

Review Article

Models for Assessing the Cost-Effectiveness of the Treatment and Prevention of Osteoporosis

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Introduction

Osteoporosis (low bone mass) implies that the risk of fractures increases. The increased risk of fractures leads to consequences for the individual and for the society as a whole. The societal costs that can be attributed to osteoporosis consist of costs for the treatment and prevention of osteoporosis and the costs associated with fractures. Common osteoporosis-related fractures are fractures of the hip, wrist and spine, which imply losses in the individual's quality of life and in some cases also an increased mortality risk. There are also costs associated with the treatment and rehabilitation of the fracture patients. In Sweden it is estimated that the annual costs of fractures amount to about 3 billion SEK, which is almost as high as the costs for diabetes or multiple sclerosis [1–3]. The treatment and prevention of osteoporosis-related fractures can either be based on medical or non-medical treatment strategies. The introduction of new medicines has increased the costs for treatment and prevention of osteoporosis. Some treatments only affect the risk of fractures whereas other treatments also have extra skeletal consequences. The annual drug costs for the treatment of osteoporosis varies depending on the chosen intervention strategy.

In a world with limited resources and health care budgets it is important to use resources efficiently.

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Economic evaluations can be used as a guide to efficient resource allocation in health care. To carry out economic evaluations in the osteoporosis field clinical studies must be complemented with modeling (see e.g. [4]). The purpose of modeling is to produce information beyond that which is available in clinical studies. Different approaches are presented in the literature and there is a need to investigate the different model alternatives and to discuss their strengths and weaknesses as a basis for assessing the cost-effectiveness of the treatment and prevention of osteoporosis.

The purpose of this paper is to review the health economic literature that assesses the cost-effectiveness of the treatment/prevention of osteoporosis. The paper identifies the underlying modeling approaches for the cost-effectiveness analysis and summarizes the features, weaknesses and strengths of different modelling alternatives. The paper unfolds as follows. Section 2 introduces the concept economic evaluation. Section 3 summarizes the reviewed studies, and detailed descriptions of the studies are presented in the next two sections. The issues are discussed in the next section and conclusions are formed in the final section.

Economic Evaluations

The Need for Economic Evaluations

Economic evaluation is a method for assessing costs and benefits of alternative ways of allocating resources to

assist decisions aimed at implying efficiency. An efficient allocation of resources implies that no further health gains can be achieved by allocating resources differently. In the osteoporosis field economic evaluations can be used for answering different health economic questions such as the following. Is it good value for money to treat osteoporosis at all given that resources can be used differently? Should we treat all women as a preventive measure or should we treat only high risk groups, e.g. those who have established osteoporosis? Which treatment should be used taking into account the costs and effects of the different treatments? To answer these and related questions, the costs of the intervention must be related to the benefits of the treatment. The costs of the intervention are, for example, costs for medication and the treatment of side effects, whereas the benefits of the intervention are, for example, the reduction in the risk of osteoporosis-related fractures, which increases the quality of life and length of life and decrease the fracture treatment and rehabilitation costs.

What is an Economic Evaluation

An economic evaluation involves a comparison of costs and benefits from alternative uses of resources and can be classified as cost-benefit analysis (CBA) or cost-effectiveness analysis (CEA). In a CBA, benefits and costs are measured in monetary units. Benefits are defined as the amount of money gainers of the program are willing to pay to make sure that the program is undertaken (willingness to pay (WTP)) and costs are defined as the compensation the losers of the program require to accept that the program is carried out. The benefits and the costs can also be expressed as compensating variation (*CV*) measures where a positive *CV* defines a benefit and a negative *CV* a cost. The measurement of WTP can be based either on observations of actual behavior or on expressed preferences. In the expressed preference approach, or contingent valuations method (CVM) survey methods are used to investigate the hypothetical WTP for a service or a good. Recently a number of health care applications have appeared [5–7].

CEA is based on maximizing health effects subject to a cost constraint [8]. Costs are measured in monetary units and health effects in non-monetary units such as gained life-years or quality adjusted life-years (QALYs). The most frequently used health outcome measures including quantity and quality of life are QALYs [9]. An economic evaluation that uses an outcome measure incorporating quantity and quality of life is usually denoted cost-utility analysis (CUA), which is a special case of CEA. QALYs are constructed by adjusting life years for the quality of life in which they are spent. To achieve this the number of years in different health states are multiplied by quality adjustment weights between 0 (=dead) and 1 (=full health), which reflect the relative desirability of the different states. The quality weights

can be estimated using direct methods such as the rating scale (RS), time trade-off (TTO) and standard gamble (SG). Another alternative is to use descriptive quality of life instruments that describe health status along a number of dimensions such as pain and mobility. One such instrument is the EuroQol questionnaire and recently a so-called social tariff was presented that generates TTO-values for EuroQol states [10–12].

CEA has often been based on a so-called decision-maker approach where the aim of the economic evaluation is to maximize whatever the decision-maker wants to maximize, and according to this approach it is up to the decision-maker to decide what costs and benefits to include. The strongest critique against this approach is that it lacks theoretical foundation in economic welfare theory and that the approach would likely lead to problems with suboptimization. Instead it has been argued that a CEA should be based on a societal perspective, which means that all costs and benefits in society should be included in the analysis. If the purpose of the CEA is to maximize social welfare given the limited resources, CEA should be based on a societal perspective meaning that all costs and benefits are incorporated in the analysis no matter who pays the costs or receives the benefits [13]. Using welfare economics as a theoretical basis of CEA provides guidance in controversial issues in CEA, e.g. whether to include costs in added life years resulting from a health care program. The most current practice in CEA is to include only costs for related illnesses. However it has been argued that all future costs should be included [14] and in a paper by Meltzer [15] that bases the CEA on the theory of welfare economics the conclusion is that all future medical and non-medical costs minus the value of production should be included. Note that the definition of costs has consequences for the threshold value in economic evaluation studies (see below).

In the case of preventive programs, it is useful to make a distinction between intervention, morbidity and mortality costs. Intervention costs are inputs that go into a health care program and consist of direct costs (e.g. costs for the drug and for physician visits) and indirect costs which depict production losses or losses in leisure time due to the treatment participation. Morbidity costs are resource consequences due to changes in morbidity (e.g. reduced risk of fractures) and consist of direct costs (e.g. the extra costs for the treatment and rehabilitation of a fracture) and indirect costs caused by the disease. Mortality costs (or costs in added life years) are the resource consequences due to changes in mortality and are estimated as the change in consumption (medical and non-medical) minus the change in production due to the change in mortality.

Decision Criteria in Economic Evaluations

Using a cost-benefit approach a program is accepted if the sum of benefits and costs (sum of *CV*'s) across individuals is positive [6]. To determine which health

program (if any) to implement using CEA the price per unit increase of health effects must be determined, e.g. the willingness to pay (WTP) for a QALY or a life year gained. Without information about the price per unit of health effects, a CEA gives no information about whether a program should be implemented or not, unless it is sorted out as a dominated alternative (e.g. the program has a higher cost and the same health effect compared to the alternative).

Data for Economic Evaluations

An economic evaluation requires cost and health effect data as reflected in the routine care of patients (e.g. when a drug is out on the market). To obtain such data a naturalistic study design can be used where patients are randomized to different treatment alternatives in a real world setting (e.g. a phase 4 study). Data for cost-effectiveness studies can also be obtained from randomized controlled trials (RCTs) where the main purpose is to investigate whether the treatment is safe and has an effect. The advantage of using a controlled trial as the base for the economic evaluation is that the results from the clinical study are of high internal validity showing whether a new therapy has an effect or not. The drawback is that the clinical study is of relatively low external validity, i.e. it does not reflect the costs and health effects for patients in routine care when the drug is out on the market. Alternatively a model-based approach can be used, which integrates clinical, epidemiological and cost data.

The Need for Modeling

To answer health economic questions as stated above modeling is needed because clinical trials cannot provide all the information that is required for the economic evaluation. Two of the most common techniques for modeling in economic evaluations are decision tree analysis and Markov modeling [9]. A limitation of decision-tree analysis is that it is not well suited for programs involving risks that are ongoing over time. In those cases the tree structure may become very complex, and Markov modeling has been suggested. In the osteoporosis field Markov modeling is used as the tool to obtain cost and health effect data for a relevant follow-up time. Markov models are useful when a decision problem involves risks that are ongoing over time (which is the case in the osteoporosis field), when the timing of events is important and when important events may happen more than once [16]. These models are represented by a finite number of (health) states in which an individual is found at any time. The model assumes that all individuals in a specific state are identical and that each individual obtains the same cost and health effect irrespective of the history of the individual, i.e. the model has no memory of prior states [16]. Markov models occur in a discrete time frame and

time progresses in units of arbitrary, but fixed, length (e.g. one year). A transition occurs when an individual moves from one state to the next and the transitions between states are determined by transition probabilities, which determine the allocation of individuals in each cycle. It is possible to model that, for example, transition probabilities, health effects and costs are a function of not only the state but also population characteristics such as age.

Selection and Overview of Studies

Studies that assess the cost-effectiveness of the prevention and treatment of osteoporosis and published in the period 1980–2001 were included in the survey. Only studies that define the effectiveness measure in terms of life years or QALYs were included. Since osteoporosis therapies may have consequences on different risks, 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 QALY 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. Papers have been searched for in HEED (Health Economic Evaluation Database). Also non-published working papers, technical reports and other papers have been included if decided relevant. The studies are divided into two periods; papers published in the period 1980–1992 and papers published in the period 1993–2001.

Between 1980 and 1992 five studies are found in the literature carried out by the same US-research group [17–21]. They all assess the cost-effectiveness of treatment with hormone replacement therapy (HRT) or screening for low bone mass and treating high-risk groups (see also [4] for a review of four of these papers). Cheung and Wren [22] use the same model framework as Weinstein and Schiff [18] to evaluate the cost-effectiveness of HRT in an Australian context. This period also includes a paper from the UK [23] that assessed the cost-effectiveness of HRT in a British setting. The period 1993–2001 consists of papers mainly from outside the US. The first study by Jönsson et al. [24] develops a fracture model that is later applied in Jönsson et al. [25]. Tosteson [26] updated previous work and assessed the cost-effectiveness of HRT and Geelhoed and Harris [27] assessed HRT and a life style intervention. The following year the Office of Technology Assessment (OTA) assessed strategies for screening women for bone density and treating those with low bone density with HRT [28]. In Daly et al. [29] the cost-effectiveness of HRT was assessed. Later Zethraeus et al. [30] presented a model for assessing the cost-effectiveness of HRT. This model is applied in Zethraeus et al. [31] where the cost-effectiveness of HRT is analyzed and by Jönsson et al. [32] who

investigated the cost-effectiveness of treatments that reduce the risk of hip fractures. The model is also applied by Kanis et al. [33] who assessed the cost-effectiveness of treatments that reduce the risk of hip fracture, and later on by Kanis et al. [34] who calculated, given the threshold value, the risk level at which a treatment is cost-effective. Willis et al. [1] presents a model to assess the cost-effectiveness of tibolone. Tosteson et al. [35] developed a model aimed at evaluating the cost-effectiveness of osteoporosis interventions among various population subgroups. Finally, Johnell et al. [36] presents a model that is used for assessing the cost-effectiveness of a bisphosphonate (alendronate).

A summary of the 22 included studies is given in Table 1, which gives information on assessed therapies, included disease states, model structure and set time. Thirteen studies only assess the cost-effectiveness of HRT, six studies investigate the cost-effectiveness of non-specific fracture therapies, and three studies assess the cost-effectiveness of tibolone, HRT and a life style intervention, and alendronate. Models used for bone specific therapies (e.g. bisphosphonates or non-specific fracture therapies) always include hip fracture as a disease state and usually also other fractures of the wrist and spine as well. Models intended for therapies with extra skeletal effects (i.e. HRT) always include hip fracture and breast cancer and usually also coronary

Table 1. Identification of included disease states

Studies in the period 1980–2001	Assessed therapy(ies)	Included disease states					Fracture incidence model	Set time after fracture		
		Fracture states		Cancer States		CHD			Stroke	Gallstones
		Hip	Other	Breast	Endometrium					
1. Weinstein, 1980 [17]	HRT	X	X	X	X			X	X	X
2. Weinstein and Schiff, 1983 [18]	HRT	X	X	X	X			X	X	X
3. Weinstein and Tosteson, 1990 [19]	HRT	X		X	X					X
4. Tosteson et al., 1990 [20]	HRT	X		X		X				NA
5. Tosteson and Weinstein, 1991 [21]	HRT	X		X		X				X
6. Cheung and Wren, 1992 [22]	HRT	X	X	X	X	X				NA
7. Daly et al., 1992 [23]	HRT	X	X	X	X	X	X		X	X
8. Jönsson et al., 1993 [24]	Fracture therapies	X	X						X	X
9. Tosteson, 1994 [26]	HRT	X		X		X				NA
10. Geelhoed and Harris, 1994 [27]	HRT and life style	X		X	X	X				X
11. OTA, 1995 [28]	Screening and HRT	X		X	X	X		X		X
12. Jönsson et al., 1995 [25]	Fracture therapies	X	X						X	X
13. Daly et al., 1996 [29]	HRT	X	X	X	X	X	X		X	X
14. Zethraeus et al., 1998 [30]	HRT	X		X		X			X	X
15. Zethraeus et al., 1999 [31]	HRT	X		X		X			X	X
16. Jönsson et al., 1999 [32]	Fracture therapies	X		X		X			X	X
17. Zethraeus et al., 2000 [44]	HRT	X	X	X		X			X	X
18. Willis et al., 2001 [1]	Tibolone	X	X							X
19. Kanis et al., 2001 [33]	Fracture therapies	X		X		X			X	X
20. Tosteson et al., 2001 [46]	Fracture therapies	X	X						X	X
21. Johnell et al. (In press) [36]	Alendronate	X	X						X	X
22. Kanis et al. (In press) [34]	Fracture therapies	X		X		X			X	X

CHD, coronary heart disease.

Table 2. Included cost data; 1–22 corresponds to the papers defined in Table 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Osteoporosis screening				X				X			X	X		X			X					
Intervention	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breast cancer	X	X	X	X	X	X	X		X	X	X		X	X	X	X			X			X
Endometrial cancer	X	X	X			X	X			X	X		X									
Cholecystectomy	X	X									X											
Stroke							X						X									
Hip fractures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other fractures	X	X				X	X	X				X	X				X	X		X	X	
CHD						X	X		X	X	X		X	X	X	X	X		X			X

Table 3. Included health effect data; 1–22 corresponds to the papers defined in Table 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
<i>Mortality data</i>																						
Hip fractures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other fractures																	X					X
Stroke									X				X									
CHD				X	X	X	X		X	X	X		X	X	X	X			X			X
Breast cancer	X	X	X	X	X	X	X		X	X	X		X	X	X	X			X			X
Endometrial cancer	X	X	X			X	X			X	X											
<i>Quality of life data</i>																						
Improvements of therapy	X	X	X	X	X	X	X	X	X			X	X	X	X	X			X	X	X	X
Hip fractures	X	X	X		X			X	X	X		X		X	X	X		X	X	X	X	X
Other fractures								X				X					X	X		X	X	
CHD													X	X	X	X			X			X
Breast cancer													X	X	X	X			X			X
Endometrial cancer	X	X	X	X																		
Cholecystectomy																						
Side effects of therapy		X		X	X	X		X	X			X	X	X	X	X			X	X	X	X

Table 4. Type of costs included in the different papers between 1980 and 2001

Studies in the period 1980–2001	Intervention costs		Morbidity costs		Mortality costs		
	Direct	Indirect	Direct	Indirect	Medical costs		Non-medical costs minus production
					Related	Unrelated	
1. Weinstein, 1980 [17]	X		X		X		
2. Weinstein and Schiff, 1983 [18]	X		X		X		
3. Weinstein and Tosteson, 1990 [19]	X		X		X		
4. Tosteson et al., 1990 [20]	X		X		X		
5. Tosteson and Weinstein, 1991 [21]	X		X		X		
6. Cheung and Wren, 1992 [22]	X		X		X		
7. Daly et al., 1992 [23]	X		X		X	X	
8. Jönsson et al., 1993 [24]	X	X	X	X	X		
9. Tosteson, 1994 [26]	X		X		X		
10. Geelhoed and Harris, 1994 [27]	X		X		X		
11. OTA, 1995 [28]	X		X		X		
12. Jönsson et al., 1995 [25]	X		X		X		
13. Daly et al., 1996 [29]	X		X		X	X	
14. Zethraeus et al., 1998 [30]	X	X	X	X	X	X	X
15. Zethraeus et al., 1999 [31]	X	X	X	X	X	X	X
16. Jönsson et al., 1999 [32]	X		X		X	X	X
17. Zethraeus et al., 2000 [44]	X	X	X	X	X	X	X
18. Willis et al., 2001 [1]	X		X		X		
19. Kanis et al., 2001 [33]	X		X		X		
20. Tosteson et al., 2001 [46]	X		X		X		
21. Johnell et al. (In press) [36]	X		X		X		
22. Kanis et al. (In press) [34]	X		X		X	X	X

heart disease. In the beginning of the period these studies usually include the risk of endometrial cancer and in some cases also the risk of gallstone disease.

In the beginning of the period bone mineral density (BMD) models were commonly used but from 1995

there is a shift to fracture-incidence models, which means that age-specific absolute risks are estimated instead of using a function that related BMD to the risk of fracture. A majority of studies assume that the risk of fracture is also reduced after the cessation of therapy.

Tables 2 and 3 show the cost and health effect (quality of life and mortality) data that have been included in the different papers. Studies assessing the cost-effectiveness of therapies with extra skeletal effects always include cost and mortality data related to hip fracture and breast cancer and since 1992 coronary heart disease cost and mortality data are always incorporated. The quality of life related to hip fracture is always considered and at the end of the period the effect of breast cancer and coronary heart disease on quality of life are also taken into consideration. Studies assessing the cost-effectiveness of bone specific therapies always include cost, mortality and quality of life data related to hip fractures. Finally, Table 4 shows the type of costs that are included in the different papers. Studies between 1980 and 1995 include direct costs for intervention and morbidity and related medical costs in added life years. Since 1998 indirect intervention and morbidity costs are often allowed for as well as non-related medical costs and non-medical costs minus production in added life years.

Studies Between 1980 and 1992

The purpose of the study by Weinstein [17] was to assess the cost-effectiveness of HRT for women at menopause. For the most part the analysis is restricted to women in whom the uterus is in situ and for whom there is an increased endometrial cancer risk. Three subpopulations were studied: women with menopausal symptoms treated between age 50 and 60 years, women with established osteoporosis treated between age 55 and 70 years, asymptomatic women treated between age 50 and 65 years. Weinstein [17] included risks for breast cancer, endometrial cancer, gallstone disease, hip fracture and wrist fractures. The health care costs were defined as costs of treatment (drugs, physician visits, routine tests), costs for side effects and complications (endometrial cancer, cholecystectomy and uterine bleeding), minus the savings to decreased risk of hip and wrist fractures. The effectiveness measure was defined as life years gained or QALYs gained. The risks were based on the epidemiological and medical literature. For example, age-specific incidence rates for hip and wrist fracture were estimated based on epidemiological data. The HRT changes the base line risks of the included disease risks. Quality adjustments were made for illustrative purposes and were specified for the relief of menopausal symptoms (assumed to be 0.01), endometrial cancer and hip fractures (assumed to be equal to a loss of 0.05). They concluded that treatment appears to be relatively cost-effective in menopausal women with prior hysterectomy or osteoporosis. The cost-effectiveness of the treatment of asymptomatic women with intact uterus is questionable.

In Weinstein and Schiff [18] the previous analysis was updated with a focus on the cost-effectiveness of estrogen combined with progestin compared with estrogen therapy alone. The study considered new medical findings that the addition of progestin decreases

or eliminates the increased risk of endometrial cancer caused by estrogen alone. The indication for treatment (5, 10 or 15 years treatment duration) was women with an intact uterus and aged 50 years. The conclusion was that the combined therapy was cost-effective compared with estrogen therapy alone unless adverse effects of continued menstruation offset the relief of menopausal symptoms.

Weinstein and Tosteson [19] update the previous work including new evidence on the relationship between fracture risk and bone mineral density estimated by Melton et al. [37]. For the most part, methods, assumptions and data sources follow those described in Weinstein and Tosteson [18]. The purpose of the study is to assess the cost-effectiveness of HRT for 50-year-old symptomatic and asymptomatic women for treatment duration of 5 and 15 years. The included disease states were breast cancer, endometrial cancer and hip fractures. Gallstone disease and wrist fractures were excluded compared to previous studies. The reason for excluding these disease states was that in previous studies they were found to be of minimal importance for the cost-effectiveness results. They found that HRT compares favorably with many accepted clinical practices. The results are sensitive to the assumed changes in quality of life during treatment.

The purpose of the study by Tosteson et al. [20] was to assess the cost-effectiveness of screening women with an intact uterus for bone density and placing those with low bone density on long-term combined HRT. Tosteson et al. [20] present a state transition computer model. A hypothetical cohort of women assumed to be well initially was followed from 50 to 100 years of age. The model uses transition probabilities to redistribute the cohort each year among a set of health states. The annual probabilities depend on the patient's current health state, age and bone mineral density. The study included risks for breast cancer, hip fracture and coronary heart disease. To each health state was linked a cost and morbidity measure. The state transition model was used to calculate the incremental cost-effectiveness ratio defined as the ratio of the difference in costs and difference in effectiveness. The numerator was defined as costs of HRT + costs of the screening test and savings due to the prevention of hip fracture. The effectiveness measure was defined in terms of life years and quality adjusted life years. The baseline risk of fractures was estimated by using a risk function relating age and bone mineral density to the risk of fracture. This relationship was obtained from Melton et al. [37], who based their estimations on a population in the US (Minnesota). HRT was assumed to stop the bone loss during treatment. In summary, it was concluded that screening women with intact uterus and placing those with bone density below 1.0 g/cm^2 is cost-effective.

Cheung and Wren [22] assessed the cost-effectiveness of HRT for women in the menopause in an Australian context. HRT was evaluated for different treatment periods (at the age of 50–55, 50–60, 50–65 years), uterus

status and symptom status. Included disease states were breast cancer, endometrial cancer, coronary heart disease, hip and wrist fractures. The model simulates the one described by Weinstein and Schiff [18] with the exception that gallstone disease was excluded and coronary heart disease was added. The same quality weights are used as in Weinstein and Schiff [18], and age-specific fracture incidence rates were obtained from the epidemiological literature. It was concluded that HRT is cost-effective for symptomatic women. Short-term treatment of asymptomatic women is an inefficient use of health care resources. The cost-effectiveness results for asymptomatic women are dependent on the cardiac benefits associated with the HRT.

The purpose of the study by Daly et al. [23] was to evaluate the cost-effectiveness of HRT in a British setting and to identify which factors most influence the cost-effectiveness results. The treatment options were: treating hysterectomized women with estrogen alone, treating non-hysterectomized women with combined therapy, and treating non-hysterectomized women with estrogen therapy. In the base case a 50-year-old woman was treated for 10 years. Daly et al. [23] include breast cancer, endometrial cancer, coronary heart disease, stroke, hip wrist and spine fractures. The fracture risks were based on epidemiological findings. Data on other risks were based on a combination of different sources in the medical literature and national statistics. The potential reduction in cardiovascular disease is the factor that most influences the cost-effectiveness results and overshadows any small increases in the breast cancer risk. Long-term prophylactic treatment of hysterectomized women and treatment of symptomatic women with a uterus compared favorably with other accepted interventions.

Studies Between 1993 and 2001

In Jönsson et al. [24] a technical description is presented of a computer model including hip, vertebrae, forearm and other fractures (Fig. 1). The model is a fracture model of a Markov type that consists of seven related parts. The health states that are included are: healthy, hip fracture first year, hip fracture second and following

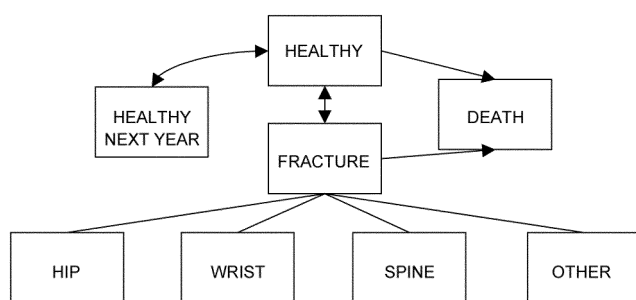


Fig. 1. Model structure for evaluating the cost-effectiveness of fracture prevention in Jönsson et al. [24].

years, vertebrae fracture first year, forearm fracture first year and other fracture first year, and dead. A healthy population is subject to risks of having a fracture over the lifetime. The model can follow the population (set to 1000 initially) and keep track of the patient distribution each year. The intervention decreases the risk of fracture, which means that the population will be distributed differently among health states each year. To each health state there is linked a cost and quality of life weight. By summing costs and health effects for all patients for all years the total costs and health effects are obtained for the natural course (without treatment). The intervention affects the transition probabilities and implies a different allocation of individuals each year. An application of the model is found in Jönsson et al. [25] where the cost-effectiveness of the treatment of a 62-year-old woman is investigated. A five-year treatment duration was assumed and a risk reduction of 50% during treatment. The annual intervention cost was assumed to be SEK 6000. The resulting cost per gained QALY was estimated at SEK 107 000 which was similar to the cost-effectiveness ratio of treating the same women for mild hypertension.

In a review and update of the cost-effectiveness of HRT, Tosteson [26] used the results from a meta-analysis [38] to model the HRT consequences on disease risks. The included disease states were: hip fracture, breast cancer and coronary heart disease. Women with an intact uterus were given combined therapy while other women were supposed to be given estrogen alone. In terms of cost per gained life year the estimates range from US\$ 15 300 for women receiving unopposed estrogen to US\$ 56 000 for women receiving combined therapy under an unfavorable scenario. The corresponding cost per quality adjusted life year gained was generally lower. The author concluded that the cost-effectiveness of HRT compared favorably with other accepted interventions in the health care.

Geelhoed and Harris [27] assessed the cost-effectiveness of HRT and a life-style regime including calcium and exercise. Effectiveness was defined as life years and quality adjusted life years. Costs included medical costs and costs for nursing home stay. Lifetime estrogen therapy initiated at 65 years involved the lowest cost per unit increase in effectiveness (\$ 8500 per gained quality adjusted life year) whereas the opposite holds for the exercise program (\$ 94 900 per gained quality adjusted life year). The results were sensitive to the effect on heart disease. A decision model based on a Markov process was used in which four intervention strategies were analyzed and compared with no intervention. The four interventions were: life time HRT initiated at the age of 50 years, HRT between age 50 and 65 years, life-time HRT initiated at the age of 65 years, and life-style intervention regimen of dietary calcium supplementation and exercise. The model included disease states such as hip fracture, heart disease, breast cancer and endometrial cancer. The base case risk of fractures was collected based on the equation estimated by Melton et al. [37]. Incidence rates of heart disease was taken from national

data sources and medical data [39,40]. HRT was assumed to decrease the risk of heart disease by 50% based on a meta-analysis [41]. The risk of breast cancer was assumed to increase by a factor 1.02 n where n denotes the number of years since HRT was initiated [42]. For estrogen users the risk of endometrial cancer was increased by a factor 8. No increased mortality was assumed to follow endometrial cancer. During HRT no bone loss was assumed. After the cessation of HRT bone mass decreased and was equal to no intervention in five years. The life-style intervention strategy was assumed to slow the rate of bone loss by 50%. The mortality after hip fracture was assumed to increase with age from 2% at the age of 50 to 20% over 85 years. Breast cancer and heart mortality were obtained from the Western Australia Hospital Morbidity Data System and endometrial mortality and incidence rates were obtained from the South Australian cancer registry. Costs included only direct costs and were expressed in 1991 Australian dollars. A woman returning home after hip fracture was assigned a quality weight of 0.9 (consistent with Weinstein and Schiff [18]). Women entering a nursing home were assigned a weight of 0.67 (based on the utility formula in [9]). No quality adjustment was made for the other disease states. Costs and health effects were discounted at a 5% rate.

Office of Technology Assessment (OTA) [28] assessed the costs and effectiveness of screening women for bone density at age 50 or at age 65 and placing women with low bone density on long-term HRT (at least 10 years). Based on a review of the literature OTA judged the following disease risks to be affected by HRT: hip fracture, coronary heart disease, breast cancer, endometrial cancer and gallbladder disease. Vertebral and wrist fractures were not included due to the lack of good health care cost data and because their exclusion are not likely to affect the conclusions. Effectiveness was defined as life years gained. No quality adjustment was made due the lack of data on quality of life weight for many of the disease states. Costs for screening, HRT, hospital care, nursing home care and other long-term care for disease related disabilities were included. No costs for family/friends and indirect costs as well as (production-consumption) were included. HRT is defined as estrogen alone or estrogen combined with estrogen. In the base case scenario OTA assumes that HRT completely stops the bone loss during treatment (BMD-based model), a 35% increase in breast cancer risk after long-term therapy, a 150% increase in the risk of gallbladder disease during treatment. The risk of endometrial cancer is assumed to increase by 600% during estrogen-only treatment and no increase if on combined therapy. The risk of coronary heart disease during treatment is supposed to decrease by 50 and 20% if the women are treated with estrogen only or combined therapy, respectively. OTA conclude that screening and treating (estrogen only) women with low bone density produced a reasonable cost per life years gained (\$27 000). Universal treatment costs \$23 000 per gained life year. The cost per gained life year is very

sensitive to the assumption of a reduction in the coronary heart disease. If it is assumed that the risk of coronary heart disease is unaffected the cost per gained life year according to the above increases to \$155 000 and \$450 000, respectively. Using combined therapy for screening and treating those with low bone mass or universal treatment, produced a cost per gained life year of about \$71 000. Assuming no effect on coronary heart disease implies a substantial increase in the cost-effectiveness ratios.

In Daly et al. [29] the cost-effectiveness of treatment strategies for HRT was assessed within the framework of a computer model. Disease states considered in the model were: endometrial cancer, breast cancer, hip fracture, wrist fracture, spine fracture, ischemic heart disease and stroke. Two treatment strategies were considered: treating hysterectomized women with estrogen only therapy (ORT), and treating non-hysterectomized women with combined estrogen-progestogen replacement therapy (CRT). The risk of endometrial cancer is not assumed to increase for CRT users. The risk of breast cancer is assumed to increase by 30% following 10 years of therapy, and 50% following 15 years of use. The risk was assumed to remain elevated after discontinuation of treatment for a period equal to the period of treatment. The risk of fractures was assumed to decrease by 20% during the first 5 years of therapy followed by a 60% reduction if continued. After the cessation of therapy the risk was assumed to persist for a period equal to the period of treatment. The risk of ischemic heart disease was assumed for ORT users to decrease by 25% after 5 years of therapy and by 50% following 10 years' use, with risk remaining reduced after cessation of therapy for a period equal to the period of treatment. For CRT users half the risk reduction was assumed. A 25% risk reduction for stroke was assumed for ORT users whereas the reduction following the use of CRT was assumed to be 12.5%. The costs included in the analysis consisted of: expected life-time costs of therapy (costs for the drug and monitoring), expected costs of treating side effects, expected savings/increases in costs from reduced/increased morbidity, and expected costs of treating patients during increased life expectancy (only costs for health care expenditure). The conclusion is that treatment of symptomatic menopausal women for any period of time offers good value for money. However, it is difficult to draw conclusions about the cost-effectiveness of treating non-hysterectomized asymptomatic women for prophylactic reasons.

In Zethraeus et al. [30] a computer model is designed to analyze the cost-effectiveness of hormone replacement therapy (HRT) in the prevention/treatment of postmenopausal women's health problem. The computer model is programmed in C++ and built as a Markov type model around menus in a Microsoft Windows environment. The computer model is developed to analyze the cost-effectiveness of HRT and is evaluated using a cohort simulation. The model integrates two previously described computer models: one used for cardiovascular-disease prevention and one for fracture

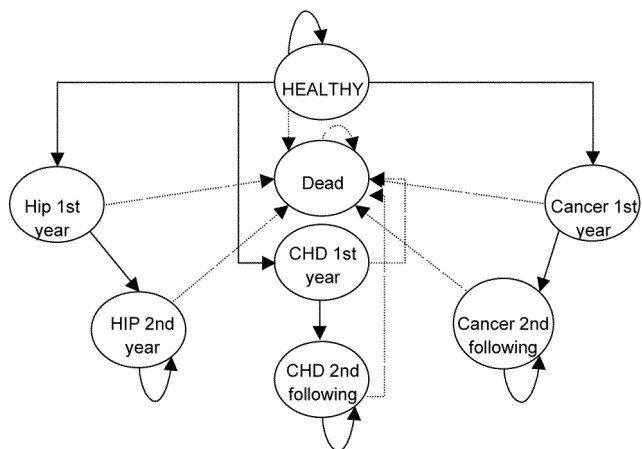


Fig. 2. Model structure for evaluating the CE of HRT in Zethraeus et al. [30].

prevention [24,43]. The model's overall structure showing the included health states are illustrated in Fig. 2. These basic health states are: 1, healthy; 2, hip fracture first year; 3, hip fracture following years; 4, breast cancer first year; 5, breast cancer following years; 6, CHD first year; 7, CHD following years; and 8, death.

Each disease state is characterized by age-dependent mortality rates, costs and quality of life weights. Hip fractures, breast cancer and CHD are divided into 'first' and 'second and following years' after a disease event since mortality rates, costs, and quality of life differ between these time periods. When a disease event occurs, the patient will stay in that state or transition until 'death'. At present, there are no transitions between health states after an event such as hip fracture to CHD or CHD to breast cancer. Solving this problem can be done in two ways. One way is to introduce new states such as a hip fracture after CHD. The problem is that the model becomes very complicated and difficulties with data arise. An alternative is to include the risks and costs of the other two diseases in the sequel after an event. The latter approach has been taken in this model. The basic model structure assumes a healthy cohort of individuals in its initial population group (the cohort size can vary between 1 and 100 000); whereby, 'healthy' means free from CHD, breast cancer and hip fractures. At each cycle of the process, the cohort is reallocated to health states according to specified transition probabilities. All transitions are assumed to occur instantaneously halfway through each cycle. In the first cycle the cohort is exposed to disease risks of CHD, breast cancer and hip fractures as well as the risk of dying from other causes. A patient experiencing a disease event can only transit to death or 'post-disease event'. Patients in 'post-disease events' can only remain in that state or transit to death. The cohort is followed until age 110 years. The cost-effectiveness formula used in the computer model can be expressed as:

$$\frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0} =$$

$$\frac{\Delta INT + \Delta MORB + \Delta MORT}{\Delta QLE} =$$

$$\frac{\Delta INT + \Delta MORB + \Delta MORT}{\Delta LE = \Delta LEQ}$$

where ΔINT = intervention costs, direct and indirect; $\Delta MORB$ = changes in morbidity costs, direct and indirect, due to the intervention; $\Delta MORT$ = changes in mortality costs, direct and indirect, due to the intervention; ΔLE = changes in life expectancy due to the intervention; ΔLEQ = Changes in quality of life measured in years due to the intervention (where 'quality of life' refers to changes in morbidity and side effects); $\Delta QLE = \Delta LE + \Delta LEQ$.

The model allows for the inclusion of costs in added life years. Costs in added life years are defined as [consumption-production]. The model permits the cost-effectiveness ratio to be expressed either as costs per life year gained or costs per quality adjusted life year gained. As the model incorporates consequences for different diseases, effectiveness measures, such as number of events avoided from an intervention, do not provide meaningful information. Instead a composed outcome measure is needed, which incorporates the interventions effectiveness for different risks.

Intervention costs (ΔINT) are divided into yearly and initial costs. Yearly costs consist of direct and indirect costs. Direct costs for an intervention include the following: cost of drug, costs for services in hospitals (physician visits), primary health care and traveling costs. Indirect costs reflect resources foregone due to the treatment (e.g., production losses). These costs are particularly relevant for primary prevention when healthy time is used for the interventions (e.g., physician visits). Initial costs consist of direct and indirect costs and may, for example, be costs for screening patients to be treated. Changes in morbidity costs ($\Delta MORB$) consist of costs saved because of reduced morbidity from CHD and hip fractures and costs added because of increased morbidity from breast cancer. The change in morbidity costs are divided into changes in direct and indirect costs. The model also permits the inclusion of changes in mortality costs ($\Delta MORT$). Changes in mortality costs are equal to changes in total consumption minus changes in the total production due to a change in mortality from the intervention [15].

The model is applied in Zethraeus et al. [31] who investigated the cost-effectiveness of HRT given for asymptomatic women in 10 years. Depending on uterus status and age (50,60,70 years) six independent treatment groups were identified. The annual average intervention cost was estimated at SEK 2000. The cost-effectiveness ratio improved with age and if hysterectomized women were treated. Another application is found in Jönsson et al. [32] who assessed the cost-effectiveness of a 5-year

intervention that reduces the risk of hip fracture by 50% compared to no intervention. The treatment was defined as cost-effective if the cost per gained QALY was below US\$ 30 000. After the 5-year treatment duration the risk adjusted back to normal after another five years. The treatment was studied in different age groups (50,60, 70,80 years) and for patients with normal initial and a twofold increase in initial fracture risk. The study showed reasonable cost-effectiveness for women with a risk twice the average at the age of 70 or more years. The cost-effectiveness was critically dependent on the offset of effect after the end of treatment. Assuming no residual effect it was difficult to show any cost-effectiveness from any intervention except for the most effective and least costly. A further use of the model was to investigate whether treatments that reduce the risk of hip fracture is cost-effective in the general population at average risk [33]. Recently the model is also applied where the purpose is to determine the threshold of fracture probability at which interventions become cost-effective [34].

The model presented in Zethraeus et al. [30] is modified in a paper by Zethraeus et al. [44]. The purpose of that paper was to analyze the consequences of the addition of spine and wrist fractures and also to analyze the consequences of replacing the Framingham risk and mortality data with Swedish risk and mortality data for CHD. Spine and wrist fractures are modeled as temporary states. This means that after being in the wrist or spine fracture state for one year the individual is transferred back to healthy. The occurrence of more than one fracture during a year after a spine or wrist fracture can be incorporated in the model by the definition of costs and quality of life. By defining the costs during one year after, for example, a wrist fracture, as the extra costs that occur during the year after fracture (in orthopedics geriatrics, nursing homes caused by the first and possible also other fractures) also the consequences of more than one fracture is considered. The paper concludes that the cost-effectiveness of HRT is not sensitive to the above changes.

Willis et al. [1] develop a Markov model of osteoporosis to estimate the costs and health benefits of tibolone therapy compared to no therapy for postmenopausal women with an increased fracture risk. A hypothetical cohort of women assumed to be initially free of osteoporosis-related fractures is followed for a period of 25 years. Each year the cohort is subject to risks of fractures of the hip, spine and wrist and the risk of dying. After a hip fracture the woman remains in one of three post-fracture disease states: healed (50%), partially healed (40%) and permanently disabled (10%). Women that sustain a wrist or spine fracture recover after the first year and return back to healthy. The risk of hip fracture is estimated based on a risk function that relates the risk of fracture to BMD and age [37]. The risk of spine and wrist fracture was estimated based on a sample of women from Malmö, Sweden. The intervention was modelled as an increase in BMD. The quality weights are obtained from Jönsson et al. [24,25], whereas the hip fracture costs are based on Zethraeus and Gerdham [45] and assumptions. Wrist and spine

fracture costs are based on assumptions on how the patient is treated. The cost per gained quality adjusted life year was about SEK 200 000 and it was concluded that the use of tibolone compared to no intervention was cost-effective.

Tosteson et al. [46] present a model for assessing the cost-effectiveness of the treatment of osteoporosis. The model is constructed around health states and to be applicable for different subpopulations at different risks and for different countries. The model mimics the natural course of osteoporosis for women between 50 and 100 years. Quality adjusted life years are used as the effectiveness measure. A Markov state transition mode is developed and implemented in a Microsoft Excel environment. The model requires data on fracture incidence, mortality, costs and quality of life. The distribution among health states in each point in time is governed by the transition probabilities, which are collected from clinical and observational trials. The model allows the user to specify country-specific fracture and mortality rates, relative risks of hip, vertebral, wrist and other fracture. Further the age of treatment initiation and treatment duration can be adjusted. The authors then discuss some issues that relate to osteoporosis modeling: modeling approach, defining health states, mortality after hip fracture, accounting for the costs of long-term care, health utilities for estimation QALYs, and model validation. A fracture incidence-based model is chosen. The reason for this the authors argue, is that BMD alone is an incomplete measure of fracture risk. Other factors that can predispose patients to fracture are, for example, family history of hip fracture, height, and visual acuity. What disease states to include depends on the indication for the treatment. If established osteoporosis is the indication for therapy other disease events such as coronary heart disease and breast cancer can be excluded. On the other hand if preventive treatment actions are considered that have extra skeletal effects also other disease states (breast cancer and coronary heart disease) should be included. Tosteson et al. [46] included hip, wrist, and vertebral fractures because they are often considered the primary clinical manifestation of osteoporosis. To allow for the inclusion of other fractures such as fracture of the rib, ankle and distal femur a disease state denoted 'other fractures' was added. The present health state and age rule transitions to future health states. Long-term health states were: healthy, healthy post-hip fracture, healthy postvertebral fracture, healthy post-second hip fracture and death. Short-term disease states were: hip fracture, vertebral fracture, wrist fracture, and other fracture. The authors assume that 50% of observed mortality after the hip fracture is due to the hip fracture. No increased mortality was assumed for the other fracture types. Costs of long-term care were calculated as a weighted average for all patients in the population. The model requires a quality weight for each health state in the model. Either the patient or the society should be used as the source for quality weight estimation. Each fracture state was

assigned a quality of life weight that was lower than age-specific quality of life weights for the general population. Finally the model was validated in terms of face validity, predictive validity and by comparing it with an existing model. Face validity addresses the question of whether model structure, data and assumptions are in line with clinical experience and published literature and was assessed by a steering committee and a global technical team. Predictive validity was assessed based on the model ability to predict life expectancy and fracture risk. Finally, the authors discuss that modeling is necessary in many settings and an advantage of modeling is the flexibility of models of considering different treatment scenarios and making cost-effectiveness projections beyond what is available in randomized controlled trials. They further state that the exclusion of other fractures (distal femur, ankle, rib) is due to the lack of data and that those disease states should be included in the future. Finally they state that modeling has limitations, which result from the fact that models are used when direct evidence for the treatment is missing. This limitation can be overcome partly by using sensitivity analysis. Finally it is concluded that the challenges highlighted in the paper will face anyone undertaking a model-based cost-effectiveness analysis of postmenopausal osteoporosis interventions. However, there will be different answers depending on the indication for the treatment (preventive treatment vs. treatment of established osteoporosis).

Johnell et al. [36] assessed the cost-effectiveness of alendronate for the treatment of osteoporosis and prevention of fractures. A Markov model was used to simulate a cohort of initially healthy females. A cycle length of 1 year was used. All patients start in the well health state. Each year the patients are subject to risks of dying or having a fracture. If the patient died she remains in that health state for the rest of the simulation. Three health states are defined as new fractures: hip fracture, spine fracture and wrist fracture. After one year in the spine and wrist fracture state the patient (if the patient did not die) moves back to the well health state. After one year in the hip fracture state the patient moves to post-hip health state following a hip fracture. In the base case scenario a hypothetical cohort of osteoporotic patients (age 71 years) transitioned through the model until they were 100 years old or dead, whichever came first. The base case analysis focused on Swedish women comparable to those in the Fracture Intervention Trial (FIT) vertebral fracture arm, i.e. age 71 years with low bone mass and at least one prior spine fracture. The base case treatment duration was assumed to be 5 years. The base line risk of fracture was collected from an observational study in the south of Sweden. The base line risk in the osteoporotic group was computed based on the relation between the risk of fracture in the FIT study and the risk in the general US population. The costs for a spine and wrist fracture were assumed to be SEK 16 000 and SEK 4000, respectively. The first-year cost of a hip fracture was assumed to be SEK 181 000. The hip fracture cost in the second and following years was assumed to be SEK

41 000. Only direct costs were included in the analysis. The annual cost for alendronate was SEK 4322. In addition to the drug cost there were costs for one specialist visit (SEK 1192) each year and a bone mineral density measurement (SEK 350) every second year. Thus SEK 1367 per patient must be added resulting from the monitoring of the therapy. Alendronate decreased the risk of fracture during treatment and also during a set-time of 5 years, where the risk adjusted linearly towards the risk without treatment. Mortality for patients free from fracture was assumed to be the same as for the general population. Normal mortality was also assumed for patients the first year after hip fracture in the age group 50–64 years; 10% mortality in the age group 65–74 years and 20% in the age group 75–84 years and 50% for women older than 84 years. The quality of life after spine and wrist fracture was assumed to be 90% and 95% of the quality of life of a healthy person, respectively. The quality of life weight for the first year after hip fracture was assumed to be 0.7 (50–64 years), 0.59 (65–74 years) and 0.43 (75 years). The quality of life weight for the second and following years after hip fracture was assumed to be 0.8 (50–64 years), 0.69 (65–74 years) and 0.53 (75+ years). The resulting incremental cost-effectiveness ratio was estimated at SEK 76 000. In a sensitivity analysis, length of intervention, starting age of cohort, quality of life of fracture and set-time were varied. The authors concluded that alendronate was good value for money and that the results are stable to changing some of the basic assumptions.

Discussion

To assess the cost-effectiveness of the treatment and prevention of osteoporosis modeling is required. The models in the review are so called state transition Markov models, characterized by disease states and transition probabilities, which reallocates a hypothetical population between defined disease states once a year. The models are data hungry and require data on transition probabilities (disease risks), mortality risks, quality of life weights, and costs. The models also need information about how an intervention affects the disease risks during and after the cessation of a therapy. The effect of the intervention should be based on the best level of data and clearly stated. First it can be based on RCTs with hard end points like hip, spine and wrist fractures. Second, RCTs with surrogate endpoints like BMD can be used. The relation between surrogate end points and hard end points are, however, not clear and questioned. Third, a 'what-if' calculation is needed if there is no RCT defined and also for the sensitivity analysis.

To assess Markov models either cohort or individual Monte Carlo simulation can be carried out. 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 [47].

The majority (64%) of previous cost-effectiveness studies have assessed the cost-effectiveness of HRT. This is also confirmed in a review by Torgerson and Reid [48], which found that about 75% of the studies assessed the cost-effectiveness of HRT. All studies published between 1980 and 1993 assessed HRT whereas only 47% of them assessed HRT in the period 1993–2001. The cost-effectiveness of HRT depends on many factors such as the uterus status, age, bone mass, symptom status and stated risk reductions. The cost-effectiveness of HRT is sensitive to, for example, the assumed coronary heart risk reduction, which at the present stage, is not supported by evidence-based medicine. Another important factor for cost-effectiveness is how the quality of life during treatment is changed. The reason for this is that every woman will be affected by the quality of life assumption and that the consequences occur in the near future. It is suggested that HRT is cost-effective for 50-year-old symptomatic women. On the other hand the cost-effectiveness of the treatment of asymptomatic women of the same age is much more questioned. Adding side-effects during therapy strongly increases the cost-effectiveness ratios. Other assessed therapies were different fracture therapies (e.g. a bisphosphonate), and a life-style intervention including exercise and calcium.

A distinction can be made between bone specific therapies only affecting the risk of fracture and therapies also having extra skeletal effects, for example, on breast cancer and coronary heart disease. Models used for bone specific therapies (e.g. bisphosphonates) always include hip fracture as a disease state and usually also other fractures of the wrist and spine as well. Models intended for therapies with extra skeletal effects (i.e. HRT) always include hip fracture and breast cancer and usually also coronary heart disease. What disease states should be included in a model in the osteoporosis field? It should be noted that a model with K states implies theoretically $K \times K$ possible transitions. Although all transitions are not possible in practice, the addition of more disease states implies that more cost and health effect data must be added as well. To minimize the data input for the model it is important to minimize the included number of health states and to keep the model as simple as possible. A necessary condition for including a disease

state is that the intervention affects the transition probability for the considered disease. However, if the disease state is associated with only minor changes in quality of life, mortality and costs at the same time as the base line risk of that disease are low, suggesting that the disease state can be excluded. For example, was wrist fracture excluded in later cost-effectiveness studies of HRT for the reason that it was associated with small cost and health effect consequences? It has also been shown that the exclusion of wrist fractures is of minor importance for the cost-effectiveness results (see e.g. [44]). There is some evidence that the mortality risk after a spine fracture increases [49]. Spine fractures may influence quality of life and costs to a greater extent and for a longer period of time compared to wrist fractures. Further studies investigating the costs and quality of life related to spine fractures are required as a base for deciding how to model the spine fracture sequence after the first spine fracture.

Age-specific risk of hip fracture is previously usually estimated based on a risk function that relates BMD to the risk of hip fracture, a so-called BMD-based model [1, 19–21, 26–28]. The risk function used in these studies is estimated based on a US-setting [37]. Age-specific fracture incidence rates are expressed as a function of BMD and an intervention is modeled as a delay in the rate of bone loss. The validity of such an approach depends on the ability of the risk factor BMD to predict the risk of fracture. Also other risk factors may be important for the risk of fracture (height, personal history of fracture, etc.) and BMD alone may be an incomplete measure of fracture risk. In later models this is eliminated and instead age-specific absolute risks are estimated.

All the papers include direct intervention and morbidity costs. Indirect costs related to the intervention and morbidity are included later in the period. The most common practice in the beginning of the period was to include future medical costs only for related illnesses. Later, future medical costs for unrelated illnesses and future non-medical costs minus production (market and non-market production) are also estimated. These findings are consistent with methodological developments in the health economics field that relate to the treatment of mortality costs. It is now suggested to include all future costs in a cost-effectiveness analysis [14,15]. To be consistent with economic theory and to avoid suboptimizations a societal perspective should be carried out, which implies that intervention (direct and indirect), morbidity (direct and indirect), and mortality costs (consumption – production) should be included. A societal perspective is also recommended in guidelines for economic evaluations of interventions in the osteoporosis field [50]. The societal perspective can be supplemented with other perspectives such as a health care perspective or whatever the decision-maker finds relevant to analyze.

The effectiveness in the cost-effectiveness estimations are usually based on 'what-if' calculations and not on RCTs. The uncertainties and limitations in the data are

usually underscored and it is argued that further studies investigating for example, the consequences of HRT on coronary heart disease and breast cancer are required. Cost and health effect data are obtained from a combination of different sources where charges are often used as proxies for costs and where quality of life estimations are based on assumptions rather than on empirical data. The importance of using empirical studies instead of arbitrary assumptions are shown by Daly et al. [51] and Zethraeus et al. [7] who showed much greater improvements in quality of life by using HRT than previously assumed in for instance Weinstein [17]. It is therefore important to re-assess the cost-effectiveness of the treatment and prevention of osteoporosis as new data are accumulated.

Only studies that define effectiveness in terms of life years or quality adjusted life years (QALYs) are selected. The ultimate consequence of osteoporosis therapies is on length and quality of life, which makes QALYs a suitable measure of relevance for the individual. The advantages of QALYs is that the measure can incorporate changes in different risks caused by the intervention and comparisons can be made between different therapies and treatment areas.

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 is suggested to be US\$ 60 000 and in a sensitivity analysis to vary between US\$ 40 000 and US\$ 100 000 [52,53]. In most cost-effectiveness studies so far the mortality costs are 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 [33,54].

What constitutes good practice in the development of a good cost-effectiveness model? In a recent consensus statement properties of good decision analytic models are presented [55]. The intention of the statement is to provide researchers and decision makers with useful guidance on the construction and evaluation of decision analytic cost-effectiveness models. It is stated that a good decision model for economic evaluation of health care programs is one that is tailored to the purposes for which it is to be used, is useful for informing the decisions at which it is aimed, and is readily communicated. According to the consensus statement a good decision model must have the following characteristics: transparency (the structure and the data included in the model can easily be investigated), internal consistency (the model must be mathematically well defined for all combinations of parameter values feasible in the model), reproducibility (an independent analyst

should be able to reproduce the results given by the model), interpretability (the results must be clear and interpretable for the decision that it is being used to inform), exploration of uncertainty (all forms of uncertainty must be appropriately explored (methodological, structural and parameter uncertainty)), statement of scope (the scope of the model should be clearly specified), external consistency (the outputs of the model should be consistent with empirical evidence), parsimony (the model should be kept as simple as possible), inferential soundness (the causal relationships in the model should be explained and supported by the best available evidence). Sculpher et al. [56] argue that the role of cost-effectiveness models is to identify optimum treatment decisions. The falsifiable hypothesis posed by modeling is that a better decision will be made by using the model than by not using it. In practice, models are made for decisions that cannot be deferred, which means that testing every model is not efficient. What instead is required is some means of assessing the quality of the model. The paper presents a framework for assessing the quality in decision models. The quality in decision models is viewed in nine dimensions: structure, disease states, options, time horizon, cycle length, data identification, data incorporation, internal consistency and external consistency. Based on the dimensions, a list of questions about quality is developed. The framework described should encourage the analyst to provide an explicit and comprehensive justification of the methods used, and allow the user of the model to make a judgement about the relevance, coherence and usefulness of the analysis [56].

The models presented in Zethraeus et al. [30,44] (and applied in Zethraeus et al. [31], Jönsson et al. [32], and Kanis et al. [33,34]) can be assessed against the list of questions described in Sculpher et al. [56]. First there is a clear statement of the decision problem, the context and the perspective of the model (*structure*). The models allow for the inclusion of intervention, morbidity and mortality costs. This opens up for a societal perspective, which is recommended in health economic evaluation studies [13]. They are flexible and can analyze different patient groups and treatment alternatives. Not only healthy women free from menopausal symptoms can be analyzed. Also different risk groups such as patients having established osteoporosis or other risk factors can be analyzed. The models, constructed to be as general and flexible as possible, may theoretically be used for any population. To make accurate conclusions using the model in other countries, the data must be valid for the specific setting to which the model is applied. The model in Zethraeus et al. [30] was developed for analyzing the cost-effectiveness of HRT but can also be used for assessing the cost-effectiveness of therapies that affect one or more of the included disease states (e.g. SERMs). To analyze therapies that only affect the fracture risk the extended version of the model can be used [44]. The inclusion of *disease states* is based on the best available medical evidence, which shows the disease risks that are affected by the therapy of interest. The *options* are well

described and involve either a comparison between treatment or no treatment or between different treatment strategies. The *time horizon* is clearly stated together with the *cycle length*. Further, the sources of parameter values (*data identification*) and their *incorporation* are clearly stated and described. Tests of *internal consistency* are carried out by the help of menus, which can be used to control the model calculations. Finally, *external consistency* is investigated by comparing the results with other studies carried out in the field. The models are open and transparent and all the details of the two models are thoroughly described [30,44].

An illustration of the two models in Zethraeus et al. [30,44] is presented in the Appendix where they are applied in a Swedish setting. First, using the model in Zethraeus et al. [30], the cost-effectiveness of a treatment with possible extra-skeletal effects are compared to no treatment. The base case assesses the cost-effectiveness of the treatment of a 60-year-old woman with a twofold increase in the risk of hip fracture. A 5-year treatment duration is assumed to reduce the risk of hip fracture by 35%. After the cessation of the therapy the risk gradually adjusts to the normal risk 5 years later. An annual treatment cost of SEK 5000 is assumed and costs and health effects are discounted at a 3% discount rate. Two scenarios are shown, one where costs in added life years are included and one where they are excluded. In a sensitivity analysis the cost-effectiveness is calculated changing some of the base case assumptions. The results presented in Table A1 show that the cost-effectiveness of the treatment is sensitive to quality of life changes during therapy and whether a coronary heart risk reduction is assumed or not. If the quality of life is assumed to improve slightly during treatment the cost-effectiveness ratios decrease radically. On the other hand if any side-effects are assumed, the 'no intervention' alternative dominates the treatment alternative. The results are less sensitive to changes in quality of life related to fracture. The cost-effectiveness results are not sensitive to the inclusion of costs in added life years, which are explained by small increases in life expectancy. Second, in the model presented in Zethraeus et al. [44], the cost-effectiveness of a bone-specific treatment is compared to no treatment. The base case assesses the cost-effectiveness of the treatment of a 70-year-old woman with a twofold increase in the risk of hip, spine and wrist fracture. A 5-year treatment duration is assumed to reduce the fracture risk by 35%. All the other assumptions are the same as in the first illustration above. The results presented in Table A2 show that the cost-effectiveness ratios are lower compared to those in Table A1. This is because the base line risk of fracture increases with age, which means that a given risk reduction avoids more fractures in the elderly. If the quality of life is assumed to improve slightly during treatment the cost-effectiveness ratios decrease. On the other hand if a small side effect is assumed, the 'no intervention' alternative dominates the treatment alternative. The results are also sensitive to changes in

relative risk of fracture and set time after cessation of therapy. The cost-effectiveness results are not sensitive to the inclusion of costs in added life years.

Conclusions

The models reviewed differ in terms of structure, data and validation. The differences in structure reflect the different issues studied in the models, but also indicate omissions in taking into account important aspects of the decision problem; both potential benefits and costs are omitted. The data used in the models are of strikingly 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. Data on clinical effectiveness are only in rare instances based on hard data from randomized clinical studies. In the best case they are based on surrogate endpoints from clinical studies, but often 'best guesses' are used based on epidemiological data and expert opinion.

It is not possible to undertake a full validation of each model. Particularly the older models, based on BMD and developed for main-frame computers, lack transparency. There is however, no reason to question their internal consistency. The fact that the same research group has often been working on the development of the model for a long time makes it reasonable to assume that internal inconsistency and computational errors are rather rare. Model to model validation has been undertaken between two of the later published models [30,35].

In the model by Zethraeus et al. [30] it is easy to test the predictive validity for the different parameter. Lifetime and ten-year risk for different fractures and other outcomes can be directly computed in the model and compared with epidemiological findings.

The Way Forward

New opportunities for prevention and treatment of osteoporosis will continue to be developed and established methods will need to be reassessed in view of new evidence. Modeling is a necessary feature for making decisions about the efficient use of resources in this field. There is a trend that a new model accompanies every new cost-effectiveness analysis of interventions in osteoporosis. This is true for public sector studies as well as studies with private sponsors. This makes it difficult to assess if the new results are a consequence of a new model or the new technology and the new data that are generated. In many instances this also represents a waste of resources on duplicate work.

A model is never complete or finished. At best it represents the state of the art at a specific point in time. There is no reason that the development of new models should come to a halt or slow down. But there are reasons to make sure that new models represent real

progress and a reasonable use of resources. We therefore suggest a framework for developing and validating new models in osteoporosis based on the following principles:

1. Full transparency of the models used in the field;
2. Co-operations between researchers working in the field;
3. Sharing of data needed for modelling;
4. The validation of new models against a generally and easily available model.

To achieve this we will take steps to make the model developed by Zethraeus et al. [30] available on the Internet. We encourage developers of new models to

take advantage of this opportunity to validate their new models. Such a validation will not prevent the development of new and original models, but it will provide an opportunity to compare results and clarify the reasons for discrepancies. It will also provide an opportunity for those who do not think they need to develop a new model to use an existing model to investigate the results with new data for a specific population (country) or for a new technology.

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Appendix

Table A1. Cost-effectiveness ratios for a 5-year treatment, with possible extra skeletal effects based on the models presented in Zethraeus et al. [30,44]. The base case indication is a 60-year-old woman with a twofold increase in the fracture risk. The base case assumes a risk reduction of 35% during therapy and a 5-year offset time. The annual intervention cost is assumed to be SEK 5000. All ratios are given in Swedish crowns (SEK)

Parameters varied in the sensitivity analysis	Costs in added life years included	Costs in added life years excluded
Base case	1 510 000	1 470 000
<i>Starting age</i>		
55-year treatment initiation	2 600 000	2 590 000
65-year treatment initiation	890 000	810 000
<i>Effect envelope</i>		
Offset time = 0 years	2 380 000	2 350 000
Offset time = 10 years	960 000	910 000
<i>Discount rate (%)</i>		
Health effects = 0	1 070 000	1 040 000
Costs and effects = 5	1 840 000	1 800 000
Costs and effects = 0	1 060 000	1 020 000
<i>Relative risk of fracture</i>		
Hip RR = 3	970 000	940 000
Hip RR = 4	700 000	670 000
<i>Intervention</i>		
10-year treatment duration	1 400 000	1 340 000
Risk reduction fracture = 50%	970 000	930 000
Risk reduction CHD = 50%	380 000	240 000
Risk increase breast cancer = 35%	Dominated	Dominated
Intervention costs = 3000	790 000	750 000
Intervention costs = 7000	2 230 000	2 190 000
<i>Quality of life during intervention</i>		
+1%	350 000	350 000
+0.5%	570 000	560 000
-1%	Dominated	Dominated
-0.5%	Dominated	Dominated
<i>Quality of life after fracture</i>		
+10%	3 010 000	2 930 000
-10%	1 000 000	970 000

Table A2. Cost-effectiveness ratios for a 5-year bone specific treatment based on the model presented in Zethraeus et al. [44]. The base case indication is a 70-year-old woman with a twofold increase in fracture risk. The base case assumes a risk reduction of 35% during therapy and a 5-year offset time. The annual intervention cost is assumed to be SEK 5000. All ratios are given in Swedish crowns (SEK)

Parameters varied in the sensitivity analysis	Costs in added life years included	Costs in added life years excluded
Base case	520 000	420 000
<i>Starting age</i>		
65-year treatment initiation	850 000	790 000
75-year treatment initiation	330 000	200 000
<i>Effect envelope</i>		
Offset time = 0 years	810 000	720 000
Offset time = 10 years	350 000	240 000
<i>Discount rate</i>		
Health effects = 0	400 000	320 000
Costs and effects = 5	610 000	510 000
Costs and effects = 0	410 000	300 000
<i>Relative risk of fracture</i>		
Hip RR = 3	330 000	240 000
Hip RR = 4	230 000	140 000
<i>Intervention</i>		
10-year treatment duration	520 000	410 000
Risk reduction fracture = 50%	320 000	220 000
Intervention costs = 3000	250 000	150 000
Intervention costs = 7000	800 000	700 000
<i>Quality of life during intervention</i>		
+1%	250 000	200 000
+0.5%	340 000	280 000
-1%	Dominated	Dominated
-0.5%	1 140 000	920 000
<i>Quality of life after fracture</i>		
+10%	800 000	650 000
-10%	400 000	320 000

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