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144(10):753-761.
46. Tosteson AN, Melton LJ III, Dawson-Hughes B, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int*. 2008;19(4):437-447. ■