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

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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 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 micro-architectural disruption and increased skeletal fragility, leading to increased fracture risk. Osteoporotic fractures result 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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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 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.](image1)

![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).](image2)
An increased risk of subsequent fractures at vertebral, hip, forearm, and “all-other osteoporotic” fractures, respectively [20]. An increased risk of subsequent fractures at the same location 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.

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].

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 estimated from the study of Oden et al. (1998) [45]. This study gave detailed and

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.

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.
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) [33].

**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 reference 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

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

*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.
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 women’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 × €30,495 = €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 Auert 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-term 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 8.86 [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 antosteoporosis 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 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.

**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

<table>
<thead>
<tr>
<th>Assumptions or parameters varied in the sensitivity analysis</th>
<th>Full adherence</th>
<th>Realistic adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>9,105</td>
<td>15,325</td>
</tr>
<tr>
<td>Model assumptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full QALY disutility of prior fractures when a new fracture occurs</td>
<td>8,641</td>
<td>14,777</td>
</tr>
<tr>
<td>No QALY disutility of prior fractures when a new fracture occurs</td>
<td>10,310</td>
<td>16,830</td>
</tr>
<tr>
<td>No increased risk due to prior fractures</td>
<td>17,979</td>
<td>22,634</td>
</tr>
<tr>
<td>50% of increased risk due to prior fractures</td>
<td>12,154</td>
<td>20,217</td>
</tr>
<tr>
<td>Projected mortality rates</td>
<td>6,440</td>
<td>13,228</td>
</tr>
<tr>
<td>Excess mortality in only the first year after fracture</td>
<td>11,266</td>
<td>16,186</td>
</tr>
<tr>
<td>Projected mortality rates and excess mortality in only the first year after fracture</td>
<td>7,510</td>
<td>14,503</td>
</tr>
<tr>
<td>Half of the excess mortality of prior fractures when a new fracture occurs</td>
<td>8,121</td>
<td>13,749</td>
</tr>
<tr>
<td>Full nursing home cost</td>
<td>736</td>
<td>7,650</td>
</tr>
<tr>
<td>Other fractures excluded</td>
<td>10,102</td>
<td>17,017</td>
</tr>
<tr>
<td>Time horizon: 95 years</td>
<td>10,095</td>
<td>15,831</td>
</tr>
<tr>
<td>Model parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rates: 5%</td>
<td>18,945</td>
<td>30,445</td>
</tr>
<tr>
<td>Treatment initiation at 65 years</td>
<td>20,371</td>
<td>26,920</td>
</tr>
<tr>
<td>Treatment initiation at 75 years</td>
<td>20,371</td>
<td>26,920</td>
</tr>
<tr>
<td>0.75 time base-case fracture disutility</td>
<td>13,289</td>
<td>22,930</td>
</tr>
<tr>
<td>0.75 time base-case fracture costs</td>
<td>13,314</td>
<td>21,659</td>
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<tr>
<td>0.50 time base-case fracture risks</td>
<td>47,340</td>
<td>60,673</td>
</tr>
<tr>
<td>0.75 time base-case fracture risks</td>
<td>20,924</td>
<td>31,826</td>
</tr>
<tr>
<td>Excess mortality attributable to fractures: 0.50</td>
<td>8,217</td>
<td>12,216</td>
</tr>
<tr>
<td>Full time base-case admissions to nursing home after hip fracture</td>
<td>13,449</td>
<td>16,562</td>
</tr>
<tr>
<td>Treatment cost 20% higher</td>
<td>15,770</td>
<td>24,243</td>
</tr>
<tr>
<td>Treatment efficacy 20% lower</td>
<td>20,526</td>
<td>24,799</td>
</tr>
<tr>
<td>Offset-time 40% lower</td>
<td>14,994</td>
<td>25,245</td>
</tr>
<tr>
<td>QALY increase by 1% during therapy</td>
<td>4,984</td>
<td>9,884</td>
</tr>
<tr>
<td>Adverse events: 10€ per year of treatment</td>
<td>9,922</td>
<td>16,554</td>
</tr>
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</table>

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

![Figure 4](image_url) Cost-effectiveness acceptability curves. Full Ad., full adherence; QALY, quality-adjusted life-year; Real Ad., realistic adherence.
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 €3526 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 base-line 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 decision-makers with accurate support for their decision-making processes. This article illustrates the rationale for using microsimulation 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

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Microsimulation Model for Osteoporosis