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ORIGINAL ARTICLE

Potential for bone turnover markers to cost-effectively identify and select post-menopausal osteopenic women at high risk of fracture for bisphosphonate therapy

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Abstract
Introduction and hypothesis Over half of all fractures among post-menopausal women occur in those who do not have osteoporosis by bone density criteria. Measurement of bone turnover may cost-effectively identify a subset of women with T-score >-2.5 for whom anti-resorptive drug therapy is cost-effective.
Methods Using a Markov model, we estimated the cost per quality adjusted life year (QALY) for five years of oral bisphosphonate compared to no drug therapy for osteopenic post-menopausal women aged 60 to 80 years with a high (top quartile) or low (bottom 3 quartiles) level of a bone turnover marker.
Results For women with high bone turnover, the cost per QALY gained with alendronate compared to no drug therapy among women aged 70 years with T-scores of -2.0 or -1.5 were $58,000 and $80,000 (U.S. 2004 dollars), respectively. If bisphosphonates therapy also reduced the risk of non-vertebral fractures by 20% among osteopenic women with high bone turnover, then the costs per QALY gained were $34,000 and $50,000 for women age 70 with high bone turnover and T-scores of -2.0 and -1.5, respectively.
Conclusion Measurement of bone turnover markers has the potential to identify a subset of post-menopausal women without osteoporosis by bone density criteria for whom bisphosphonate therapy to prevent fracture is cost-effective. The size of that subset highly depends on the assumed efficacy of bisphosphonates for fracture risk reduction among women with both a T-score >-2.5 and high bone turnover and the cost of bisphosphonate treatment.

Keywords Bisphosphonates · Bone turnover · Cost-effectiveness · Non-vertebral fracture · Vertebral fracture

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Introduction

Fractures related to osteoporosis represent a substantial public health problem, especially among post-menopausal women [1]. A significant proportion of these fractures can cost-effectively be prevented by the combination of calcium and vitamin D supplementation with anti-resorptive drug therapy among those with a femoral neck T-score ≤−2.5 or a prevalent vertebral fracture [2]. At least half of all fractures among post-menopausal women, however, occur among women with a T-score >−2.5, [3, 4] yet pharmacologic therapy among this subset in the absence of additional fracture risk factors is not cost-effective [5].

Several prospective investigations have now suggested that serum and urine markers of bone turnover (especially bone resorption) are associated with incident fracture, [6–11], and these markers have the potential to identify an additional subset of post-menopausal women for whom anti-resorptive drug therapy can cost-effectively lower their risk of fracture. Therefore, the primary aim of this modeling study was to evaluate the cost-effectiveness of measuring bone turnover in post-menopausal women with femoral neck T-scores > −2.5, and treating those with a marker level in the highest quartile with a bisphosphonate for five years, compared to a strategy of no bone marker measurement or bisphosphonate therapy.

Methods

We constructed a Markov micro-simulation cost-utility model, comparing 5 years of treatment with bisphosphonate compared to no drug therapy. For both strategies, eight health states were used (no fracture, post distal forearm fracture [DFF], post clinical vertebral fracture [i.e., clinically evident at onset], post radiographic vertebral fracture [i.e., not clinically evident at onset], post hip fracture, post other fractures [i.e., of the proximal forearm, humerus, scapula, clavicle, sternum, ribs, pelvis, distal femur, patella, tibia, or proximal fibula], post hip and vertebral fracture, and death). Beginning in the no fracture state, women can develop a DFF, hip, clinical vertebral, radiographic vertebral, or other fracture, at which time transition to that post-fracture state occurs. The direct and indirect costs of that fracture are assigned as a transition cost. Quality adjusted life year (QALY) values are assigned for one year spent in each health state and are lower in the fracture states relative to the no fracture state, reflecting the disutility caused by fractures. Long-term care costs beyond the first year after hip fracture are assigned as a cost per year in the post hip and post vertebral/hip fracture states. Individuals are eligible (at risk) of transition to a different state once every six 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 analysis.

For the base analyses, we ran the model for 70-year-old women with a femoral neck T-score of either −1.5 or −2.0 until age 105, using Monte Carlo simulations with 40,000 trials each (that is, running 40,000 individuals through the model one at a time) [12], aggregating the lifetime costs and health benefits of each strategy. A lifelong time horizon was chosen for these analyses, in order to capture the permanent disutility and long-term care costs associated with certain fractures.

Probabilities of fractures

The risks for each type of fracture as a function of age were developed from comprehensive population-based age-specific data for women from the Rochester Epidemiology Project [13]. This database captures virtually all health care utilization within Olmsted County, Minnesota [14]. The incidence rates for clinical vertebral, hip, and distal forearm fractures included the first instance of each of these, excluding recurrent fractures at that skeletal site. The rates for "other" fractures represent the sum of the incidences of all of the specific fracture types listed above, and do include any recurrent fractures seen over a three-year period [13]. Fracture rates were plotted against the midpoint of each associated age-range, and a best fitting power curve was determined for each fracture as a continuous function of age.

Each fracture risk function was adjusted for bone mineral density (BMD) by the method of De Laet and colleagues [15]. Femoral neck BMD was modeled to decrease by 0.00554 gm/cm^2 per year [16]. We estimated the relative risks of hip, vertebral, DFF, and other fractures for each Z-score decrease of 1 to be 2.6, 1.8, 1.4, and 1.6, respectively [17].

We assumed relative risks of 4.1, [18] 1.7, [19] and 2.1 [20], respectively, for a subsequent clinical vertebral fracture following an incident clinical vertebral fracture, for a subsequent hip fracture following an incident hip fracture, and for a subsequent DFF following an incident DFF. We did not model an increased risk of subsequent fractures at sites different than that of the incident fractures, because our fracture risk equations were based 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 of a subsequent "other" fracture following an incident "other" fracture [13].

Further details on the derivation of the fracture rates used in this model are available in the on-line appendix of a previously published study [5].

Relative risks of fractures with a high level of bone turnover

For the base case analysis, we use the relative risk estimates reported by Gerdham and colleagues for vertebral and non-vertebral fracture (2.21 and 1.55, respectively) associated with a serum tartrate resistant acid phosphatase (TRACP5b) level in the top quartile compared to those with a marker value in the bottom 3 quartiles [11]. The relative risks of fractures in those with a bone marker level in the top quartile (prevalence equal to 0.25) relative to the whole population were derived from the following formula:

$$\mathrm{RR}_{\text{with vs whole}} = \mathrm{RR}_{\text{with vs without}} / [1 + (\mathrm{RR}_{\text{with vs without}} - 1) * \text{prevalence}]. \quad (1)$$

Therefore, the risks of vertebral and non-vertebral fractures in those with high bone turnover relative to the whole population were calculated to be 1.70 and 1.36, respectively.

Similarly, the relative risks of fractures in those with a bone marker level in the bottom 3 quartiles relative to the whole population were derived from the following formula:

$$\mathrm{RR}_{\text{without vs whole}} = 1/1 + [(\mathrm{RR}_{\text{with vs without}} - 1) * \text{prevalence}], \quad (2)$$

yielding relative risks of vertebral and non-vertebral fractures in those low bone turnover of 0.77 and 0.88, respectively.

For the analyses to be potentially generalizable to other bone turnover markers, sensitivity analyses were done with different relative risk estimates of incident fractures associated with a high marker level.

Relative risk of fracture on bisphosphonate therapy

The relative risks of clinical and radiographic vertebral fractures were estimated to be 0.5 while on bisphosphonate therapy, based on post hoc analyses of osteopenic participants in clinical trials of alendronate [21, 22]. Unfortunately, no adequate estimate of the risk of non-vertebral fractures on any anti-resorptive drug agent in osteopenic women is available. For the base-case analysis, we assumed a relative risk of 1.0 for non-vertebral fractures while on bisphosphonate therapy compared to no drug therapy. One study has suggested, however, that alendronate may reduce incident non-vertebral fractures to a greater degree in those with high compared to low bone turnover [23]. Hence, we also did sensitivity analyses assuming lower relative risks of vertebral and non-vertebral fractures on bisphosphonates therapy in those with high bone turnover. We further assumed a linear, gradual offset of fracture reduction benefit over the subsequent five years following treatment discontinuation as recommended by Tosteson and colleagues [24]. Because we modeled fracture reduction from oral bisphosphonate therapy on the basis of direct data rather than indirectly through changes in bone density, changes in BMD from bisphosphonate therapy were not modeled.

Mortality

An age-specific background mortality risk function was constructed from U.S. vital statistics for 2002 to model the risk of transition to death for each cycle of the model [25]. The mortality associated with acute hip fracture was estimated to be 1.375 times the base rate [26]. Since no precise estimates of the excess mortality that may be attributable to non-hip fractures exist [27], we assumed no excess mortality directly attributable to clinical vertebral or other non-hip fractures. Because there may be excess mortality attributable to that subset of clinical vertebral fractures requiring hospitalization, in a sensitivity analysis we did assume a mortality rate 1.28 times the base rate for the first year after a clinical vertebral fracture [28].

Direct costs

We assumed the yearly cost of oral bisphosphonate therapy to be equal to the average U.S. wholesale price of alendronate for 2004 ($1,000) [29], and that side effects from bisphosphonates would generate only trivial direct medical costs (Table 1).

The direct medical costs assigned to acute hip, clinical vertebral, distal forearm, and “other” fractures were $18,651, $8,065, $4,494, and $8,178, respectively (2004 U.S. dollars). These estimates were derived from costs of all medical utilization for the year following a specific fracture minus the utilization of an age-and sex-matched control group [30], but otherwise were assumed to be the same regardless of age at the time of the incident fracture. The costs of each unit of medical utilization used to construct these costs estimates are not based on charges, but rather on societal opportunity cost estimates. We estimated the cost of one follow-up level 3 physician visit for each year on drug therapy ($53), and the cost of bone densitometry at the time of and 2 years after baseline or any incident fracture ($139), to be the median 2001 U.S. Medicare reimbursement rates for these services [31]. There is no current Medicare reimbursement rate for a serum TRACP5b test. Hence, we used the Medicare reimbursement rate for a urine N-telopeptide test for 2004 ($28), and did a sensitivity analysis assuming a cost four times that of the base case ($112).

Table 1 Model Parameters

Parameter	Value	References
QALY gained per year		
No fracture state	0.84	Macran, 2003 [47]
Post Distal Forearm Fracture	0.82 (1st year), then 0.839	Kanis, 2004 [28]
Post hip fracture	0.67 (1st year), then 0.68	Kanis, 2004 [28]
Post clinical vertebral fracture	0.58 (1st year), then 0.76	Kanis, 2004 [28]
Post radiographic vertebral fracture	0.76 (first 6 years), then 0.84	Oleksik, 2000 [37]
Post hip and clinical vertebral fracture	0.41 (1st year), then 0.60	Tosteson, 2001 [40]
Post "other" fracture	0.753 (1st year), then 0.813	Kanis, 2004 [28]
Direct medical costs		
Acute hip fracture	$28,964	
Direct medical costs	$18,651	Gabriel [30]
1st year long-Term Care	$10,313	Leibson [32]
Acute clinical vertebral fracture	$8,065	Gabriel [30]
Acute distal forearm fracture	$4,494	Gabriel [30]
Acute "other" fracture	$8,178	Gabriel [30]
Alendronate per year	$1,000	
Long-term care >1 year after hip fracture	$7,302	Leibson [32]
Indirect fracture costs		
Hip fracture	$5,219 (age 60) to $215 (age 75+)	Meerding [34]
Spine fracture	$2,215 (age 60) to $92 (age 75+)	
Distal forearm fracture	$1,409 (age 60) to $58 (age 75+)	
"Other" fracture	$1,914 (age 55–59) to $78 (age 75+)	
Relative risk of fractures on alendronate	Non-spine fractures 1.0 Spine fractures 0.5	Cummings [21] Quandt [22]
Other costs		
Yearly physician visit	$53	Center for Medicare and Medicaid Services [31]
Bone densitometry	$139	
Serum TRACP5blevel	$28	
Discount rates		
Costs	0.03	
Health benefits	0.03	

Long-term care costs for the first year following hip fracture were estimated from a study of nursing home utilization following hip fracture compared to an age- and sex-matched control group [32]. Based on the U.S. cost per day of long-term care [33] and the mean length of stay following hip fracture for those who were community dwelling pre-fracture, the long-term care cost for the first year after hip fracture was estimated to be $10,313 (2004 U.S. dollars), averaged over all hip fracture patients. From this same study, we estimated that 12.2% of the entire cohort was both community-dwelling pre-fracture and required permanent long-term care following the hip fracture, costing $7,302 per year averaged over all hip fracture patients (Table 1).

Indirect costs

The proportions of a year with lost productivity were estimated to be 0.348, 0.149, 0.127, and 0.095, respectively, for hip, clinical vertebral, other and distal forearm fractures, respectively, from the study of Meerding and colleagues [34] (personal communication). Indirect costs from lost productivity were calculated as this proportion multiplied by the mean yearly earnings for employed white women in the U.S. for 2004 (stratified according to age) [35], and adjusted by the workforce participation rate as a function of age [36]. These costs varied from $5,219 for a hip fracture in women age 60 to $58 for a distal forearm fracture in women age 80 (Table 1).

Quality adjusted life years associated with each health state

We derived fracture disutilities associated with incident hip, distal forearm, clinical vertebral, and other fractures from direct prospective estimates of Kanis and colleagues (Table 1) [28]. Radiographic vertebral deformities were assumed to have a disutility of 0.08 [37], but only for six years after their

occurrence since radiographic but otherwise clinically silent vertebral fractures more than 4 to 8 years old do not appear to be associated with increased pain or limited activity [38, 39]. The assumed disutility associated with the post hip and vertebral fracture states were the sums of the disutilities of the post-hip and post-clinical vertebral fracture states, and were similar to the estimates from the cross-sectional study of Tosteson and colleagues [40].

Sensitivity analyses

Seven sets of sensitivity analyses were done. First, the base-case analyses were repeated for women with a starting ages 60 and 80. Second, to assess how sensitive our results were to changes in discount rates, fracture rates, cost, or disutility, univariate analyses were done varying fracture costs and fracture rates from 0.7 to 1.3 times the base-case values, varying the disutility attributable to fractures from 0.5 to 1.5 times the base-case values, and varying the discount rates for costs and health benefits from 0% to 6%. Third, to assess how sensitive the base results are to the assumed association between a high bone marker value and incident fracture, analyses were also done varying the relative risk of vertebral fracture from 1.25 to 3.0 for those in the highest quartile of bone turnover relative to the bottom three quartiles.

Fourth, to assess how sensitive the base-case results are to assumed efficacy of oral bisphosphonates, analyses were done assuming greater fracture-reduction efficacy of bisphosphonates in those with high bone turnover, modeling the relative risks of incident vertebral fractures to be 0.4 or 0.5 on oral bisphosphonates relative to no drug therapy, and the risk of non-vertebral fractures to be 0.6, 0.8, or 1.0, respectively, on oral bisphosphonates relative to no drug therapy. Fifth, analyses were done assuming reduced drug costs. Sixth, to assess the effect of non-persistence or poor adherence to oral bisphosphonate therapy, analyses were done assuming persistence with bisphosphonate therapy for only 18 months, or adherence of only 50%. Finally, an analysis was done assuming that those in the top tertile of bone turnover would be selected for bisphosphonate therapy, such that the relative risks of vertebral and non-vertebral fracture, respectively, for those in the top tertile would be 1.58 and 1.31 (using Eq. (1)).

Probabilistic sensitivity analyses were used to assess the effect of uncertainty regarding multiple parameters on these results, varying fracture rates, direct costs, indirect costs, long-term care costs following hip fracture, and disutility associated with fractures. These were done for all four base-case scenarios (those with high and those with a low bone turnover, at both T-score levels of −1.5 and −2.0), and from these analyses the 90% confidence intervals for the costs per QALY gained were derived for all four base-case scenarios.

Model validation

The model estimated the percentage of 50-year-old women who would have a fracture during their remaining lifetime to be 17.0% for hip fractures and 16.0% for DFF, which are close to those of Melton and colleagues (17.5% and 16.0% for DFF and hip fractures, respectively) [41]. The model estimated that 18.0% would have one or more lifetime clinical vertebral fractures, a modest overestimate relative to the earlier value (15.6%) [41].

Calculation of cost-effectiveness

For each analysis, incremental cost-effectiveness ratios (ICER) were computed as the difference in costs between two strategies divided by the difference in accumulated QALY's between the strategies. An ICER represents the cost of gaining one QALY.

Results

For 70-year-old post-menopausal women with a T-score of either −1.5 or −2.0 and high bone turnover, the cost per QALY gained was between $50,000 and $100,000 with an oral bisphosphonate compared to no drug therapy (Table 2), although the probabilistic sensitivity analyses showed that the 90% confidence intervals crossed both of these thresholds. With high bone turnover at T-scores of −2.0 and −1.5, the probabilities that the cost per QALY gained was < $100,000 were 0.88 and 0.65, respectively (Fig. 1). For those with low bone turnover, the estimated costs per QALY gained were well in excess of $100,000, with low probabilities (0.18 and 0.02) that these values were actually less that $100,000 for women with a T-score of −2.0 and −1.5, respectively.

Compared to women age 70, the costs per QALY gained with a bisphosphonate compared to no drug therapy were slightly lower for 60-year-old women and higher for 80-year-old women (Fig. 2). These results were relatively insensitive to reasonable changes in assumed medical costs associated with fractures, the cost of bone marker measurement, or to assumed preventable mortality due to vertebral fracture, mildly sensitive to changes in assumed fracture rates and discount rates, and moderately sensitive to changes in reasonable changes in fracture disutility (Table 3). Selecting those in the top tertile rather than the top quartile of bone marker value for oral bisphosphonate therapy raises the cost per QALY gained for 70-year-old women with a T-score of −2.0 slightly from $57, 818 to $62,935.

If that same woman (age 70 with a T-score −2.0 and high bone turnover) does not persist with drug therapy beyond 18 months, the cost per QALY gained changes little if she

Table 2 Costs per QALY gained for 70-year-old women with alendronate therapy versus no drug therapy in those with high or low bone turnover, and with femoral neck T-score −2.0 or −1.5

Bone turnover level		Femoral Neck T-Score			
		−2.0		−1.5	
	Strategy	Oral bisphosphonate	No drug Rx	Oral bisphosphonate	No drug Rx
High (top quartile)	*Costs**	$24,148	$19,854	$17,815	$13,266
	*QALYs***	9.362	9.288	9.471	9.414
	*ICER***(90% C.I.)*	$57,818 (34,350–123,300)		$80,599 (48,000–168,125)	
Low (bottom 3 quartiles)	*Costs*	$16,828	$12,107	$13,151	$8,366
	QALYs	9.525	9.490	9.593	9.567
	ICER (90% C.I.)	$136,119 (78,250–280,000)		$186,875 (111,750–355,500)	

*Lifetime accumulated costs
**Lifetime accumulated quality adjusted life years
***Incremental cost-effectiveness ratio (cost per QALY gained with alendronate versus no drug therapy)

takes that drug in an adherent manner during that time frame (Table 3). Similarly, if only half of prescribed doses are purchased and consumed (adherence of 50%), the costs per QALY change little if the effectiveness and consumption of the bisphosphonate are assumed to be reduced proportionately. On the other hand, if the effectiveness of the bisphosphonate is reduced an additional 30% by purchasing drug that is not consumed or is consumed improperly, then with either persistence of only 18 months or adherence of 50% the costs per QALY gained are increased to over $70,000 (Table 3).

The cost per QALY gained is below $50,000 for a postmenopausal woman with a T-score of −1.5 if bisphosphonates reduce the risk of non-vertebral fracture by 40%, or if it reduces non-vertebral fracture by 20% and vertebral fracture by 60% in those with high bone turnover (Fig. 3). For a 70-year-old woman with a T-score of −2.0, the cost per QALY gained is below $50,000 if bisphosphonate therapy is assumed to reduce the risk of non-vertebral fracture by 20% in those with a high bone turnover marker (Fig. 3). Moreover, if the cost of bisphosphonates are assumed to be $500 or less, then the costs per QALY gained are below $50,000 for those with high bone turnover, and below $100,000 for those with low bone turnover (Fig. 4).

If a relative risk of incident vertebral fracture of 3.0 in those with high bone turnover was assumed, the cost per

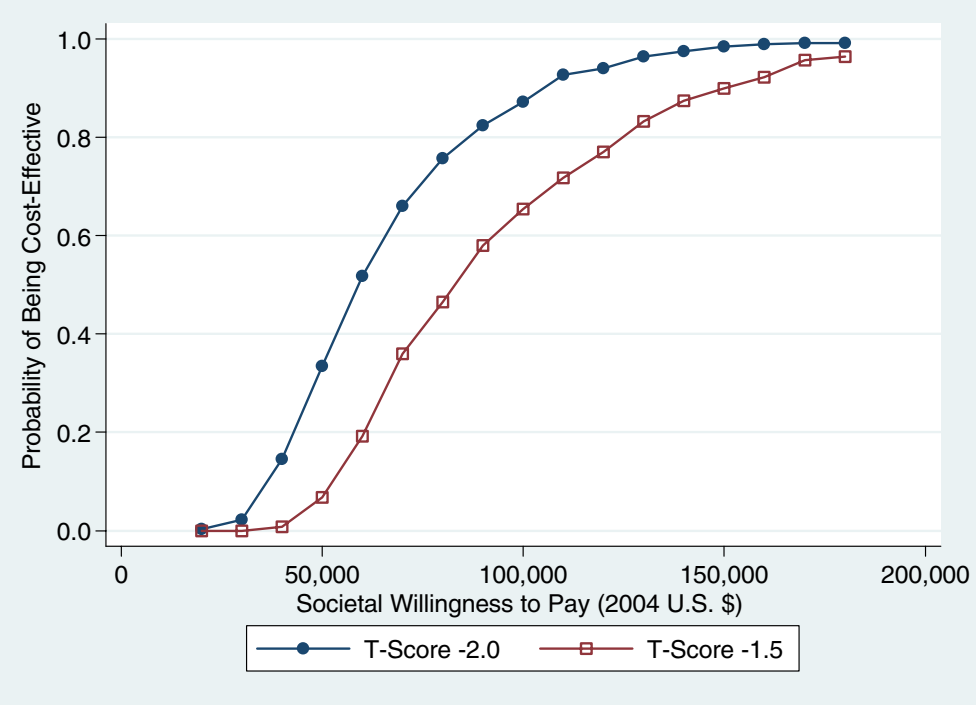

Fig. 1 Cost effectiveness acceptability curves (70-Year-old women) for oral bisphosphonate therapy of postmenopausal women with high bone turnover

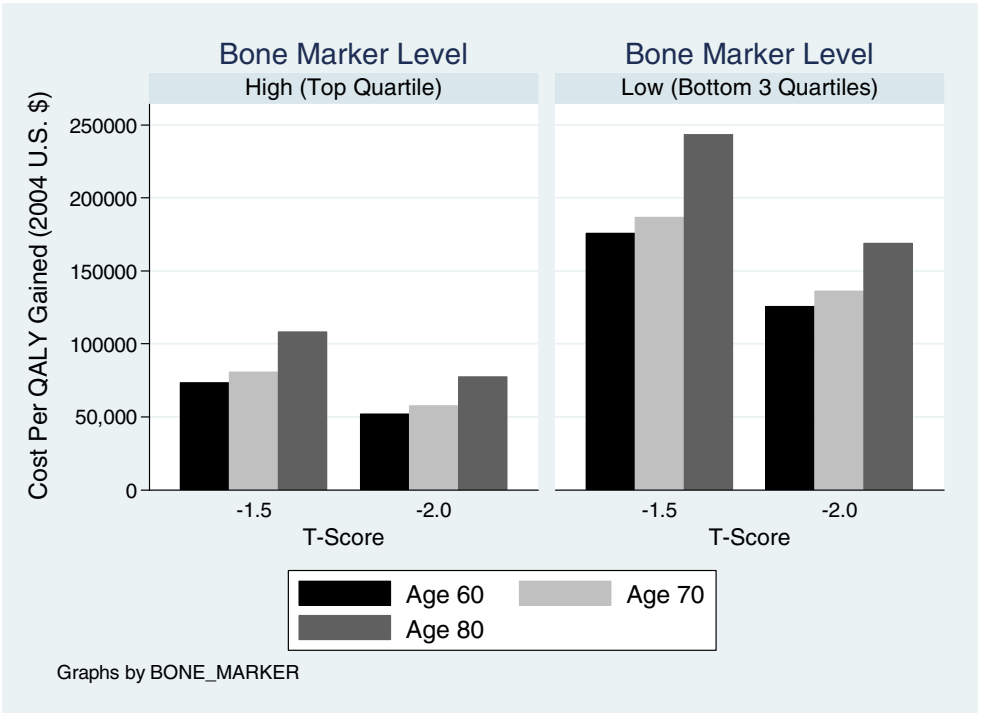

Fig. 2 Cost per QALY gained for oral bisphosphonate versus no drug therapy, according to age, starting T-score, and bone marker level

QALY gained was $47,155, whereas if that relative risk is 1.25 in those with a high bone turnover marker, the cost per QALY gained was $89,416.

Discussion

At least half of all fractures among post-menopausal women occur in those who do not have osteoporosis by bone density criteria. Hence, if the societal burden of osteoporotic fractures is to be substantially lowered, more widespread use of drug therapy will be required. For those who have a prevalent vertebral deformity, bisphosphonate therapy appears to be cost-effective for post-menopausal women with T-scores ranging from −1.5 to −2.4 [42]. In the absence of other BMD-independent fracture risk factors, however, anti-resorptive drug therapy does not appear to be cost-effective in those who have T-scores better than −2.5 [5].

Anti-resorptive drugs appear to prevent incident fractures, especially vertebral fractures, in large part by reducing bone turnover [43, 44]. Many studies have found evidence that elevated levels of a variety of markers of bone resorption are associated with incident fracture independent of bone density. Although these studies are sometimes in conflict with respect to which markers are most predictive of fracture, bone markers are nonetheless attractive candidates to identify a subset of post-menopausal women without osteoporosis by BMD criteria who are at high risk of fracture.

Table 3 Univariate sensitivity analyses (70-year-old with a T-score of −2.0, high bone turnover, oral bisphosphonate vs. no drug therapy)

Parameter	Range (low, high)	Cost per QALY gained	
		Parameter low	Parameter high
Discount rates	0, 0.06	$47,135	$68,985
Fracture costs	0.7, 1.3 times base-case costs	$61,198	$56,751
Fracture rates	0.7, 1.3 times base-case rates	$83,325	$42,779
Fracture disutility	0.5, 1.5 times base-case values	$115,330	$38,310
Preventable mortality due to vertebral fracture	No, yes	$57,818	$56,833
Cost of bone marker measurement	$28,$112	$57,818	$61,830
Persistence with drug therapy only 18 Months	No drug wasted, 30% drug wasted	$59,145	$73,251
Adherence 50%	No drug wasted, 30% drug wasted	$55,193	$71,302

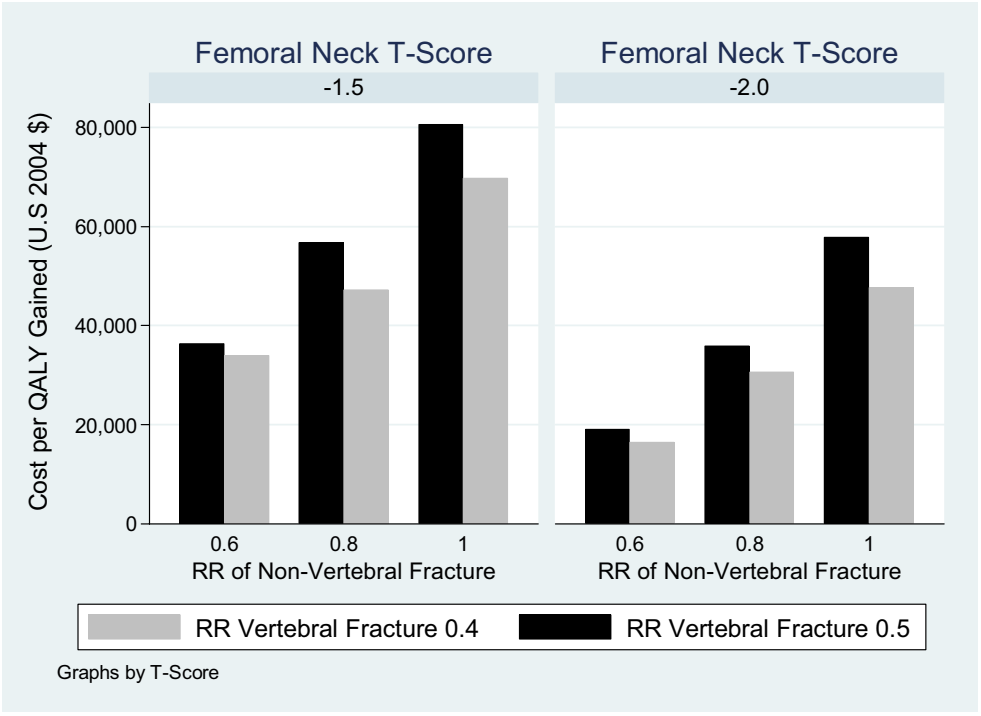

Fig. 3 Cost Per QALY gained for oral bisphosphonate therapy vs. no drug therapy for 70-year-old women with high bone turnover, according to relative risk of fractures on oral bisphosphonate therapy

Under the assumptions underlying this model, our results suggest that at current estimates of bisphosphonate cost in the U.S. measuring bone turnover would effectively identify a subset of women with T-scores between −1.5 and −2.0 for whom five years of bisphosphonate therapy is cost-effective, assuming a societal willingness to pay (WTP) per QALY gained of $100,000. There is no clear consensus, however, on the true amount of resources society is willing to pay for health benefits [45, 46]. If the societal WTP is $50,000 per QALY gained, then use of a bone turnover marker to select post-menopausal women for bisphosphonate therapy is cost-effective only if there are additional fracture risk factors present independent of both BMD and bone turnover, if one assumes a lower yearly cost of bisphosphonates, or if these drugs *do* reduce non-vertebral fracture incidence among women without osteoporosis but with high bone turnover.

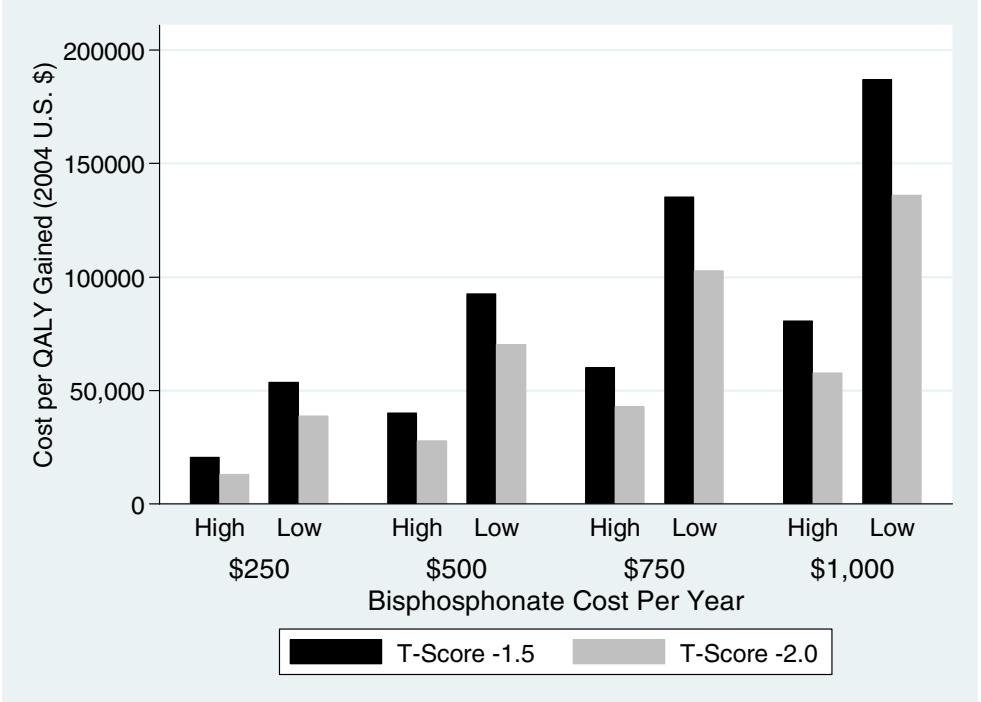

Fig. 4 Cost per QALY gained with bisphosphonate vs. no drug therapy in 70-year-old women with high or low bone turnover, according to yearly cost of oral bisphosphonate therapy

Reduced adherence to or premature discontinuation of bisphosphonate therapy do not alter these results significantly unless bisphosphonate effectiveness is reduced to a greater extent than drug expenditure through either drug wastage or inappropriate use.

To further clarify the cost-effectiveness of bone turnover markers to select post-menopausal women for treatment, prospective studies on the associations between elevated levels of these markers and incident non-vertebral and especially vertebral fractures are needed. In particular, additional studies evaluating the efficacy of anti-resorptive drug therapy in fracture risk reduction among post-menopausal women with T-scores better than −2.5 and high levels of bone turnover are necessary. Such studies would allow more accurate estimation of the cost-utility of using these markers to identify additional subsets of post-menopausal women for whom anti-resorptive drug therapy is cost-effective.

Until such studies are conducted, it may be premature to recommend widespread use of bone markers to select post-menopausal women with T-scores >-2.5 for anti-resorptive drug therapy. Thus far, most of the studies that have linked high bone turnover to incident fracture have used non-vertebral fracture as the dependent variable [6–10], but that association is not relevant to the cost-effectiveness of their use if bisphosphonates do not reduce the incidence of non-vertebral fracture in those with bone density T-score better than −2.5. Serum TRAPC5b [11] and bone alkaline phosphatase [6] have been shown in one study each to be associated with incident vertebral fracture, but neither association has yet been confirmed by other investigators. Additionally, if bone turnover markers are measured less precisely in clinical practice than in the observational studies on which we based our estimates of fracture risks attributable to high bone turnover, the costs per QALY gained for bisphosphonate treatment of post-menopausal women with a high bone marker value will be higher than what we have estimated in this study.

There are many strengths to this modeling study. First, we have included all relevant fractures, and have employed population-based estimates of their age-and BMD-adjusted incidence. Second, we have focused specifically on the cost-effectiveness of drug therapy in the post-menopausal osteopenic female population under a variety of 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 post-menopausal women. Specifically, we have included in our sensitivity analyses estimates of the effect of both bisphosphonate cost and efficacy on the costs per QALY gained, such that these results may still be applicable if drug costs change or additional data regarding the efficacy of alendronate among post-menopausal women with T-scores >-2.5 emerges in the future.

There are important limitations to this study. Our model may overestimate the true cost effectiveness of bisphosphonate therapy in post-menopausal women because it slightly overestimates the incidence clinically evident vertebral fractures. We also did not consider other risk factors such as prevalent radiographic vertebral fracture. Our results are generalizable only to the post-menopausal female white population of the U.S. Finally, inferences from this cost-modeling study are limited by the lack of consensus regarding the true societal willingness to pay for health benefits, and also by the lack of precise data regarding the effectiveness of oral bisphosphonates in that subset of post-menopausal women with a T-score >-2.5.

In conclusion, measurement of bone turnover has the potential to aid identification of an additional subset of post-menopausal women who do not have osteoporosis by bone density criteria but for whom oral bisphosphonate therapy may cost-effectively reduce their risk of vertebral fracture. Additional studies regarding the strengths of association between high bone turnover and incident fractures, and regarding the efficacy of anti-resorptive agents in subsets of women with T-scores >-2.5 defined by levels of bone turnover markers are needed to further define how these markers can be used cost-effectively to identify post-menopausal women with T-scores >-2.5 for anti-resorptive drug therapy.

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