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Development and Validation of a Markov Microsimulation Model for the Economic Evaluation of Treatments in Osteoporosis

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ABSTRACT

Objective: Markov models are increasingly used in economic evaluations of treatments for osteoporosis. Most of the existing evaluations are cohort-based Markov models missing comprehensive memory management and versatility. In this article, we describe and validate an original Markov microsimulation model to accurately assess the cost-effectiveness of prevention and treatment of osteoporosis.

Methods: We developed a Markov microsimulation model with a lifetime horizon and a direct health-care cost perspective. The patient history was recorded and was used in calculations of transition probabilities, utilities, and costs. To test the internal consistency of the model, we carried out an example calculation for alendronate therapy. Then, external consistency was investigated by comparing absolute lifetime risk of fracture estimates with epidemiologic data.

Results: For women at age 70 years, with a twofold increase in the fracture risk of the average population, the costs per quality-adjusted life-year gained for alendronate therapy versus no treatment were estimated at €9105 and €15,325, respectively, under full and realistic adherence assumptions. All the sensitivity analyses in terms of model parameters and modeling assumptions were coherent with expected conclusions and absolute lifetime risk of fracture estimates were within the range of previous estimates, which confirmed both internal and external consistency of the model.

Conclusion: Microsimulation models present some major advantages over cohort-based models, increasing the reliability of the results and being largely compatible with the existing state of the art, evidence-based literature. The developed model appears to be a valid model for use in economic evaluations in osteoporosis.

Keywords: cost-effectiveness, Markov model, microsimulation, modeling, osteoporosis.

Introduction

Osteoporosis is an increasingly major health problem around the world. It is a disease characterized by low bone mass with microarchitectural disruption and increased skeletal fragility, leading to increased fracture risk. Osteoporotic fractures results in significant morbidity, mortality [1], and reductions in quality of life [2,3]. They also impose a huge financial burden on health-care systems. Moreover, with an aging population and increasing life expectancy, their consequences are expected to increase in the future.

In the cost-constrained environment of health care, economic evaluation of various diagnostic and treatment strategies is commonly used to help allocate resources in the most efficient manner [4–6]. Modeling is an important tool of economic evaluation by its ability to: extrapolate results from one trial; combine multiple sources of data; generalize results from one context to another; define research strategy; and delineate areas of uncertainty [7]. Nevertheless, models have limitations related to the quality of the assumptions and the data utilized [8,9]. Thus, models should be designed and conducted to reflect the complexity of the real world [9].

During the past decade, significant improvements were achieved in the field of pharmacoeconomic assessment of osteoporotic interventions [6,10]. However, remaining limitations relate to the effects of drugs on nonvertebral, nonhip fractures, the assessment of adherence to treatment, and also the failure to appropriately consider a lifetime horizon. Moreover, most of the models are cohort-based [11], thereby limited in their ability to deal simultaneously and accurately with the complex interactions of patient, intervention, and clinical events. Specifically, this approach is limited by the "memoryless" feature of the process, which is known as the Markov assumption [12]. This assumption means that once a patient has moved from one state to another, the model will have "no memory" regarding where the patient came from. When transition probabilities depend on prior events (such as in osteoporosis), this dependence or "memory" should be reflected in the model [13]. In many cohort models, "post-fracture states" have therefore been used for persistent changes in transition probabilities and utilities after hip and vertebral fractures. Nevertheless, future events are potentially inaccurately estimated by this approach [14].

Examples of the weaknesses of this approach follow. First, because of the desire to avoid an unmanageable number of health states, cohort models have restricted the number of disease states and transitions between them. For example, it has been frequently assumed that patients who have had a hip fracture cannot experience any future nonhip fracture [11]. This does not reflect realistic clinical perspectives because patients can definitely have other fractures after a nonfatal hip fracture. Additionally, patients in "postfracture state" might have a previous history of one, two, or more prior fractures but may be assigned the same transition probabilities, costs, and utility. This is also inconsistent with epidemiologic studies. Various studies have

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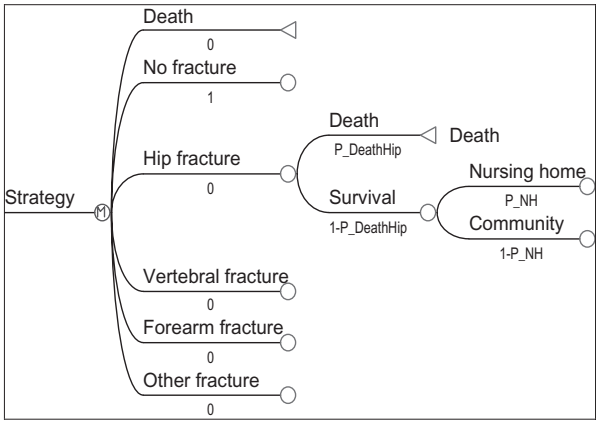

Figure 1 Markov model structure for each strategy. P_DeathHip and P_NH are, respectively, probabilities of death in the year after hip fracture and probabilities of being admitted to a nursing home after hip fracture for surviving patients.

shown a relationship between utility values and the number and location of prior fractures [15–18]; thus, if a model fails to record all the prior fractures, the utility value of patients with multiple prevalent fractures will be overestimated. Moreover, prior fractures were also shown to dramatically increase the risk of subsequent fractures [19,20] and there should be a record of all fractures to accurately assess this increased risk. Third, the residential status of a patient, defined as community- or nursing home dwelling, may affect long-term costs. The failure to track residential status will, for example, inappropriately add costs to a patient with an incident fracture who already lives in a nursing home [14].

Microsimulation models address the above weaknesses and have the potential to be more accurate than cohort models. Their use has increased dramatically with the speed of computing technology and they now begin to supplant cohort models in health-care technology assessment [21]. In the setting of osteoporosis, a Monte Carlo microsimulation identifies individual subjects to track their characteristics and individual disease histories [22]. Factors such as prior fracture and current residential status are used to calculate transition probabilities, utility values, and costs. Therefore, microsimulation models require no restrictive assumptions regarding patient movement to health states and allow assessing the impact of prior fractures without creating a large, incomprehensible and unmanageable number of health states. The infrequent use of microsimulation in osteoporosis is due to the greater variance in results because of random variation in individual outcomes, and of the much greater detail required for data sets (to be modeled) than would be required for cohort-based models. These factors have been proposed as the rationale for supporting the use of cohort-based approaches [23]. Potential drawbacks with microsimulation models include the computation burden when the joint uncertainty in all parameters is assessed using probabilistic sensitivity analysis [12].

We believe that there is value in developing microsimulation models in the field of osteoporosis [23]. The objective of this study was therefore to develop and validate a new Markov microsimulation model for the assessment of the cost-effectiveness of the prevention and treatment in osteoporosis. In this article, we present the model and we validate it through an empirical illustration.

Methods

The developed model was constructed using decision analysis software (TreeAgePro 2006 Suite, release 0.4, TreeAge Software, Inc., Williamstown, MA).

Model Structure

Because osteoporosis is a chronic disease characterized by a recurrence of events and when the fracture risk is continuous over time, a Markov modeling technique is appropriate [24]. The structure of the model is shown in Figures 1 and 2. It has been suggested that the model should be kept as simple as possible to be understandable, while capturing the underlying essentials of the process and interventions [13]. Therefore, the model consists of six states: "no fracture," "death," "hip fracture," "vertebral fracture," "forearm fracture," and "other fracture." This last state represents all other osteoporotic fractures [25] (e.g., humerus, pelvis, or distal femur).

The cycle length of the model is 1 year because events rarely occur more than once a year and most of the data sources, such as fracture disutility and fracture cost, are calculated on this frequency. The model follows the patients until they are dead or they reach the age of 105 years.

All the transitions between health states other than death are possible. So, in every cycle and regardless of the current state, each individual has a probability of having a fracture based on fracture risk, of having no fracture, or of dying based on mortality rates. If an individual is in a fracture state, she might have a new fracture (all fracture types are possible), or move to the "no fracture" state, or die. If an individual were to die, she would remain in the "death" state for the rest of the simulation.

A branch was created to keep track of residential status (either in the community or in a nursing home) for an individual with a hip fracture because this fracture type is associated with admission to a nursing home. Once a patient enters a nursing home, we assume that he/she will stay there for the rest of his/her life. We also assume a discount rate of 3% for costs and of 1.5% for health benefits for the base-case analysis, as recommended for health economic evaluations in Belgium, the country of reference for the present article [26].

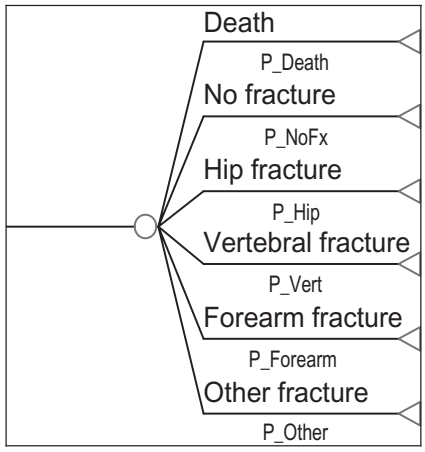

Figure 2 Expanded subtree for all health state other than death. P_Death, P_NoFx, P_Hip, P_Vert, P_Forearm, P_Other are transition probabilities of death, no fracture, hip fracture, vertebral fracture, forearm fracture, and other fractures, respectively. Figure 2 needs to be applied to all health states other than death in Figure 1 (represented by a green circle).

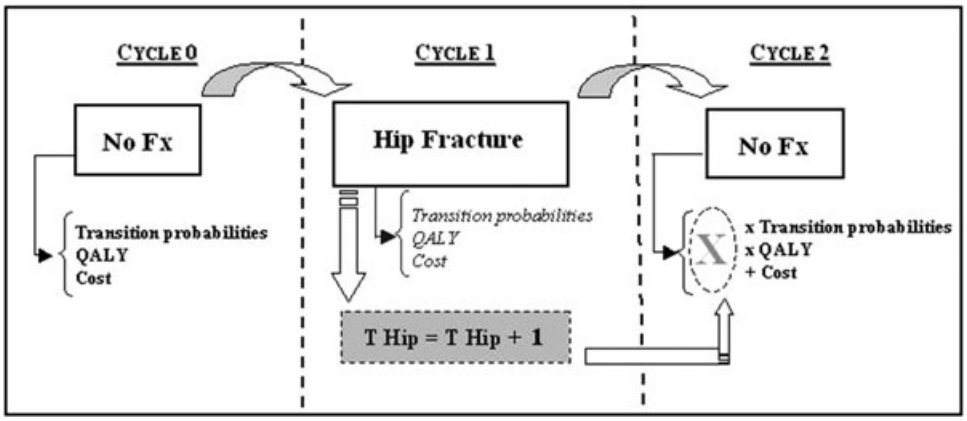

Figure 3 Example of memory integration. QALY, quality-adjusted life-year.

Memory Integration

In a practical sense, tracking patient history can be done with so-called tracker variables [22]. In our model, such variables were created to record the number of each fracture type and the residential status for all patients. They were then used in calculations of transition probabilities, utilities, and costs to reflect the patient history.

To illustrate how the model integrates memory, an example is shown in Figure 3. Our hypothetical patient began the process in the state "no fracture" and had corresponding transition probabilities, utility, and cost. It was assumed that the patient had suffered a hip fracture at stage 1, and so he moved to the state "hip fracture" associated with a lower utility, a higher cost, and different transition probabilities. The tracker variable that counts the number of hip fractures was then increased by one unit and was then used in all ensuing cycles to adjust transition probabilities, utilities, and costs to reflect the long-term impact of hip fracture on these components. Using this technique, "post-fracture states" and restrictive assumptions regarding patient transitions to health states used in cohort models are not needed.

Fracture Probabilities

Transition probabilities depend on the individual's characteristics (age, gender, bone mineral density, number of clinical risk factors), presence or absence of prior fractures, presence or absence of therapy and probabilities should also depend on the residential status of the individual. Patients are entered in the model one at a time with the same or different characteristics. Their transition probabilities may differ according to fracture events during the process. The effect of treatment is modeled as a relative risk reduction in population-specific fracture risk [27]. Treatment length in the model should be based on the duration of clinical trials, often limited to 3 or 5 years for anti-osteoporotic therapy.

Initial probabilities should be taken from epidemiologic data specific to the country and need to be adjusted to accurately reflect the fracture risk in the target population in comparison with that of the general population. The incidence of a first fracture in Belgium was estimated in a previous study [28].

Our model incorporates an increased risk of subsequent fracture for individuals who have a prior fracture of the same location. These increased relative risks are 4.4, 2.3, 3.3, and 1.9 for vertebral, hip, forearm, and "all-other osteoporotic" fractures, respectively [20]. An increased risk of subsequent fractures at sites different from that of prior fractures is not modeled because fracture incidence (at a specific site) was estimated regardless of the presence of fractures at other sites, and a multiplicative hypothesis could not be supported at this time with one exception. An increased relative risk of 2.3 is modeled for a hip fracture after a vertebral fracture based on existing literature [20,29–31]. All these increased relative risks were increased by a factor of 1.7 during the year after the fracture (calculated based on the study of Johnell et al. [2004]) [30], except in the case of vertebral fracture, and were reduced by 10% per each decade above the age of 70 years [19]. Further fractures of the same type are assumed to have no additional effect because of the absence of data providing an accurate relationship between the number of prior fractures and an increased risk.

Mortality Rates

Transition probabilities to death depend on individual characteristics (age and gender) and the presence or absence of prior fractures. Mortality rates according to age and gender are available from official estimates specific to the country [32]. Projected mortality rates were also tested in sensitivity analysis. Such estimates take account of progressive mortality reductions in advanced age and have been carried out in Belgium [33].

The impact of prior fracture on mortality is controversial [34]. Most studies have noted a substantial increase in mortality in the first year after a hip or a clinical vertebral fracture [1,35–37]. The duration of excess mortality remains unclear and the studies differ regarding the existence of a long-term effect of fractures [38]. Some studies have shown persistent and long-term increased mortality [35,38–40]. Others have suggested that the increased mortality after a hip fracture is limited to the first year after fracture and that no or only modest increased mortality was evident during subsequent years of follow-up [34,41,42].

To avoid an overestimation of the beneficial effect of treatment on mortality, it is important to take only into account most of the excess mortality [27] attributable to fractures, which could be reduced through fracture prevention. Therefore, we conservatively assumed that only 25% of the excess mortality after a hip or vertebral fracture can be directly or indirectly attributable to the fractures themselves [1,41,43,44].

In our base-case analysis, we assumed a first year and a subsequent year excess mortality after hip and clinical vertebral fracture. Excess mortality after a hip fracture was obtained from the study of Oden et al. (1998) [45]. This study gave detailed and

conservative estimates in comparison with other studies [1,46]. The increased mortality after a clinical vertebral fracture has been found to be very similar and even slightly higher than those of a hip fracture [1,35,41,43]. Therefore, we suggested in a conservative approach an impact of clinical vertebral fracture similar to that of hip fracture.

It is also assumed that other osteoporotic fractures, including forearm fractures, are not associated with an increased mortality that could be attributable to the fracture, and this is consistent with published studies [35,37]. We also suggested in a conservative manner that a second and further fractures at the same site will cause no greater excess mortality. Nevertheless, we do assume an interaction of excess mortality between a vertebral and an hip fracture, based on the result of Cauley et al. (2000) [35].

Health State Utility Values

The utility values associated with each health state depend on age, presence or absence of prior fractures, and may also depend on the presence or absence of therapy. A recent study [47] systematically reviewed the utility estimates for health states associated with osteoporosis and suggested reference values for countries that would like to carry out cost-utility analyses but are not able to process country-specific study (which requires both time and money). We used these references values for the general population level as well as relative reductions due to fractures (Table 1).

Our microsimulation model gives the possibility of having several fractures at the same or at different sites. Such an improvement requires an estimation of or an assumption about the consequences of fracture interactions on utility value. Previous models have assumed that when a patient suffers a fracture for a second or further time, only the reduction in quality of life resulting from one fracture is taken in consideration [48]. Nevertheless, it seems likely that a person who suffered two fractures has a lower level of quality of life (all other things being equal) than an individual who has suffered only one of these two fractures. This assumption was confirmed by recent studies showing that the number of fractures is a significant determinant of quality of life [3,15–18,49]. We, therefore, assumed that when a second fracture occurs at the same site as a previous one (e.g., hip or clinical vertebral), the subsequent disability and reduction in quality of life can be attributed partially to the first fracture and partially to the new fracture event. Therefore, to avoid overestimation of disability, due to both fracture events, in case of the occurrence of a second fracture at the same site, we reduced by 50% the disability allocated to the first fracture event. This assumption seems coherent and even conservative for vertebral fractures because some studies have shown that quality of life reduces with the number of previous vertebral fractures and that it has almost an additive effect [18]. For an individual with both a hip and vertebral clinical fracture, the total impact on utility value equals the sum of the impacts related to each of the fractures. This result is coherent with the study of Tosteson et al. (2001) [15], which suggests that the impact of the two fractures is even greater than the sum of the impacts related to each of the fractures. When an individual with a prior hip or clinical vertebral fracture has a forearm or other fracture, the long-term impact of the previous fracture is reduced by half. Nevertheless, there will be no more interaction after the year of this latest fracture because forearm and other fractures have no effect on utility value in subsequent years.

Table 1 Model parameters

Parameter	Values	Distribution	Source
Fracture risk	Depending on age and fracture type	Uniform (0.85*BV to 1.15*BV)	[28]
Probability of admissions to a nursing home	Depending on age	Uniform (0.75*BV to 1.25*BV)	[51]
Relative risk of a prior fracture on future fracture risk (for age range 50 to 60)			
Prior hip implies future hip (RR)	2.30	Uniform (1.20 to 3.40)	[20]
Prior CV implies future CV (RR)	4.40	Uniform (3.50 to 5.30)	[20]
Prior forearm implies future forearm (RR)	3.30	Uniform (1.65 to 4.95)	[20]
Prior other implies future other (RR)	1.90	Uniform (1.65 to 2.15)	[20]
Prior CV implies future hip (RR)	2.30	Uniform (1.90 to 2.70)	[20]
Mortality rates			
Excess mortality attributable to fracture	0.25	Uniform (0.20 to 0.30)	[41,43]
Utility values			
Hip fracture, first year* (RR)	0.797	Beta ($\alpha = 655$, $\beta = 167$)	[47]
Hip fracture, subsequent years* (RR)	0.899	Beta ($\alpha = 2{,}007$, $\beta = 225$)	[47]
CV fracture, first year* (RR)	0.720	Beta ($\alpha = 169$, $\beta = 66$)	[47]
CV fracture, subsequent years* (RR)	0.931	Beta ($\alpha = 1{,}021$, $\beta = 76$)	[47]
Forearm fracture, first year* (RR)	0.940	Beta ($\alpha = 326$, $\beta = 21$)	[47]
Other fracture, first year* (RR)	0.91	Beta ($\alpha = 318$, $\beta = 31$)	[47]
Direct fracture costs (in €)			
Hip fracture, first year	From 16,457 to 20,998	Uniform (0.85*BV to 1.15*BV)	[51,52]
CV fracture, first year	2,429	Uniform (0.85*BV to 1.15*BV)	[56,57]
Forearm fracture, first year	2,159	Uniform (0.85*BV to 1.15*BV)	[55]
Other fracture, first year	3,573	Uniform (0.85*BV to 1.15*BV)	[56,57]
Long term care > 1 year after hip fracture (for those who enter nursing homes)	19,821 (<70 years)–15,247 (>70 years)	Uniform (0.85*BV to 1.15*BV)	[54]
Intervention			
Hip fracture efficacy (RR)	0.62	Log-normal (95% CI 0.40–0.98)	[58]
CV fracture efficacy (RR)	0.56	Log-normal (95% CI 0.46–0.68)	[58]
Forearm fracture efficacy (RR)	0.67	Log-normal (95% CI 0.34–1.31)	[58]
Other fracture efficacy (RR)	0.81	Log-normal (95% CI 0.68–0.97)	[58]
Compliance	0.705	Uniform (0.80*BV to 1.20*BV)	[67]

*Relative reduction in utility value represents the proportional loss of quality-adjusted life-year due to the fracture.
BV, base value; RR, relative risk; CI, confidence interval; CV, clinical vertebral.

Costs

Belgian methodological guidelines for pharmacoeconomic evaluations recommend a direct health-care cost perspective [26]. These encompass intervention costs related to diagnosis and intervention (e.g., drugs, surgical procedure), together with adverse events attributable to the intervention as well as direct health-care costs related to the disease. Indirect costs (e.g., productivity losses) as well as unrelated health-care costs in life-years gained should not be included in the reference case analysis [26] and were therefore not included in our model.

The cost of a fracture is divided into cost during the first year after the fracture and long-term costs, which may persist for several years and even for the rest of the patient's lifetime. Cost estimates are expressed in €2006 and were inflated by consumer price indexes when necessary [50]. Direct hip fracture costs include hospitalization cost and additional costs during the year after the fracture. In Belgium, this has ranged from €16,457 to €20,998 according to age based on the hospitalization [51] and extra costs during the year after the fracture [52], both estimated in 1996.

Hip fractures are also associated with long-term costs. These long-term costs have been based on the proportion of patients being institutionalized after the fracture. This proportion was shown to range from 5% (for the age range 50–60 years) to 30% (for women aged 90 years or more) in Belgium [51]. In economic models, it is assumed that women who enter into a nursing home will remain there for the rest of their lives [11] and thus, the annual cost of being in the nursing home is added into the model for each remaining year of the woman's life. Nevertheless, this is a simplification providing a cost overestimation because the individuals might have been institutionalized later in life in any case, regardless of their hip fracture. Therefore, it is important to estimate only the long-term costs attributable to hip fracture, which could be reduced through fracture prevention [53].

To estimate the total cost attributable to fracture, we first reduced the proportion of individuals in a nursing home after a fracture (= 100%) each year by the institutionalization rate in the general population. The annual hip fracture cost was obtained by multiplying the proportion of fractures related to institutionalization with the annual cost of institutionalization (= €83.5 per day [54], so €30,495 per year). Then, we summed these values for each year until the age of average life expectancy. The proportion of long-term costs attributable to hip fracture was estimated respectively at 65% and 50% for women less than and more than the age of 70 years. So, a 50-year-old woman institutionalized after a hip fracture would have an annual long-term cost equal to $0.65 \times €30{,}493 = €19{,}820$.

Forearm fracture costs were estimated at €2159 [55]. Other fractures have been quantified relative to hip fracture on the basis of their costs [56,57]. We assumed that the costs of other osteoporotic fractures represent 25% of hip fracture costs, in line with the study of Gabriel et al. (2002) conducted between 1989 and 1992 [56]. This study does not integrate the cost of the nursing home in comparison with the study of Autier et al. (2000). We, therefore, reduced hip fracture costs by 50% of their extra costs before applying the proportion factor. The costs of other fractures were then estimated at €3573. Clinical vertebral fracture costs were estimated at €2429 based on a proportion factor of 17% relative to hip fracture [56,57]. The long-term costs of fractures other than hip have been rarely studied. Therefore, we conservatively assumed that there are no associated long-tem costs.

Empirical Illustration

To illustrate the model and the impact of model assumptions, an example calculation was carried out. In the base-case analysis, we assumed that women aged 70 years old with a twofold increase in fracture risk received a 5-year alendronate therapy, the most widely prescribed osteoporosis treatment worldwide. The increased risk corresponds approximately to the fracture risk of women with two clinical risk factors or women with one previous fracture (who have on average a fracture risk increase of 1.86 [19]). The clinical effectiveness of alendronate in the treatment of women with osteoporosis has been extensively documented [58]. A recent review suggested relative risks of 0.62 for hip fracture, 0.56 for clinical vertebral fracture, 0.67 for forearm fracture, and 0.81 for other fractures [58]. These relative risks have been used in recent studies assessing the cost-effectiveness of alendronate therapy [48,59,60] and were therefore selected for this analysis. After a 5-year treatment period, we assumed that the treatment effect persisted for 5 years (i.e., "offset-time"), in line with clinical studies [61–64] and assumptions used in previous models [27,59,65]. The risk reduction was assumed to decline linearly to zero during this period.

Adherence to antiosteoporosis medications is currently low and is associated with decreased antifracture efficacy [66]. In a recent study assessing adherence to bisphosphonates including alendronate [67], only 70%, 58%, 40%, 25%, and 20% of patients were respectively found to be persistent after 3 months, 6 months, 1 year, 2 years, and 5 years of therapy. Therefore, we assumed that 30%, 12%, 18%, and 15% of patients stopped drug therapy after 3 months, 6 months, 1 year, and 2 years. No treatment effect was assumed for patients who discontinued treatment after 3 months, and offset time for nonpersistent patients was assumed to be the same as their treatment period. Compliance, defined as how appropriately the treatment was correctly taken, was estimated at 70.5% for persistent women in the same study [67]. Medication costs and fracture reduction efficacy were assumed to be proportional to compliance.

The annual cost of the original alendronate therapy was estimated at €421.18 (Fosamax, 70-mg tablet packages, once per week; Merck & Co., Whitehouse Station, NJ). In accordance with previous standard assumptions regarding the monitoring of osteoporotic treatments [11], we assumed that treatment was associated with one annual physician's visit (€20) and an additional bone densitometry measurement every second year (estimated at €47). No adverse events were assumed in the base-case analysis.

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses were performed using a beta distribution for quality-adjusted life-year (QALY) disutility and a log-normal distribution for the relative fracture risk of treatment (Table 1), as recommended by Briggs's book [12]. Uniform distributions were also used for fractures risks, for probability of admissions to a nursing home, for excess mortality after a fracture, for fracture costs, and for the impact of a prior fracture on future fracture risk. Analyses were performed with 150 simulations (each parameter was randomly selected from the distribution) and with 25,000 trials per analysis. An acceptability curve was then constructed from the incremental cost and QALYs between different strategies for the 150 simulations.

Model Consistency

Assessing the consistency of the model was classified into three categories: internal consistency, external consistency,

and between-model consistency. To investigate the internal consistency, different sensitivity analyses in terms of model parameters and modeling assumptions were carried out. External consistency was investigated by comparing absolute lifetime risk of fracture estimates with estimates based on epidemiologic data and other studies. And between-model consistency was assessed by comparing some features of our model with those of existing models and by comparing results provided by our model with that of Zethraeus, available online [11], for the same example calculation.

Results

Internal Consistency

Table 2 gives the cost per QALY gained (in €) for alendronate therapy versus no treatment. For each case, a large number of microsimulations (200,000) were carried out to guarantee the stability of the results. The cost per QALY gained in the base case was €9105 and €15,325, respectively, under full and realistic adherence assumptions. The univariate sensitivity analyses based on model assumptions suggested that the cost per QALY gained was higher when we did not integrate QALY disutility for prior fractures and when there was no increased risk due to prior fractures. The impact of the number of prior fractures on utility value was however limited. When taking account of the full nursing home costs and not only of the proportion attributable to fracture, the efficiency was greatly overestimated.

Cost per QALY gained was lower when we used the projected mortality rates. It is also interesting to note that using projected mortality rates compensates for the incremental cost-effectiveness ratio increase due to the deletion of excess mortality after the first year. Therefore, our base-case assumption (medium-term excess mortality and actual mortality rates) gives similar results to an assumption using projected mortality rates and only first-year excess mortality.

The cost per QALY gained was shown to decrease with increasing age, fracture risk, fracture disutility, treatment efficacy, offset time, and with decreasing intervention cost and discount rates. The cost per QALY gained was also shown to be lower where quality of life increases during therapy and higher when adverse events are assumed.

The cost-effectiveness acceptability curves showed the probability that an intervention is cost-effective as a function of the decision-maker's willingness to pay. At an assumed willingness to pay of €45,000 and for women aged 70 years, there were a 96.7% and a 91.3% chance, respectively, that treatment would be cost-effective under full and realistic adherence assumptions (Fig. 4). These values were 96.0% and 79.3% for women aged 65 years.

Table 2 Cost per QALY gained (in €) of alendronate therapy versus no treatment: base-case and sensitivity analyses based on model assumptions and model parameters

Assumptions or parameters varied in the sensitivity analysis	Full adherence	Realistic adherence
Base case	9,105	15,325
Model assumptions		
Full QALY disutility of prior fractures when a new fracture occurs	8,641	14,777
No QALY disutility of prior fractures when a new fracture occurs	10,310	16,830
No increased risk due to prior fractures	17,979	23,634
50% of increased risk due to prior fractures	13,154	20,317
Projected mortality rates	6,440	13,238
Excess mortality in only the first year after fracture	11,266	16,186
Projected mortality rates and excess mortality in only the first year after fracture	7,510	14,503
Half of the excess mortality of prior fractures when a new fracture occurs	8,121	13,749
Full nursing home cost	736	7,650
Other fractures excluded	10,102	17,017
Time horizon: 95 years	10,095	15,831
Model parameters		
Discount rates: 5%	18,945	30,445
Treatment initiation at 65 years	20,371	26,920
Treatment initiation at 75 years	CS	1,718
0.75 time base-case fracture disutility	13,289	22,930
0.75 time base-case fracture costs	13,314	21,659
0.50 time base-case fracture risks	47,340	60,673
0.75 time base-case fracture risks	20,924	31,826
Excess mortality attributable to fractures: 0.50	8,217	12,216
0.50 time base-case admissions to nursing home after hip fracture	13,449	16,562
Treatment cost 20% higher	15,770	24,243
Treatment efficacy 20% lower	20,526	24,799
Offset-time 40% lower	14,994	25,245
QALY increase by 1% during therapy	4,984	9,884
Adverse events: 10€ per year of treatment	9,922	16,554

CS, cost saving; QALY, quality-adjusted life-year.

External Consistency

Absolute lifetime risk of hip fracture and of any osteoporotic fracture was estimated respectively at 16.5% and 45.3% for women aged 60 years. The average age at first hip and at

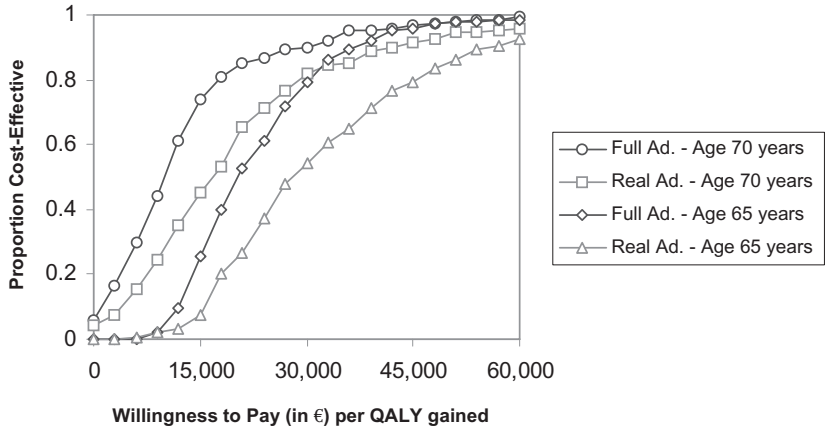

Figure 4 Cost-effectiveness acceptability curves. Full Ad., full adherence; QALY, quality-adjusted life-year; Real Ad., realistic adherence.

Table 3 Comparison of some features between models in osteoporosis

Model	Markov approach	Time horizon	Restrictive assumptions about transitions between states	Increased risk after a prior fracture
Our model	Microsimulation	Lifetime	No	Yes
Zethraeus et al. [11]	Cohort	Lifetime	Yes	No
NICE [68]	Microsimulation	10 years	No	Yes
Tosteson et al. [27]	Cohort	Lifetime	No	No
Schousboe et al. [65]	Microsimulation	Lifetime	No	Yes

first osteoporotic fracture was 82.37 years and 74.61 years, respectively.

Between-Model Consistency (Table 3)

The most often used models in the field of osteoporosis are the model of Zethraeus et al. [11], the model of Tosteson et al. [27] and the National Institute for Clinical Excellence (NICE) model [68]. The first two models are cohort-based, while the third is a microsimulation model. The first model was limited by restrictive assumptions about transitions between states. For example, patients with a prior hip fracture cannot experience any future nonhip fracture. This model, populated with Swedish data, has the advantage to be based on a great local database and was based on a societal perspective. The model of Tosteson defines more health states and allows patients with prior hip fracture to have future nonhip fracture. These two models do not integrate an increased risk after a prior fracture, in comparison with the NICE model. The time horizon of the NICE model is constrained to a 10-year period. Nevertheless, different studies have shown that a prior fracture has a long-term effect on future fracture risk and quality of life and that hip fracture is associated with long-term costs. Therefore, the required time horizon to evaluate fully the benefit of a particular intervention may be very long [69] and the use of a lifetime horizon is then recommended for a chronic disease such as osteoporosis [26,70]. A recent microsimulation model of Schousboe et al. [65] used a lifetime horizon and incorporates an increased relative risk for a subsequent fracture after a prior fracture of the same location.

In the model of Zethraeus [11] populated with Swedish data, alendronate therapy was cost saving compared with an incremental cost per QALY gained of €9105 in our model under full adherence assumption. The differences can be explained by several factors. A key one relates to the significantly greater fracture incidence, estimated to be 30% to 40% for first fractures, in Sweden compared to Belgium [28,71]. This single factor would alter the incremental cost-utility by respectively €5526 and €9032.

Discussion

Economic evaluation has become increasingly important in the field of osteoporosis because of the growing awareness of osteoporosis, the development and introduction of new treatments, and the extending role of economic evaluations in health-care decision-making process. Reliability and the subsequent interest in these evaluations depend both upon the methodological aspects of the model itself and on the quality of the data feeding the model. During the last decade, a lot of significant improvements have been achieved in the quality of economic evaluations in the field of osteoporosis. Nevertheless, most of the existing models are cohort-based models lacking comprehensive memory management and versatility. The major weakness of this approach is that it does not integrate memory and thus future events do not depend on prior events. Such simplifications could lead to potentially inaccurate estimations. Some examples were reviewed in the introduction.

Improving the quality of modeling is becoming a priority issue. Microsimulation models are beginning to supplant cohort-based models in health-care decision-making [21]. These models undoubtedly have a better ability to represent the complexity and the heterogeneity of pathology such as osteoporosis. The major advantage of these models is that the full patient history may be recorded and thus, in the case of osteoporotic models, factors such as prior fracture and residential status can be used in calculations of transition probabilities, costs, and utilities. Therefore, no restrictive assumptions regarding patient transitions to health states are needed and this method allows assessing the impact of prior fractures without creating a large and unmanageable number of health states. Moreover, these models help in dealing with future data regarding the consequences of fracture interactions. In spite of their advantages, microsimulation models have rarely been used in the field of osteoporosis because they also present limitations. First, microsimulation models require more detailed and sophisticated data. An improvement over time is, however, evident in the collection of data. Then, these models are associated with a greater variance in results. Finally, the computation burden is another potential drawback.

In this article, we present a new Markov microsimulation model to accurately assess the efficacy of osteoporosis management. This model has been constructed in accordance with good modeling practice [13,70,72,73], was based on the latest developments and modeling challenges addressed in previous models and reviews and improvements in data collection related to osteoporosis, and has been validated. First, internal consistency was confirmed by univariate sensitivity analyses in terms of model parameters and modeling assumptions and by probabilistic sensitivity analyses. All of these were consistent with expected conclusions. Second, our absolute lifetime risks of fracture estimates are within the range of previous estimates [27,45,71,74–78]. External consistency was also confirmed by an additional analysis that has recently estimated the effect of changes in baseline population risk and changes in life expectancy on absolute lifetime fracture risks [28]. Third, our model has many important features of models in osteoporosis such as a lifetime horizon, an increased risk after a prior fracture, and no restrictive assumptions about transitions between states. Moreover, the results provided by our model seem coherent and do not significantly diverge from the model of Zethraeus, which confirmed between-model consistencies. More specific comparison with existing models is however needed and should include the comparison of the same treatment in the same population.

In addition to the advantages gained by choosing the microsimulation modeling, we only modeled long-term fracture costs attributable to the hip fracture event and our model is the first to incorporate a relation between utility values and the number of prior fractures. Although the effect on cost-effectiveness is limited, this assumption was supported by the literature. Furthermore, our model discriminates between first year and subsequent

year effects of a fracture on future risks, costs, and quality of life and it takes into account the characteristics of the selected population and all the specificities of treatments such as compliance, persistence, offset time of action, and adverse events.

There are potential limitations to our model. First, an increased risk of subsequent fractures at sites different from that of prior fractures is not modeled, with one exception. On the other hand, the NICE model assumed that for simulated patients suffering fractures at two different sites, only the greatest risk adjustment was applied in calculating the risks of subsequent fractures. The reason of our conservative assumption is that fracture incidence (at a specific site) was estimated regardless of the presence of fractures at other sites. Second, our analysis was restricted to a direct health-care cost perspective, as recommended for Belgian pharmacoeconomic evaluations [26]. We have therefore not incorporated unrelated health-care costs in life-years gained and indirect fracture costs related to productivity losses or to informal care provided by patient's relatives. Eventually, we have not incorporated long-term costs attributable to clinical vertebral fracture.

Improving the quality of modeling is worthwhile but is not sufficient. The use of ever more sophisticated models to conduct evaluations without improving the quality of the information inputs will not increase the reliability of the results [8]. We observed that fracture risk, fracture costs, and fracture disutility have a significant impact on the cost per QALY gained of treatments. Such data are only available for a limited number of countries. Further research is therefore needed to improve the availability of data in the field of osteoporosis, and in all countries. So, the widespread use of generic instruments in large populations, and with long-term follow-up, has been recommended to investigate the disutility of fractures [47,79]. Furthermore, few head-to-head comparisons of treatments have been undertaken. Such comparisons would be very interesting. Research is also needed to estimate long-term costs attributable to hip and vertebral fracture and to establish long-term effectiveness of treatments to assess the long-term cost-effectiveness of anti-osteoporotic therapy.

Flexibility and adaptability of the model to different countries were also primary considerations with the design of our model. This model is flexible and can analyze different patient groups (such as patients having established osteoporosis or other clinical risk factors), treatment alternatives, and cost perspectives, in any country. It could also be adapted to test different assumptions related to parameters or to model structure. Moreover, to make accurate conclusions reflecting country specificities, the data must be valid for the specific setting to which the model is applied [11]. Therefore, country-specific data for all model inputs are required. The developed model allows the specification of country-specific data (e.g., fracture and mortality rates, costs, utilities, discontinuation rates). It would be great to have a large database for different countries to assess potential differences in cost per QALY gained of treatment between countries.

The developed model could be used to evaluate the cost-effectiveness of the treatment and prevention of osteoporosis. To assess the cost-effectiveness of new treatments, reliable data are required on fracture reduction efficacy (at specific sites), on treatment cost, on the effect of treatment after stopping therapy, on therapy adherence, and on adverse events. Non-adherence to therapy results in a significant change in cost-effectiveness. Therefore, the effects of noncompliance and nonpersistence to therapy should be investigated and should be an integral part of economic evaluations in osteoporosis. Adverse events have also been barely incorporated in cost-effectiveness analyses but there may be of potential significance. The model could also be used to assess the cost-effectiveness of osteoporosis screening strategies and to support recommendations about osteoporosis screening. Because osteoporosis is a silent disease, screening for osteoporosis has been recommended to identify and treat patients at high risk of fracture, before any fracture occurs [80–82]. Few studies have investigated the cost-effectiveness of screening for osteoporosis. Such studies will be very useful for decision-makers to guide rationale decisions. These analyses would require the estimation of the screening cost per treated patient that could then be used as a prior cost for the intervention strategy. This model could also be used to estimate absolute lifetime risk of fractures [28] and to assess the burden of osteoporosis in a selected population.

Conclusion

High quality evaluations are required to provide the decision-makers with accurate support for their decision-making processes. This article illustrates the rationale for using micro-simulation models to accurately assess the efficacy of osteoporosis management. This approach presents some major advantages over cohort-based models, increasing the reliability of results and being largely compatible with the existing state of the art, evidence-based literature. The model described in this article appears valid for use in economic evaluations in osteoporosis. This model, like all models, should never be regarded as completed [13]. It would need to be updated as new evidence becomes available to inform its structure or input values.

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References

1 Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. Osteoporos Int 2004;15:38–42.
2 Borgstrom F, Zethraeus N, Johnell O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int 2006;17:637–50.
3 Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int 2005;16:447–55.
4 Cranney A, Coyle D, Welch V, et al. A review of economic evaluation in osteoporosis. Arthritis Care Res 1999;12:425–34.
5 Drummond M, O'Brien B, Stoddart G, et al. Methods for the Economic Evaluation of Health Care Programmes. New York: Oxford University Press, 1997.
6 Zethraeus N, Ben Sedrine W, Caulin F, et al. Models for assessing the cost-effectiveness of the treatment and prevention of osteoporosis. Osteoporos Int 2002;13:841–57.
7 Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? Pharmacoeconomics 2000;17:445–59.
8 Sheldon TA. Problems of using modelling in the economic evaluation of health care. Health Econ 1996;5:1–11.
9 Soto J. Health economic evaluations using decision analytic modeling. Principles and practices—utilization of a checklist to their development and appraisal. Int J Technol Assess Health Care 2002;18:94–111.
10 Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int 2006;17:29–40.
11 Zethraeus N, Borgstrom F, Strom O, et al. Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model. Osteoporos Int 2007;18:9–23.

12 Briggs A, Sculpher M, Claxton K. Modelling Methods for Health Economic Evaluation. New York: Oxford University Press, 2006.
13 Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—modeling studies. Value Health 2003;6:9–17.
14 Stevenson MD, Oakley J, Chilcott JB. Gaussian process modeling in conjunction with individual patient simulation modeling: a case study describing the calculation of cost-effectiveness ratios for the treatment of established osteoporosis. Med Decis Making 2004;24:89–100.
15 Tosteson AN, Gabriel SE, Grove MR, et al. Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int 2001;12:1042–9.
16 Cockerill W, Lunt M, Silman AJ, et al. Health-related quality of life and radiographic vertebral fracture. Osteoporos Int 2004;15:113–9.
17 Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 2000;15:1384–92.
18 Silverman SL, Minshall ME, Shen W, et al. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611–9.
19 Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375–82.
20 Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000;15:721–39.
21 Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006;24:1043–53.
22 Hunink M, Glasziou P, Siegel J, et al. Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge: Cambridge University Press, 2001.
23 Vanness DJ, Tosteson AN, Gabriel SE, et al. The need for microsimulation to evaluate osteoporosis interventions. Osteoporos Int 2005;16:353–8.
24 Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322–38.
25 Melton LJ III, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:16–23.
26 Cleemput I, Crott R, Vrijens F, et al. Recommandations pour les évaluations pharmacoéconomiques en Belgique. Health Technology Assessment (HTA). Bruxelles: Centre Fédéral d'Expertise des Soins de Santé (KCE); 2008. KCE reports 78B (D/2008/10.273/24).
27 Tosteson AN, Jonsson B, Grima DT, et al. Challenges for model-based economic evaluations of postmenopausal osteoporosis interventions. Osteoporos Int 2001;12:849–57.
28 Hiligsmann M, Bruyère O, Ethgen O, et al. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone 2008;43:991–4.
29 Black DM, Arden NK, Palermo L, et al. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999;14:821–8.
30 Johnell O, Kanis JA, Oden A, et al. Fracture risk following an osteoporotic fracture. Osteoporos Int 2004;15:175–9.
31 Melton LJ III, Atkinson EJ, Cooper C, et al. Vertebral fractures predict subsequent fractures. Osteoporos Int 1999;10:214–21.
32 FPS Economy, Directorate-general Statistics and Economic Information. Démographie mathématique. Mortality tables 2004 et 2002–2004., Belgium, 2006.
33 Lambrecht M, Paul J. Quotients de mortalité prospectifs. *Working Paper 20-04*, The Federal Planning Bureau, Belgium, 2004.
34 Tosteson AN, Gottlieb DJ, Radley DC, et al. Excess mortality following hip fracture: the role of underlying health status. Osteoporos Int 2007;18:1463–72.
35 Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556–61.
36 Center JR, Nguyen TV, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999;353:878–82.
37 Cooper C, Atkinson EJ, Jacobsen SJ, et al. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001–5.
38 Empana JP, Dargent-Molina P, Breart G. Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. J Am Geriatr Soc 2004;52:685–90.
39 Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 1997;87:1630–6.
40 Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. Osteoporos Int 2007;18:1583–93.
41 Kanis JA, Oden A, Johnell O, et al. The components of excess mortality after hip fracture. Bone 2003;32:468–73.
42 Wolinsky FD, Fitzgerald JF, Stump TE. The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. Am J Public Health 1997;87:398–403.
43 Kanis JA, Oden A, Johnell O, et al. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int 2004;15:108–12.
44 Browner WS, Pressman AR, Nevitt MC, et al. Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med 1996;156:1521–5.
45 Oden A, Dawson A, Dere W, et al. Lifetime risk of hip fractures is underestimated. Osteoporos Int 1998;8:599–603.
46 Roberts SE, Goldacre MJ. Time trends and demography of mortality after fractured neck of femur in an English population, 1968–98: database study. BMJ 2003;327:771–5.
47 Hiligsmann M, Ethgen O, Richy F, et al. Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int 2008;82:288–92.
48 Stevenson M, Davis S, Lloyd-Jones M, et al. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technol Assess 2007;11:1–134.
49 Fechtenbaum J, Cropet C, Kolta S, et al. The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. Osteoporos Int 2005;16:2175–9.
50 FPS Economy, SMEs, independant Professions and Energy, Consumer prices, Belgium 2008. Available from: http://www.statbel.fgov.be/indicators/cpi/cpi_hist1920.xls [Accessed May 1, 2008].
51 Reginster JY, Gillet P, Ben Sedrine W, et al. Direct costs of hip fractures in patients over 60 years of age in Belgium. Pharmacoeconomics 1999;15:507–14.
52 Autier P, Haentjens P, Bentin J, et al. Costs induced by hip fractures: a prospective controlled study in Belgium. Belgian Hip Fracture Study Group. Osteoporos Int 2000;11:373–80.
53 Borgstrom F, Strom O. Long term hip fracture costs related to institutionalization. Osteoporos Int 2007;18(Suppl. 1):S29–S175.
54 Rombeaux J. Maison de repos et maison de repos et de soins. Radioscopie du secteur public. Union of Cities and Municipalities of the Walloon region, 2004.
55 Bouee S, Lafuma A, Fagnani F, et al. Estimation of direct unit costs associated with non-vertebral osteoporotic fractures in five European countries. Rheumatol Int 2006;26:1063–72.
56 Gabriel SE, Tosteson AN, Leibson CL, et al. Direct medical costs attributable to osteoporotic fractures. Osteoporos Int 2002;13:323–30.
57 Melton LJ III, Gabriel SE, Crowson CS, et al. Cost-equivalence of different osteoporotic fractures. Osteoporos Int 2003;14:383–8.
58 Stevenson M, Lloyd Jones M, De Nigris E, et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 2005;9:1–160.

59 Strom O, Borgstrom F, Sen SS, et al. Cost-effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries—an economic evaluation based on the fracture intervention trial. Osteoporos Int 2007;18:1047–61.
60 Kanis JA, Adams J, Borgstrom F, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone 2008;42:4–15.
61 Stock JL, Bell NH, Chesnut CH, 3rd, et al. Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. Am J Med 1997;103:291–7.
62 Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:875–83.
63 Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189–99.
64 Tonino RP, Meunier PJ, Emkey R, et al. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. J Clin Endocrinol Metab 2000;85:3109–15.
65 Schousboe JT, Ensrud KE, Nyman JA, et al. Universal bone densitometry screening combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. J Am Geriatr Soc 2005;53:1697–704.
66 Lekkerkerker F, Kanis JA, Alsayed N, et al. Adherence to treatment of osteoporosis: a need for study. Osteoporos Int 2007;18:1311–7.
67 Rabenda V, Mertens R, Fabri V, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int 2008;19:811–8.
68 Kanis JA, Brazier JE, Stevenson M, et al. Treatment of established osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 2002;6:1–146.
69 Dere W, Avouac B, Boers M, et al. Recommendations for the health economics analysis to be performed with a drug to be registered in prevention or treatment of osteoporosis. Calcif Tissue Int 1998;63:93–7.
70 Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. Pharmacoeconomics 2000;17:461–77.
71 Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int 2000;11:669–74.
72 Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment. Decision analytic modelling in the economic evaluation of health technologies. A consensus statement. Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment. Pharmacoeconomics 2000;17:443–4.
73 Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics 2006;24:355–71.
74 Doherty DA, Sanders KM, Kotowicz MA, et al. Lifetime and five-year age-specific risks of first and subsequent osteoporotic fractures in postmenopausal women. Osteoporos Int 2001;12:16–23.
75 Lauritzen JB, Schwarz P, Lund B, et al. Changing incidence and residual lifetime risk of common osteoporosis-related fractures. Osteoporos Int 1993;3:127–32.
76 Nguyen ND, Ahlborg HG, Center JR, et al. Residual lifetime risk of fractures in women and men. J Bone Miner Res 2007;22:781–8.
77 Melton LJ III, Therneau TM, Larson DR. Long-term trends in hip fracture prevalence: the influence of hip fracture incidence and survival. Osteoporos Int 1998;8:68–74.
78 Giversen IM. Time trends of age-adjusted incidence rates of first hip fractures: a register-based study among older people in Viborg County, Denmark, 1987–1997. Osteoporos Int 2006;17:552–64.
79 Brazier JE, Green C, Kanis JA. A systematic review of health state utility values for osteoporosis-related conditions. Osteoporos Int 2002;13:768–76.
80 US Preventive Services Task Forces. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002;137:526–8.
81 Kanis J, Burlet N, Cooper C, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008;19:399–428.
82 National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington, DC: 2008, p. 30.