

# Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model

N. Zethraeus · F. Borgström · O. Ström · J. A. Kanis ·  
B. Jönsson

Received: 12 September 2006 / Accepted: 11 October 2006 / Published online: 9 November 2006  
© International Osteoporosis Foundation and National Osteoporosis Foundation 2006

## Abstract

**Objective** The purpose of the paper is to update and review the latest developments related to modelling and economic evaluation of osteoporosis in the period 2002–2005 and further to present a reference model for the assessment of the cost-effectiveness of the prevention and treatment of osteoporosis.

**Discussion** The reference model is intended to be used for fracture specific interventions affecting the risk of fracture. An interface version and an extensive description of the model

is available on the internet (<http://www.healtheconomics.se>) and also accessible via the International Osteoporosis Foundation (<http://www.osteofound.org>). The purpose of the reference model is to improve the quality and comparability of cost-effectiveness analysis in the osteoporosis field and to serve as a tool for validation of present and future cost-effectiveness models. The reference model allows the cost-effectiveness analysis to be carried out from a societal perspective including intervention, morbidity and mortality costs. The model has been extensively tested and calibrated, and meets the properties of good decision analytic modelling. The model is a state transition Markov cohort model, which is characterised by a 50-year time horizon divided into one year cycle lengths. The following health states are included: “healthy”, “hip fracture”, “spine fracture”, “wrist fracture”, “other fracture”, and “dead”.

**Conclusion** The model is flexible and allows for the estimation of the cost-effectiveness over different ranges for a selected number of variables (e.g., age, fracture risk, cost of intervention).

---

The named authors wrote this article on behalf of the Committee of Scientific Advisors of the International Osteoporosis Foundation.

---

N. Zethraeus · B. Jönsson  
Centre for Health Economics, Stockholm School of Economics,  
P.O. Box 6501, S-113 83 Stockholm, Sweden

N. Zethraeus  
e-mail: [henz@hhs.se](mailto:henz@hhs.se)

B. Jönsson  
e-mail: [hebj@hhs.se](mailto:hebj@hhs.se)

F. Borgström · O. Ström  
Stockholm Health Economics,  
Vasagatan 38 2tr,  
SE-111 20 Stockholm, Sweden

O. Ström  
e-mail: [oskar.s@healtheconomics.se](mailto:oskar.s@healtheconomics.se)

J. A. Kanis (✉)  
Centre for Metabolic Bone Diseases (WHO Collaborating  
Centre), University of Sheffield Medical School, UK,  
Sheffield S10 2RX, UK  
e-mail: [W.j.pontefract@sheffield.ac.uk](mailto:W.j.pontefract@sheffield.ac.uk)

F. Borgström  
Medical Management Centre at the Karolinska Institute (KI),  
Stockholm, Sweden  
e-mail: [fredrik.b@healtheconomics.se](mailto:fredrik.b@healtheconomics.se)

**Keywords** Cost-effectiveness · Osteoporosis · Prevention

## Introduction

Osteoporosis increases the risk of fractures, which leads to major consequences for the individual and society. Fractures increase the burden to society both with respect to mortality and quality of life. The mortality caused by hip fractures accounts for approximately 1% of all deaths and 1000 life-years lost per year in Sweden [1]. Fractures account for about 1–2% of the total health care costs of which inpatient care costs dominate. Although fractures affect older people to a large extent, indirect costs (loss in

value of production due to sick leave) also play an important role that has been estimated at about 10% of the total costs [2]. Although hip fractures account for a major part of the burden to society, recent data indicate that vertebral fractures also play a more important role than previously assumed [3–5]. For example, it has been recently shown that the loss in quality of life in the year after a hospitalised spine fracture is the same or even greater than the loss in quality of life that is caused by a hip fracture [4].

Clinical studies have shown that pharmacological treatments such as D-vitamins, calcium, bisphosphonates and SERMs reduce the risk of fracture. In addition, non-medical interventions such as hip protectors may reduce the risk of hip fracture, though recent studies suggest little if no effect [2, 6]. The introduction of new interventions has increased the costs for the treatment and prevention of osteoporosis. For example, in Sweden the sales of pharmaceuticals for bone specific disorders (bisphosphonates and SERMs) have increased by 84% from SEK 182 to 335 million during the last five-year period 2000–2004 [7]. These agents account for a rise from 0.8 to 1.2% of the total pharmaceutical sales. If calcium and D-vitamin preparations are included, the total sales have increased from SEK 280 to 460 million, which corresponds to an increase in the share of total pharmaceutical sales from 1.2 to 1.6%.

With limited resources and health care budgets, it is important to strive for the efficient use of scarce resources, so that health outcomes are maximised. Economic evaluations can support decisions concerning the efficient allocation of scarce resources in health care. In economic evaluations, the costs of the interventions are weighed against the benefits and cost-effectiveness indicates that no further health gains can be achieved by allocating resources differently. The importance of cost-effectiveness studies in health care decision making has been strengthened over the past few years. In particular, economic evaluations play an increasing role in pricing and reimbursement decisions [8].

Modelling is a necessary feature for making decisions about the efficient use of health care resources in the area of osteoporosis [9, 10]. The purpose of modelling is to produce information beyond that which is available from clinical studies. An example of the need for modelling is to generate information about costs and health effects that occur after the cessation of the clinical study. In a previous review of the osteoporosis health economic literature by Zethraeus et al. [11], the weaknesses and strengths of different model alternatives were discussed. The authors concluded that Markov modelling is usually used but that models differ in many respects in terms of structure, data and validation. Both in the public and the private sector new models have accompanied several of the new cost-effectiveness analyses of interventions in osteoporosis,

which makes it difficult to assess to what extent the results are a consequence of a new model or the new technology and data. To increase the probability that the cost-effectiveness results reflect the true benefits and costs of different interventions the cost-effectiveness, analysis should be assessed on a reference model. This provides an opportunity to validate present and future models, and in the absence of a new model, to investigate the results with new data for a given indication or new interventions. There may be reasons to change certain aspects of the model to capture the properties of a new technology. However, there is still the need to validate the model for a standard case.

The major aim of this paper is to present a reference model for the assessment of the cost-effectiveness of the prevention and treatment of osteoporosis. In particular, the paper addresses the following questions: What types of health care technologies are assessed and for what indications? What is the perspective of the economic evaluation? What specific features are involved in modelling in osteoporosis? What properties should a reference model have? To investigate these questions we carried out a review and update [9–12] of the literature related to the assessment of the treatment and prevention of osteoporosis. The literature search identified studies published in the period from 2002 to 2005. A reference model is suggested and illustrated by a hypothetical intervention for different scenarios. The model is intended to be used for fracture specific interventions affecting the risk of fracture. An interface version and a detailed description of the model are available on the internet (<http://www.healthconomics.se>) and also accessible through the International Osteoporosis Foundation (<http://www.osteofound.org>). In this version it is possible to estimate the cost-effectiveness over different ranges of a selected number of parameters (e.g., age, fracture risk, cost of intervention).

## Overview of studies 1980–2001

A review carried out by Zethraeus et al. [11] identified 22 studies that assessed the cost-effectiveness of the treatment and prevention of osteoporosis. At the beginning of the period (1980–1992), more than 70% of the cost-effectiveness studies came from the same US research group, which estimated the cost-effectiveness applied to a US setting [13–17]. Later studies were mainly from outside the US by a Swedish research group [18–22] that developed models to assess the cost-effectiveness of the prevention and treatment of osteoporosis using Swedish data.

Thirteen out of 22 studies assessed the cost-effectiveness of hormone replacement treatment (HRT), 6 studies investigated the cost-effectiveness of hypothetical fracture therapies, and 3 studies assessed the cost-effectiveness of

tibolone, HRT and a life style intervention, and alendronate, respectively. HRT was the only technology assessed at the beginning of the period, with the introduction of bisphosphonates, the first models were developed in the mid-1990s that focused on fracture-specific therapies in general, i.e., hypothetical therapies that affected only the risk of fracture. It was not until in the beginning of the 2000s that fracture specific agents (e.g., alendronate) were assessed, based on clinical trials and using fracture-specific models [23].

All the cost-effectiveness studies were based on the so-called Markov state transition models. The structure of the models differed depending on the therapy assessed and the potential effects and side effects of therapy. Models used for fracture specific therapies (e.g., bisphosphonates or hypothetical fracture therapies) always included hip fracture as a disease state and usually also included fractures of the wrist and spine. Models intended for therapies with extra-skeletal effects (i.e., HRT) always included hip fracture and breast cancer, and usually also coronary heart disease. At the beginning of the period, these studies usually included the risk of endometrial cancer and, in some cases, also the risk of gallbladder disease. The structure of the HRT models usually differed with respect to other disease states: Some models included coronary heart disease (CHD) and stroke. This reflected the uncertainty during that time of the effects of HRT on those disease states, due to the lack of randomised controlled trials. Subsequently, the publication of randomised controlled studies reduced the uncertainty related to HRT and its effect on different disease states [24–26].

In early studies, the fracture risk was usually modelled from the relationship between bone mineral density (BMD) and fracture risk (BMD models) developed by Melton et al. [27]. However, other risk factors are also important for the risk of fracture (height, smoking status, previous fracture etc), so that BMD alone is an incomplete measure of fracture risk. In addition, there are uncertainties concerning the relationship between changes in BMD and changes in fracture risk [28–30]. Later studies incorporated age-specific absolute risks, which were based on epidemiological data. The majority of studies assumed that the risk of fracture was reduced for some time after treatment was stopped.

In earlier studies, cost-effectiveness analysis was based on a health care perspective, but after 1998, more than 50% of the studies were based on a societal perspective so that costs outside health care were included, such as indirect costs and costs in added years of life. This reflects the methodological development in health economics, where Meltzer [31], for example, argues for the inclusion of costs in added years of life. Studies in the period 1980–1995 included direct costs for intervention and morbidity and related medical costs in added life years. Since 1998, indirect intervention and morbidity costs were often included, as well as costs minus production in added life-years.

Studies assessing the cost-effectiveness of therapies with extra skeletal (non-fracture) effects have always included cost and mortality data related to hip fracture and breast cancer, and since 1992, cost and mortality data for CHD. The quality of life related to hip fracture was always considered and, at the end of the period, the effect of breast cancer and coronary heart disease on quality of life was also taken into account. Studies that assessed the cost-effectiveness of fracture specific therapies included cost, mortality and quality of life data related to hip fractures.

## Overview of studies 2002–2005

For comparative purposes, the search strategy was the same as that used in the previous review [11]. Studies that assessed the cost-effectiveness of the prevention and treatment of osteoporosis and published in the period 2002–2005 were included in the survey. Only studies that defined the effectiveness measure in terms of quality adjusted life years (QALYs) were included. Since osteoporosis therapies may have consequences on different fracture outcomes, events avoided are not a suitable outcome measure. The ultimate consequence of osteoporosis therapies is on length of life and quality of life, which makes QALY an attractive outcome measure. Since QALYs incorporate quantity and quality of life into one measure, this makes it possible to compare the cost-effectiveness of different therapies for one patient group and to compare the cost-effectiveness of therapies in different treatment areas [32]. QALYs are also recommended by some drug benefit boards and health technology assessment agencies (the Swedish Pharmaceutical Benefits Board (LFN) and the National Institute for Health and Clinical Excellence (NICE)). Papers were searched in HEED (Health Economic Evaluation Database) and PubMed® with a cut-off date of September 2005. The following keywords were searched for: “cost” and “osteoporosis”. Papers that focused on indications other than osteoporosis were excluded. Studies not defined as economic evaluation studies (e.g., cost studies) were also excluded. Unpublished working papers, technical reports and other research papers have been added if considered relevant. In total, 22 studies were identified and are summarised in Table 1 [33–54].

Table 1 lists the studies by year of publication, intervention assessed, indications and country to which the results apply. The most frequently assessed technology was pharmacological agents, which were assessed in 19 of the studies (86%). Hip protectors were assessed in the three remaining studies (14%). Assessments of bisphosphonates dominated the pharmacological interventions and constituted more than 60% of these studies. SERMs were assessed in 4 of the studies followed by calcium/vitamin D and HRT

**Table 1** Summary of studies included in the review

Nr	Authors	Year of publication	Intervention and comparator	Indication	Country
1	Grima, Burge & Tosteson [39]	2002	Risedronate vs. alendronate	Established osteop 65 year, women	US
2	Iglesias, Torgerson, Bearne et al. [40]	2002	Risedronate vs. calcium/vitamin D	Established osteop 75 year, women	UK
3	Kanis, Brazier, Stevenson et al. [44]	2002	Bisph./HRT/SERM/calcium./vitamin D/calcitonin/thiazide diuretics/anabolic steroids vs. no treatment	Established osteop, 50–80 year, women	UK
4	Nagata-Kobayashi, Shimbo & Fukui [46]	2002	HRT vs. screening & HRT vs. no treatment	50 year women, osteopenia/osteoporosis	Japan
5	Segui-Gomez, Keuffel & Frick [48]	2002	Hip protectors vs. no treatment	Nursing homes, 65–85+ year, women/men	US
6	Willis [52]	2002	Calc/Vit D vs. no treatment	High risk population, 50–70 year, women	Sweden
7	Borgstrom & Zethraeus [54]	2003	Risedronate vs. calcium/vitamin D	Established osteop, ost, 74 year old women	Sweden
8	Brecht, Kruse, Felsenberg et al. [35]	2003	Risedronate vs. Standard treatment (no treatment & calcium vitamin D)	Established ost, 70-year old women	Germany
9	Jonsson, Borgstrom & Zethraeus [41]	2003	Alendronate vs. calcium/vitamin D	Established osteop, ost, 69 and 71 year old women	Denmark
10	Waldegger, Cranney, Man-Son-Hing et al. [51]	2003	Hip protectors vs. no intervention	Nursing homes, 70–82 year old women	Canada
11	Borgstrom, Johnell, Jonsson et al. [33]	2004	Alendronate vs. calcium/vitamin D	Established ost, 60–80 year old men	Sweden
12	Borgstrom, Johnell, Kanis et al. [34]	2004	Raloxifene vs. calcium/vitamin D	Osteoporotic, 60–80 year old women	Sweden
13	Brecht, Kruse, Mohrke et al. [36]	2004	Risedronate/alendronate/Raloxifene vs. calcium/vitamin D	Established osteoporosis, 70 year old women	Germany
14	Fleurence [38]	2004	Calc/Vit D/hip prot. vs. no treatment	High risk and average, men and women 70 years	UK
15	Kanis, Borgstrom, Johnell et al. [42]	2004	Risedronate vs. calcium/vitamin D	Established osteop, ost women 60–80 years of age	UK
16	Singh, Sun & Anis [49]	2004	Hip protectors vs. no treatment & calcium/vitamin D	Nursing home residents, 85 years men/women	Canada
17	Christensen, Brixen, Gyrd-Hansen et al. [37]	2005	Alendronate vs. calcium/vitamin D	RR fracture=2, 71 year old women	Denmark
18	Kanis, Borgstrom, Johnell et al. [43]	2005	Raloxifene vs. calcium/vitamin D	50–80 year old women, osteop+est osteop	UK
19	Lundkvist, Johnell, Cooper et al. [45]	2005	parathyroide hormone (PTH) vs. calcium-vitamin D	69 year old women, established osteoporosis	Sweden
20	Schousboe, Nyman, Kane et al. [47]	2005	Alendronate vs. calcium/vitamin D	55–75 years old women osteopenia	US
21	Stevenson, Lloyd Jones, De Nigris et al. [50]	2005	Bisph./raloxifene/teraparotide vs. calcium/vitamin D	50–80 year old women	UK
22	Zethraeus, Borgström, Jönsson et al. [53]	2005	HRT vs. screening & HRT vs. no treatment	50–60 year old women with menopausal symptoms	Sweden

(two studies each) and PTH, which was assessed in one study. The base line comparator was usually calcium and vitamin D. Only one study directly assessed the cost-effectiveness of one bisphosphonate compared with another bisphosphonate [39]. Almost all the studies analysed the

cost-effectiveness of the use of the technology for women between the ages of 50–85 years. Men were assessed in four studies [33, 38, 48, 49]. Most of the studies focused on women living independently in private residence, whilst three studies only analysed women living in nursing homes

(hip protectors). The populations considered were usually at a higher risk of fractures compared with the average population, and most studies assessed the cost-effectiveness for women with osteoporosis or established osteoporosis. Most of the economic evaluations (73%) were set in countries within Europe (Denmark, Germany, Sweden, and the UK) and more than 50% of the studies applied to either the UK or Sweden. Outside Europe, the US, Canada and Japan are represented.

The cost-effectiveness analyses were all based on a Markov state transition model, which is characterised by health states, transition probabilities, Markov cycles and a time horizon. Table 2 defines the disease states included in the models from the different studies. The papers can be divided into 17 studies that used fracture-specific models, i.e., models that only include fracture disease states (studies usually analysing treatments that only reduce the fracture risk) and five studies that used non-fracture specific (extra-skeletal) models, also including non-fracture disease states such as breast cancer and CHD (studies analysing treatments with fracture and non-fracture effects). All but one of the fracture specific models assessed fracture-specific therapies (bisphosphonates, calcium vitamin D, PTH, hip protectors). One study that assessed the cost-effectiveness of HRT only included hip fracture as a disease state [46]. All the non-fracture specific models assessed treatments

with both fracture and non-fracture specific effects (i.e., SERMs and HRTs). Table 3 shows included costs in the different studies.

All models included a hip fracture state and usually also spine and wrist fracture states, and sometimes also other fractures. For the assessment of SERMs and HRT, breast cancer and coronary heart disease states were also included. After the publication of the Women's Health Initiative studies [24, 25] the assessment of HRT also included colorectal cancer, stroke and venous thromboembolic events [53]. In all studies, the fracture risks were based on fracture incidence derived from epidemiological studies. Thus, the baseline fracture risks were based on incidence rather than on the relationship between BMD and the risk of fracture. The effect of therapy was usually based on analysis of randomised controlled trials. A remaining effect of therapy was modelled after stopping treatment, so that the intervention reduced the risk of fracture for a variable time after stopping treatment.

The majority of studies were not carried out based on a societal perspective, so that important cost items have been excluded from the analysis. A societal perspective should include direct and indirect costs for the programme, morbidity and mortality. In the majority of studies only direct costs for the programme (intervention) and morbidity (e.g., fracture costs in hospital) and also related medical

**Table 2** Included disease states

Study	Included disease states									Fracture incidence model	Remaining effect on fracture
	Fracture states				Cancer states		Cardiovascular states				
	Hip	Spine	Wrist	Other	Breast	Colorectal	CHD	Stroke	VTE		
1	X	X								X	Unknown
2	X	X	X	X						X	Unknown
3	X	X	X	X	X			X		X	X
4										X	Unknown
5	X									X	Not relevant
6	X									X	Unknown
7	X	X	X							X	X
8	X	X	X	X						X	Unknown
9	X	X	X							X	X
10	X	X	X							X	Not relevant
11	X	X	X							X	X
12	X	X	X		X			X		X	X
13	X	X								X	Unknown
14	X	X	X	X						X	X
15	X	X	X							X	X
16	X									X	Not relevant
17	X	X	X							X	X
18	X	X	X		X			X		X	X
19	X	X	X							X	X
20	X	X	X	X						X	X
21	X	X	X	X	X			X		X	X
22	X	X	X		X	X		X	X	X	X

**Table 3** Included costs in the different studies

Study	Intervention costs		Morbidity costs		Mortality costs		All costs minus production
	Direct	Indirect	Direct	Indirect	Medical related	Costs unrelated	
1	X		X		X		
2	X		X		X		
3	X		X		X		
4	X		X		X		
5	X		X		X		
6	X		X		X		
7	X		X		X	X	X
8	X		X		X		
9	X		X		X	X	X
10	X		X		X		
11	X		X	X	X	X	X
12	X		X	X	X	X	X
13	X		X		X		
14	X		X		X		
15	X		X		X		
16	X		X		X		
17	X		X		X		
18	X		X		X		
19	X		X		X	X	X
20	X		X		X		
21	X		X		X		
22	X		X	X	X	X	X

costs in added years of life. Six out of 22 studies also included costs minus production in added years of life [33, 34, 41, 45, 53, 54].

### A reference model

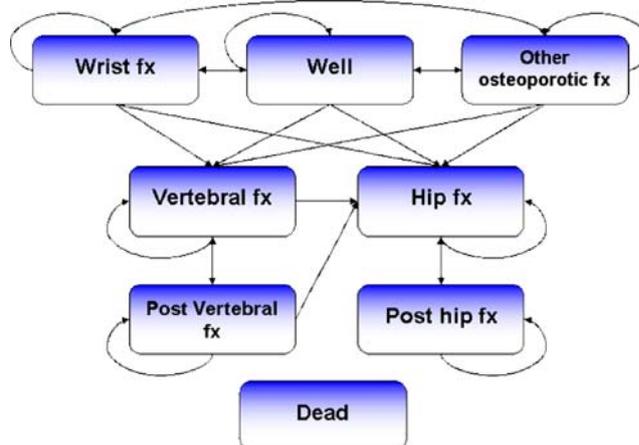
The reference model is extensively validated and based on previous modelling experience developed for almost 15 years, and meets the criteria of good decision analytic modelling [18–20, 31, 41, 53, 55]. The model can be used for analysing different populations: female/male, high risk populations, and different ages. The model produces the change in costs and effectiveness (in terms of QALYs) for the intervention compared with no intervention. The model uses a societal perspective where direct and indirect costs related to intervention, morbidity and mortality are included. As an option mortality costs may be excluded. The model also provides an opportunity to incorporate negative (side effects) or positive effects during therapy.

### Model structure

The reference model presented below is a state transition Markov cohort model, which is characterised by a life-long time horizon (maximum 50 years) divided into a Markov

cycle length of 1 year. The structure of the model is shown in Fig. 1. The arrows show the allowed transitions in the model. Each year there is always a possibility of dying or staying in the same health state. The fracture-state consists of a hip fracture, vertebral fracture, wrist fracture and one “other” fracture state. The “other” fracture state provides the possibility of including another fracture that is considered to be important, but could also be used as a proxy for all other osteoporotic fractures.

An intervention is modelled by its impact on the disease risks during and possibly also after stopping treatment. The



**Fig. 1** The structure of the model

remaining effect of an intervention on the fracture risk after the treatment period is modelled as a linear decline in the level of risk reduction for a given “offset time”. The remaining effect is usually assumed to persist for the same time as for the intervention period.

#### Empirical illustration

To illustrate how the model can be used an example calculation was carried out for a hypothetical population based on Swedish data. Cost and quality of life data were largely based on empirical studies. Data on disease risks and mortality rates were obtained from different national registers and epidemiological studies. A brief description of the data and sources is given below. Figures 2 and 3 present the Screen input and output of the reference model.

<b>Population characteristics</b>	
Country	Sweden
Starting age	70
Relative risk of fractures	2
<b>Treatment</b>	
Treatment cost per year (SEK)	6 000
Treatment length (years)	5
Off set time (years)	5
<b>Treatment effect (% risk reduction)</b>	
Hip fracture	35%
Vertebral fracture	35%
Wrist fracture	35%
treatment effect on quality of life	0%
<b>Model setup</b>	
Annual discount rate, costs	3%
Annual discount rate, effects	3%
Cost in added life years	yes

**Fig. 2** Input framework of reference model

#### Definition of population and effect of intervention

The base case assesses a 70-year old woman with a twofold increase in the fracture risk. It is assumed that the intervention reduces the fracture risk by 35% (RR=0.65) during therapy and that a remaining effect wanes linearly for another 5 years. This is consistent with findings in clinical randomised studies of the effect of bisphosphonates on the overall risk of fracture [56]. Note that the offset time can be changed in the model allowing for other remaining effects. The same relative risk reduction is assumed for all the fractures. The intervention is compared with standard treatment (e.g., calcium and D-vitamins).

#### Disease risks

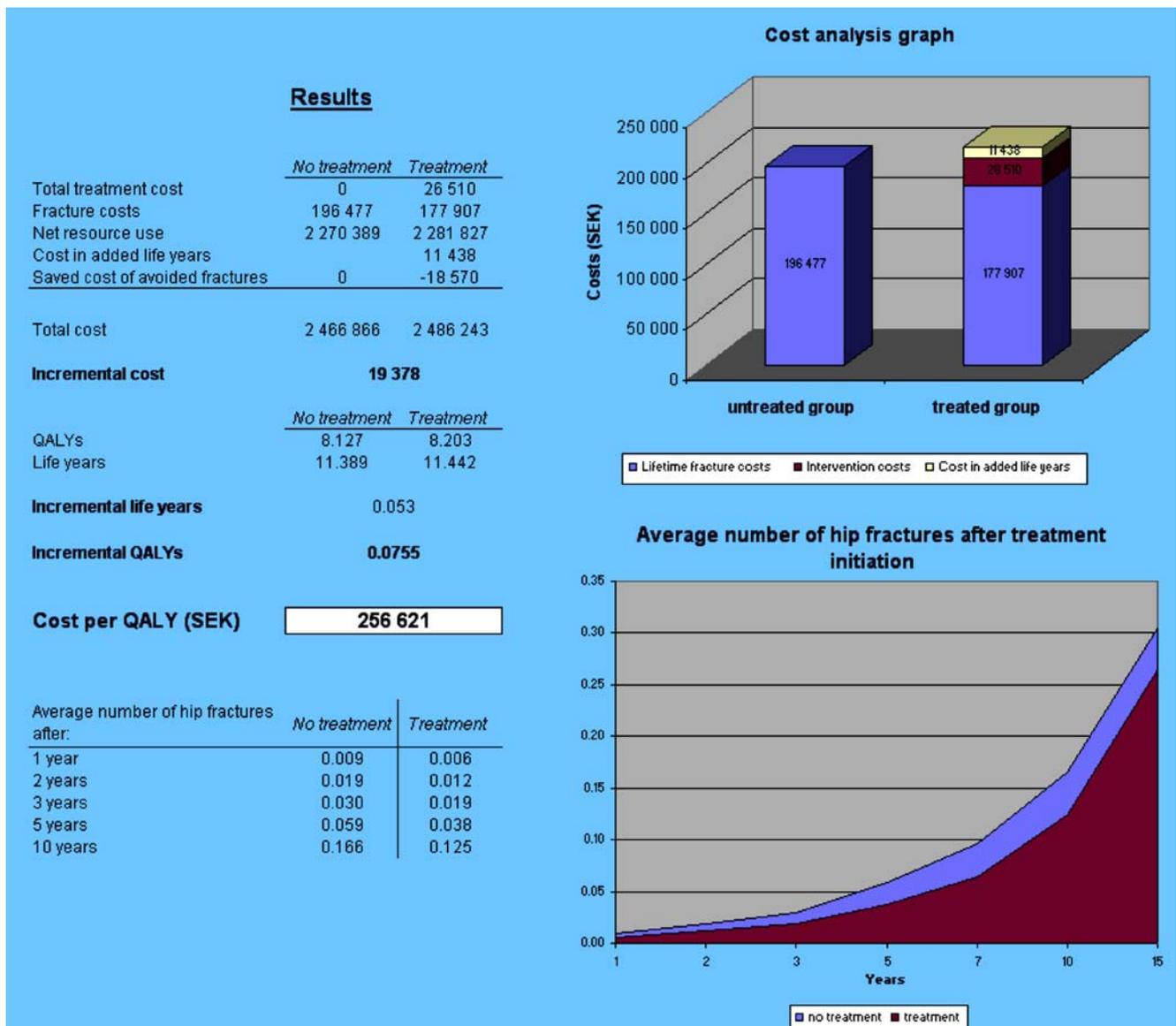
The age-differentiated risk of fractures at the hip, clinical vertebrae and the wrist in a general Swedish female population were derived from a population based study from Malmö published in a study by Kanis et al. [57]. Other fractures are presently not activated in the reference model.

#### Mortality rates

Patients with hip fractures and clinical vertebral fractures have a higher mortality compared to the normal population [58–62]. A part of the excess mortality after fracture compared to normal mortality cannot entirely be ascribed the fracture event but also to other co-morbid conditions [1, 62, 63]. We assumed that 30% of the observed excess mortality after a hip or vertebral fracture was associated with the fracture event. Wrist fracture was not assumed to be associated with any excess mortality [58, 59]. Age-specific annual mortality rates for the general population, first and second and following for hip and spine fractures were taken from statistics Sweden and two publications by Odén et al. and Johnell et al. [64–66]. The adjusted normal mortality (death due to other causes not included in the model) can be calculated as normal mortality multiplied by the fraction of all causes of death that is not explained by hip and spine fractures. The mortality caused by hip fractures accounts for approximately 1% of all deaths. The fraction of all deaths that spine fractures accounts for is uncertain and in the base case analysis no mortality adjustments are made.

#### Quality of life weights

Estimates of the reduction in quality of life the year after osteoporotic fractures were derived from a study based on patients recruited at the orthopaedic department at the Malmö University Hospital in the south of Sweden [67].



**Fig. 3** Output framework of reference model

From this study the yearly proportional loss in quality of life after a hip fracture, vertebral fracture and wrist fracture were estimated at 0.203, 0.374 and 0.023, respectively [67]. By relating these estimates to Swedish population utility values (50–59 years: 0.82; 60–69 years: 0.78; 70–79 years: 0.78 and 80 years and above: 0.74) [68] age differentiated fracture specific quality of life weights were obtained [5, 69]. The quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [70]. Based on the findings that radiographically defined vertebral fractures reduce quality of life by approximately 9% when the fracture may have occurred at a previously unknown time [71] it was conservatively assumed that the quality of life loss related to clinical vertebral fractures the second and following years was 0.05.

There are no studies suggesting that wrist fracture is associated with a measurable reduction in quality of life in the long term, and it was assumed that wrist fracture had an impact on the quality of life only during the first year after fracture.

#### Costs

The inclusion of costs was based on a societal perspective including intervention costs, disease related costs and costs in added years of life. All costs are in Swedish crowns (SEK) expressed in the prices of 2004 (1€=9.1SEK). When needed, the costs were inflated using the Consumer Price Index from Statistics Sweden. The annual intervention cost (a typical bisphosphonate) is assumed to be SEK 6,000. In a

sensitivity analysis the intervention cost is varied between SEK 3 000 and 9 000. The intervention cost consists of drug costs and costs for assessment and physician visits.

Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral and wrist fracture were derived from Zethraeus et al. [3, 72]. Hip fracture costs in the second and following years were based on the age-differentiated proportion of patients that come from home before fracture, that reside in nursing home one year after fracture (data on file). The proportions of patients admitted from home going to long-term care after hip fracture at different ages were; 50–69: 7% , 70–79: 10% , 80–89: 15% , over 90: 23%. These patients were assumed to remain in a nursing home for the rest of their lives [70] at a daily cost of SEK 1 605 [73]. It was conservatively assumed that vertebral and wrist fractures were associated with costs only during the first year after fracture. Costs in added years of life, defined as the difference between annual production and consumption in different age groups, are based on Ekman et al. [74].

## Results

Table 4 gives the cost-effectiveness ratios for a 5-year fracture specific treatment. All ratios are given in Swedish crowns (SEK).

The cost per gained QALY is SEK 260,000 in the base case analysis. The sensitivity analysis demonstrates that the cost-effectiveness ratio decreases with increasing age, offset time, population risk, and decreasing intervention cost. If the quality of life during therapy is increased, the cost-effectiveness ratio also becomes lower. On the other hand small side effects during therapy (represented by a 1% decrease in quality of life during therapy) will increase the ratio substantially. In all the scenarios the cost per QALY gained is below the defined cost-effectiveness threshold value of SEK 600,000. Dominated (D) means that the intervention is associated with lower costs and better effects compared with no intervention. Excluding the costs in added years of life (mortality costs) implies lower cost-effectiveness ratios.

## Discussion

This paper presents a reference model for the assessment of the cost-effectiveness of the treatment and prevention of osteoporosis. The model is intended to be used for the evaluation of health care technologies that affect the risk of fractures. An interface version and a description of the model are available on the internet (<http://www.health.economics.se>) and through a link from the International Osteoporosis Foundation (<http://www.osteofound.org>). The

model permits the estimation of the cost-effectiveness over different ranges for a selected number of parameters (e.g., age, fracture risk, cost of intervention).

There are several reasons why a reference model is needed. First, it may be used as a common reference for the assessment of new therapies. If every new technology is accompanied by a new model, it may be difficult to conclude whether the cost-effectiveness results are a consequence of the model or of the new technology. Second, new models can be validated against the reference model based on a given set of data. Such a validation provides an opportunity to discuss and compare results and clarify the reasons for discrepancies. Third, it will provide an opportunity to use a well validated model to investigate the effect of new data for a specific population (country) or for a new technology.

This paper has also reviewed the latest developments in modelling and economic evaluation of the prevention and treatment of osteoporosis. In total the review identified 22 studies in the period 2002–2005, which is equal to the number of studies identified in the period 1980–2001 [11].

**Table 4** Cost effectiveness ratios for different populations and assumptions (SEK)

Parameters varied in the sensitivity analysis	Costs in added life years excluded	Costs in added life years included
Base case	110,000	260,000
Starting age		
65 year treatment initiation	280,000	430,000
75 year treatment initiation	D	D
Effect envelope		
Offset time=0 years	330,000	460,000
Offset time=10 years	2,000	4,000
Discount rate		
Health effects 0%, costs 3%	80,000	100,000
Costs and effects=0%	40,000	210,000
Costs and effects=5%	150,000	300,000
Fractures		
RR=1	370,000	540,000
RR=2	110,000	150,000
RR=3	20,000	20,000
RR=4	D	D
Assuming only half of the reduction in quality of life related to fractures	140,000	340,000
Intervention		
QOL due to therapy +1%	70,000	180,000
QOL due to therapy -1%	190,000	450,000
Risk reduction fracture=50%	D	150,000
Intervention costs=3,000	D	80,000
Intervention costs=9,000	280,000	430,000

D=the intervention dominates the no intervention alternative  
Base case: 70-year old woman with 2-fold increase in fracture risk.  
Risk reduction=35%. Five-year offset time. Annual intervention cost 6,000 SEK

Sixteen of the studies were published in medical journals, five were published in health economic journals and two were identified as HTA reports. A reason for the increase in the number of studies and related models is the increase in the development and introduction of new treatment alternatives. In particular, the introduction of bisphosphonates, which were assessed in more than 50% of the studies, explains the increase in the number of studies. Another factor that may explain the development is that, during the few years, the role of economic evaluation in health care decision making has increased, reflecting the importance that reimbursement agencies give to cost-effectiveness as one explicit criterion behind reimbursement decisions.

All the cost-effectiveness models are so called Markov state transition models, which are characterised by health states, transition probabilities, Markov cycles and a time horizon. The models can be divided into fracture-specific models and models with non-fracture (extra-skeletal) effects. The models are rather similar in structure; about the same disease states are identified, the cycle length is one year and the time horizon is usually life long. The majority of models are fracture-specific models with the aim of analysing treatments that only reduce the fracture risk. In particular the bisphosphonates have been assessed, but also hip protectors have been evaluated. All of the fracture-specific models have included a hip fracture state and most also included spine and wrist fracture states and in some cases also other fractures. The fracture risks have been based on epidemiological data, and not on the relation between BMD and the risk of fracture, a feature seen in some early models.

Data on clinical effectiveness were in the previous period (1980–2001) only in rare instances based on data from randomised clinical studies. Usually “best guesses” were used based on epidemiological data and expert opinion. Thus, the effectiveness for the cost-effectiveness estimations were usually based on what-if calculations and not on RCTs. Studies in the period 2002–2005 have largely based the effectiveness on randomised controlled trials, studying the effect of therapy on fracture risk [75–78], systematic reviews or meta-analyses. Only one of the identified studies assessing the cost-effectiveness of HRT, used an observational study as the only base for the effectiveness measure [46]. After the cessation of therapy a remaining effect is usually modelled. The effect of therapy after stopping treatment is associated with a higher degree of uncertainty, due to the lack of appropriate randomised studies.

The majority of studies did not include a societal perspective, so that important cost items were excluded from the analysis. A societal perspective includes direct and indirect costs for the intervention, morbidity and mortality. In most studies, only direct costs for the programme

(intervention) and morbidity (e.g., fracture costs in hospital) were included. However, due to the definition and structure of the Markov model in these studies, related medical costs for mortality have been included implicitly (at least costs for the included disease states). For all the studies, hip fracture was assumed to be associated with an increased mortality risk (in some cases also spine fracture is assumed to increase the mortality risk), and by avoiding a hip fracture that life is prolonged. When the life is extended the individual will be confronted with further risks of hip fractures which are included in the model. To be consistent with economic theory and to avoid sub-optimisation, a societal perspective should be carried out, which implies that also unrelated medical costs and non-medical costs minus production should be included in added years of life as recommended in guidelines for economic evaluations of interventions in osteoporosis [79, 80]. The societal perspective can be supplemented with budget impact analyses from other more limited perspectives (e.g., health care budget, drug budget etc).

The data used in the models are of different quality. Often the epidemiological data are better referenced to empirical studies than data on costs and utilities. However, an improvement over time is evident in the collection of data on costs and utilities for different health states. Cost and health effect data are obtained from a combination of different sources where charges often are used as proxies for costs and where quality of life estimations are based on assumptions rather than on empirical data. It is important to aim at using empirical data as a base for the costs and quality life figures. If not there is a risk of obtaining biased cost-effectiveness results. For example, previous studies show that the first assumptions made of the reduction in quality of life related to menopausal symptoms severely underestimated the real effect of symptoms on quality of life shown in later empirical studies [81, 82]. Also the costs and quality of life related to spine fractures have been underestimated in many studies that do not base their estimates on empirical studies. Recently, empirical studies have demonstrated that hospitalised spine fractures have about the same impact on quality of life as hip fractures.

The reference model is constructed in accordance with good modelling practice, which according to Akehurst and Brazier [83] includes the following characteristics: transparency (the structure and the data included in the model can easily be investigated), internal consistency (the model is mathematically well defined for all combinations of parameter values feasible in the model), reproducibility (independent analysts have the opportunity to reproduce the results given by the model), interpretability (the results are clear and interpretable for the decision that it is being used to inform), exploration of uncertainty (uncertainty can be appropriately explored by the use of sensitivity and

stochastic analysis), statement of scope (the scope of the model is clearly specified), external consistency (the outputs of the model are consistent with empirical evidence), parsimony (the model is kept as simple as possible), inferential soundness (the causal relationships in the model should be explained and supported by best available evidence).

The reference model presented in this paper can further be assessed against a list of nine dimensions (questions) described by Sculpher et al. [84]. The purpose of the list is to encourage the analyst to provide an explicit and comprehensive justification of the methods used, and allows the user of the model to make a judgement about the relevance, coherence and usefulness of the analysis. First there is a clear statement of the decision problem, the context and the perspective of the model (*structure*). The model is intended for assessing the cost-effectiveness of fracture-specific treatments affecting the risk of fracture. The analysis is based on a societal perspective and the model allows for the inclusion of intervention, morbidity and mortality costs. A societal perspective is recommended in health economic evaluation studies and also by some drug benefit boards [32, 80]. The model is flexible and can analyse different patient groups and treatment alternatives in any country. Different risk groups such as patients having established osteoporosis or other risk factors can be analysed by multiplying the average risk with a relative risk factor. To make accurate conclusions in other countries, the data must be valid for the specific setting to which the model is applied. That is data on risks, mortality, costs and quality of life must be valid for the setting that is analysed. In the base case the model is populated with data appropriate for Sweden. The inclusion of *disease states* is based on the most important fracture states in terms of cost and health effect consequences. Hip, but also spine fractures, are associated with major costs and quality of life consequences, which are important to incorporate. Also fractures of the wrist are included. The model also permits the user to activate an “other fracture” disease state. This option increases the flexibility of the model to incorporate other important fracture disease states considered relevant. The *options* are well described and involve either a comparison between treatment/no treatment or between different treatment strategies. The *time horizon* is clearly stated and is based on a life long perspective. All individuals are followed until they are dead or achieve the age of 100 years. A life long perspective is preferable due to the long term effects on costs, mortality and quality of life. The *cycle length* is defined as one year, which is consistent with annual data on e.g., disease risks and mortality rates. Further the sources of parameter values (*data identification*) and their *incorporation* are clearly stated, referenced and described. Tests of *internal consis-*

*tency* are carried out by the help of menus, which can be used to control the model calculations. Several tests in different sensitivity analysis have been carried out and compared with expected outcomes. Finally, *external consistency* is investigated by comparing the results with other studies carried out in the field. e.g., the life time risk of fracture and life expectancy for an average population has been calculated and compared with estimates based on epidemiological data and other studies analysing the effect on life expectancy.

To assess Markov models either cohort or individual Monte Carlo simulation can be carried out. Most of the reviewed studies above use cohort simulation for the assessment of the Markov model, which means that a hypothetical number of patients are run through the model producing a point estimate of the incremental cost-effectiveness ratio. In individual Monte Carlo simulations (a standard feature of many software packages) a large number of patients are followed through the model individually where the path followed by different patients will differ due to chance. The advantage of the individual simulation is that it gives an estimate of the variance associated with the costs and health effects in each arm of the model. This representation of the uncertainty in the estimated cost and effects relates to the inherent uncertainty of the probabilistic structure of the model and is sometimes termed as “first-order” Monte Carlo simulation. “Second-order” Monte Carlo simulation can also be performed. In addition to allowing for uncertainty due to the ways individuals travel through the model, the underlying model variables are allowed to vary over a given range with a given distribution [85]. It has become popular to express the results of the uncertainty analyses in so called cost-effectiveness acceptability curves. This trend is in line with methodological developments in the field.

To assess whether an intervention is cost-effective from a societal point of view the costs (including intervention, morbidity and mortality costs) must be compared with the societal value per unit increase in health effects. An intervention is cost-effective if the value exceeds the costs per unit increase in health effects. The value of a QALY gained in the illustration above suggested to be SEK 600 000, which also can be derived from the value that the Swedish road authorities put on a statistical life (corresponds to US\$ 70,000 using the average exchange rate during 2003: US\$=8.1 SEK). Other studies have used US\$ 60,000 as a base case and in a sensitivity analysis varied the threshold value between US\$ 40,000 and US\$ 100,000 [86, 87]. In most cost-effectiveness studies so far, the mortality costs have been excluded. For life extending interventions this means an underestimation of the cost per QALY gained in patient groups where the value of the consumption exceeds the production, and an overestimation

in patient groups where the value of production is greater than the consumption. For calculations excluding costs in added years of life, lower benchmark values of US\$ 20,000–40,000 have generally been used [88].

## Conclusions

For about 25 years, modelling has served as a necessary tool for the assessment of the cost-effectiveness of the treatment and prevention of osteoporosis. Modelling is a necessary feature for making decisions about the efficient use of health care resources in the area of osteoporosis. Several models have been developed to assess the cost-effectiveness of health technologies in the osteoporosis field. Although the models have become more similar over time, they still differ in many respects in terms of data, perspective and validation. This makes it difficult to assess if the cost-effectiveness results are a consequence of a new model or the new technology and data.

Cost-effectiveness analysis is a method for assessing costs and benefits of alternative ways of allocating resources in order to assist decisions aiming at achieving efficiency. It is important that these decisions are based on reliable and valid assessment of cost effectiveness. If not, there is an increased risk of erroneous health care decisions and policy recommendations, which may result in wasteful use of scarce resources in society. In the light of the increasing role and use of economic evaluations in health care decision making, this should be a priority issue. Improving the quality of the cost-effectiveness information might also imply that the role and use of economic evaluations may increase in the future.

To improve the quality and comparability of cost-effectiveness analysis in the osteoporosis field a reference model is suggested, which is made available on internet (<http://www.healthconomics.se>). The model is intended to be used for assessing the cost-effectiveness of health care technologies affecting the risk of fracture. The purpose of the reference model is to serve as a tool for validating present and future cost-effectiveness models. The model may also be used instead of developing new models in the field.

The reference model allows the cost-effectiveness analysis to be carried out from a societal perspective including intervention, morbidity and mortality costs. The model is based on several years of modelling experience and meets the properties of good decision analytic modelling. The model is a state transition Markov cohort model, which is characterised by a 50-year time horizon divided into one-year cycle lengths. The following health states are included: healthy, fracture states of the hip, spine, wrist, “other fracture”, and dead. The model is flexible and can be used for analysing different populations: female/male, high risk populations, and different ages.

The model is in the base case populated with Swedish cost and health effect data. To use the model for other countries and settings the data on costs and health effects must be adapted to reflect the new conditions. A model is only a tool for synthesising the best available data on cost and health effects valid for a specific setting at a certain point in time. To produce reliable and valid cost-effectiveness results, the model should always be based on best available data valid for the country/setting subject to analysis.

New opportunities for the prevention and treatment of osteoporosis will continue to be developed and established methods need to be reassessed in view of new evidence. Modelling will always play an important role in the assessment of the cost-effectiveness of the prevention and treatment of osteoporosis. A reference model may contribute to increasing the quality and reliability of cost-effectiveness analyses of new technologies in the osteoporosis field. It further provides opportunities for validation and discussion of results from other models, which may clarify reasons for discrepancies.

**Acknowledgements** Supported in part by a grant from the International Osteoporosis Foundation.

## References

1. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK (2003) The components of excess mortality after hip fracture. *Bone* 32:468–473
2. SBU [The Swedish Council on Technology Assessment in Health Care] (2003) Osteoporos-prevention, diagnostik och behandling [Osteoporosis-prevention, diagnosis and treatment]. SBU, Stockholm, report No 165/1
3. Zethraeus N, Borgström F, Johnell O, Jönsson B (2002) Costs and quality of life associated with osteoporosis related fractures-results based on a Swedish survey. Published in the Working Paper Series in Economics and Finance at the Stockholm School of Economics, Working paper No 512
4. Borgström F, Zethraeus N, Johnell O (2005) Costs and quality of life associated with osteoporosis related fractures in Sweden. *Osteoporosis International* (forthcoming 2005)
5. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, Jonsson B (2004) The risk and burden of vertebral fractures in Sweden. *Osteoporos Int* 15:20–26
6. Sawka AM, Boulos P, Beattie K, Thabane L, Papaioannou A, Gafni A, Cranney A, Zytaruk N, Hanley DA, Adachi JD (2005) Do hip protectors decrease the risk of hip fracture in institutional and community-dwelling elderly? A systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int*
7. Total läkemedelsförsäljning (2000–2004) In: Apoteket (ed)
8. Eberhardt S, Stoklossa C, Schulenburg JGvd (2005) Euromet 2004. The influence of economic evaluation studies on health care decision making. A European Study. In: Eberhardt S, Stoklossa C, Graf von der Schulenburg JM (eds). Amsterdam, The Netherlands
9. Fleurence RL, Iglesias CP, Torgerson DJ (2005) Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. *Osteoporos Int*

10. Johannesson M, Jonsson B (1993) Economic evaluation of osteoporosis prevention. *Health Policy* 24:103–124
11. Zethraeus N, Ben Sedrine W, Caulin F, Corcaud S, Gathon HJ, Haim M, Johnell O, Jonsson B, Kanis JA, Tsouderos Y, Reginster JY (2002) Models for assessing the cost-effectiveness of the treatment and prevention of osteoporosis. *Osteoporos Int* 13:841–857
12. Tosteson AN, Jonsson B, Grima DT, O'Brien BJ, Black DM, Adachi JD (2001) Challenges for model-based economic evaluations of postmenopausal osteoporosis interventions. *Osteoporos Int* 12:849–857
13. Weinstein MC (1980) Estrogen use in postmenopausal women—costs, risks, and benefits. *N Engl J Med* 303:308–316
14. Weinstein MC, Schiff I (1983) Cost-effectiveness of hormone replacement therapy in the menopause. *Obstet Gynecol Surv* 38:445–455
15. Weinstein MC, Tosteson AN (1990) Cost-effectiveness of hormone replacement. *Ann N Y Acad Sci* 592:162–172, discussion 185–192
16. Tosteson AN, Rosenthal DI, Melton LJ 3rd, Weinstein MC (1990) Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. *Ann Intern Med* 113:594–603
17. Tosteson AN, Weinstein MC (1991) Cost-effectiveness of hormone replacement therapy after the menopause. *Baillieres Clin Obstet Gynaecol* 5:943–959
18. Jönsson B, Hedbrant J, Johnell O (1993) A Computer Simulation Model to Analyse the Cost-effectiveness of Fracture Prevention of Osteoporosis. *EFI Research paper Nr 6525*
19. Zethraeus N, Johannesson M, Jönsson B (1998) A computer model to analyse the cost effectiveness of hormone replacement therapy. *EFI Research Paper No 6578*
20. Zethraeus N, Lindgren P, Johnell O (2000) A computer model to analyse the cost-effectiveness of hormone replacement therapy—a revised version. *SSE/EFI Working Paper Series in Economics and Finance*, at the Stockholm School of Economics, Working paper No 368
21. Jonsson B, Kanis J, Dawson A, Oden A, Johnell O (1999) Effect and offset of effect of treatments for hip fracture on health outcomes. *Osteoporos Int* 10:193–199
22. Zethraeus N, Johannesson M, Jonsson B (1999) A computer model to analyze the cost-effectiveness of hormone replacement therapy. *Int J Technol Assess Health Care* 15:352–365
23. Johnell O, Jonsson B, Jonsson L, Black D (2003) Cost effectiveness of alendronate (fosamax) for the treatment of osteoporosis and prevention of fractures. *Pharmacoeconomics* 21:305–314
24. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* 288:321–333
25. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Jama* 291:1701–1712
26. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Jama* 280:605–613
27. Melton LJ 3rd, Kan SH, Wahner HW, Riggs BL (1988) Lifetime fracture risk: an approach to hip fracture risk assessment based on bone mineral density and age. *J Clin Epidemiol* 41:985–994
28. Johnell O, Kanis JA, Oden A, Johannesson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20:1185–1194
29. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Bmj* 312:1254–1259
30. Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Qin G, Christiansen C (2005) The long-term predictive value of bone mineral density measurements for fracture risk is independent of the site of measurement and the age at diagnosis: results from the Prospective Epidemiological Risk Factors study. *Osteoporos Int* 1–7
31. Meltzer D (1997) Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ* 16:33–64
32. Gold M, Siegel J, Russell L (1996) *Cost-effectiveness in health and medicine*. Oxford University Press, New York
33. Borgstrom F, Johnell O, Jonsson B, Zethraeus N, Sen SS (2004) Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. *Bone* 34:1064–1071
34. Borgstrom F, Johnell O, Kanis JA, Oden A, Sykes D, Jonsson B (2004) Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. *Pharmacoeconomics* 22:1153–1165
35. Brecht JG, Kruse HP, Felsenberg D, Mohrke W, Oestreich A, Huppertz E (2003) Pharmacoeconomic analysis of osteoporosis treatment with risedronate. *Int J Clin Pharmacol Res* 23:93–105
36. Brecht JG, Kruse HP, Mohrke W, Oestreich A, Huppertz E (2004) Health-economic comparison of three recommended drugs for the treatment of osteoporosis. *Int J Clin Pharmacol Res* 24:1–10
37. Christensen PM, Brixen K, Gyrd-Hansen D, Kristiansen IS (2005) Cost-effectiveness of alendronate in the prevention of osteoporotic fractures in Danish women. *Basic Clin Pharmacol Toxicol* 96:387–396
38. Fleurence RL (2004) Cost-effectiveness of fracture prevention treatments in the elderly. *Int J Technol Assess Health Care* 20:184–191
39. Grima, Burge, Tosteson (2002) Short-term cost-effectiveness of bisphosphonate therapies for postmenopausal osteoporotic women at high risk of fracture. *27:448–455*
40. Iglesias CP, Torgerson DJ, Bearne A, Bose U (2002) The cost utility of bisphosphonate treatment in established osteoporosis. *Qjm* 95:305–311
41. Jonsson L, Borgstrom F, Zethraeus N (2003) [Cost-effectiveness of alendronate treatment of osteoporosis in Denmark. An economic evaluation based on the Fracture Intervention Trial]. *Ugeskr Laeger* 165:4112–4116
42. Kanis JA, Borgstrom F, Johnell O, Jonsson B (2004) Cost-effectiveness of risedronate for the treatment of osteoporosis and prevention of fractures in postmenopausal women. *Osteoporos Int* 15:862–871
43. Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B (2005) Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. *Osteoporos Int* 16:15–25
44. Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M (2002) Treatment of established osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess* 6:1–146
45. Lundkvist J, Johnell O, Cooper C, Sykes D (2005) Economic evaluation of parathyroid hormone (PTH) in the treatment of osteoporosis in postmenopausal women. *Osteoporos Int*

46. Nagata-Kobayashi S, Shimbo T, Fukui T (2002) Cost-effectiveness analysis of screening for osteoporosis in postmenopausal Japanese women. *J Bone Miner Metab* 20:350–357
47. Schousboe JT, Nyman JA, Kane RL, Ensrud KE (2005) Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med* 142:734–741
48. Segui-Gomez M, Keuffel E, Frick KD (2002) Cost and effectiveness of hip protectors among the elderly. *Int J Technol Assess Health Care* 18:55–66
49. Singh S, Sun H, Anis AH (2004) Cost-effectiveness of hip protectors in the prevention of osteoporosis related hip fractures in elderly nursing home residents. *J Rheumatol* 31:1607–1613
50. Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J (2005) A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 9:1–160
51. Waldegger L, Cranney A, Man-Son-Hing M, Coyle D (2003) Cost-effectiveness of hip protectors in institutional dwelling elderly. *Osteoporos Int* 14:243–250
52. Willis MS (2002) The health economics of calcium and vitamin D3 for the prevention of osteoporotic hip fractures in Sweden. *Int J Technol Assess Health Care* 18:791–807
53. Zethraeus N, Borgstrom F, Jonsson B, Kanis J (2005) Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: Results based on the Women's Health Initiative randomized controlled trial. *Int J Technol Assess Health Care* 21:433–441
54. Borgstrom F, Zethraeus N (2003) [Economic assessment based on a clinical study of risedronate. Fracture prevention in elderly women with osteoporosis is cost-effective]. *Lakartidningen* 100:36–40
55. Johannesson M, Hedbrant J, Jonsson B (1991) A computer simulation model for cost-effectiveness analysis of cardiovascular disease prevention. *Med Inform (Lond)* 16:355–362
56. Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, Jonsson B (2005) Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. *Osteoporos Int* 16:6–14
57. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B (2000) Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 11:669–674
58. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D (2000) Risk of mortality following clinical fractures. *Osteoporos Int* 11:556–561
59. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 353:878–882
60. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd (1993) Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 137:1001–1005
61. Jalava T, Sarna S, Pylkkanen L, Mawer B, Kanis JA, Selby P, Davies M, Adams J, Francis RM, Robinson J, McCloskey E (2003) Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res* 18:1254–1260
62. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B (2004) Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 15:108–112
63. Parker MJ, Anand JK (1991) What is the true mortality of hip fractures? *Public Health* 105:443–446
64. Johnell O, Kanis JA, Oden A, Sembo I, Redlund-Johnell I, Pettersson C, De Laet C, Jonsson B (2004) Mortality after osteoporotic fractures. *Osteoporos Int* 15:38–42
65. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA (1998) Lifetime risk of hip fractures is underestimated. *Osteoporos Int* 8:599–603
66. Statistics Sweden. Sweden's Statistical Databases. In <http://www.scb.se/eng/databaser/ssd.asp>
67. Zethraeus N, Borgström F, Johnell O, Kanis J, Jönsson B (2002) Costs and Quality of Life Associated with Osteoporosis Related Fractures—Results from a Swedish Survey. Working Paper Series in Economics and Finance, 512
68. Burstrom K, Johannesson M, Diderichsen F (2001) Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res* 10:621–635
69. Kind P, Dolan P, Gudex C, Williams A (1998) Variations in population health status: results from a United Kingdom national questionnaire survey. *Br Med J* 316:736–741
70. Jonsson B, Christiansen C, Johnell O, Hedbrandt J, Karlsson G (1996) Cost-effectiveness of fracture prevention in established osteoporosis. *Scand J Rheumatol Suppl* 103:30–38
71. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J (2000) Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res* 15:1384–1392
72. Zethraeus N, Stromberg L, Jonsson B, Svensson O, Ohlen G (1997) The cost of a hip fracture. Estimates for 1,709 patients in Sweden. *Acta Orthop Scand* 68:13–17
73. Stockholms stads budgetavräkning 2003 [online]. In
74. Ekman M, Zethraeus N, Dahlstrom U (2002) Cost-effectiveness of bisoprolol in chronic heart failure. *Lakartidningen* 99(7):646–650
75. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348:1535–1541
76. Lauritzen JB, Petersen MM, Lund B (1993) Effect of external hip protectors on hip fractures. *Lancet* 341:11–13
77. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 344:333–340
78. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *Jama* 282:637–645
79. WHO (1999) Recommendations for health economics evaluations of interventions in osteoporosis. WHO Collaborating Centre for Public Health Aspects of Osteoporosis and other Rheumatic Diseases, Liège, Belgium
80. LFN [the Swedish drug benefits board]. General guidelines for the economic evaluation from pharmaceutical benefits board. LFNAR 2003:2
81. Zethraeus N, Johannesson M, Henriksson P, Strand RT (1997) The impact of hormone replacement therapy on quality of life and willingness to pay. *Br J Obstet Gynaecol* 104:1191–1195
82. Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M (1993) Measuring the impact of menopausal symptoms on quality of life. *Bmj* 307:836–840
83. Akehorst RPA, Brazier J (2000) Decision analytic modelling in the economic evaluation of health technologies. A consensus statement. *Pharmacoeconomics* 17:443–444

84. Sculpher M, Fenwick E, Claxton K (2000) Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics* 17:461–477
85. Briggs AH (2000) Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 17:479–500
86. Johannesson M (2001) At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? *Eur Heart J* 22:919–925
87. Almbrand B, Johannesson M, Sjostrand B, Malmberg K, Ryden L (2000) Cost-effectiveness of intense insulin treatment after acute myocardial infarction in patients with diabetes mellitus; results from the DIGAMI study. *Eur Heart J* 21:733–739
88. National Osteoporosis Foundation (1998) Osteoporosis: Review of the Evidence for Prevention, Diagnosis and Treatment and Cost-Effective Analysis. *Osteoporosis International* 8(Suppl 4): 1–88