The Cost-Effectiveness of Bisphosphonates in Postmenopausal Women Based on Individual Long-Term Fracture Risks

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ABSTRACT

Objectives: Cost-effectiveness analyses are routinely based on data from group averages, restricting its generalizibility to those with below- or above-average risk. A pharmacoeconomic model that used individualized risks for fractures was developed in order to take into account patient heterogeneity.

Methods: Data were obtained from The Health Improvement Network research database of general practitioners, comprising a UK general population of women aged more than 50 years (N = 330,000). Mortality and hip, vertebral, and other osteoporotic fracture risks for each individual were estimated by age, body mass index (BMI), smoking, and other clinical risk factors. Estimates on costs, EuroQol (EQ-5D) utilities, and treatment efficacy were obtained from a UK national report (the National Institute for Clinical Excellence) and outcomes were simulated over a 10-year period.

Results: It was found that the cost per quality-adjusted life-year (QALY) gained was lower in elderly women and in women with fracture history. There was a large variability in the cost-effectiveness with baseline fracture risk and with clinical risk factors. Patients with low BMI (<20) had considerable better cost-effectiveness than patients with high BMI (≥26). Using a cost-acceptability ratio of £30k per QALY gained, bisphosphonate treatment became cost-effective for patients with a 5-year risk of 9.3% (95% confidence interval [CI] 8.0–10.5%) for osteoporotic fractures and of 2.1% (95% CI 1.5–2.7%) for hip fractures. Including bone mineral density in the risk assessment, the cost per QALY gained was £35k in women at age 60 with a fracture history and a T-score of –2.5 (at age 80, this was £3k).

Conclusion: A pharmacoeconomic model based on individual long-term risks of fracture improves the selection of postmenopausal women for cost-effective treatment with bisphosphonates.

Keywords: cost-effectiveness, fracture, osteoporosis, postmenopausal women, risedronate.

Introduction

Economic evaluations are increasingly used as a guide to allocate resources in health care [1]. In the field of the osteoporosis, a large number of cost-effectiveness analyses have now been conducted [2,3]. The typical approach in cost-effectiveness analyses is that of economic modeling, with simulation studies that vary the probabilities of various health states. These probabilities are typically derived from literature and based on population averages. The use of population averages in economic modeling can limit the generalizibility of cost-effectiveness results to patients with below- or above-average risk. For example, a low body mass index (BMI) is associated with a higher mortality than individuals with an average BMI. Thus, individuals with low BMI have a different cost-effectiveness compared with individuals with average BMI.

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It has been suggested that intervention thresholds should be based on long-term fracture probability rather than on age and specific levels of bone mineral density (BMD) [4]. The reason for this view is that BMD is only one component of the risk of fracture and there are several clinical risk factors that contribute to fracture risk independent of BMD. To date, there have been no cost-effectiveness analyses that took into account the heterogeneity in clinical risk factors in the population. The objective of this study was to estimate the intervention threshold for cost-effectiveness of bisphosphonate therapy, using individual estimates for the risks of fracture.

Methods

Study Population

The study population included all women aged between 50 and 100 years who were registered at a general practice in the UK that provide their computerized medical records to The Health Improvement Network (THIN) research database. General practitioners (GPs)

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play a key role in the UK health-care system, as they are responsible for primary health care and specialist referrals [5]. The data recorded in THIN include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. The study population was followed from 1990 up to 2003. The period of follow-up was divided into 6-month intervals and the age and the risk factors for fracture and mortality were assessed at each interval.

Overall Design of the Model

Using data from this large cohort, an individual patient-based pharmacoeconomic model was developed. The model included six outcomes: hip fracture (or femur or pelvis), clinically symptomatic vertebral fracture, clinically asymptomatic vertebral fracture, wrist fracture (or clavicle, scapula or rib), humerus fracture (or tibia or fibula), and death. Two separate analyses were conducted. The first analysis included those from the study population without a fracture history. The second analysis included all patients who developed a fracture (excluding morphometric vertebral fractures) during the simulation. In each analysis, the outcomes between those using bisphosphonates or not were compared.

Probabilities of Fracture or Death

The individual probabilities for fracture and death were calculated using Cox proportional hazards models. The methodology was similar to that previously applied to an analysis of oral glucocorticoid users [6]. We first fitted regression models with age and the various clinical risk factors. Backward regression was conducted using a significance level of 0.05. Then, the final Cox models were used to estimate the long-term probability of fracture or death (i.e., survivor function). The survivor function provides the long-term risk for each set of patient characteristics [6]. We investigated possible statistical interactions between age and the risk factors (i.e., whether the relative risk (RR) of risk factors differed across age). Interactions between the various risk factors were not evaluated because of the large number of possible combinations. Various methods were used to test the fitting of the Cox models, including visual evaluation of the proportional hazards assumption and a comparison of the observed and predicted fracture probabilities. The Cox models were developed separately for each of the four different fracture types and death. Because of the strong interaction between age and various risk factors, the Cox model for death was fitted separately for each 10-year age stratum.

Two sets of clinical risk factors were used in the calculation of individual probabilities for fracture and mortality. The first set included risk factors that have been validated in a large meta-analysis of prospective epidemiological studies, including BMI, smoking, fracture history, use of oral glucocorticoids, and history of rheumatoid arthritis [7]. In order to evaluate the extent of variation of cost-effectiveness, additional risk factors, which were associated in a previous study with an increased risk of fracture, were also measured [8]. These included prescribing in the 6 months before central nervous system medication (anticonvulsants, hypnotics/anxiolytics, antidepressants, antipsychotics, and anti-Parkinsonian drugs), recorded history of early menopause, and of falls in the 6 to 18 months before. The presence of the following diseases was also noted: chronic obstructive pulmonary disease and asthma, cerebrovascular accident, heart failure, and inflammatory bowel disease. For patients with any of these diseases, presence of a record indicating a GP visit or hospitalization for these diseases in the 6 months before was also measured. BMI was included as categorical variable (low BMI < 20, normal BMI 20–26, and high BMI ≥ 26).

As vertebral fractures are under diagnosed in the UK general clinical practice and systematic morphometry was not routinely done by GPs, we adjusted the vertebral fracture rate. The rate of (morphometric) vertebral fractures, as reported in the European Prospective Osteoporosis Study, was about 18 times higher than those in THIN [9]. We multiplied the THIN vertebral rates by half of this ratio, a more conservative approach, in line with estimates from a recent pharmacoeconomic analysis [10]. One-third of these fractures were considered to be clinically symptomatic and the remaining morphometric vertebral fractures.

Modeling the Cost-Effectiveness

Using the individual mortality and fracture probabilities, the outcomes were simulated over a 10-year period, with simulation of outcomes at each 3-month period of time. It was assumed that bisphosphonates were given for 5 years, with a linear offset of the protective effect over the remaining 5 years of the model [3]. Out of the total study population, 5000 patients were randomly sampled and the age and risk factors were used to calculate the individual fracture and mortality rates. Over the course of the model, the individual rates were adjusted for increasing age and, in case of fracture occurrence in the model, for fracture history. This simulation was repeated 20 times using different cohorts of 5000 people. In the analysis for cost-effectiveness with different levels of baseline 5-year fracture risk, the total population was divided into 20 subgroups of fracture risk (as determined from age and both sets of clinical risk factors). Linear regression analysis (with polynomial terms) was used to estimate the predicted cost-effectiveness at different levels of 5-year fracture risk.

Table 1 Cost data and assumptions used in the model

Costs	Bisphosphonate prescriptions (for 1 year): £284* BMD measurement: £34* GP visit: £18* Hip fracture leading to nursing home entry: age 40–69, £31,299 (year 1), £23,562 (subsequent years); age 70–79, £32,606 (year 1), £24,240 (subsequent years); age 80+, £34,654 (year 1), £25,357 (subsequent years)* Other hip fracture: age 40–69, £5157 (year 1); age 70–79, £6487 (year 1); age 80+, £8538 (year 1)* Clinically symptomatic vertebral fracture: age 40–69, £477 (year 1), £222 (subsequent years); age 70–79, £539 (year 1), £222 (subsequent years); age 80+, £581 (year 1), £222 (subsequent years)* Wrist fracture: age 40–79, £359 (year 1); age 80+, £585 (year 1)* Humerus fracture: age 40–79, £1024 (year 1); age 80+, £1024 (year 1)*
Health utility†	Hip fracture leading to nursing home entry: 0.4 (first and subsequent years)* Other hip fracture: 0.83 (year 1), 0.925 (subsequent years)* Clinically symptomatic vertebral fracture: 0.83 (year 1), 0.93 (subsequent years)* Wrist fracture: 0.981 (year 1)* Humerus fracture: 0.794 (year 1), 0.973 (subsequent years)*
Assumptions	BMD measurement (baseline) only in patients <65 years* No GP costs for patients aged 75 years or older; one-third of patients aged below 75 years require one additional GP visit per year* One-third of vertebral fractures are clinically symptomatic [23] Percentage of patients that move from the community to a nursing home after a hip fracture: age 40–59, 0%; age 60–79, 4%; age 80–89, 12%; age 90+, 17%* Annual discounting: costs, 6%; benefits, 1.5%* Fracture risk reduction due to bisphosphonate: hip, RR = 0.67; vertebral, RR = 0.59; wrist and humerus, RR = 0.81*

*Data and assumptions from the assessment report on the clinical effectiveness and cost-effectiveness of prevention and treatment of osteoporosis, as prepared by the National Institute for Clinical Excellence [3].
†Multipliers for the proportionate effect of a fracture on the health utility [3].
BMD, bone mineral density; GP, general practitioner; RR, relative risk.

Costs and Assumptions

The cost data and other assumptions used in the model are listed in Table 1 [3]. The costs for prescriptions, GP visits, and BMD scans were accrued at the beginning of each 3-month period. If a patient died, it was assumed that this occurred at the midpoint of the 3-month interval. If a fracture occurred, it was assumed that any losses in quality or quantity of life started to occur at the next 3-month interval of time. If a patient suffered a fracture and died in the same 3-month interval, the order of these events was determined randomly. Lifetime costs were estimated for each patient in the simulation who experienced a fracture.

In this study, it was assumed that bisphosphonates reduced the risk of hip fractures by 33% (Table 1). No differentiation was made between risedronate and alendronate. The reason for this was that UK prescription costs were similar for risedronate and alendronate and a large meta-analysis found a statistically comparable fracture efficacy [11]. There are also no comparative studies with fracture as outcome. The cost-effectiveness of cyclical etidronate was not evaluated, given the absence of clinical data on hip fracture efficacy.

Postfracture Mortality

In order to estimate postfracture excess mortality, fracture cases in the study population were randomly matched to four controls (without a fracture) by age, GP practice, and calendar time. Cases and controls were then compared for 1-year mortality using Cox proportional hazards models. Interaction terms between fracture status and age were also included, if statistically significant. The excess mortality in the year after the hip or clinically symptomatic vertebral fractures was then estimated for each age, based on the survivor function of the Cox model (i.e., the difference in 1-year risk between cases and controls). For the other fractures, no post-fracture excess mortality was assumed, as the excess risk was small. These estimates for excess mortality were used to adjust the mortality in the 1 year after a hip or clinically symptomatic vertebral fracture. It was assumed that fracture prevention also avoided this excess mortality.

Calculation of Quality-Adjusted Life Years

Lifetime quality-adjusted life-years (QALYs) were estimated for each patient in the simulation who experienced a hip, clinically symptomatic vertebral, humerus, or wrist fracture. The calculation of the gain in QALYs was estimated using a similar approach as the National Institute for Clinical Excellence (NICE) [3]. Age-specific information on the quality of life (QoL) in the general population was obtained from literature [12]. The number of years alive with and without postfracture excess mortality was calculated and age-specific EuroQol (EQ-5D) utilities were then assigned, with and without postfracture loss of QoL, as reported in Table 1. The incremental cost-effectiveness ratio for the cost to gain one QALY was then calculated by dividing the difference in total costs between the two strategies (bisphosphonates or not) by the differences in number of QALYs. Morphometric

Table 2 Excess 1-year mortality in fracture cases (absolute difference in 1-year mortality between fracture cases and controls)

Age (year)	Hip (%)	Vertebral (%)
50–59	2.4	2.3
60–69	4.4	3.5
70–79	7.5	5.2
80–89	11.4	6.7
90+	13.6	6.6

vertebral fractures were not associated in the model with any loss in quality or quantity of life, but were indicators of fracture history and increased risk of fracture.

Random Variability

The random variability of the cost-effectiveness ratios was determined in two steps. First, the fracture and mortality probabilities used in each simulation were randomly selected from a normal distribution based on the mean and standard deviation of the parameter as observed in the THIN population. The second step used the cost-effectiveness estimates as observed in the 20 reiterations of the model. Nonparametric bootstrapping techniques were used to estimate the 95% confidence interval (CI), repeating the analysis 10,000 times. The 95% CI was based on the 2.5 and 97.5 percentiles of the distribution of the bootstrapping results [13]. The 95% CI for the cost-effectiveness at different levels of 5-year fracture risk was based on the linear regression analyses of 2.5 and 97.5 percentiles of the distribution of the bootstrapping results.

Validation of Model

In literature, it has been recommended that statistical models that predict outcomes are validated in independent data sets [14]. Therefore, we obtained information from a random age-stratified sample of 50,000 women aged 50 years from the General Practice Research Database (GPRD). During the period of follow-up, the occurrence of the various fracture types was noted. Each vertebral fracture was assumed to have occurred nine times (a similar adjustment for underdiagnosis of vertebral fractures as used in the main analysis). The proportion of fractures that would have been prevented by bone protection was based on the estimate for bisphosphonate efficacy. The cost per fracture prevented was the number of fracture prevented divided by the total costs for bone protection during the period of follow-up. The cost per QALY gained could not be validated given the additional requirement for lifetime data post fracture on mortality and QoL, which were not available. We also validated the model by populating it with the data from a previous NICE assessment report (using their fracture incidence and mortality rates, RR increases because of low BMD or fracture history, cost data, and efficacy estimates) [15].

Results

Study Population

The study population consisted of 332,306 women who were aged between 50 and 100 years and who did not have a fracture history at baseline. The average duration of follow-up was 5.9 years (median 4.7 years). There were 5597 women with hip and 1509 women with clinically symptomatic vertebral fractures. Strong risk factors for fracture included age, low BMI, fall and fracture history. Mortality was strongly related to age, low BMI, smoking history, and fall history. Within the different age groups, the patients with higher fracture risk, due to presence of clinical risk factors, had higher mortality, compared with patients with lower fracture risk. As shown in Table 2, mortality was increased in the 1 year after a hip and clinically symptomatic vertebral fracture.

Cost-Effectiveness

The outcomes of the model in fracture incidence and mortality over the 10 years of the simulation are displayed in Table 3. As shown in Table 4, bisphosphonate therapy was more cost-effective in the older women and in women with a fracture history. Also, it was found that cost-effectiveness varied within age groups by baseline risk of fracture. Considering the effect of risk factors, a large influence of BMI was

Table 3 Rates of fracture and mortality in the simulation in patients not using bisphosphonates*

	Without fracture history (%)					With fracture history (%)				
Age (year)	Died	Hip fracture	Vertebral fracture†	Wrist fracture	Humerus fracture	Died	Hip fracture	Vertebral fracture†	Wrist fracture	Humerus fracture
50–59	4.4	0.8	3.3	3.8	2.9	5.2	1.7	7.6	6.6	5.1
60–69	10.7	2.4	7.1	5.1	3.5	10.4	4.2	13.2	8.0	5.8
70–79	25.6	5.9	10.7	5.7	3.8	25.3	9.9	19.7	8.5	6.1
80–89	50.2	9.2	10.3	5.2	3.4	54.2	15.0	18.3	7.7	5.4
90+	75.6	9.6	7.6	4.0	2.7	84.4	13.9	11.6	5.1	3.6

*Individual fracture and mortality probabilities of model based on age, body mass index, smoking, fracture history, use of oral glucocorticoids, and history of rheumatoid arthritis.
†Including clinically symptomatic and asymptomatic vertebral fracture.

Table 4 Cost (£000) per QALY gained stratified by fracture history, age, and baseline fracture risk*

	No fracture history		Fracture history	
	5-year hip fracture risk (%)	Cost per QALY gained (95% CI)	5-year hip fracture risk (%)	Cost per QALY gained (95% CI)
Age 50–59 years	0.4	270 (70–653)	0.9	38 (31–45)
Low baseline fracture risk	0.3	406 (132–805)	0.6	58 (44–77)
High baseline fracture risk	0.5	192 (63–434)	1.4	35 (26–48)
Age 60–69 years	1.2	60 (44–82)	2.2	26 (21–33)
Low baseline fracture risk	0.7	136 (60–272)	1.3	51 (31–84)
High baseline fracture risk	1.8	36 (28–46)	3.1	23 (18–28)
Age 70–79 years	3.2	20 (17–23)	5.4	8 (6–11)
Low baseline fracture risk	1.7	31 (27–35)	3.0	17 (14–22)
High baseline fracture risk	4.7	18 (14–24)	7.1	8 (6–11)
Age 80–89 years	5.9	9 (7–12)	9.8	<0 (<0–2)
Low baseline fracture risk	3.9	17 (12–23)	5.6	8 (5–12)
High baseline fracture risk	8.6	6 (2–10)	12.3	<0 (<0–<0)
Age 90+ years	7.6	8 (6–10)	12.6	1 (<0–2)
Low baseline fracture risk	5.1	17 (13–22)	7.6	10 (6–13)
High baseline fracture risk	10.7	4 (<0–9)	16.3	<0 (<0–<0)

*Each age group was divided into four quartiles of fracture risk as based on clinical risk factors (excluding age).
CI, confidence interval; QALY, quality-adjusted life-year.

noticed (Table 5). Patients with low BMI (<20) had considerable better cost-effectiveness than patients with high BMI (≥26).

Long-Term Fracture Risk Required for Cost-Effectiveness

The cost per QALY gained was estimated for patients with different baseline risks for hip or osteoporotic fractures (Fig. 1). Using a cost-acceptability ratio of £30k per QALY gained, bisphosphonate treatment became cost-effective for patients with a 5-year risk of 9.3% (95% CI 8.0–10.5%) for osteoporotic fractures and of 2.1% (95% CI 1.5–2.7%) for hip fractures. The threshold for a cost-acceptability ratio of £20k was 11.1% (95% CI 9.8–12.4%) for osteoporotic fractures and 3.0% (95% CI 2.3–3.8%) for hip fractures.

Costs-Effectiveness and BMD

Using published data on the risk of osteoporotic fractures at different T-scores, the cost per QALY gained was estimated for different T-scores (Table 6). Bisphosphonate therapy was not cost-effective at age 60 in patients at threshold of osteoporosis who did not have a fracture history or other clinical risk factors. But cost-effectiveness would be achieved in these patients if risk factors independent of BMD were present with a RR of 2.8 (using a cost-acceptability ratio of £30k).

Sensitivity Analyses

Table 7 shows the results of the sensitivity analyses. The proportion of clinically symptomatic vertebral fractures or post-fracture mortality estimates did not

Table 5 Cost (£000) per QALY gained for patients with different risk factors

		No fracture history		Fracture history	
	Prevalence (%)	Age 60–79	Age 80+	Age 60–79	Age 80+
Body mass index					
Low (<20)	6.7	23	1	11	<0
High (≥26)	44.5	71	23	22	12
Recorded history of early menopause					
Yes	0.1	29	0	10	<0
No	99.9	54	11	27	4
RA					
Yes	1.7	38	10	16	3
No	98.3	55	10	18	3
IBD					
Yes	0.6	33	8	15	2
No	99.4	50	8	20	3
COPD/asthma					
Yes	10.2	34	7	16	2
No	89.8	49	10	19	1
Recorded history of osteoporosis					
Yes	2.5	31	5	17	1
No	97.5	47	11	25	5

COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; QALY, quality-adjusted life-year; RA, rheumatoid arthritis.

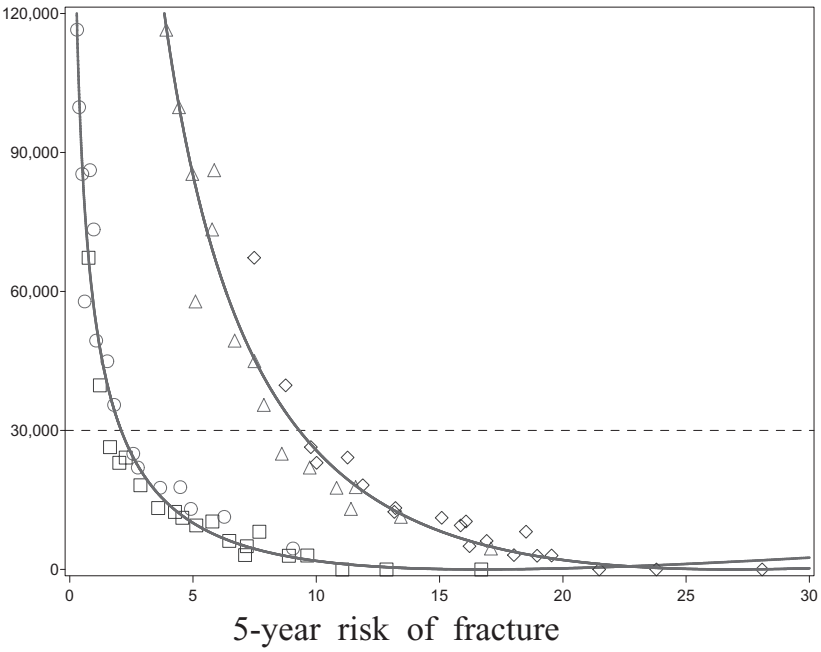

Figure 1 Cost (£) per quality-adjusted life-year gained by 5-year baseline risk of hip or osteoporotic fracture (○ = hip fracture risk without fracture history, □ = hip fracture risk with fracture history, △ = osteoporotic fracture risk without fracture history, ◇ = osteoporotic fracture risk with fracture history); fracture and mortality probabilities based on age, body mass index, smoking, fracture history, use of oral glucocorticoids, and history of rheumatoid arthritis, central nervous system medication use, falls, early menopause, and history of chronic diseases.

have major effects on the results of the study. It was also found that the thresholds based on the median costs per QALY gained (i.e., the middle value in the repeated simulations) were considerably lower than those based on the mean costs.

Validation of Model

In the validation data set, it was found that the cost per fracture prevented was £30k. When applying our estimates from our economic model to the validation population, the cost per fracture prevented was found to be comparable (£29k).

For patients without a fracture history and a T-score of –2.5, the cost per QALY gained was £35k in our model versus £39k (95% CI 26–67k) in the NICE model at age 70, £10k versus £15k (95% CI 4–47k) at age 80. The corresponding data for patients with a fracture history was £51k versus £70k (95% CI 53–112k) at age 50, £52k versus £50k (95% CI 36–86k) at age 60, £16k versus £15k (95% CI 8–32k) at age 70, and £1k versus less than £0 (95% CI <0–16k) at age 80.

Discussion

In this study, it was found that cost-effectiveness for bisphosphonates would be achieved for patients with a 5-year risk of 9.3% for osteoporotic fractures. An important assumption in this study was that bisphosphonates reduced fractures in all study patients. The efficacy of bisphosphonates in individuals with low BMD is well established, but they may be less efficacious in individuals with normal BMD [16]. The results of this study on cost-effectiveness of bisphosphonates can thus only be applied to patients, who have a substantial risk of fracture and in whom bisphosphonates are likely to be clinically effective.

This study is the first economic model in the field of osteoporosis that applied individualized fracture and mortality risks, with risks varying between individual patients. Many economic models also simulate outcomes for individuals, but typically assume that all individuals have identical risks [3,15]. There are several limitations to this approach of assuming all patients are average. First, results may not be generalizable to patients with below- or above-average risks. For example, patients with above-average risks (due to the presence of other risk factors) may have shorter life-expectancy, which will increase the cost per QALY gained. The second limitation of this approach is that the resulting intervention thresholds are based on a restricted number of clinical characteristics, such as age and BMD. A more attractive approach to economic modelling is to base intervention thresholds on long-term fracture probability and to use data from a diverse population (with different risks) for the pharmaco-economic model. A recent analysis highlighted the importance that the data used for the cost-effectiveness model accurately reflect the risk of the target population [17]. Large well-validated health-care databases, such as the GPRD, may provide useful information for cost-effectiveness modelling, as they contain individual data on risks of outcomes and death.

The data in this study (on costs, fracture incidence, and mortality) were based on UK information. Our findings on the fracture cost-effectiveness threshold may only be generalizable to other countries if the various input parameters of the model would be

Table 6 Cost (£000) per QALY gained in patients with T-scores of −1.5, −2.5, and −3.5

	T = −1.5				T = −2.5				T = −3.5			
			RR required for cost-effectiveness†				RR required for cost-effectiveness†				RR required for cost-effectiveness†	
Age (year)	Annual fracture risk (%)*	Cost per QALY gained	Threshold £20k	Threshold £30k	Annual fracture risk (%)*	Cost per QALY gained	Threshold £20k	Threshold £30k	Annual fracture risk (%)*	Cost per QALY gained	Threshold £20k	Threshold £30k
Without fracture history												
50	0.6	162	3.9	3.3	0.9	101	2.6	2.2	1.5	48	1.6	1.3
60	0.7	137	3.4	2.8	1.1	77	2.1	1.8	1.8	35	1.3	1.1
70	1.3	61	1.8	1.5	1.9	32	1.2	1.0	3.0	11	—	—
80	1.9	32	1.2	1.0	2.8	13	—	—	4.5	2	—	—
With fracture history												
50	1.1	77	2.1	1.8	1.7	39	1.4	1.1	3.0	11	—	—
60	1.2	68	2.0	1.6	1.8	35	1.3	1.1	3.1	10	—	—
70	2.1	26	1.1	—	3.0	11	—	—	4.8	1	—	—
80	2.9	12	—	—	4.0	3	—	—	6.7	0	—	—

*Data obtained from the National Institute for Clinical Excellence report, representing women with no clinical risk factors [3].
†RR for osteoporotic fractures (independent of bone mineral density) required to reach cost-effectiveness, estimated by dividing the risk of fracture at the threshold of cost-effectiveness by the risk of fracture in women with no clinical risk factors.
QALY, quality-adjusted life-year; RR, relative risk.

Table 7 Sensitivity analyses for cost-effectiveness threshold (at £20k and £30k) of 5-year risk of hip or osteoporotic fractures

	Hip fractures		Osteoporotic fractures	
Sensitivity analysis	Threshold £20k (%)	Threshold £30k (%)	Threshold £20k (%)	Threshold £30k (%)
Overall (mean)	3.0	2.1	11.0	9.3
Overall (median)	2.6	1.7	10.4	8.5
No discounting	2.6	1.8	10.2	8.5
Offset of bisphosphonate effects within 2 years	4.8	3.6	13.9	11.9
RR = 0.50 of fracture reduction at all sites by bisphosphonates	1.7	1.2	8.4	7.1
RR = 0.80 of fracture reduction at all sites by bisphosphonates	8.0	5.5	18.3	15.0
20% of vertebral fractures clinically symptomatic	3.6	2.5	11.2	9.5
Post-fracture excess mortality after hip and clinically symptomatic fractures using NICE estimates [3]	3.3	2.3	11.6	9.6
Nursing home admission in 25% of hip fracture cases	1.8	1.3	8.6	7.4
Doubling of risk of wrist and humerus fractures	3.0	2.0	16.1	13.9

NICE, the National Institute for Clinical Excellence; RR, relative risk.

comparable to those from other countries. Our model could easily be populated with information from other countries. Although cost data may be readily available, individualized information on fracture incidence and mortality may not be available in all countries, as these data may not be systematically collected for large general populations. But it would be useful if longitudinal medical information would be collected in more countries. This would allow better cost-effectiveness assessment of medical therapies, based on individualized information.

Kanis et al. recently developed thresholds for fracture risks at which treatment would become cost-effective. With a drug that reduces fractures by 35% and an annual cost of $500, it was found that the 10-year hip probability at which this intervention became cost-effective was 1.2% in women aged 50 years and 7.2% in women aged 85 years [18]. But in this study, a single intervention threshold was estimated. The reasons for multiple age-dependent intervention thresholds in the study by Kanis et al. were that it used average population data for both mortality and fracture risks, with information on age and sex only. Nevertheless, a single intervention threshold could be used if risk factor and age effects are exchangeable. In this study, we found that younger patients with several clinical risk factors had comparable fracture and mortality risks as older patients without risk factors and these patients had similar intervention thresholds when also taking into account the clinical risk factors. If this also applies to QoL (on which we do not have any data), a single intervention threshold can be used. The findings in this study suggest that intervention thresholds should be based on hip fracture risk. A doubling in the risk of wrist and humerus fractures did not change the hip fracture threshold. The threshold for risk of osteoporotic fractures changed considerably, because of the smaller impact of wrist and humerus on the loss of QALYs.

Bisphosphonate treatment was found to be cost-effective in almost all elderly women (>80 years). The cost per QALY gained was below or around £20k, irrespective of fracture history and presence of risk factors. This finding could suggest that all elderly women should be put on bisphosphonate treatment. Nevertheless, our study assumed that bisphosphonates reduced the risk of fractures in all women, irrespective of their characteristics. This is unlikely to be the case. Most clinical studies with bisphosphonates have been conducted in women with osteoporosis [3]. A large randomized clinical study found that bisphosphonates had no effect on the risk of hip fractures in elderly women selected primarily on the basis of clinical risk factors, while significant effects were observed in women with low BMD [19]. Thus, the findings of this study can help to identify women for further diagnostic testing, such as BMD measurement. Bisphosphonate treatment should be considered not only if a patient has a fracture risk above the cost-effectiveness threshold, but also if bisphosphonates are likely to be clinically effective. An elderly woman with normal BMD but increased risk of fracture due to falling tendency should not be prescribed a bisphosphonate, as there is no clinical evidence for fracture reduction in patients with these characteristics.

We found that bisphosphonate therapy was considerably more cost-effective in patients with low BMI. This was related both to the inverse relationship between BMI and risk of fracture and to the higher prevalence of other clinical risk factors in patients with low BMI. Several studies have consistently reported that patients with low weight or BMI have an increased risk of osteoporosis. A review of clinical predictors of osteoporosis concluded that body weight less than 59 kg may be a simple and reasonably sensitive but nonspecific measure for selecting women for further diagnostic testing [20]. This observation and the finding of better cost-

effectiveness with low BMI suggest that elderly women with low BMI should be targeted for further diagnostic testing [21].

There are various limitations of this study. Our findings are based on a complex mathematical model. We evaluated the key underlying assumptions utilized and its overall predictive capacity performed well. Nevertheless, we did not evaluate all possible interactions and the model may therefore have overestimated or underestimated risks for certain combinations of risk factors. Another limitation was that we did not have information on all risk factors for fracture (such as BMD, exercise, or diet), which would improve the accuracy of prediction for an individual patient. Also, our estimates for the confidence intervals for cost-effectiveness did not take into account the statistical uncertainty around the magnitude of bisphosphonate efficacy. Our estimates for the loss of QoL due to a fracture were similar to those used by the NICE, but the evidence base for some of the estimates is limited [3,15]. Similarly, there are only few data on the level of nursing admission after a hip fracture, although this was an important determinant of the intervention threshold. In this study, we assumed that the prevention of hip fractures resulted in a reduction of mortality. There are, however, no empiric data to indicate that there is indeed a survival advantage associated with the prevention of fracture. But an analysis of hip fracture cases suggested that part of the excess mortality can be attributed to the hip fracture rather than to comorbidity [22].

In conclusion, this study allowed the calculation of the threshold for cost-effective intervention with bisphosphonates in a general population of elderly women. These intervention thresholds can be calculated from age and clinical risk factors and may be used to identify those patients who might benefit from BMD assessment and from therapy with bisphosphonates. Pharmacoeconomic models based on individual risks of outcomes may improve the targeting in a cost-effective manner of therapy to patients.

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