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HEALTH ECONOMICS OF OSTEOPOROSIS

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ABSTRACT

Health economics is concerned about how the scarce resources should most efficiently be allocated to maximise the health outcomes. Health economic evaluation is a method for assessing costs and benefits of alternative treatment strategies for allocating resources to assist decisions aiming at improving efficiency. Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue leading to increased bone fragility and thus an increased risk of fractures. Fractures are a burden to society, with respect to mortality, costs as well as quality of life. There are several treatments available for the prevention and treatment of osteoporosis. The general purpose of this thesis was to develop important aspects of the health economics of osteoporosis. More specifically, the aspects addressed were fracture related costs and quality of life for use in economic evaluation, economic modelling of osteoporosis therapies and health economics as a tool in treatment guidelines and patient selection (intervention thresholds).

Data concerning costs and quality of life related to osteoporotic fractures in Sweden was collected in a prospective study that followed hip, vertebral and wrist fracture patients 18 months after fracture. The results for the first year after fracture indicate that hip fracture is associated with the highest costs whereas vertebral fracture leads to the largest loss in quality of life of the three types of fracture.

Using computer simulation models the cost-effectiveness was assessed for two drugs: raloxifene and strontium ranelate. The cost-effectiveness of raloxifene compared to no treatment was estimated on Swedish women who were similar in characteristics to the women included in the Multiple Outcomes of Raloxifene study. The study was based on Swedish women who were similar in characteristics to the patients in the Spinal Osteoporosis Therapeutic Intervention study (SOTI) and Treatment Of Peripheral Osteoporosis Study (TROPOS). Compared to no treatment, both drugs were indicated to be cost-effective treatments.

Intervention thresholds for osteoporosis can be defined as the ten-year risk of hip fracture at which intervention becomes cost-effective. Based on a Markov cohort model intervention thresholds were estimated for seven countries. The ten-year risk of hip fracture at which treatment becomes cost-effective varied between countries mainly due to differences in the willingness to pay (WTP) for a QALY gained, fracture related costs and intervention costs.

Economic evaluation has become an important tool for evaluating the value for money of new medical technologies. However, much of the quality of an economic evaluation relies on the quality of the data used in the analysis. Using a new framework for collecting data on fracture related costs and quality of life this thesis has provided new information on costs and quality of life for fractures in Sweden, which will improve future economic evaluations of osteoporosis therapies. Moreover, this demonstrates that economic evaluation can be a tool for improving the selection of patients in clinical practice who are suitable for treatment, based on a cost-effectiveness criterion.

Keywords: Economic evaluation, cost-effectiveness, osteoporosis, fracture related costs, quality of life

LIST OF PUBLICATIONS

I. Borgström, F., N. Zethraeus, O. Johnell, L. Lidgren, S. Ponzer, O. Svensson, P. Abdon, E. Ornstein, K. Lunsjo, K.G. Thorngren, I. Sernbo, C. Rehnberg, and B. Jönsson, Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int*, 2006. 17(5): p. 637-50

II. Borgström, F., O. Johnell, J.A. Kanis, A. Oden, D. Sykes, and B. Jönsson, Cost-effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. *Pharmacoeconomics*, 2004. 22(17): p. 1153-65

III. Borgström, F., B. Jönsson, O. Ström, J.A. Kanis, An economic evaluation of strontium ranelate in the treatment of osteoporosis in a Swedish setting. Based on the results in the SOTI and TROPOS. *Manuscript submitted for publication*

IV. Borgström, F., O. Johnell, B. Jönsson, J.A. Kanis, C. Rehnberg, At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. *Manuscript accepted for publication in Osteoporosis International*

CONTENTS

LIST OF ABBREVIATIONS

BMD	Bone mineral density
CHD	Coronary heart disease
FIT	The fracture intervention trial
GDP	Gross domestic product
HIP	The hip intervention program study
HRT	Hormone replacement therapy
ICER	Incremental cost-effectiveness ratio
KOFOR	The costs and quality of life related to osteoporosis fractures in Sweden study
LYG	Life-years gained
MORE	The multiple outcomes of raloxifene study
PTH	Parathyroid hormones
QoL	Quality of life
QALY	Quality-adjusted life-years
SEK	Swedish kronor
SERM	Selective estrogen receptor modulator
SOTI	The spinal osteoporosis therapeutic intervention study
TROPOS	The treatment of peripheral osteoporosis study
VERT	The vertebral efficacy with risedronate therapy study

1 INTRODUCTION

We are living in a world of scarce resources. How these scarce resources should be optimally allocated to provide the maximum output is the essence of the subject of economics. Health economics is the application of the theory of economics on health, i.e. how the resources available for health production should be most efficiently allocated to maximise health outcomes. Health economic evaluation is a method for assessing the costs and benefits of alternative strategies for allocating resources to assist in decisions aiming at improving efficiency. An efficient allocation of resources implies that no further health gains can be achieved by allocating resources differently.

As novel medical technologies are developed it is important to assess whether they are good value for money as compared to older technologies. That is, will the new technology improve the resource allocation and thereby improve health at an acceptable cost for society. This thesis deals with health economic evaluation applied on osteoporosis. Currently, there are several treatments available for the prevention and treatment of osteoporosis and there are several in development. Therefore, in an economic perspective, it is important to carry out research on the consequences of osteoporosis that facilitates the creation of a good platform for the economic evaluation of osteoporotic treatments.

1.1 OSTEOPOROSIS

1.1.1 Diagnosis, epidemiology and pathology

Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, leading to increased bone fragility and thus, an increased risk of fractures [1]. Fractures are a burden to society, with respect to mortality, costs as well as 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 [2]. Fractures account for about 1-2% of the total health care costs, where inpatient care costs dominate. Although fractures are more common in the elderly, indirect costs (loss in value of production due to sick leave) also play an important role which has been estimated at about 10% of the total fracture costs [3].

The diagnosis of osteoporosis is based on bone mineral density (BMD) measurements and is defined by the World Health Organisation (WHO) as [4]:

1. *Normal*: a value of BMD or bone mineral content (BMC) ≤ 1 standard deviation (SD) below the young adult average value

2. *Osteopenia*: a value of BMD or BMC >1 SD below the young adult average value but >2.5 SD above

3. *Osteoporosis*: a value of BMD or BMC ≥ 2.5 SD below the young adult average value

4. *Severe osteoporosis (established osteoporosis)*: a value of BMD or BMC ≥ 2.5 SD below the young adult average value and presence of one or more fragility fractures

Osteoporosis is clinically manifested in fractures. However, low bone mass in itself is related to increased mortality [5, 6]. There are two forms of osteoporosis. *Primary osteoporosis* due to factors such as natural aging, menopause and life-style factors such as smoking, alcohol and physical activity. *Secondary osteoporosis* due to medical disorders (e.g. hypogonadism and corticosteroid therapy). [7]

Osteoporosis is a disease mainly affecting elderly postmenopausal women. About two fractures out of three occur in women. The lifetime risk of sustaining a hip, vertebral or wrist fracture for 50-year old women in Sweden has been estimated at 46%. The corresponding risk for men has been estimated at 13% [8]. The higher incidence of fractures in women can be explained by accelerated bone loss that occurs in the menopause due to the diminishing production of estrogens. [7]

Risk factors for osteoporotic fractures can be divided into risk factors which it is possible and not possible to affect. Gender, ethnicity, increasing age, previous fracture and family history of fracture are examples of risk factors that cannot be affected. Risk factors possible to affect are for example low BMD, life-style factors, low body weight, vitamin D deficiency, smoking, alcohol use and poor visual acuity.[7, 9]

The fracture types that can be considered as osteoporotic can be defined as low-energy trauma fractures caused by a fall from the same level. A more specific definition is fractures occurring at sites that are associated with a low BMD which at the same time have an increased fracture risk above the age of 50 [8, 10]. Based on this criterion fractures at for example the hip, vertebrae, wrist, humeral, rib, pelvic, tibial and fibular can be considered osteoporotic fractures [8, 10]. Hip, vertebral and wrist fractures are the classical types of osteoporotic fracture accounting for about 60% of all fractures.

Hip fracture is the fracture type associated with the most severe consequences in terms of morbidity, mortality and costs [8]. About 10% of all patients sustaining a hip fracture are long term institutionalised and 20-30% of the hip fracture patients die within one year after fracture [8]. The risk of hip fracture increases exponentially (see Figure 1) with age with a mean age of a hip fracture for men and women in Sweden of 76 and 80 years, respectively. The incidence varies quite substantially between populations. In Europe, the variation in hip fracture risk between countries is about seven fold and worldwide more than tenfold [11, 12]. The highest hip fracture risk in the world has been observed in the Scandinavian countries [13].

The major types of hip fracture are cervical and trochanteric hip fractures. About half of all hip fractures are trochanteric. Cervical fractures are mostly treated with osteosynthesis or arthroplasty and trochanteric hip fractures are in most cases treated with osteosynthesis [8]. Some studies have shown that patients with trochanteric fractures are more osteoporotic and are associated with a higher mortality than cervical fractures [14, 15].

Vertebral fractures have also been shown to be associated with an impact on mortality, morbidity and costs [16]. However, the consequences of vertebral fractures are not as well investigated as for hip fractures. A vertebral fracture is not as clearly defined as a hip fracture. Usually, a definition based on radiographically identified vertebral deformities or clinical diagnosis is used. The clinical definition includes all patients with vertebral fracture that comes to clinical attention while a definition based on deformities includes all patients in a population fulfilling some specific deformity criteria (e.g. the McCloskey-Kanis criterion

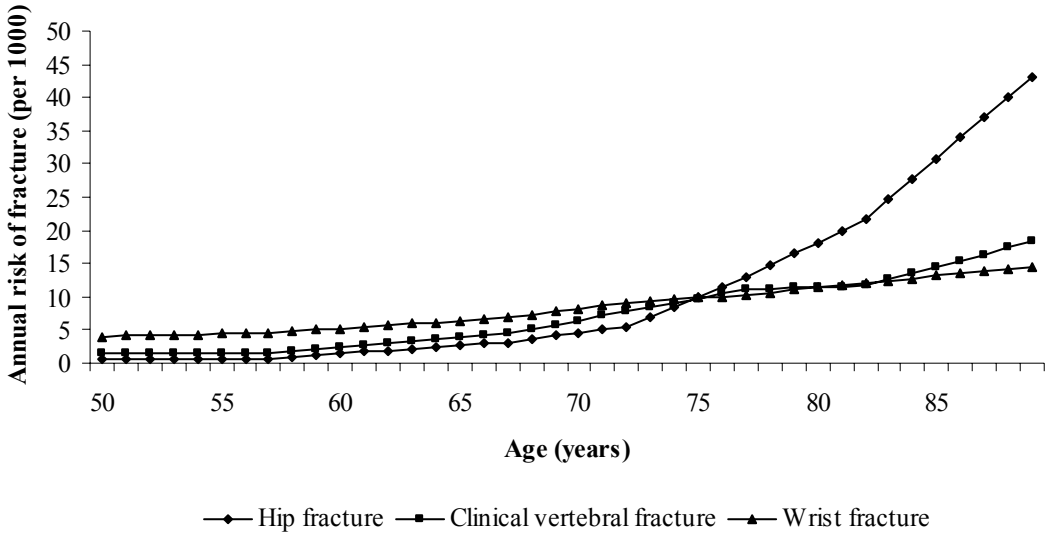
[17]). About one third of all vertebral fracture deformities (also referred to as morphometric fractures) come to clinical attention [18]. Since it is difficult to identify morphometric vertebral fractures most research has been done on clinical vertebral fractures. However, there are studies indicating that radiographically identified fractures cause a reduction in quality of life and are associated with some costs [19-21].

The risk of vertebral fracture increases with age, but does not show an exponential trend as do hip fracture (see Figure 1). The lifetime risk of a clinically defined vertebral fracture at the age of 50 for a Swedish woman is 15.1% [8].

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 believed [16, 22, 23]. For example, it has recently been 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 caused by a hip fracture [23].

Wrist fractures have not been shown to have any consequences of the same magnitude as hip and vertebral fractures. Studies have shown that wrist fractures are associated with some costs and quality of life reductions the first year after fracture [23-26]. Wrist fractures have not been indicated to increase mortality compared to the general population [27-29]. The incidence of fracture increases linearly with age (see Figure 1). The lifetime risk of a wrist fracture for 50 year old women in Sweden has been estimated at 21% [8].

Figure 1 Average annual fracture incidence for Swedish women



Source: [30]

1.1.2 Treatments for osteoporosis

Treatments for osteoporosis are either pharmacological or non-pharmacological. The pharmacological interventions currently available on the market can be divided into six categories:

Calcium and Vitamin D are most often given as a combination treatment of both substances. It is not entirely clear to what extent Vitamin D and Calcium reduce the risk of osteoporotic

fractures on their own. Therefore, they are often given as an add-on to other osteoporotic drugs. [7, 31]

Hormone replacement therapy (HRT) stops the bone loss by restraining the bone resorption. Several studies have shown that HRT reduces the risk of fractures [32, 33]. However, HRT has recently been shown to have several extra-skeletal effects. Combined oestrogen and progesteron for the treatment of women with an intact uterus has been shown to increase the risk of cardiovascular disease and breast cancer and decrease the risk of colorectal cancer [32, 34]. Oestrogen treatment given to hysterectomised women has been shown to increase the risk of stroke [32]. For these reasons, HRT is no longer considered a first line treatment for osteoporosis in Sweden [35].

Bisphosphonates are anti-resorptive agents preventing bone loss and thereby reducing the risk of fractures. There are several different bisphosphonates. Those currently available on the market for the treatment of osteoporosis are etidronate, alendronate and risedronate. Bisphosphonates have been shown to reduce the fracture risk primarily in postmenopausal women with low BMD. Etidronate, the oldest bisphosphonate, has been shown to reduce the risk of vertebral fracture while, alendronate and risedronate have demonstrated a risk reduction for hip and wrist fractures as well [36-38]. The safety profile is more favourable for bisphosphonate than for HRT. The most frequent adverse event is mild to moderate gastrointestinal discomfort [18].

Selective Estrogen Receptor Modulators (SERMs) act as oestrogen agonist on bone and lipid metabolism and as antagonists in breast tissue. Raloxifene, which currently is the only available SERM on the market, has been shown to reduce the risk of vertebral fractures and breast cancer in early postmenopausal women with low BMD [39]. Moreover, raloxifene has in one study shown to reduce the risk of coronary heart disease (CHD) among patients at high risk of cardiovascular disease [39]. On the negative side raloxifene shows an increased risk of thromboembolic events.

Parathyroid Hormones (PTH) given by intermittent injection restores bone strength by stimulation of new bone formation. A clinical study has shown PTH to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with previous vertebral fractures and low bone mass [40]. Teraparatide is currently the only available PTH on the market.

Strontium ranelate reduces bone resorption while allowing continued bone formation [41]. Clinical studies have shown strontium ranelate to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with low BMD. Strontium ranelate has not been found to have any serious adverse events. The most common adverse events were diarrhoea and nausea, which mostly occurred during the first three months of treatment. A less common adverse event was venous thromboembolism, which was slightly more frequent among strontium ranelate users.[42, 43]

Examples of non-pharmacological interventions are nutrition, exercise and hip protectors [7]. Interventions such as hip protectors may reduce the risk of hip fracture, though recent studies suggest little or no effect [3, 44].

1.1.3 Patient management and treatment of osteoporosis

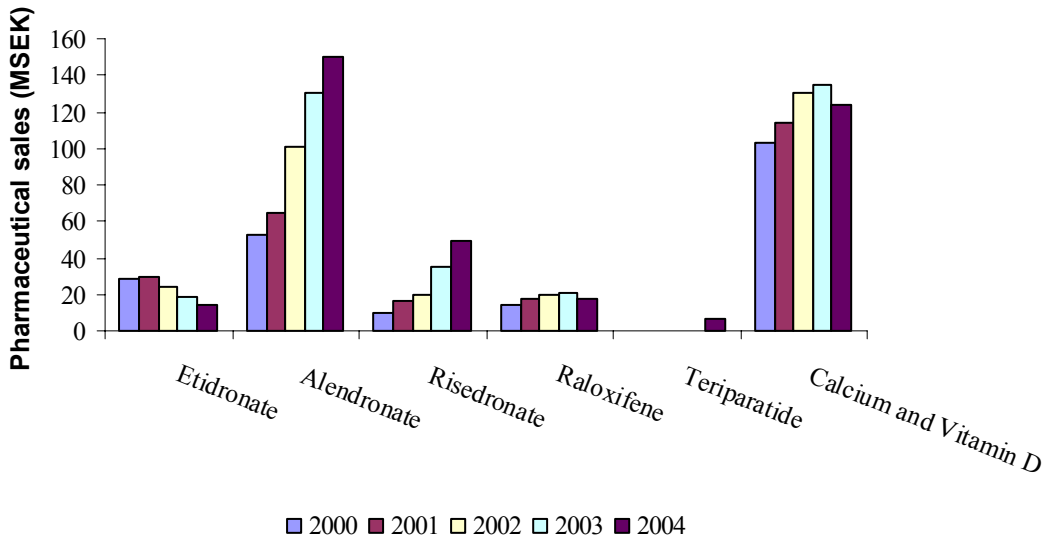
According to Swedish treatment guidelines the decision of treatment should be based on an assessment of the absolute fracture risk for the patient [45]. Only patients at high risk of fracture should be treated and the risk assessment should be based on all risk factors and not only on bone mass. The general categories of high risk fracture patients appropriate for treatment are patients diagnosed with osteoporosis (i.e. a value of BMD >2.5 SD below the young adult average value) and patients with previous low energy fracture and a value of BMD >2.0 SD below the young adult average value.

The recommended first line treatment for patients at high risk of fracture is bisphosphonates together with vitamin D and calcium supplements. Second line treatments are SERMs together with vitamin D and calcium supplements and estrogens with some restrictions. The suggested treatment length of an intervention is about five years. Except a suggested telephone contact a few months after treatment has been initiated there are no specific recommendations for how an osteoporosis therapy should be monitored. However, a BMD measurement every second year during treatment is common [31].

1.1.4 Treatment patterns in Sweden

Pharmaceutical sales of treatments for osteoporosis have increased in the last five years (Figure 2) [46]. This increase is mainly due to the introduction of bisphosphonates at the end of the 1990:s. Total sales have increased from 209 MSEK in the year 2000 to 363 MSEK in the year 2004, which is an increase of 73%. 1.27% of the total pharmaceutical sale in Sweden in the year 2004 can be related to osteoporosis treatments. The sale figures are slightly overestimated, since it was not possible to separate the drugs prescribed for other conditions than osteoporosis in the statistics. Moreover, HRT was not included because it was not possible to differentiate between sales related to osteoporosis and menopausal symptoms. However, it can be mentioned that the sales have dropped by 27% between years 2000 and 2004 (from 453 MSEK to 331 MSEK). This drop in sales can mainly be related to the negative effects on extra-skeletal events that HRT has recently shown to have [32, 34].

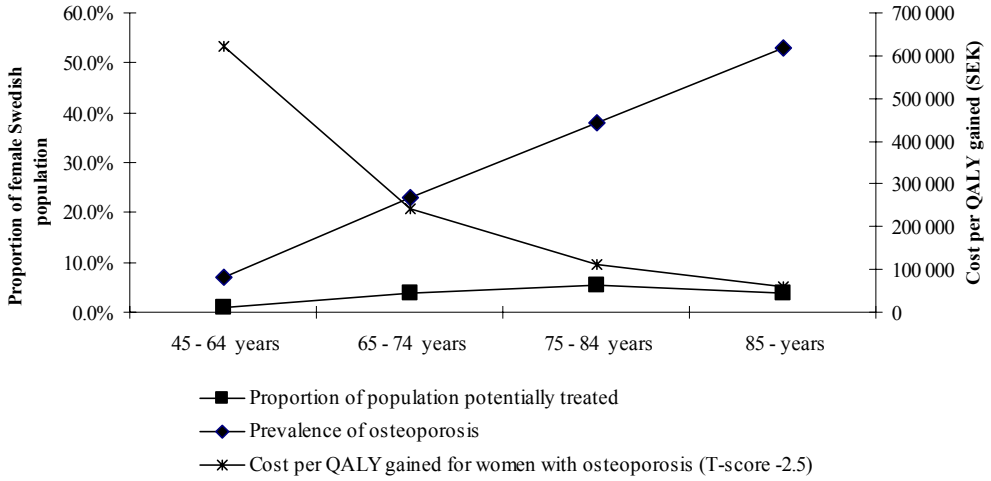
Figure 2 Pharmaceutical sales of osteoporotic treatments in Sweden 2000-2004



Source: [46]

Based on pharmaceutical sales and defined daily doses (DDD) an estimate of the proportion of the population that could be treated with any drug can be calculated. In Figure 3, the age-differentiated proportion of the female population that could potentially be treated, based on year 2004 sales, with bisphosphonates, SERMs and teraparatide is depicted. The share that could be treated increases from 0.8% in ages 45-64 to 5.6% in ages 75-84, where after a decrease can be noticed. These numbers can be compared to the proportion of the female population that is osteoporotic (i.e. a T-score<-2.5) and thus, constitutes potential candidates for treatment. As can be seen in the figure there is a substantial gap between the proportion of osteoporotic patients and how many of the population that could be treated. Moreover, depicted in Figure 3, is the estimated cost per QALY gained by bisphosphonate treatment compared to no treatment for women at the threshold of osteoporosis (T-score=-2.5) at different starting ages of intervention. In younger ages (45-65 years) the cost per QALY gained is in line what can be considered to be cost-effective (about SEK 600 000). At older ages the cost per QALY gained decreases indicating that it is cost-effective to treat patients at a lower risk of fracture than just based on the standard indication of osteoporosis (i.e. a T-score of -2.5). That is, it would be cost-effective to treat a larger proportion of the population than those with a T-score of -2.5 or lower.

Figure 3 Proportion of female population that could be treated based on DDD and sales of bisphosphonates, SERMs and teraparatide, the prevalence of osteoporosis and the cost-effectiveness of osteoporotic women (T-score=-2.5) at different starting ages of treatment



Source: [46] and own calculations

1.2 ECONOMIC EVALUATION IN HEALTH CARE

Economic evaluation can be defined as "the comparative analysis of alternative courses of actions in terms of both their costs and consequences" [47]. A health economic evaluation is always a comparison between two treatment alternatives or more within a defined patient group. It generates information that can be used by health care providers in their decisions on how to allocate resources.

1.2.1 History of economic evaluation

The economic field concerned with the optimal allocation of society´s scarce resources has come to be called welfare economics. The original concepts can be traced back to the nineteenth century but it was not until the beginning of the 1900s that the area was more theorised by names such as Pareto, Kaldor and Hicks. Economic evaluation of health care

programmes started to attract an interest in the 1960's. One of the first health economic evaluations was based on a public health programme for vaccination of child measles. In the 1970s the concept of a one dimensional outcome measure, called Quality-Adjusted Life-Years (QALYs), was introduced and thus, cost-utility analysis was born. [48]

1.2.2 The different types of economic evaluation

Economic evaluation in health care is usually divided into four categories; *cost-minimisation*, *cost-utility*, *cost-effectiveness* and *cost-benefit analysis* [47, 48]. All four methods (summarised in Table 1) measure costs similarly, but they are distinguished by their different approaches as to how to measure the consequences of the compared alternatives [47].

Table 1 Types of Economic Evaluation

Type of economic evaluation	Outcome measure
Cost-minimisation analysis	Outcome assumed to be equal for all alternatives
	Only costs compared
Cost-effectiveness analysis	One-dimensional clinical outcome measure
	E.g. life-years gained
Cost-utility analysis	Multidimensional utility index as the outcome measure
	E.g. quality-adjusted life years
Cost-benefit analysis	Outcome measured in monetary units

Source: Drummond et al [47]

Cost-minimisation analysis compares treatments solely on the basis of costs. The method is used when there is reason to assume that the outcome of the therapies can be considered as equivalent. According to this method, if two health care-programmes have equal outcomes the least costly alternative is to be preferred [47].

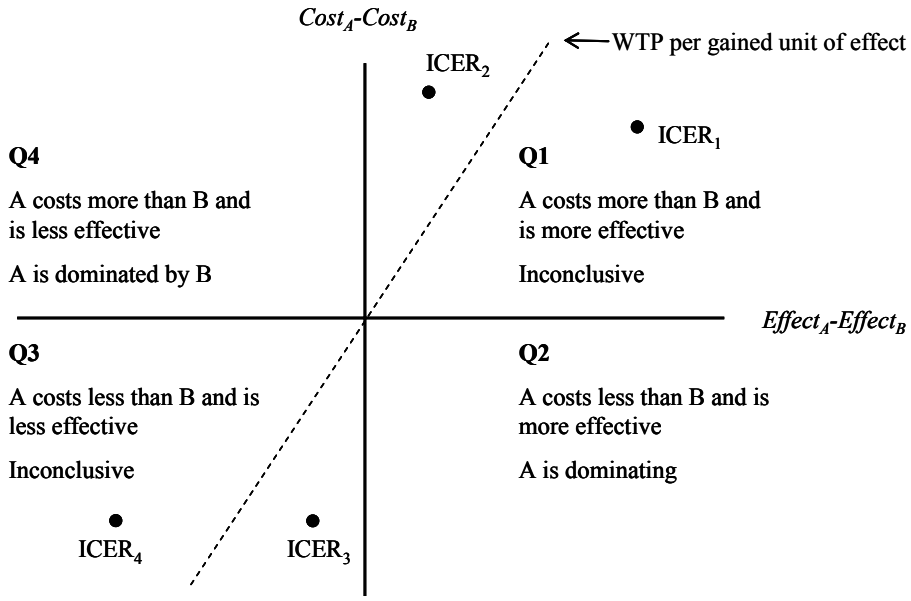
Cost-effectiveness analysis on the other hand assesses both treatment costs and outcomes. Effects (treatment outcomes) are measured in one-dimensional units, such as life years gained. The *Incremental Cost-Effectiveness Ratio* (ICER) is obtained by taking the ratio of the incremental difference in total cost (ΔC) to the incremental difference in benefits (ΔE) between programs [47].

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_A - C_B}{E_A - E_B} \quad (1)$$

The ICER can be interpreted as the incremental cost of producing effect by a treatment alternative compared to the next most effective alternative, and can be expressed e.g. as the cost per life year gained. This incremental ratio, as opposed to the average cost-effectiveness ratio, is the relevant variable to consider when deciding on the allocation of resources which maximises the health effects for a given amount of resources [49].

When two different mutually exclusive alternatives (i.e. the patient can only receive one of the treatment alternatives), for example treatment A and treatment B are compared with regards to costs and effects, four different groups of results can emerge, which can be illustrated in a so-called cost-effectiveness plane in Figure 4 below.

Figure 4 The cost-effectiveness plane



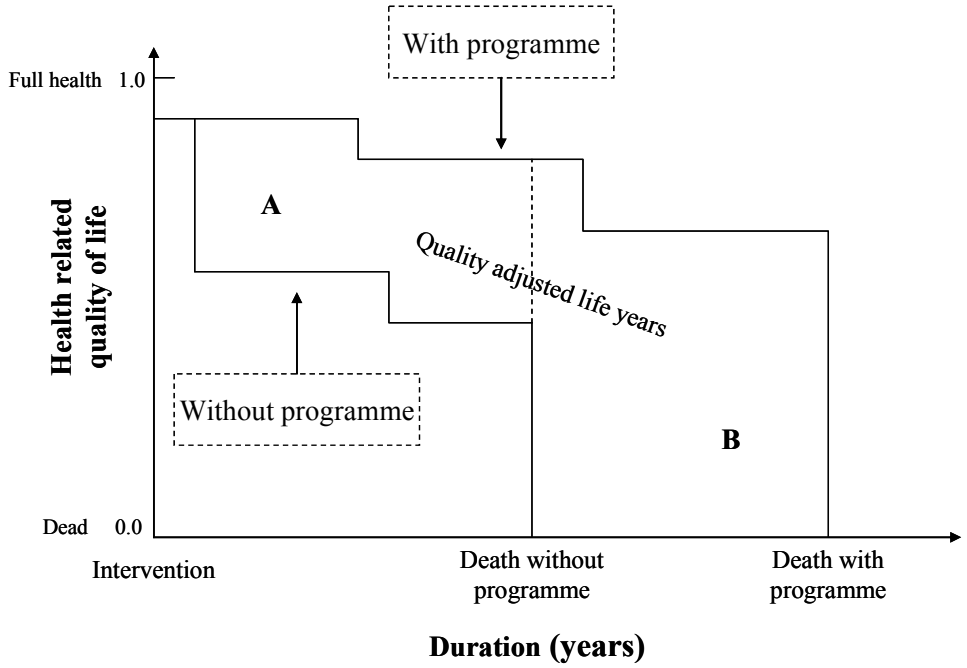
If A has a higher effect than B at equal or lower cost (quadrant 2;Q2), A is said to dominate B, and A should be preferred. If A costs more and has the same or a lower effect (Q4), then B dominates A, and B should be preferred. If, however, A costs less at a lower effect or more at a higher effect (Q1 and Q3), the ICER must be valued by the decision-maker. The optimal choice will depend on the willingness to pay for an additional unit of effect.[1] If the maximum WTP can be defined, program A should be preferred to program B if the ICER is below this threshold value [48]. In the figure, the WTP is illustrated as the dotted line crossing origo. The WTP is the same for any given gradient, i.e. it is the same all along the line. If the ICER falls below the WTP line ($ICER_1$ and $ICER_3$), treatment A should be chosen, while if it falls above ($ICER_2$ and $ICER_4$) treatment B should be chosen.

Cost-utility analysis uses a generic outcome measure incorporating multi-dimensional consequences. This solves the problem with the one-dimensional cost-effectiveness analysis, which makes it difficult to compare results from studies in different medical areas when the outcome measure varies. Cost-utility analysis on the other hand can be used to compare the relative merit of many different types of health care programs [50]. One frequently used measure is quality-adjusted life-years (QALYs), a utility index that weighs together the consequences of survival and quality of life [48]. QALYs are constructed by multiplying the number of life years gained with a utility value for the level of health status. The utility value ranges between 0 (dead) and 1 (full health). The main methods used to measure utility values are time trade-off measurements, standard gamble or rating scale methods [48].

An illustrative example of the concept of a QALY is given in Figure 5. Area *A* in the figure is the quality improvement of implementing a health care programme compared to not implementing it and area B is the quantity improvement i.e. B is the extra quality adjusted life years gained by the programme and A is the improved health status gained during the expected lifetime without the programme.

[1] A fixed budget rule can also serve as the decision rule [4]

Figure 5 Quality-adjusted life years gained from an intervention



Source: Drummond et al [47]

In *cost-benefit analysis*, both costs and outcomes are calculated in monetary terms. Benefits are best measured by the maximum willingness to pay (WTP). WTP are subjective valuations of the monetary value of health outcomes, measured by different techniques such as contingent valuation questions. If the value of the total calculated benefits produced by a program exceed the value of the total costs, it is considered to be good value for money [50].

1.2.3 Costs

Estimating costs is crucial in all health economic evaluations and often involves several steps. First, all relevant resources must be identified and quantified into physical units, e.g. hospital days. Thereafter, the physical units must be priced and valued. The perspective of the evaluation determines which different sets of costs ought to be incorporated in the analysis. Frequently used perspectives are the *societal perspective* (including all costs) and the *health care perspective* (only including costs of health care). Costs are usually divided into *direct* and *indirect costs* [47, 50]. Sometimes *intangible costs* are also mentioned. Costs associated with increased life expectancy should also be included in evaluations if the intervention affects survival [51].

Direct costs include direct medical costs and direct non-medical costs. The main groups of direct medical costs are cost of inpatient (hospital) care, outpatient care (e.g. physician and nurse visits), procedures and tests, devices, and services such as home care. Direct non-medical costs (costs unrelated to health care) include e.g. the cost of transportation, services such as social assistance and unpaid care by relatives etc. [47, 50].

Indirect costs are related to productivity losses in society due to illness. Examples of indirect costs are costs of sick leave, reduced productivity at work or early retirement. Diseases mainly affecting the elderly who no longer participate in the labour force thus have low indirect costs [47, 50].

Intangible costs are consequences that are difficult to measure and for which it is difficult to assess a value. An example is the value associated with reduced or improved health. This type of cost is very rarely explicitly included as a cost in an economic evaluation but more often incorporated as a utility in the denominator of the ICER.

When health care interventions prolong the life of patients, the increased survival may also be associated with a cost for society. This *cost in added life years* corresponds to the difference in consumption and production over the gained years. Such costs should be included in the economic evaluation from a societal perspective [51]. The size of this cost will depend on the age of the patient. Elderly patients (in retirement) most often consume more resources than they produce while younger people produce more than they consume.

1.2.4 Costing

When the relevant resource use is defined and collected, unit costs must be attributed to it. According to economic theory a resource should be priced based on its opportunity cost, i.e. the value of the benefits that are foregone because the resource is not available in its best alternative use [47]. However, in practice the market price of the resource is mostly used.

Market prices are available for several resources but for some non-market items, such as informal care (care by relatives) costing is more problematic. Different valuation principles can be applied when costing informal care. One way of estimating the opportunity cost of informal care is based on the income lost due to relatives and others performing informal care [47]. The opportunity cost could then be estimated by the wage rate of the caregivers. However, the time spent on informal care is often also at the expense of leisure time which also has a value. The opportunity cost of lost leisure time has been suggested to be valued from zero to average overtime earnings. Another valuation principle is to value informal care at the market price of a close substitute also known as the replacement cost method [52].

Another issue is how to cost productivity changes, i.e. indirect costs. One method is the human capital approach, which estimates the value of lost production based on gross earnings for those employed. [47] It has, however, been argued that the human capital approach overestimates the cost of lost productivity due to illness because it does not take into consideration that sooner or later the indisposable worker will be replaced and the productivity loss will diminish. This is considered in the friction cost method [53].

1.2.5 Cost of illness

Another quite common health economic analysis is the cost of illness study. A cost of illness study estimates the costs related to a specific disease and is not a comparison between treatment strategies. Thus, a cost of illness study gives no direct guidance on how resources should be allocated to improve efficiency but provides information about the burden of disease and includes necessary information for the use in economic evaluations.

Cost of illness is most often based on a top-down or a bottom-up approach. The top-down starts with the identification of the total disease related costs for the given perspective (e.g. health care or societal), which are divided by the number of cases for the relevant time period to obtain the cost per incident case. The bottom-up approach starts at the other end with the estimation of the cost per case which is multiplied by the number of relevant cases.

1.2.6 Resource allocation decisions using economic evaluation

When can a health care programme be considered worthwhile to pursue? If the programme has lower costs and a better effect compared to the comparator, the decision on implementation is clear. However, when the better effect is achieved at the price of an additional cost, the decision is less clear.

There exist two different principles on how resources could be allocated based on economic evaluations. The first is called the fixed budget approach. If the budget and the cost effectiveness for the relevant health care interventions are known it is possible to calculate the best allocation of the different interventions to maximise the effect. However, this type of maximisation of the effect is difficult. Like the cost-effectiveness analysis, the budget must capture all relevant costs irrespective of when in time they occur. Assessing this kind of budget is very hard. Making comparisons between treatments disease areas is difficult because there are often differences in the costs and outcome measures used in studies estimating the cost-effectiveness. Moreover, differences in the methodology make comparison between studies complicated.

The second approach is to base the decision on a willingness to pay (WTP) for a gained unit of effectiveness (e.g. the value gained QALY). If the price per unit increase in effectiveness exceeds the cost the treatment is cost-effective. This approach has become the preferred of the two. Setting the cost-effectiveness threshold value is no easy task, however. Currently, there exist no definite values, merely different suggestions for their estimations. One suggestion for estimating the societal value of a QALY is based on the value of a statistical life. For example, using this approach [54], the value of a QALY has been estimated at about SEK 655 000 (about $ 86 000) in Sweden [55]. Another way of inferring threshold values could be based on past reimbursement decisions and guidelines made by national government agencies, such as in the UK ($32 000 – $48 000/QALY), Australia ($28 200 - $ 51 000/LYG) and New Zeeland ($10 900/QALY) [56]. Other threshold values that can be derived from the literature vary quite substantially (from $ 18 000 - $ 650 000), depending on country, perspective, outcome measure (e.g. life-year or a QALY) and methodology [56]. Yet another approach could be to base the threshold value on a measure of a country's economic performance. For example, The WHO Commission on Macroeconomics and Health has suggested that interventions with a cost-effectiveness ratio lower than 3 times the gross domestic product (GDP) per capita for each averted disability adjusted life year (DALY) could be considered good value for money [57] in developing countries.

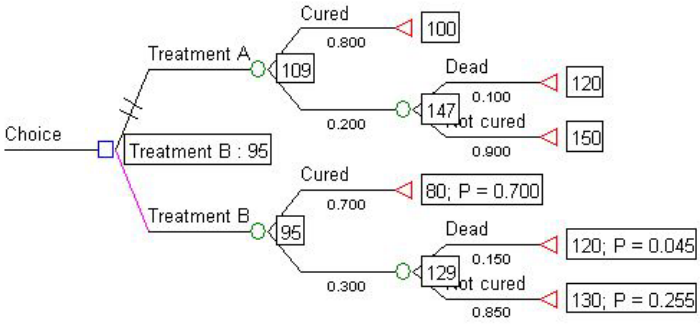
1.2.7 Modelling

There are two main approaches that can be taken when performing an economic analysis. *The within trial analysis* or patient-level analysis is carried out alongside a randomised clinical trial. Resource use and effects are collected simultaneously with the clinical trial. The time frame of a within trial analysis is the same as the length of the clinical trial. However, the consequences of a treatment often stretch longer than the intervention period. In health economic evaluation all relevant costs and effects should be considered, regardless of when in time these occur, should be considered. This together with the fact that clinical trial populations are often not fully representative of the target treatment population in clinical practice in various settings often makes *decision-analytic simulation* modelling the preferred choice when estimating the cost-effectiveness of a treatment. Simulation modelling integrates

epidemiological, clinical and cost data from different sources and over time related to the evaluated treatment strategies. [47, 58] A model is a simplification of reality with the aim of excluding irrelevant details while maintaining interesting information relevant for the programme under study. The most common modelling techniques are decision tree models, Markov cohort models and individual based simulation models (e.g. discrete event modelling).

In a *decision-tree model* the expected probabilities and payoffs (i.e. costs and health outcomes) are calculated and compared between treatment alternatives. An example of a decision tree is shown in Figure 6. The two compared treatments (A+B) are represented by two different arms emanating from the so called choice node. The possible events, which could be a health state or treatment option, associated with the treatment are structured in branches or nodes. Each branch is assigned an event probability and event related costs and effects. The expected costs and effects in each arm are calculated starting from the end node, successively moving forward to the choice node. Decision-tree models are most appropriate for short-term analyses, or other situations when the number of possible outcomes is limited (e.g. acute illness).

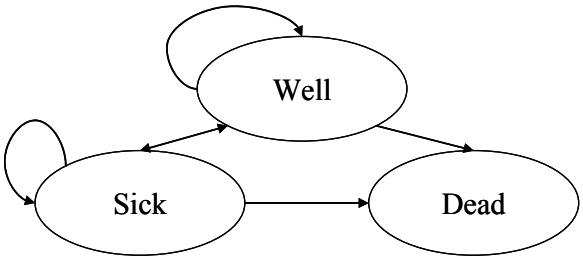
Figure 6. An example of a decision tree model



Markov models are a specific type of discrete state-transition simulation models. A simulated cohort of patients is divided into a finite number of states based on, for example, the current health status of the patient. The states are mutually exclusive and collectively exhaustive. Time is handled as discrete periods of the same length (cycles). One important assumption of the Markov model is the no memory assumption or the Markovian property, i.e. future events only depend on the current state of the patient, and not on prior events [59].

A Markov model is often illustrated in the form of a state transition diagram (Figure 7). The patient cohort progresses between the health states over a certain number of cycles according to defined transitions probabilities resulting in a cohort distribution. The cohort distribution is then related to a set of cycle and state dependent costs and effects. Summarising costs and effects over states and cycles, the average total cost and effect per patient is obtained.

Figure 7. State transition diagram of a Markov cohort model



This process can be formalised as:

$$\text{Undiscounted total effect per patient} = \sum_{c=1}^{C} \sum_{s=1}^{S} f_{cs} * E_{cs} \qquad (2)$$

where C is the number of cycles and S is the number of states, f_s is the fraction of the cohort in state s and E_s is the utility of state s.

Markov models are especially appropriate when the disease in focus is characterised by recurrence of certain events which are based on continuous risk over time [58]. Examples of such diseases are osteoporosis and rheumatoid arthritis.

Sometimes it might be necessary to model changes in probabilities, costs and effects over time after an event. Because of the no memory assumption, this cannot be directly included in a health state in a Markov cohort model. This can be solved by adding more health state states (e.g. Sick 1st year, Sick 2nd year and so on), however, this often leads to so many health states that the transparency of the model is heavily undermined. One solution within the Markov cohort model framework is the use of tunnelling technique [60], but it is often necessary to move from the cohort approach to individual based simulation.

In *Individual based simulation modelling* patients are moved through the model one by one and not as a cohort. By letting each patient move through the model individually, it is possible to keep track of the model path history which can be used as information when probabilities, costs and effects are assigned through the simulation. The simulated costs and effects will differ between patients since they will take different paths through the model, a consequence often referred to as first-order uncertainty. Using individual simulation a large number of patients must be run through the model, using so-called Monte-Carlo simulation, to obtain stable results.

One type of individual simulation modelling that has quite recently been introduced as a health economic modelling tool is *discrete event simulation (DES)*. The model technique originally comes from engineering science and operations research [61]. DES is more focused on events than a number of defined health states as in Markov cohort simulation. Patients are followed over time and events occur at discrete time points and based on a list (called the event queue) keeping track of when the events occur. The entire system that is being modelled is said to change state when an event occurs. The activation of an event might lead to new events that are added to the event queue in appropriate order. The events are also related to some sort of activity. For example an activity could be a hospitalisation including a number of events such as hospitalisation, operation and discharge. The main advantage of DES is that a

patient can be in several activities at the same time, which can be compared to a Markov cohort model, where a health state must be defined for each possible combination of activities. DES is most appropriate for modelling diseases where the time to event is a key factor in the epidemiology, for example cancer.

As long as all relevant consequences of a treatment strategy are considered, the results of the economic evaluation should not be dependent on the choice of model technique. Therefore, the choice of model technique is largely a matter of convenience. A discrete event model can be replaced by a Markov cohort model with many health states and short cycle lengths which, in turn, can be replaced by a large decision tree. However, an important factor for the choice of modelling framework is data availability. The model technique that best represents available data in the most transparent way is most likely the best choice.

1.2.8 Uncertainty in economic evaluations

In cost-effectiveness model simulation studies, information from different sources is synthesised. The aim is to build and populate models with the most appropriate data and methods that are available. Despite these efforts there is always an uncertainty in the estimated results in a cost-effectiveness analysis. The uncertainty in model based cost-effectiveness analyses can be classified into four different categories: methodological uncertainty, modelling uncertainty, transferability/generalisability and parameter uncertainty [62].

Methodological uncertainty is the uncertainty arising when comparing study results based on different methods. This most often originates in a disagreement between researchers about the most appropriate method to be used. This type of uncertainty has been suggested to be handled by sensitivity analysis and agreement upon a reference case model. Modelling uncertainty relates to the structure and process which have been suggested to be handled by sensitivity analysis and letting different groups conduct the same analysis. Transferability/generalisability uncertainty arises when the results from an analysis are applied to another setting.

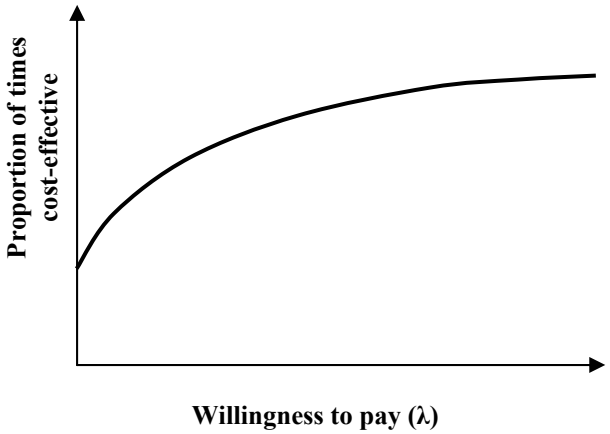
The uncertainty that has been given most attention in decision analytic modelling is parameter uncertainty, that is, the uncertainty that relates to limitations in the underlying data in the model. One way of exploring the uncertainty in the data and seeing its impact on cost-effectiveness is sensitivity analysis, that is, by varying some of the parameters, the robustness of the results can be evaluated. However sensitivity analysis is somewhat arbitrary since there is no method that defining what parameters to select and in what ranges they should be varied. Another way of exploring the uncertainty is through probabilistic analysis, where the uncertainty in the relevant underlying parameters is taken into account by allowing some or preferably all of them to vary over a given range with a given distribution. A variation in the cost-effectiveness estimates can be obtained by sampling values from the distributions a number of times and using them to estimate the cost-effectiveness.

Making inference (e.g. estimating and confidence intervals and hypothesis testing) on the ICER statistic is problematic because the sampling distribution of the ICER, a ratio statistic, is not known. Other problems are that the ICER is undefined when the denominator (i.e. the incremental effect) is zero and the ICER has different interpretations depending on what quadrant in the cost-effectiveness plane estimate falls upon. Solutions for handling these

problems have been confidence boxes and ellipses and the net benefit approach, for example [63, 64].

A graphical illustration of probabilistic analyses that has become quite common is the acceptability curve [65-67]. An acceptability curve shows the proportion of estimates of the ICER that falls below different values of willingness to pay for one unit of health effect (Figure 8). The acceptability curve summarises the uncertainty surrounding the estimate of the ICER in a convenient way.

Figure 8 A cost-effectiveness acceptability curve



1.3 ECONOMIC EVALUATION OF OSTEOPOROSIS

To get an overview of the history and development of the economic evaluation of osteoporosis, a literature review of previous research within the area was performed. The review was divided into studies estimating fracture related costs, fracture related quality of life and cost-effectiveness of osteoporosis treatments. Relevant studies were identified from the Health Economic Evaluation Database (HEED) and the PubMed database. All costs were inflated to 2005 year prices and converted into the Swedish currency (SEK) using the average exchange rate for 2005.

1.3.1 Fracture related costs

When estimating fracture costs for use in health economic studies, it is important that the costs are those that are potentially avoided by avoiding the fracture event. That is, only the additional resource use associated with the fracture should be considered in the cost estimation. A review was conducted to identify studies that have estimated such fracture related costs appropriate for the use in cost-effectiveness studies. The review included published studies from the year 1995 and onwards. Moreover, studies that only estimated the costs associated with the initial hospitalisation related to the fracture event and studies estimating costs based on expert judgement were not included in the review. In total, 9 studies, summarised in Table 2, fulfilled the inclusion criterias.

In the Swedish registry based study by Zethraeus et al [68] the potential cost savings of preventing a hip fracture were estimated based on sample of 1 709 fractured men and women in the city of Stockholm in the year 1992. The patients acted as their own control and the extra cost of hip fracture was calculated comparing resource use one year before and one year

after the fracture. The direct costs included inpatient and outpatient hospital care at the orthopaedics, geriatrics and other acute hospital care. Moreover, special living accommodation (i.e. nursing home, home for the elderly and group living) and municipal home-help were included in the costs. Outpatient primary care costs were not included. The study had a societal perspective but did not include indirect costs or costs related to relative care. The mean potential cost savings from preventing a hip fracture for patients who survived the whole year after fracture were estimated at SEK 166 265. The hip fracture related cost including patients who died within a year after fracture was estimated at SEK 131 846.

In Dolan and Torgerson [26] health care and social care costs related to hip, vertebral, wrist and other osteoporotic fractures in a UK setting were assessed. A variety of sources was used to estimate the costs. Acute care costs were derived from published sources and social care costs (i.e. special living accommodation) related to hip fracture were based on a survey comparing resource use before and after fracture. Outpatient care costs were derived from a general practitioner database using case-control design. The mean cost related to a hip fracture, vertebral fracture and a wrist fracture the first year after fracture was estimated at SEK 206 990, SEK 8 178 and SEK 7 990, respectively.

In another Swedish based study by Zethraeus and Gerdtham [69], the extra cost of a hip fracture was estimated based on the same patient sample as the above mentioned study by Zethraeus et al [68]. However, the sample was restricted to the 1 080 women that were admitted from a private residence. Based on an econometric model the potential cost savings of preventing a hip fracture for patients surviving the whole year after fracture were estimated at SEK 239 215.

The cost related to a hip fracture in a social security perspective was estimated in Reginster et al [70]. The study included 2 379 patients hospitalised for a hip fracture during the year 1996. Resource use included inpatient care and outpatient care covered by social security. Outpatient costs were estimated by comparing resource use before and after fracture. The hip fracture related cost the year after fracture in Belgium was estimated at SEK 83 610.

The extra costs related to hip and vertebral fracture in the Netherlands were estimated using a matched case cohort design in a study by De Laet et al [21]. Inpatient care, outpatient care, nursing home admissions and pharmaceutical consumption were included in the cost estimates. Resource use was collected one year before and two years after the fracture for both the fractured patients and their controls. In all, the sample consisted of 44 and 42 pairs (cases and controls) in the hip fracture group and the vertebral fracture group, respectively. The incremental cost (i.e. case-control) the year after a hip fracture was estimated at SEK 92 317. Vertebral fractures in the study were radiologically defined. For this reason the exact date of the fracture was not known, and thus the cost could not be estimated for the year after fracture event. The vertebral fracture was instead calculated as the yearly average cost between the first and second radiograph. A yearly returning incremental cost related to vertebral fracture was estimated at SEK 4 990.

Another study estimating the cost of a hip fracture in Belgium has been conducted by Autier et al [71, 72]. The study had a matched case control design including 159 pairs. The sample consisted of women who sustained a fracture in the years 1995 and 1996. Resource use was collected during the year after fracture and included inpatient care, outpatient care, rehabilitation, assistance at home and nursing home. The extra costs of a hip fracture were estimated at SEK 160 187. This cost is almost twice as high compared to the previously

discussed Belgian study [70]. The cost for the initial hospitalisation is quite similar between studies, but the study by Autier et al [71, 72] is more comprehensive concerning costs following the first hospitalisation, e.g. the inclusion of nursing home costs.

In Gabriel et al [73] direct medical costs attributable to osteoporotic fractures in the USA the year after fracture were estimated using a population based case control study. The sample consisting of 1 263 pairs was based on patients from Olmsted County, Minnesota. The mean incremental cost (cases-controls) of a hip, vertebral and wrist fracture was estimated at SEK 123 517, SEK 50 518 and SEK 27 429, respectively. However, these cost estimates did not capture all relevant cost items. For example, nursing home care, transportation services and some outpatient care were not included.

Hip fracture related costs the first year after fracture was assessed in Nurmi et al [74] based on Finnish patients. 106 patients who sustained a hip fracture between January 1999 and January 2000 were prospectively followed for a year after the fracture. Data on inpatient care, outpatient care, rehabilitation, home care, transportation, medication, nursing home care and forensic autopsies was gathered. Whether only resource use related to the fracture event itself or all resource use was collected is not clearly specified in the article. The average one year total hip fracture cost was estimated at SEK 135 196.

In Borgström et al [23] costs related to hip, vertebral and wrist fracture were estimated from a societal perspective. Medical care, community care, informal care and indirect costs were included. The sample consisted of 635 patients from seven hospitals, who survived the year after fracture, between the years 2002-2004. Only resource use that could be related to the fracture event was included. The hip fracture related cost was estimated at SEK 130 350, the vertebral fracture cost at SEK 115 381 and the wrist fracture related cost at SEK 19 677.

The results vary somewhat between the studies. However, a direct comparison of the results between studies is problematic because they are conducted within different health care systems at different points in time. The studies also differ in included cost categories and study designs. One conclusion that can be drawn is that hip fracture appears to be the most costly fracture type, followed by vertebral fracture and wrist fracture. However, few studies have investigated the costs associated with vertebral and wrist fractures. All studies consider medical care costs to some extent but only one study [23] included the whole relevant spectrum of costs from a societal perspective. In general, very few studies have investigated long-term fracture related costs. However, fractures, especially at the hip, are likely to be associated with extra costs stretching longer than one year after the event. One study [21] in the review estimated that both hip and vertebral fractures were associated with costs for more than one year.

Table 2 Fracture cost literature review.

Author, year	Country	Study design			Costs	Sample	Gender	Mean costs (SEK) first year after fracture		
		Structure	Perspective	Time frame				Hip	vertebral	wrist
Zethraeus et al, 1997 [68]	Sweden	retrospective register based	Societal	1 year before and after	Direct	1709	both	131 846		
Dolan & Torgerson, 1998 [26]	UK	mix: register, surveys and literature	Health care	1 year after	Direct	varying	women	206 990	8 178	7 990
Zethraeus et al, 1998[69]	Sweden	retrospective register based	Societal	1 year before and after	Direct	1080	women	239 215		
Reginster et al, 1999[70]	Belgium	retrospective register based	Social security	1 year after	Direct	2379	both	83 610		
Da Laet et al, 1999 [21]	Holland	prospective matched case cohort	Health care	1 year before and 2 years after	Direct	44*2 hip, 42*2 vert	both	92 317	4 990	
Autier et al, 2000 [71]& Haentjens et al, 2001 [72]	Belgium	prospective matched case control	Health care	1 year after	Direct	159*2	women	160 187		
Gabriel et al, 2002 [73]	USA	retrospective population based case control	Health care	1 year before and after	Direct	1263*2	both	123 517	50 518	27 429
Nurmi et al, 2003 [74]	Finland	prospective cohort	Health care	1 year after	Direct	106	both	135 196		
Borgström et al, 2006 [23]	Sweden	prospective cohort	Societal	18 months after	Direct/indirect	635	both	130 350	115 381	19 677

1.3.2 Fracture related quality of life

When using QALYs as the outcome measure in a health economic evaluation, it is important that quality of life is assessed using an instrument in line with utility theory. Examples of such appropriate methods are the standard gamble and time-trade off methods. The utility can be directly estimated using one of these methods or by using generic instruments such as the EQ-5D which is based on 243 health states that have been ascribed utility values using the time-trade off method based on a general population sample [75]. Another generic instrument based on a standard gamble method is the Health Utility Index (HUI) [76].

In cost-effectiveness analyses of osteoporotic treatments it is necessary to have estimates on the utility loss related to fractures following the fracture. To calculate the area under the curve, it is important to have quality of life estimates at different points in time, e.g. before the fracture, and 2 and 12 months after the fracture. The literature review was restricted to published studies that estimated quality of life using a valid method in line with utility theory and collected data that made it possible to calculate the quality of life loss related to fracture during the first year after fracture or longer.

Only four studies that fulfilled the inclusion criteria's of the review were identified (Table 3). The first study by Dolan et al [24] estimated the quality of life loss related to wrist fracture in 50 women from the UK. Quality of life was measured, using the EQ-5D instrument, in connection with the first visit to an outpatient clinic after the fracture and at a follow-up visit (the mean days between visits were 48 days). The annual loss in quality of life, estimated at 0.018, was calculated by assuming the health state value at the follow-up visit to be similar to the value a patient would have had if the wrist fracture had not occurred.

In Brazier et al [77] quality of life before fracture, at 6 and 12 months after hip fracture was estimated, using the EQ-5D. The sample was based on 39 patients enrolled in a clinical trial. The proportionate loss in quality of life compared to a healthy individual (i.e. the QoL-weight) could be calculated to 0.80.

In Tidermark et al [78], quality of life using the EQ-5D was estimated in 89 Swedish hip fracture patients treated with internal fixation. Quality of life was measured before fracture (based on recall), 1 week after fracture, 4 months after fracture and 17 months after fracture. By interpolating between the 4 and 17 months estimates, a QoL-weight the first year after fracture of 0.68 can be calculated.

Quality of life related to hip, vertebral and wrist fractures was estimated in a Swedish based study by Borgström et al [23]. The sample consisted of 635 patients and quality of life, based on the EQ-5D, was estimated before (based on recall) and after fracture (within two weeks, after 4 months and after 12 months). The QoL-weights the first year after fracture were estimated at 0.79, 0.64 and 0.93 for hip, vertebral and wrist fracture, respectively.

There are a number of studies that have estimated the health related quality of life associated with osteoporotic fracture using time-trade off or standard gamble methods [79-83]. However, few of these have collected information in such a way that the calculation of Qol loss over a period of time is feasible. Some studies have just looked at a certain point in time after fracture or estimated quality of life based on patients who have experienced a fracture in previous years [80, 83]. There are also few studies that have followed patients in terms of quality of life for longer time frames than one year. However, the existing evidence suggests

that quality of life is reduced for more than one year after a hip and a vertebral fracture [80, 81].

Table 3 Fracture related quality of life literature review

Author, year	Country	QoL instrument	Sample	Gender	QoL weight the first year after fracture		
					hip	vertebral	wrist
Dolan et al, 1999	UK	EQ-5D	50	women			0.98
Brazier et al, 2000	Multinational	EQ-5D	39	women	0.80		
Tidermark et al, 2002	Sweden	EQ-5D	89	both	0.68		
Borgström et al, 2005	Sweden	EQ-5D	634	both	0.79	0.64	0.93

1.3.3 Cost-effectiveness studies

The history of the economic evaluation of osteoporotic therapies can be divided into two phases. In the first phase, starting in the 1980's, the fracture risk was usually modelled from the relationship between bone mineral density (BMD) and fracture risk (BMD models) [84]. This modelling approach is linked to the unavailability of clinical trials using fracture events as endpoints. 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 [85-87]. The second phase started in the early 1990's with the introduction of models incorporating age-specific absolute fracture risks, based on epidemiological data [88].

The review of cost-effectiveness was restricted to published studies from the year 2000 and onwards. The reason for this was to limit the number of studies but also because before the year 2000 the main part of the economic evaluation studies were based on HRT and hypothetical therapies [58]. Other inclusion criteria's were that the QALY had to be used as the outcome measure and that the evaluated intervention/s had to be a existing pharmaceutical therapy and not hypothetical.

18 studies were identified in all. The studies categorised into therapy classes are summarised in Table 4. Bisphosphonates were evaluated in 12 out of the 18 studies. The most common countries on which the analysis was based was Sweden (seven studies) and the UK (four studies). In all studies except one the base comparative treatment was no treatment. All studies derived the effect of the treatment from clinical trials. The treatment effect was modelled as a risk reduction in the event risk in all studies. In ten studies, the cost-effectiveness was estimated based on the results from a specific clinical trial and in the remainder of the studies the effect of treatment was estimated using meta-analysis or choosing appropriate treatment effects from different clinical trials. All models included hip fracture as a disease state and usually also included fractures of the wrist and spine. Studies evaluating therapies with extra-skeletal effects (i.e. HRT and raloxifene) always included fracture but neither of the two studies evaluating HRT incorporated any non-fracture events. Both studies evaluating raloxifene included breast cancer and usually coronary heart disease (CHD) in the model. All the cost-effectiveness studies were based on state transition models. Markov cohort simulations were used in 16 studies and two studies applied an individual simulation technique. In most studies, the base-case target populations were women aged about 70 with and without established osteoporosis. This indication also corresponds well with the patient

characteristics in the clinical trials on which the studies were based. The societal perspective was chosen in nine of the analysis, followed by health care (used in seven studies) and social insurance (used in two studies) perspectives. Only four of the studies included future costs, i.e. the difference in consumption and production over ages. In 13 of the studies the consequences of the treatments were included over the lifetime of the target patients and in the five other studies, the time horizon varied between 10 to 30 years.

It is difficult to directly compare the different results estimated in the studies due to different settings and study design. However, some generalised conclusions for the different drug classes can be drawn. Both studies evaluating HRT showed very low cost-effectiveness ratios compared to no treatment, but neither of them included the full effect profile of HRT which reduces the value of these two studies. Based on the study results bisphosphonates compared to no treatment seem to be cost-effective treatments, especially among women with established osteoporosis. Only one study compared different types of bisphosphonates and the result indicated that risedronate was a dominant alternative compared to alendronate. However, no major conclusion should be drawn from this since the treatment effects were rather arbitrarily chosen. The estimated cost per QALY gained for SERMs (i.e. raloxifene) was in general somewhat higher as compared to those estimated for the bisphosphonates but could be still considered to be cost-effective compared to no treatment. One study estimated a cost per QALY gained above 5 000 000 SEK for raloxifene treatment. However, this study did not include the beneficial effect on breast cancer that raloxifene has shown to have, a factor which is an important driver for the cost-effectiveness of this drug. The estimated cost per QALY gained of PTH treatment was also fairly high and could be considered to be on the borderline of being cost-effective. Finally, the single study analysing the calcium and vitamin D treatment showed a cost-saving result.

Several studies are based on the same modelling frameworks. Modelling platforms can be recognized in all nine studies. Two major model frameworks that have been used for the evaluation of bisphosphonates can be identified, five studies [89-93] were based one model and four [94-97] on the other. Also, one Swedish based research group can be identified as being behind eight of the studies [89-93, 98-100] .

Table 4 Cost-effectiveness literature review

	Country	Intervention	Treatment effect	Disease states*	Model	Base case indication	Time horison and perspective	Cost per QALY gained (SEK 2005)
HRT								
Willis et al, 2001	Sweden	HRT vs Notreat	Various clinical trials	Fractures**	Markov	53-year old women, osteopenia/osteoporosis	25-year health care	Osteopenic: 54 000 Osteoporosis: cost-saving
Nagata-Kobayashi et al, 2002 [101]	Japan	HRT vs screening & Notreat	Meta-analysis	Hip fracture	Markov	50 year old women, osteopenia/osteoporosis	30-year societal	4 000-32 000
Bisphosphonates								
Grima et al, 2002 [96, 97]	USA	Risedronate vs Alendronate	VERT, HIP and FIT	Fractures**	Markov	65-year old women with established osteoporosis	Life-time health care	Cost-saving
Iglesias et al, 2002 [97]	UK	Risedronate vs Notreat	VERT and HIP	Fractures**	Markov	75-year old women with established osteoporosis	Life-time health care	Cost-saving
Borgström & Zethraeus, 2003 [90]	Sweden	Risedronate vs Notreat	HIP	Fractures**	Markov	74-year old women with and without established osteoporosis	Life-time societal with future costs	Estab. osteoporosis=18 000 Osteoporosis=298 000
Johnell et al, 2003 [91]	Sweden	Alendronate vs Notreat	FIT	Fractures**	Markov	71-year old women with established osteop, 69 year old women with osteoporosis	Life-time societal	71-year old: 82 000 69-year old: 136 000
Brecht et al, 2003 [94]	Germany	Risedronate vs Notreat	VERT and HIP	Fractures**	Markov	70-year old women with established osteoporosis	10-year social insurance	Cost-saving
Jönsson et al, 2003 [92]	Denmark	Alendronate vs Notreat	FIT	Fractures**	Markov	71-year old women with established osteop, 69 year old women with osteoporosis	Life-time societal with future costs	71-year old: 140 000 69-year old:250 000
Borgström et al, 2004 [89]	Sweden	Alendronate vs Notreat	FIT	Fractures**	Markov	71-year old women with established osteop, 69 year old men with osteoporosis	Life-time societal with future costs	71-year old: 16 000 69-year old:62 000

Brecht et al, 2004 [95]	Germany	Risedronate/alendronate/ raloxifene vs Notreat	VERT, HIP, FIT and MORE	Fractures**	Markov	70-year old women with established osteoporosis	10-year social insurance	Risedronate: cost-saving Alendronate=42 000 Raloxifene: >5 000 000
Kanis et al, 2004 [93]	UK	Risedronate vs Notreat	Meta-analysis	Fractures**	Markov	70-year old women with and without established osteoporosis	Life-time health care	Prior vertebral fracture=143 000 No prior vertebral fracture= 560 000
Stevenson et al, 2004 [102]	UK	Alendronate/raloxifene/calcitonin/HRT vs Notreat	Meta-analysis	Fractures**, CHD and breast cancer	Individual state transition	70-year old women with established osteoporosis	10-year health care	Alendronate: 130 000 Calcitonin:>3 000 000 HRT: 700 000 Raloxifene: 330 000
Christensen et al, 2005 [103]	Denmark	Alendronate vs Notreat	FIT	Fractures**	Markov	71 year old women at high risk of fracture (RR fracture = 2)	Life-time societal	SEK 100 000
Schousboe et al, 2005 [104]	USA	Alendronate vs Notreat	FIT	Fractures**	Markov	55-75 years old women with osteopenia	Life-time societal	Varying: 2 500 000 - 540 000
SERMs								
Borgström et al, 2004 [98]	Sweden	Raloxifene vs Notreat	MORE	Fractures**, breast cancer and CHD	Markov	60-80 year old women with osteporosis	Life-time societal with future costs	<600 000
Kanis et al, 2005 [99]	UK	Raloxifene vs Notreat	MORE	Fractures**, breast cancer and CHD	Markov	50-80 year old women with and without established osteoporosis	Life time health care	<330 000
PTH								
Lundkvist et al, 2005 [100]	Sweden	PTH vs Notreat	PTH clinical trial	Fractures**	Individual state transition	69 year old women with established osteoporosis	Life-time societal	<600 000
Calcium & Vitamin D								
Willis, 2002 [105]	Sweden	Calc/Vit D vs Notreat	Clinical trial	Hip	Markov	50-70 year old women at high risk of fracture	Life-time health care	Cost-saving

* Disease states on which treatment is assumed to have an effect n

** Hip, vertebral and wrist fractures

2 AIMS OF THE THESIS

The general purpose of this research has been to develop important aspects of the health economics of osteoporosis. The research can be divided into three categories: *Fracture related costs and quality of life for the use in economic evaluation, economic modelling of osteoporosis therapies* and *health economics as a tool in treatment guidelines and patient selection (intervention thresholds).* More specifically, the following aims were set up for the research:

Fracture related costs and quality of life for use in economic evaluation (paper I)

- To develop a data collection methodology for the assessment of fracture related costs and quality of life

- To collect data using the methodology and estimate the societal fracture related costs and quality of life in Sweden relevant for health economic evaluation.

Economic modelling of osteoporosis therapies (paper II-III)

- To build and further develop models for the assessment of the cost-effectiveness of osteoporosis drugs.

- To estimate the cost-effectiveness of raloxifene based on the MORE trial.

- To estimate the cost-effectiveness of strontium ranelate based on the SOTI and the TROPOS.

Health economics as a tool in treatment guidelines and patient selection (paper IV)

- To further develop the concept of intervention thresholds (i.e. at what hip fracture risk it is cost-effective to treat).

- To develop a model for the estimation of intervention thresholds in a multinational perspective

- To assess what factors are most important for differences in intervention thresholds between countries.

3 METHODS AND MATERIALS

3.1 FRACTURE RELATED COSTS AND QUALITY OF LIFE (PAPER I)

The study on costs and quality of life associated with osteoporosis-related fractures in Sweden (KOFOR) was initiated with the primary aim of collecting information about the costs and quality of life related to osteoporotic fractures at the hip, vertebrae and the wrist which are relevant for the use in health economic evaluation.

3.1.1 Study design and data collection procedure

Data regarding resource use and quality of life related to fractures was collected by questionnaires at the baseline, 4 months, 12 months and 18 months after the fracture event. In a pilot study a data collection questionnaire was developed and then tested at the Malmö University Hospital [22]. At the baseline patient characteristics, background information and perceived health status just before and health status after the occurrence of the fracture were collected. At the 4 month, 12 month and 18 month follow-up resource use since the last visit and current health status were collected. Patient reported information at the baseline was primarily collected via interviews in connection with the hospital visit related to the fracture event. If the interview could not be conducted in relation to the hospital visit, the information was collected via a telephone interview. Quality of life and patient reported resource use at the follow-ups were collected via telephone interviews.

Fractured patients were enrolled at seven study centres (Södersjukhuset in Stockholm, Malmö University Hospital, Lund University Hospital, Norrlands University Hospital, The Hospital in Ystad, Helsingborg Hospital and Hässleholm Hospital). To be included a patient had to be diagnosed for a fracture caused by low-energy trauma and be at least 50 years old. Vertebral fractures had to be confirmed by an X-ray examination. Patients seeking care for multiple fractures were not eligible for the study. Fractures caused by other diseases such as cancer were not included. Moreover, patients who were judged not to be able to complete the questionnaires due to dementia or other psychological problems were excluded from the study. To be eligible for the study the patient had to be included and interviewed within four weeks after the fracture event. Patients had to give their informed consent to participate in the study prior to inclusion. The study was approved by local ethic committees.

3.1.2 Resource use

Resources were collected using patient records, register sources and by asking the patient. The resources were categorised into medical costs (hospitalisations, outpatient care and pharmaceuticals), non-medical costs (community care and informal care) and indirect costs (i.e. loss of production). Community care consisted of special living arrangements, home care and transportation. Patient-reported resource use (community care, and informal care) and resources lost, i.e. indirect costs were recorded for a shorter time period within the study duration (one month) to minimise recollection bias.

3.1.3 Costing

The cost of fractures was estimated by multiplying the quantity of the different resource used by a corresponding value of the resource, i.e. a unit cost. All costs are given in 2004 prices, inflated, when necessary, using the Swedish consumer price index [106]. The costs were converted from the Swedish krona (SEK) to Euros (€) using the yearly average exchange rate for 2004 (9.1268 SEK/€) [106]. Indirect costs were estimated by the human capital approach.

3.1.4 Quality of life

Quality of life was estimated using the EQ-5D questionnaire, which is a general quality of life instrument dividing health status into five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [107]. Each dimension is divided into three degrees of severity: no problem, some problems, major problems. The five health dimensions divide health status into 243 (3^5) possible health states. Social tariff values for these health states, estimated as TTO utility values, have been presented by Dolan et al.[75] This tariff was applied to the observed health states in the study.

In the study, 5 quality of life point estimates were given before fracture, within four weeks after the fracture, 4 months after the fracture, and 12 and 18 months after the fracture. Fracture related quality of life loss was estimated by assuming that the patient would have remained at the stated pre fracture quality of life level if the fracture had not occurred. The annual quality of life loss related to fracture was then calculated by subtracting the pre fracture quality of life by the estimated quality of life the year after fracture. Quality of life the year after fracture, the area under the curve (QALY), was estimated in two different ways. In the first way, quality of life was interpolated between the point estimates at baseline, 4 months and 12 months. In the second way, it was conservatively assumed that patients reach their stated 4 month quality of life already at 1 month after fracture. The pre fracture quality of life was collected from patients after the fracture and not before. This might potentially lead to some recollection bias since the pre-fracture health status might have been perceived to have been better than it actually was. Therefore, the annual quality of life loss was also estimated using population quality of life norms (where available) as a proxy for the patients' quality of life before fracture.

3.1.5 Patient sample

The included patients in the KOFOR-study were followed for 18 months. However, the results presented in this study are for the first year after fracture. The patient sample that was analysed consisted of 635 fractured patients (278 hip fractures, 81 vertebral fractures and 276 wrist fractures) who survived the whole year after fracture. The proportion of women exceeded 78% in all three fracture groups and the mean ages were 77.6, 75.9 and 69.5 years among hip, vertebral and wrist fracture patients, respectively. 98% of the hip and vertebral fracture patients came from private residence before fracture, while all wrist fracture patients came from home (see Table 5).

Table 5 Patient characteristics and baseline information

	Hip fracture (n=278)	*Vertebral fracture (n=81)*	*Wrist fracture (n=276)*
Mean age	77.6	75.	69.5
Age range	51-96	50-92	50-92
Proportion women	0.78	0.81	0.91
Proportion living in private residence before fracture	0.98	0.98	1.00
Proportion having a previous fracture in the last five years:	0.23	0.20	0.14
Proportion admitted the first day	1.00	0.72	0.09
Proportion working	0.03	0.09	0.23
Mean days from fracture to interview (standard deviation)	4.24 (2.95)	6.56 (6.8)	8.08 (4.19)
Mean days from fracture to hospitalisation if hospitalised (standard deviation)	0.41 (1.58)	0.19 (0.58)	0.96 (3.17)

3.1.6 Statistics

Cost data is often skewed and thus not normally distributed. The Shapiro-Wilk test was used for testing the normality of the cost and quality of life distributions [108]. If the data was not found to be normally distributed, the non parametric Kruskal-Wallis one-way analysis of variance test was used [108] to test the difference in costs and quality of life between different sub groups (e.g. age, gender); if shown to be normally distributed, the regular t-test was used [108]. If the data was not normally distributed, confidence intervals were obtained by using the bias corrected accelerated (bca) percentile bootstrapping method [109].

Because cost data is often heavily skewed, it is not appropriate to use in regression modelling in its original shape. Therefore, in the analysis investigating the relationship between costs and other variables, the Box-Cox method [110] was used to find the best transformation of the cost data to fit a normal distribution. The transformed cost variable was then used as the dependent variable in a multivariate ordinary least square (OLS) regression model. The Breusch-Pagan test was used to test for heteroscedasticity [111]. In the presence of heteroscedasticity, White's corrected standard errors were applied [111].

All analyses were conducted in the statistical software package STATA 8.0 for windows and 5% was used as the level of significance.

3.2 MODELLING THE COST-EFFECTIVENESS OF OSTEOPOROSIS TREATMENTS (PAPERS II-III)

Raloxifene and strontium ranelate are two drugs that have been shown to reduce the risk of fractures in large clinical trials [39, 42, 43]. Based on the results in these trials, two studies were conducted to estimate the cost-effectiveness of each drug for women in a Swedish setting. For the estimation of the cost-effectiveness a model is needed to extrapolate the effects beyond the time frame of the clinical trial and upon Swedish women similar in characteristics to the patients in the trials.

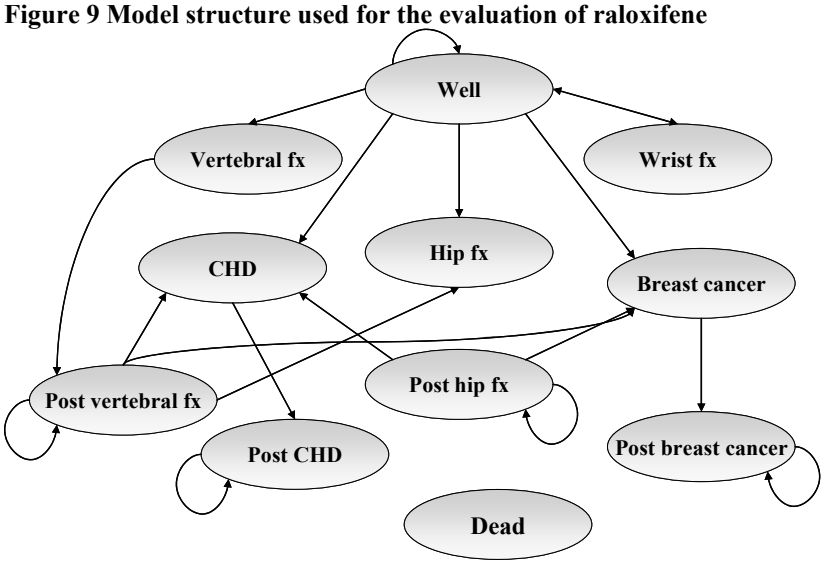
The cost-effectiveness was estimated for women taking the drug compared to women not given the drug (i.e. placebo in the clinical trials).

3.2.1 Modelling approach

The consequences of osteoporosis stretch over long time spans with changing epidemiological patterns with increasing age. This makes approaches such as decision tree models inappropriate for the modelling of osteoporosis. Since osteoporosis can be characterised as a chronic disease that progresses in relatively well defined events (i.e. fractures) usually measured as incidence and not time to event, Markov models have been the most frequent modelling approach [112, 113].

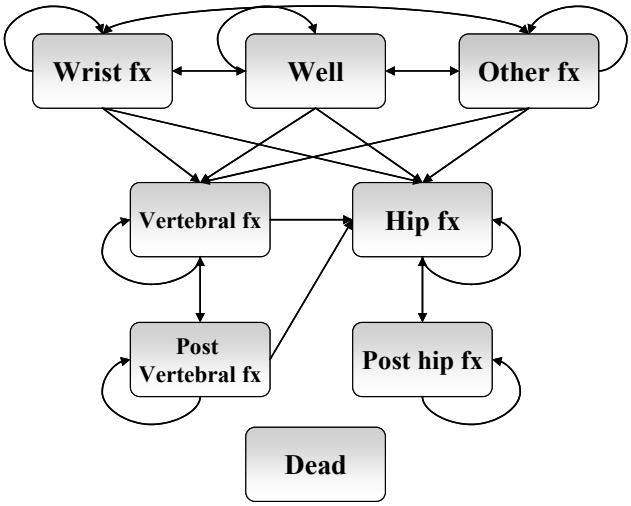
A Markov cohort approach was also chosen for the evaluations of raloxifene and strontium ranelate. The models have similar base structures but are, in each case, adapted to reflect the specific treatment effect observed in the clinical trials. This is illustrated in Figure 9 and Figure 10.

Figure 9 Model structure used for the evaluation of raloxifene



Note that it is possible to go to the dead state from all health states, however to simplify the figure, these transition arrows have been omitted.
CHD=Coronary heart disease
Fx=fracture

Figure 10 Model structure used for the evaluation of strontium ranelate



Note that it is possible to go to the dead state from all health states, however to simplify the figure, these transition arrows have been omitted.
Fx=fracture

Both models are based on the same principle, that the transition of patients between the health states in annual cycles from a certain starting age of intervention until the event of death or until they reach the age of 100 years. The included disease states are also characterised by age-dependent fracture risks, mortality rates, costs and quality of life weights. Moreover, the consequences of the disease events are divided into an *acute* and a *post* phase that are explicitly modelled as health states. The acute phase captures the consequences, in terms of morbidity and costs, the first year after the event while the post phase capture the consequences beyond the first year after event. The only disease event that is modelled to have an impact only during the first year after event is wrist fracture. The main difference between the two models is that in the model used for the evaluation of raloxifene, non fracture related events such as coronary heath disease (CHD) and breast cancer were included. Therefore the model structures can be defined as an extra-skeletal model and a bone-specific model (i.e. only fracture events included).

The extra-skeletal model precedes the bone-specific model and was developed for the purpose of estimating the cost-effectiveness of hormone replacement therapy [114, 115]. The model originates from a cost-effectiveness model for cardiovascular disease prevention [116, 117]. As can be seen in Figure 9 the following disease events are included in the model: *Hip fracture, Vertebral fracture, Wrist fracture, Breast cancer, CHD and Death*. CHD is divided into five health states: Recognised acute myocardial infarction, Unrecognised acute myocardial infarction, Angina pectoris, Coronary insufficiency and Sudden death.

When estimating the cost-effectiveness in the model a cohort of patients start the simulation in the *Well* health state and are thereafter at yearly risks of an event occurring. If an event occurs the patient will move to the corresponding health state and remain there for the next year where after new events might occur. From the well health state it is possible to have any event but there are some restrictions on possible transitions from other health states. One restriction is that when a patient is in an acute disease health state the transition options are going to the corresponding post disease health state (e.g. from hip fracture to post hip fracture) or dying. Other transition restrictions are that it is not possible to have any other events, except dying, in extra-skeletal post disease states. From the post hip fracture state, it is

possible to incur a CHD and a breast cancer event but not a vertebral fracture or a wrist fracture. From the vertebral fracture state, it is possible to incur CHD, breast cancer and a hip fracture, but not a wrist fracture. These restrictions are of course deviations from the actual epidemiological pattern. It would have been possible to introduce health states such as a vertebral fracture or hip fracture after CHD; however, this would make the model less transparent and require data that is not available. Moreover, by having too many health states with competing risks and restrictions on the transitions paths for having multiple diseases (e.g. not possible to have further disease events after having a CHD event) there is a potential risk of underestimating the risk of diseases in the model simulations, which might have an impact on the cost-effectiveness results. For this reason and to keep the model as simple and transparent as possible, without skewing the cost-effectiveness estimates, data was adjusted to account for the possibility of sustaining the omitted transitions (e.g. hip fracture after CHD) in the model.

The bone-specific model was developed as a consequence of the introduction of bisphosphonates which significantly reduce the risk of fracture only but have not been shown to have any impact on the risk of extra-skeletal events. Different versions of the model have been used to assess the cost-effectiveness of different osteoporotic therapies in various countries [89-93]. The model uses a similar structure as the extra-skeletal model, but with the CHD and breast cancer health states excluded. However, some modifications have been made in the bone-specific model. One modification is that a health state including other osteoporotic fracture types than the "classical" hip, vertebral and wrist fracture types has been added. Other alterations are that it is possible to have more than one hip fracture and that it is possible to incur fracture in the acute fracture health states.

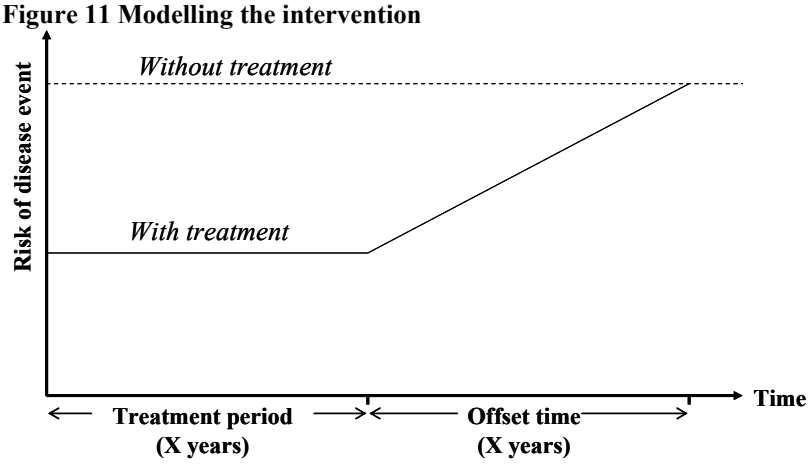
All the patients begin in the *well* health state. Each year a patient has a probability of having a fracture, remaining healthy or dying. If a patient dies, she will move to the *dead* health state and remain there for the rest of the simulation. If the patient incurs a fracture she will, depending on the type of fracture, move to the *hip fracture*, *vertebral fracture*, *wrist fracture* or *other osteoporotic fracture* health state. After one year in one of these states the patient can have a new fracture, move to the *post hip fracture* state, the *post vertebral fracture* state or die. Wrist fracture and other osteoporotic fracture are assumed to have an impact on costs and morbidity only in the first year after fracture; thus, after one year in these health states patients move, if not fractured once more, back to the well health state. Patients in the post-vertebral fracture state can remain in this state, have a vertebral fracture, hip fracture or die. From the post-hip state it is only possible to remain in the post-hip state, have another hip fracture or to die. Consequently, patients who have had a hip fracture cannot experience any future wrist, vertebral or other osteoporotic fractures, and patients in the vertebral and post vertebral states cannot have a wrist fracture. The probability of having a vertebral or a wrist fracture after a hip fracture is low, and the consequences on mortality and quality of life after having experienced multiple, different fractures have been poorly investigated. Nevertheless, the approach is conservative since it will slightly underestimate the number of vertebral and wrist fractures.

3.2.2 Modelling an intervention

An intervention is modelled by its impact on the disease risks during and possibly also after stopping treatment. The remaining effect of an intervention on the fracture risk after the treatment period has most commonly been modelled as a linear decline in the level of risk reduction for a given "offset time" [118]. How the treatment effect on disease risks was

modelled in both the extra-skeletal and bone-specific model is illustrated in Figure 11. The remaining effect on fracture risk of osteoporosis treatments has usually been assumed to persist for the same time as for the intervention period. However, the models are flexible and allow for different assumptions of risk changes, lengths of treatment and offset time periods.

Figure 11 Modelling the intervention



3.2.3 Data

The data needed for modelling the cost-effectiveness of osteoporosis treatments can be divided into three categories: Clinical data (e.g. effect of treatment), epidemiological data (e.g. risk of disease and mortality) and health economic data (e.g. costs and quality of life). A model should be populated with the best available data at the time of the analysis. Therefore, the data used in the two studies estimating the cost-effectiveness of raloxifene and strontium ranelate differs somewhat.

3.2.3.1 Clinical data

The Multiple Outcomes of Raloxifene Evaluation (MORE) study was a four-year multi-centre, randomised, blinded, placebo controlled trial including 7705 osteoporotic postmenopausal women aged 31-80 (mean age 67 years). The mean femoral neck T-score for bone mineral density (BMD) was -2.33 SD and for the lumbar spine the BMD was T-score of -2.58 SD. [31, 39, 119, 120]. Patients were randomly assigned to receive 60 mg/d or 120 mg/d of raloxifene or matching placebo. All participants were also given calcium and vitamin-D supplements. The relative vertebral fracture risk of raloxifene compared to placebo for patients given 60 mg/d without prior vertebral fracture at the baseline was estimated at 0.52 (CI: 0.35-0.78). The corresponding relative risk for patients with prior vertebral fractures at the baseline was estimated at 0.65 (CI: 0.52 -0.81).[31] Raloxifene was not shown to significantly reduce the risk of non-vertebral fractures. However, raloxifene reduced the risk of invasive breast cancer by 72% (CI 54%-83%) [119]. In a patient subgroup (13.4% of the patients in the study) at high risk of cardiovascular events, the MORE study reported a 40% reduction in the risk of cardiovascular events (CI 5%-62%) [120].

The Spinal Osteoporosis Therapeutic Intervention (SOTI) study was a five-year multinational randomised double blind, placebo controlled study, with a main statistical analysis over three years, including 1 649 postmenopausal women aged 50 years or more (mean age=69 years) with at least one radiographically confirmed vertebral fracture and a lumbar spine BMD lower

than 0.840g/cm^2 [42]. The primary endpoint was the number of patients experiencing new vertebral fractures over three years. A secondary endpoint was the number of patients with new non-vertebral osteoporotic fractures. Compared to placebo, strontium ranelate reduced the incidence of new radiographical vertebral fractures by 41% (RR=0.59; 95% CI= 0.48-0.73) and new clinical vertebral fractures by 38% (RR=0.62; 95% CI=0.47-0.83) over three years. Pooling the vertebral and non-vertebral fractures demonstrated a significant fracture risk reduction of 32% (RR=0.68; 95% CI= 0.57-0.81). [42]

The Treatment Of Peripheral OSteoporosis (TROPOS) Study was a five-year multinational (11 European countries and Australia included) randomised double blind, placebo controlled study, with a main statistical analysis over three years, including 5 091 osteoporotic women aged above 70 (mean age=77 years) with a femoral neck BMD below 0.600 g/cm^2. At the baseline, 33% of the patients had at least one vertebral fracture. The primary endpoint was the time to occurrence of the first non-vertebral fracture. A secondary endpoint was the occurrence of vertebral fractures. Compared to placebo, strontium ranelate reduced the incidence of major osteoporotic fractures by 19%. (RR=0.81; 95% CI=0.66-0.98), the risk of non-vertebral fractures by 16% (RR= 0.84; 95% CI=0.70-0.91) and the risk of radiographical vertebral fractures by 39% (RR=0.61; 95% CI=0.51-0.73).[43]

3.2.3.2 Epidemiological data

Population fracture risks were derived from various sources in the literature [30, 121, 122]. The risk of invasive breast cancer risk was based on data from the Swedish National Board of Health and Welfare for the year 2000 [123]. The risk of CHD was extracted from hospital inpatient statistics provided by the Centre of Epidemiology at the National Board of Health and Welfare in Sweden for the period 1990-1994 [117].

Fracture risks have to be adjusted to reflect the increased fracture risk in the target patient groups, compared to that of the general population. In the strontium ranelate study, the relative risk of fracture for the target patient groups compared to the population fracture risk was calculated from the BMD and the prevalence of vertebral fractures in the patient groups[124, 125]. In the raloxifene study patients without prior vertebral fractures were assumed to have a two-fold increase in risk (RR=2) of vertebral fracture compared to the average population risk [86], while patients with prior vertebral fractures were assumed to have a fourfold increase in vertebral fracture risk [126].

Mortality rates for the general female population in Sweden were derived from life tables published by official statistics [106]. In the extra-skeletal model mortality was adjusted to exclude the risk of dying from CHD and breast cancer to fit the model [117].

Hip and clinical vertebral fractures lead to an increased mortality compared to the normal population [28, 29, 127-129]. Hip and vertebral mortality rates in the first and following years after fracture event were derived from different published sources [27, 128, 130], respectively. In the raloxifene, study a relative risk of mortality after clinical vertebral fractures estimated at 2.5 the year after fracture and 1.3 in subsequent years for all ages was used. In the strontium ranelate study increased mortality after clinical vertebral fracture was age differentiated.

In line with evidence suggesting that the total excess mortality compared to the general population cannot entirely be attributed to the fracture event [2, 3, 131, 132] it was assumed

that 30% of the observed increase in mortality after fracture could be related to the fracture itself.

Osteoporotic patients have been found to have a higher degree of frailty compared to the general population, implicating that excess mortality after fractures among osteoporotics is not entirely attributed to the fracture event. It has been estimated that 33% of the deaths one year after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25% directly related. In another study on Swedish hip fracture patients only 17%- 32% of all deaths depending on age were found to be causally related to the fracture.

Mortality in the first and following years after breast cancer was calculated using data from the *Centre for Epidemiology at the National Board of Health and Welfare* for all patients with invasive breast cancer (ICD-10: C50) between 1995-2000. CHD mortality the first and subsequent years were the same as that given in Zethraeus et al [117].

3.2.3.3 Health economic data

Costs were included based on a societal perspective in both studies, including intervention costs, disease related costs (medical care costs, non-medical care costs and indirect costs) and costs in added years of life.

Direct and indirect fracture related costs in Sweden during the first year after a hip, vertebral and wrist fracture were derived from various empirical cost studies [21, 22, 68]. Hip fracture costs in the second and following years were based on the proportion of patients who are admitted from their own home and become long term institutionalised after fracture and the cost of staying in a nursing home stay [49, 133]. In the raloxifene study, the proportion of institutionalised patients was assumed to be 10% for all ages [49] and in the strontium ranelate study it was age differentiated (data on file). Costs of CHD events and breast cancer were taken from the literature [134, 135]. Swedish estimates on the costs in added life years were derived from Ekman et al [136].

The annual intervention cost was based on drug costs, a yearly visit to the physician and a bone mineral density measurement every second year.

3.2.3.4 Quality of life

Quality of life for the general population was derived from the literature [137, 138]. Fracture related quality of life the year after osteoporotic fractures was derived from a prospective Swedish based study [22]. Quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [49]. In line with evidence indicating a long-term reduction in quality of life after vertebral fractures, quality of life loss related to clinical vertebral fractures in the second and following years was conservatively assumed to be 0.05 [20, 80, 81, 139].

The utility loss after CHD and breast cancer was assumed to be 0.1 for all years after the disease event and for all ages [115, 140].

3.3 MULTINATIONAL INTERVENTION THRESHOLDS (PAPER IV)

Intervention thresholds (IT) can be defined as the absolute disease risk at which an intervention becomes cost-effective. Assessing at what risk of disease it is acceptable or cost-effective to treat with an intervention can serve as a helpful tool for the synthesis of treatment guidelines. In osteoporosis, the IT has been expressed as the ten-year probability of hip fracture at which intervention is cost-effective [10, 141-143]. However, the clinical manifestation of osteoporosis constitutes of several different fracture types with different consequences for health and costs. Only considering hip fracture in the IT assessment will lead to too high probabilities at which intervention is considered to be cost-effective since the benefit of osteoporosis treatments will be underestimated. This have been accounted for by the calculation of hip fracture morbidity equivalents (HFMQ) which is a measure of the morbidity of osteoporotic fractures relative to hip fractures [10]. By adjusting the risk of hip fracture using these hip fracture equivalents, the multiple outcomes of osteoporosis are reduced to a common currency which facilitates the estimation of ITs. So far, ITs, using hip fracture equivalents, have been estimated for Sweden and the UK [141-143].

3.3.1 Study objective and analysis framework

The main objective of this study was to estimate and investigate the potential differences in intervention thresholds for osteoporosis for women in different countries.

Intervention thresholds were estimated for women in seven high income countries representative of different regions around the world: Australia, Germany, Japan, Sweden, Spain the UK and USA. The cost-effectiveness analysis was estimated based on a societal perspective with the intention of including morbidity costs, indirect costs and costs of increased survival where available. The willingness to pay for a QALY gained was assumed to be two times the gross domestic product (GDP). All costs are given in year 2004 values. Costs were, when necessary, inflated using country-specific consumer price indices and converted to the US dollar ($) at the average annual exchange rates for 2004. Both costs and effects were discounted at an annual rate of 3% in the base analysis.

In line with a recent meta-analysis of the effects of bisphosphonates in post-menopausal osteoporosis [144] a relative risk reduction of treatment of 35% was assumed. A five-year intervention was assumed, which was chosen to approximate the time period for which there is direct or indirect clinical data on intervention effects. However, durations of three and ten years were also tested in sensitivity analyses. After stopping treatment, the risk reduction was assumed to reverse in a linear manner (also called the offset time of treatment effect) over a five-year period [118, 144, 145] in the base case.

3.3.2 The model

A Markov cohort model was used to estimate the probability at which intervention is cost-effective. The model consists of four health states: *Well, Fracture, Post fracture* and *Dead*. A patient starts the simulation at a given age in the *Well* state and transitions through the model at yearly risks of fracture or dying. If a fracture occurs, the patient moves to the fracture state for one year. The following year the patient is at risk of dying or sustaining another fracture. If neither occurs, the patient moves to the *post fracture* state which captures the long term consequences of fracture. From the *post fracture* state it is possible to remain in the same state, fracture or die. The simulation ends when the patient dies or reaches 100 years of age.

3.3.3 Model data

Ideally, data for all components (epidemiological, clinical and cost) should be derived from the country on which the study is based. The countries included in this study were chosen because local estimates of age -differentiated hip fracture risk and cost of hip fractures were available. Local data were used to the greatest possible extent and when data was missing a uniform way was used to convert Swedish data to other countries for missing variables.

4 RESULTS

4.1 FRACTURE RELATED COSTS AND QUALITY OF LIFE ONE YEAR AFTER FRACTURE (PAPER I)

The average fracture related costs estimated for the first year after a hip, vertebral or a wrist fracture are shown in Figure 12. Hip fracture is associated with the highest cost followed by vertebral fracture and wrist fracture. Medical care costs constituted the main cost factor, however, their proportion of total costs differed between fracture types. There was no significant difference in fracture related costs between genders for any fracture type. The estimated hip fracture cost varied significantly over age groups, mostly because of a rise in resource use of community care, in particular home help and special living accommodation (Figure 13). The hip fracture cost also varied significantly ($p<0.001$) across age groups for women but not for men ($p=0.35$).Wrist fracture costs were not found to significantly vary over ages ($p=0.88$) or between gender ($p=0.35$). The cost of vertebral fractures did not differ between men and women ($p=0.14$).

Figure 12 Average cost first year after fracture (SEK 2004)

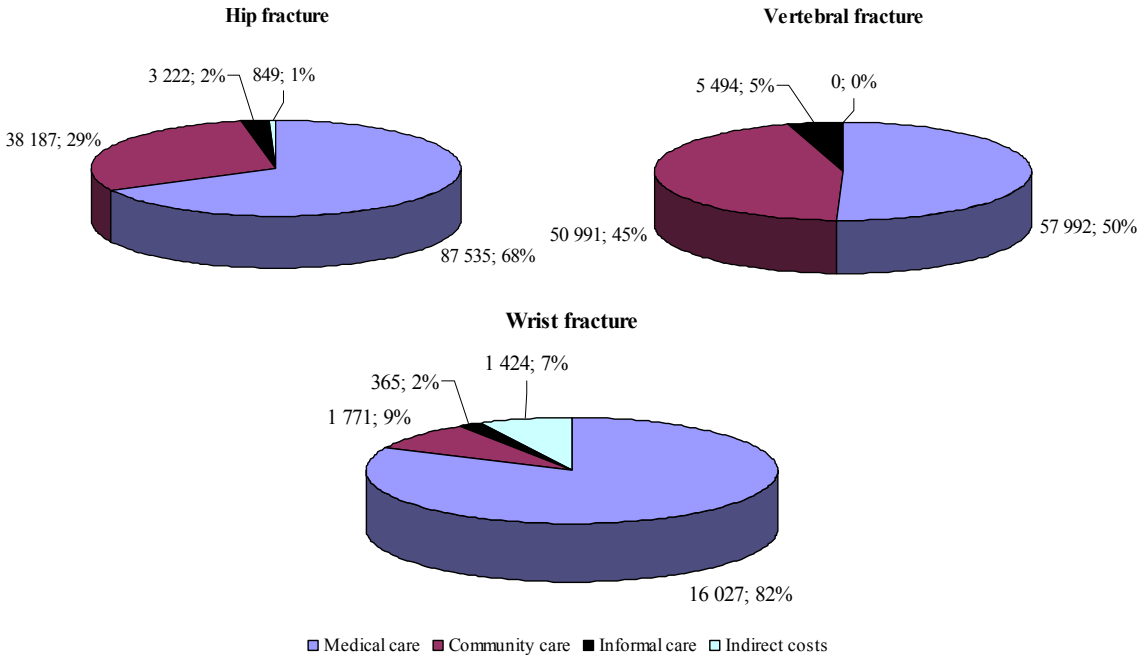
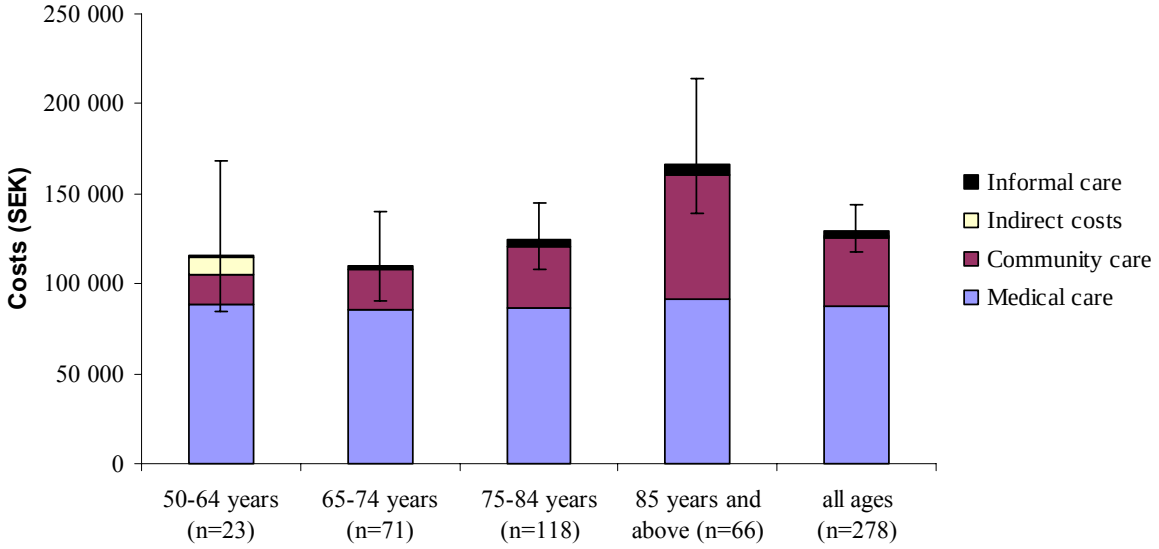


Figure 13 Average age differentiated annual cost of hip fractures (SEK 2004)



The study sample included a higher proportion of patients who were hospitalised when seeking care for vertebral fracture than what is observed in actual practice. Therefore, hospitalised and non-hospitalised vertebral fractures were analysed separately. The vertebral fracture cost was significantly higher for non-hospitalised patients 65 years or older as compared to younger patients ($p<0.01$). Hospitalised patients were found to have higher costs than non-hospitalised patients ($p<0.01$) (Figure 14).

Figure 14 Average age differentiated annual cost of vertebral fractures (SEK 2004)

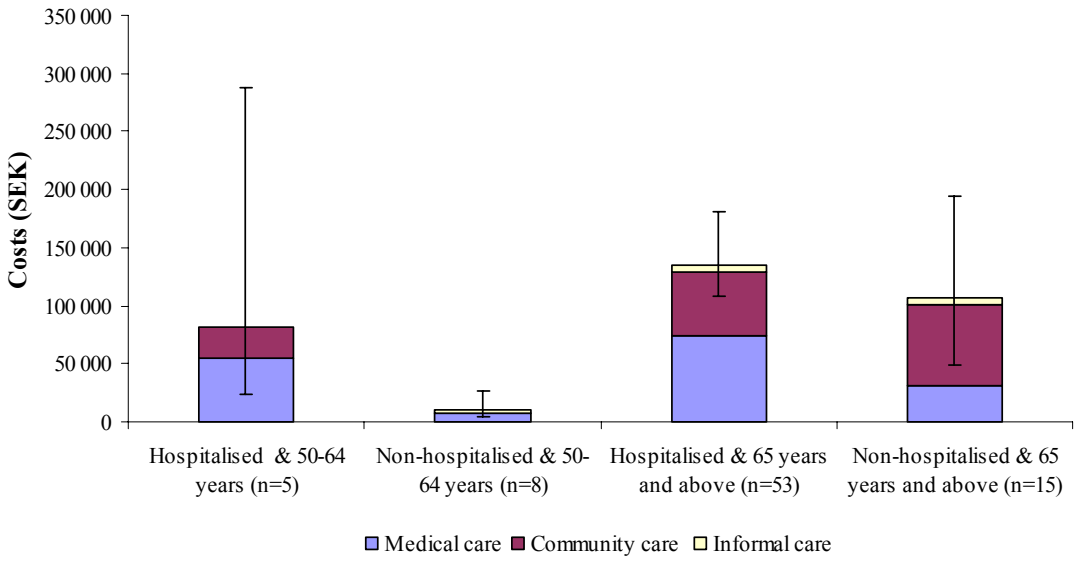
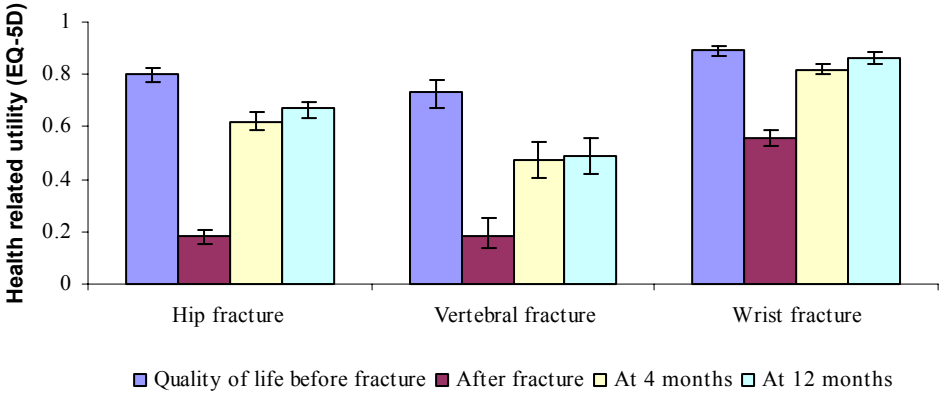


Figure 15 shows the EQ-5D social tariff values before and after a fracture. All three fracture types were associated with significant reductions in the measured quality of life after fracture, as compared to their perceived quality of life before fracture (p-values<0.0001). Quality of life before fracture was highest for wrist fracture, which can partly be explained by a lower mean age of the wrist fracture patients. Vertebral and hip fractures are associated with the lowest quality of life at each measurement. After both vertebral and hip fractures, quality of life decreased to low levels directly after a fracture, but hip fracture patients showed higher

quality of life levels at the 4 and 12 month measurements as compared to vertebral fracture patients. There was no significant difference in the annual quality of life loss between hospitalised and non-hospitalised vertebral fracture patients.

Figure 15 Estimated health related utility (EQ-5D social tariff values)



4.2 THE COST-EFFECTIVENESS OF RALOXIFENE (PAPER II)

Based on the extra-skeletal Markov model described in the methods and materials section, the cost-effectiveness of raloxifene was estimated for Swedish women similar in characteristics to the women included in the MORE-trial. The cost-effectiveness was assessed in a societal (including cost in added life years, direct and indirect costs) and a health care perspective (including direct costs only). Base case results from the analysis are shown in Table 6 for women starting a five-year long treatment with raloxifene at ages 60, 70 and 80. After the treatment period a five-year decline in the vertebral fracture risk was assumed. The effect of treatment on breast cancer was not assumed to have any residual effects. The cost-effectiveness was estimated for patient groups with a low BMD but with and without prevalent vertebral fractures before the treatment is initiated, which is in line with the patients included in the MORE study. Costs are given in year 2001 prices and both costs and effects were discounted at an annual rate of 3%.

Table 6 The cost-effectiveness of raloxifene , costs in SEK

Age (years)	*QALY:s gained*	*Life-years gained*	*Incremental cost*	*Cost per QALY gained*	*Cost per life-year gained*
No prior vertebral fracture					
Societal perspective					
60	0.061	0.054	31 317	513 393	579 944
70	0.067	0.062	33 913	506 164	546 984
80	0.065	0.071	35 337	543 646	497 704
Health care perspective					
60	0.061	0.054	22 687	371 918	420 130
70	0.067	0.062	20 316	303 224	327 677
80	0.065	0.071	17 125	263 462	241 197
Prior vertebral fracture					
Health care perspective					
60	0.066	0.055	22 360	338 788	406 545
70	0.075	0.066	19 477	259 693	295 106
80	0.074	0.078	15 955	215 608	204 551

The risk reducing effect of raloxifene on vertebral fracture and breast cancer events acts as a complement, leading to fairly stable cost-effectiveness ratios over different treatment starting ages. The breast cancer effect has a higher relative importance for cost-effectiveness at younger ages, whereas the vertebral fracture effect becomes more important with increasing age. The cost-effectiveness ratio was slightly lower among patients with prior vertebral fracture because of a higher absolute vertebral fracture risk. The sensitivity analysis showed that changes in key parameters did not lead to any major changes in the cost-effectiveness ratio. In relation to suggested threshold values for the willingness to pay for a QALY/life year, the study results indicate that raloxifene may be a cost-effective treatment among postmenopausal women in Sweden at an increased risk of vertebral fracture.

4.3 THE COST-EFFECTIVENESS OF STRONTIUM RANELATE (PAPER III)

The extra-skeletal Markov model presented in the methods and materials section was used to estimate the cost-effectiveness of strontium ranelate treatment in Sweden. The cost-effectiveness of strontium ranelate was estimated for Swedish women based on patient characteristics and results in the SOTI and TROPOS. In the base case, the cost-effectiveness was estimated for 69-year old women with a low BMD and prevalent vertebral fractures (SOTI) and for 77- year old women with low BMD (TROPOS). Treatment was assumed to be given for three years, followed by a decline in the fracture risk reducing effect for three years. The cost-effectiveness analysis had a societal perspective. Costs are given in year 2004 prices and both costs and effects were discounted at an annual rate of 3%

Table 7 The cost-effectiveness of strontium ranelate, costs in SEK

	SOTI analysis	***TROPOS analysis***
Costs		
Fracture costs avoided	-1 025	-10 088
Intervention cost	16 633	16 144
Consumption - production	6 317	3 434
Incremental cost	*21 925*	9 490
Effects		
Life years	0.032	0.019
Quality adjusted life years	0.046	0.037
Cost-effectiveness		
Cost per life year gained	678 259	503 507
Cost per QALY gained	472 586	259 643

As can be seen in Table 7 the cost-effectiveness ratios were somewhat lower in the TROPOS patient group compared to the SOTI patient group. The difference in cost-effectiveness between the groups is mainly explained by the fact that in TROPOS, there was a risk reducing effect on hip, vertebral and wrist fractures, while for SOTI there was only a treatment effect on the risk of vertebral fractures. In sensitivity analysis, varying the value of potentially uncertain parameters, the cost per QALY gained remained fairly stable below SEK 600 000. In relation to the suggested threshold values for the willingness to pay for a QALY/life year, the study results indicate strontium ranelate to be a cost-effective treatment compared to no treatment. However, this conclusion is clearer for patients similar to TROPOS patients than for SOTI patients.

4.4 UPDATED COST-EFFECTIVENESS SIMULATIONS USING DATA FROM THE KOFOR-STUDY

Neither of the cost-effectiveness analyses based on raloxifene or strontium ranelate included fracture related costs and quality of life estimated in the KOFOR-study. Moreover, since the time of the analyses some new data on mortality and long term fracture costs have become available. With the purpose of investigating the impact of this new data the cost-effectiveness of the drugs the base-cases and the probabilistic analyses were re-simulated. The parameters that were given measures of uncertainty are shown in Table 8. To take the covariance between fracture costs and quality of life losses in the KOFOR-estimates, the data was bootstrapped using the same random seed. Model parameters not mentioned in Table 8 are the same as those used in the strontium ranelate analysis described in section 3.2.3. The cost-effectiveness estimated using a societal perspective and costs was inflated to year 2005 values. Both costs and effects were discounted at an annual rate of 3%.

Table 8 Parameters given measures of uncertainty in the probabilistic analysis

	Source	Method
Costs		
First year		
Hip fracture	KOFOR	Bootstrapping mean estimate
Vertebral fracture	KOFOR	Bootstrapping mean estimate
Wrist fracture	KOFOR	Bootstrapping mean estimate
Long-term		
Probability of long term care in nursing home after hip fracture	Stockholm county council*	Bootstrapping logistic regression
Quality of life		
First year		
Hip fracture	KOFOR	Bootstrapping mean estimate
Vertebral fracture	KOFOR	Bootstrapping mean estimate
Wrist fracture	KOFOR	Bootstrapping mean estimate
Long-term		
Hip fracture	KOFOR	Bootstrapping mean estimate**
Vertebral fracture	KOFOR	Bootstrapping mean estimate**
Wrist fracture	KOFOR	Bootstrapping mean estimate**
Mortality		
First year		
Hip fracture	Swedish national inpatient register and causes of death register	Bootstrapping Poisson regression
Long-term		
Hip fracture	Swedish national inpatient register and causes of death register	Bootstrapping Weibull survival regression
Effect of treatment		
Raloxifene	The MORE study	lognormal distribution
Strontium ranelate	SOTI and TROPOS	lognormal distribution

* data on file

** based on spread in corresponding first year estimates

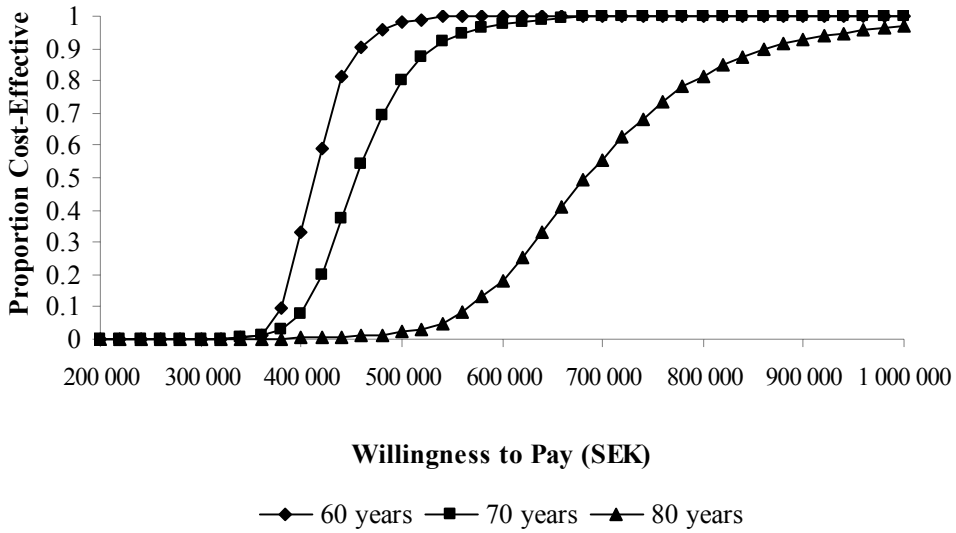
The re-estimated base-case results for raloxifene treatment, shown in Table 9, gave somewhat lower cost-effectiveness ratios at ages 60 and 70 and higher at the age of 80 years (compare with Table 6). This can partly be explained by the fact that in the old analysis a constant increase in mortality after vertebral fracture was used whereas in the new estimations, mortality was age-differentiated leading to a decreasing gain in life years of avoiding a vertebral fracture with increasing age. This effect can be noted in both outcome measures (QALYs and life-years). Another aspect is that in the old analysis, the incremental cost remained fairly constant over ages, while in the new analysis, they decrease with age. This is a result of the higher estimated vertebral fracture related cost, which will have a higher impact on the incremental cost at higher ages because of the increasing fracture incidence with age.

Table 9 Re-estimated cost-effectiveness of raloxifene , costs in SEK

	Incremental cost	*Life years gained*	*QALYs gained*	*Cost per life-year gained*	*Cost per QALY gained*
No previous vertebral fracture					
60	34 730	0.092	0.087	377 295	400 300
70	31 733	0.066	0.070	479 423	454 367
80	21 756	0.022	0.031	991 162	696 415
Previous vertebral fracture					
60	37 167	0.112	0.102	330 638	365 637
70	33 735	0.084	0.085	402 182	398 523
80	21 384	0.026	0.037	809 387	585 222

The probabilistic analysis (based on 2000 samples) is presented in the form of acceptability curves in Figure 16 . At an assumed willingness to pay for a QALY of SEK 650 000, there was a 100%, 99% and a 38% chance of a cost-effective result at the age of 60, 70 and 80, respectively. The curve at 80 years is flatter than the other two because no uncertainty was considered for the breast cancer parameters (except the treatment effect) and avoided breast cancer events constiture the most important driving force behind the cost-effectiveness at younger ages (below the age of 70) and avoided vertebral fracture at higher ages (above the age of 70).

Figure 16 Acceptability curves based on raloxifene simulations



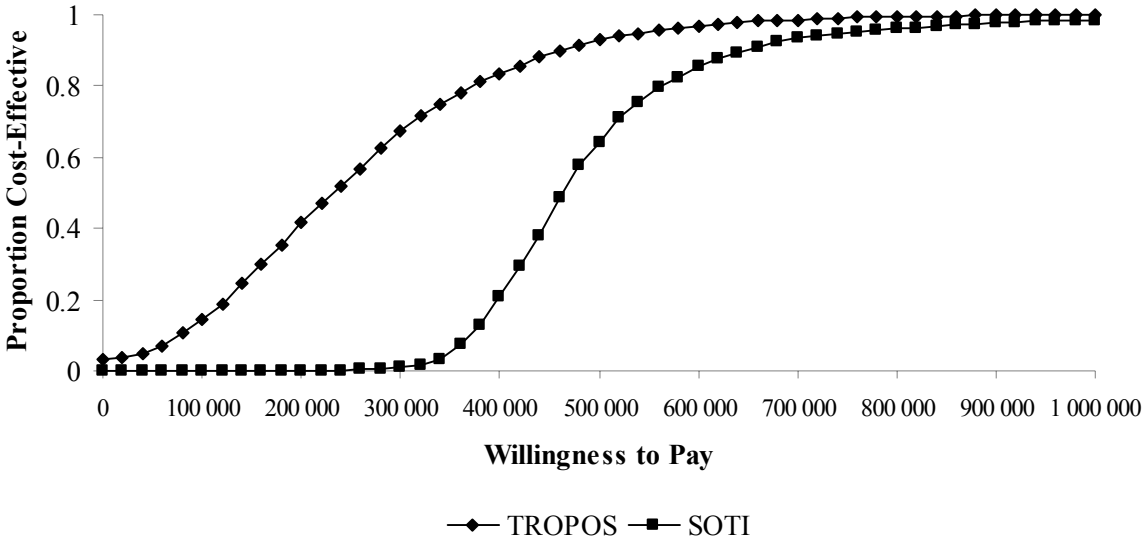
The re-estimated base-case ICER estimates for the strontium ranelate cost-effectiveness were somewhat lower compared as to the older estimates. There are marginal differences in the outcomes measures (QALYs and life-years), while the incremental cost is slightly lower because of a higher vertebral fracture related cost in the new simulations.

Table 10 Re-estimated cost-effectiveness of strontium ranelate, costs in SEK

	Incremental cost	*Life-years gained*	*QALYs gained*	*Cost per life-year gained*	*Cost per QALY gained*
TROPOS	7 327	0.017	0.036	441 392	205 817
SOTI	20 811	0.032	0.045	656 495	462 464

The results from probabilistic analyses (based on 2000 samples) are presented in the form of acceptability curves in Figure 17. At an assumed willingness to pay of SEK 650 000, there was a 90% chance that treatment with strontium ranelate was cost-effective for SOTI patients. For women with TROPOS characteristics, the cost-effectiveness ratio fell below SEK 650 000 in 98% of the simulations. That uncertainty is taken into account for more parameters than in older analyses is reflected by slightly flatter curves.

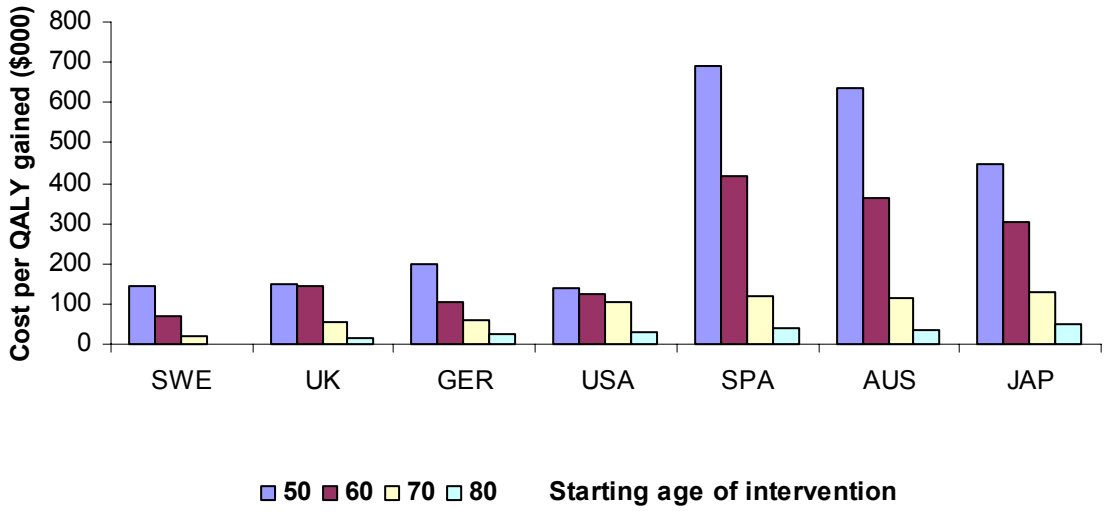
Figure 17 Acceptability curves based on the strontium ranelate simulations



4.5 MULTINATIONAL INTERVENTIONS THRESHOLDS (PAPER IV)

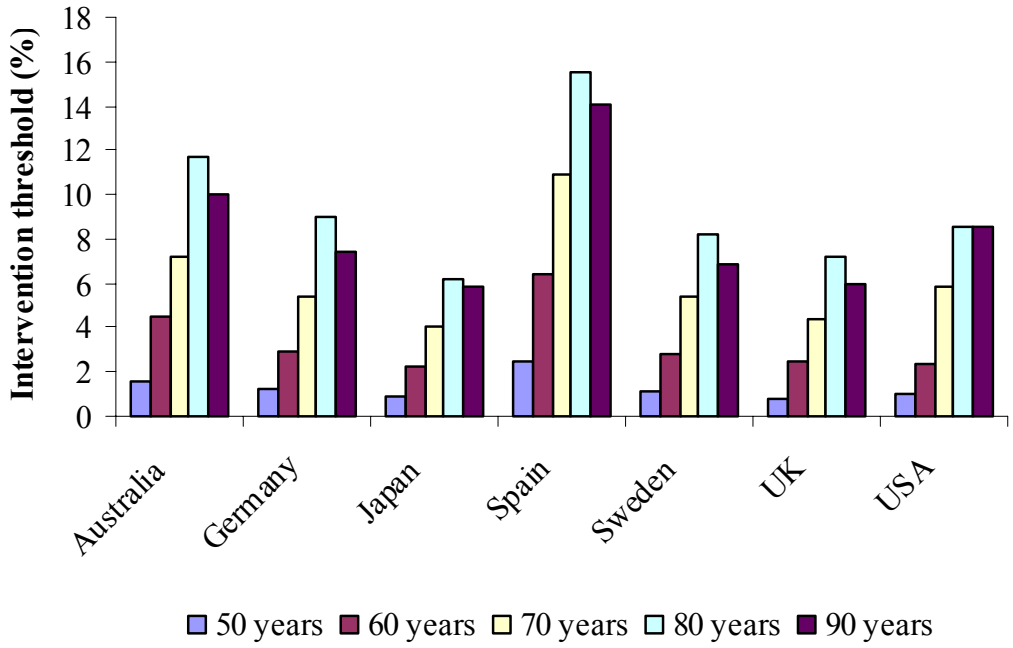
The cost per QALY gained for all seven countries, accounting for all osteoporotic fractures, is shown in Figure 18. Costs of increased survival are excluded; however, this did not have any major impact on the results of analyses in women at the population risk of fracture. A consistent finding for all countries was that the cost per QALY gained decreased with the increasing starting age of intervention. Overall, cost-effectiveness ratios were similar between countries, with the exception of Australia and Spain that stood out as having markedly higher cost-effectiveness ratios as compared to other countries. This is mainly explained by a combination of lower fracture risk, lower estimated hip fracture related costs and relatively high intervention costs.

Figure 18 Cost effectiveness of intervention for patients at population fracture risk based on the hip fracture equivalent approach



The estimated age-differentiated intervention thresholds, i.e. the ten-year risk of hip fracture at which treatment becomes cost-effective are presented in Figure 19. The intervention threshold rises with an increased starting age of treatment for all countries. Intervention thresholds were found to be lowest for the UK and Japan and highest for Spain. Sensitivity analysis showed that the variables that appeared to have the largest impact on the intervention thresholds were treatment effect, WTP per QALY gained and intervention cost. The major contributors to the difference in estimated thresholds between countries seem to be fracture-related costs, intervention costs and the WTP per QALY gained. When assuming these variables to be the same, the intervention thresholds were more or less equal for all countries.

Figure 19 Relative risk and ten-year hip fracture probability (%) at which treatment becomes cost-effective



Note: Costs of increased survival are excluded

5 DISCUSSION

5.1.1 Fracture related costs and quality of life

An economic evaluation is an important tool for guidance in decisions concerning resource allocation. However, the inference that can be drawn from an economic evaluation depends on the quality and validity of the study, which largely relies on the quality of the data used to estimate cost-effectiveness. The data needed to perform economic evaluations on osteoporotic treatments can be put into three categories; clinical data, epidemiological data and health economic data. Clinical data is the effects of treatments on the relevant patient groups. Epidemiological data is information (e.g. fracture risks and mortality rates) about the disease treated and health economic data is costs and health effects associated with disease events (e.g. fractures) included in the model.

The KOFOR-study had the aim of providing good estimates on costs and quality of life losses related to hip, vertebral and wrist fractures in Sweden that can be used in economic evaluation. When estimating the costs related to fractures, it is important that only the extra cost incurred by the fracture is accounted for. There are different types of study designs that can be considered when setting up a data collection study to estimate the potential cost savings of avoiding a fracture.

One study design approach is to use patients as their own controls by relating all costs the year before to all costs the year after fracture. The main problem when performing prospective studies using this design is that it demands large numbers of patients at risk of fracture to be followed over time. To identify one patient with a fracture, several other patients must also be followed that do not fracture. The before and after approach is probably more practical when using a register based retrospective study design than a prospective design. The advantage is that register studies often can provide fairly large sample sizes. The main disadvantage of such studies is that it is hard to collect all relevant resource use. For example, it is rare that information about indirect costs and informal care is available from any register.

Another design for the estimation of the extra cost of a fracture is to use a matched case cohort, i.e. fractured patients are compared with patients as similar in characteristics as possible to the fractured patients except that they have not sustained a fracture. The main difficulty with a matched case cohort design is that the matched unfractured patients must reflect the same resource use as the fractured if they had not fractured. This is important because patients with osteoporosis have a higher morbidity and mortality compared to the normal population [8]. If this is not reflected in the matched cohort, there is a risk that the extra costs of fracture will be overestimated.

A third study design is to follow patients from the time of fracture and identify and collect the fracture related resource use only. This was the approach taken in the KOFOR-study. Advantages with this approach are that it is possible to include all relevant cost items and that information prior to the fracture does not have to be collected, thus reducing the time period for the data collection and the sample size because no matched cohort is used. A disadvantage could be that in some cases, it might be hard to determine whether a resource is related to the fracture or not. If the trend is towards over-inclusion of resource use that is judged to be

related to fracture or the opposite it is hard to assess. However, when comparing the KOFOR results with previous Swedish register based studies [68, 69], it seems that fracture related resource use regarding long term institutionalisation is lower in the KOFOR-study which might indicate that resources are conservatively included using a fracture related study design.

Which study design is the most appropriate is not easy to answer, each one has its flaws. A before and after design demands large sample sizes, if performed prospectively, which is more or less necessary if the aim is to include all relevant costs in a societal perspective. A matched case cohort design will have difficulties selecting the appropriate matched non-fractured patients while the resource use identified in a fracture related design could be questioned. What might speak in favour of a fracture related data collection study is that it will take the shortest time and demand the lowest budget of the three approaches. One alternative for achieving the best estimate of the extra cost of a fracture could be a combination of a register based study and a fracture related study. A register based study could be used to estimate extra fracture costs for those resources that are available in registers, e.g. inpatient costs, while a fracture related study could act as a complement estimating costs such as informal care and indirect costs.

Measuring the quality of life loss related to a fracture is also associated with some difficulties. The main problem is to achieve good and reliable estimates on quality of life before the fracture. It is hard to prospectively estimate quality of life because it is not possible to know in advance when a patient will fracture. One solution could be to follow a large sample of non-fractured patients and measure their quality of life at regular intervals and wait until some of them sustain fractures. However, this will require very large samples and need quite frequent quality of life estimates, thus making this approach more or less unfeasible. Another solution could be to use the matched case cohort approach; however, for the estimation of fracture costs, the problem is that the cohort must consider that fractured patients have a higher morbidity than the normal population. A third solution would be to ask patients to state their perceived quality of life before the fracture, after the fracture occurrence. Naturally, this could potentially lead to some recollection bias since the pre-fracture health status might have been perceived to have been different than it actually was.

Another issue relating to the measurement of fracture related utility is whose preferences should be used to estimate quality of life. Quality of life could be measured either based on individuals who actually experience the relevant health state (i.e. individual values) or based on a general population sample that values the relevant health state from a description (i.e. social values). Some studies have indicated there to be a divergence between individual and social time-trade off values [146, 147]. Individual TTO-values seems to be higher than social EQ-5D values for a given health state, a difference that increases with the severity of the health state. The implication of this for the results in the KOFOR-study, which used the social EQ-5D instrument to estimate quality of life, is that the quality of life loss would be lower if a direct elicited individual TTO question had been used. Using an algorithm for the conversion between social values and individual values presented in a study by Burström et al. [147], individual quality of life losses related to hip, vertebral and wrist fracture could be approximated at 0.10, 0.09 and 0.04, respectively. These quality of life losses are lower than the social values estimated using the EQ-5D in the KOFOR-study (i.e. 0.17 (hip fracture), 0.26 (vertebral fracture) and 0.06 (wrist fracture)). Using these individual values in a cost-effectiveness analysis would lead to a decreased gain in QALYs from avoiding a fracture event and thus, an increased cost-effectiveness ratio.

Whose preferences, those of the individual or the social, should be used in economic evaluation? According to the theory of welfare economics the individual values should be preferred because individuals are considered the best to judge their own welfare. However, interventions do not only affect the patient but everyone in society, that is, we are all tax payers and potential patients. Therefore it can be argued that social values should be used since the aim of economic evaluation is to provide guidance on how to most efficiently allocate the scarce resources.

The KOFOR-study included all costs relevant for a societal perspective. The study showed that hip fracture was the most costly fracture, followed by vertebral and wrist fractures while the quality of life loss in the year after fracture was the highest for vertebral fracture, followed by hip and vertebral fracture. The findings for hip fracture regarding cost and quality of life are relatively similar to the results in previous studies [22, 68, 77, 148]. Perhaps the most interesting finding in the study is the quality of life loss after a vertebral fracture; however, these results must be interpreted with some caution. First, the sample size was relatively small (81 patients) and second the distribution between hospitalised and non –hospitalised patients was skewed compared to clinical practice. Moreover, only patients seeking care at hospitals were included which might suggest that the sample could be worse off than patients only given care in primary care.

The KOFOR-study results can be used in economic evaluations; however, there are still areas of future research related to fracture costs and quality of life. Since the KOFOR-study was Swedish based, it will be most valid to use its results in cost-effectiveness analyses conducted in a Swedish setting. Fracture related costs will vary between countries due to differences in resource use and price levels and whether the fracture related quality of life differs between countries has so far not been thoroughly investigated. Therefore, it is of relevance to conduct studies in other countries. The study design developed and used in the KOFOR-study could provide a good platform for future studies in other countries. Using the same study design when estimating the fracture related costs and quality of life would considerably facilitate a cross country comparison.

The severe consequences of vertebral fractures found in the KOFOR-study also constitute an area which needs further research. Especially, more studies with larger sample sizes are needed to confirm the marked impact of a vertebral fracture on quality of life. The long-term consequences of fractures (i.e. beyond the first year after fracture event) also need to be further investigated. In terms of impact on the cost-effectiveness ratio, the long-term fracture related costs and quality of life reductions are at least as important as the acute first year consequences. The KOFOR-study will, to some extent, fill this data void when the eighteen-month follow up will be completed.

5.1.2 Modelling the cost-effectiveness of osteoporosis therapies

A cost-effectiveness model study should consider all treatment effects that will have a significant impact on the results. However, the analysis must also reflect data availability at the time of the study. Lack of data often means that assumptions must be made to fill the data gap. The more assumptions, the more uncertain will the cost-effectiveness results be. There is a trend towards building quite detailed and sophisticated models which might lie close to the epidemiological pattern of the disease but which tend to be non transparent and very data hungry. The population of this type of models must often rely on assumptions and expert opinions for many model parameters. Because the quality and reliability of the results in a

cost-effectiveness analysis largely rely on the quality of the data, an economic evaluation should always use the best information available at the time of the study. As new information becomes available, the model can be adapted accordingly and the cost-effectiveness re-assessed. In this thesis, the cost-effectiveness of raloxifene and strontium ranelate has been re-estimated using new evidence on fracture related costs and quality of life. Because the old version of the cost-effectiveness of strontium ranelate had been estimated quite recently, there was no major difference in cost-effectiveness between the old and the updated version for strontium ranelate treatment. There is a longer time period between the old and new versions for the cost-effectiveness of raloxifene assessments which also have resulted in a larger difference in the results because new data that has become available. The changes are mainly due to new fracture related costs and quality of life and an implementation of age-differentiated fracture mortality rates. These changes might perhaps not change the conclusions concerning the cost-effectiveness of raloxifene, but the magnitude of the changes shows that it is relevant to perform re-assessments as new information comes along.

When assessing the cost-effectiveness of a treatment strategy, it should be compared to current standard care or the best alternative treatment strategy in the targeted patient group. Both raloxifene and strontium ranelate were compared to a no treatment strategy in the respective studies (papers II and III) and not to any other intervention. It could be argued that the current standard care is actually no treatment since the majority of patients that can be diagnosed to have osteoporosis do not receive treatment. However, a number of interventions are available on the market which are recommended in guidelines as first line treatments (e.g. alendronate and risedronate) for osteoporosis, which could be considered as standard care or the best alternative treatments. The main problem of comparing different treatment alternatives in cost-effectiveness analysis is that the clinical evidence comes from clinical trials that only compare the drugs with placebo. Differences in for example study design, patient characteristics and statistical analysis make it difficult to assess the relative efficacy between treatments. The choice of treatment is crucial for the results in a cost-effectiveness analysis when a comparison with other treatments is addressed; unfortunately, this choice is very difficult and subject to bias. For example, there are studies which have estimated the cost-effectiveness between osteoporotic interventions and shown completely opposite result for which treatment is actually most cost-effective [149, 150]. However, a simple solution does not exist. A head to head trial comparing two osteoporotic treatments is not very likely to be conducted, because it would need a large number of patients to have power to detect a significant difference in fracture risk.

Estimating the cost-effectiveness between two treatments is not hard, technically, but it is the interpretability of the results that will be harder. When an economic evaluation of a novel treatment is to be assessed, the first step is to base the cost-effectiveness analysis on the best data available and regarding clinical evidence, the best information can be derived from the clinical trial. If the clinical trial compares treatment with placebo, the base-case analysis should also use these comparators. Not comparing with the most relevant comparator will limit the usefulness of the economic evaluation. Therefore, it is understandable that decision-makers sometimes demand that the cost-effectiveness between treatments is estimated by making indirect comparisons. However, it is important that there is an awareness of the inherent uncertainty in those analyses when decisions are made.

If we were to make an indirect comparison between raloxifene compared to strontium ranelate (based on the TROPOS patient group) for women with established osteoporosis (a T-score of -2.5 and a previous vertebral fracture) raloxifene would come out as the cost-effective

alternative at starting ages between 60-80 years. The interpretability of this analysis largely lies in the validity of the comparability of the treatment effects. For example, the MORE-study is based on patients with a mean age of 69 years, while the mean age of the TROPOS is 77 years. Also worth noting is that by using a net health benefit approach, the probabilistic analysis showed that there was no significant difference in the cost-effectiveness between drugs. Another indirect comparison which might seem relevant could be to compare with bisphosphonates which are the most prescribed drug class and the suggested first line treatment for osteoporosis. Using the estimated fracture risk reduction for alendronate based on a meta-analysis [144] showed alendronate to be the most cost-effective treatment at all starting ages between 60-80 years, which is mainly due to a lower drug price and better point estimates on fracture risk reduction. What can be noticed is that current Swedish treatment guidelines and reimbursement decisions are in line with these results, i.e. bisphosphonates are recommended as first line treatment and SERMs are as second line treatment [151]. Strontium ranelate, which has been shown to be effective in higher age groups where the evidence for other drugs is weaker, is reimbursed for osteoporotic women younger than 74 years who do not tolerate bisphosphonates and there is a general reimbursement for treatment in osteoporotic women 74 years and older [152].

One aspect that will be important in the future development of health economics osteoporosis is compliance. When approaching compliance, a distinction should be made between persistence, how long the drug is taken, and adherence, the proportion of medication taken correctly over a period of time. As mentioned the effect of a treatment modeled in economic evaluations is usually based on results from clinical trials. The effectiveness, based on the intention to treat calculations, observed in clinical trials is related to the adherence of patients in the trial. In the cost-effectiveness base-case analysis, patients are usually assumed to have an intervention cost during the whole intervention period. This can be considered as a conservative approach since the persistency is very likely not to be 100%. The intervention costs could be adjusted to the persistence of therapy, i.e. for the period the patients have the drug prescribed in the clinical trial, which would result in a lower treatment cost. However, then the lower treatment effect for those that discontinue treatment should also be considered. Patients in clinical practice may be less persistent to therapy and less adherent than in the clinical trial, leading to lower benefits of therapy and a potentially overestimated cost-effectiveness when using clinical trial data on persistence and effectiveness. Poor compliance will not only have an impact on the effect side, but also on costs because both intervention costs and effects disappear when the patients stop taking the medication. The main problem with incorporating compliance specifically in the health economic analysis is the lack of relevant data. Both information about the actual compliance in clinical practice and the linkage between compliance and treatment effect is needed in the health economic analysis. Ideally, you would like to have a clinical trial with enough patients to undertake an analysis of effectiveness related to persistence and adherence to therapy, but then you would also need estimates on real life compliance which are very hard to assess. Measuring compliance in clinical practice without changing the incentives for the patient to take the drug is very hard. Moreover, the issue of relative efficacy of treatments will be even harder to address when also including the compliance aspect in the analysis. With the development of new treatments given at less frequent intervals (e.g. bi-annually or annually) with a possibility to have an improved compliance compared to other drugs given in more frequent dosing regimens it will be important to incorporate these aspects in the economic analysis to adequately assess the additional value of these new drugs. Finding good data on compliance and how to appropriately incorporate this in health economic modelling will be an area for future research.

5.1.3 Intervention thresholds

One of the most common uses of cost-effectiveness evaluations is and has been on a health care macro- and meso-level, for example, giving guidance for reimbursement for decision makers and for national and regional treatment guidelines. The use of health economic tools has not been that common at the health care micro level, i.e. in the decision by the physician of whether to treat the individual patient. By the introduction and use of intervention thresholds in combination with risk score algorithms cost-effectiveness analysis can also become an important and practical tool in clinical practice.

For treatment and prevention of osteoporosis, it is relevant to base treatment guidelines on the absolute fracture risk, rather than other risk factors such as bone mass density or prevalent fracture. BMD does not satisfactorily predict fracture risk, and for example, it cannot explain the ten-fold difference in hip fracture risk between northern and southern Europe [13]. A hurdle to be overcome with intervention thresholds (i.e. the ten-year hip fracture probability at which intervention is cost-effective) is to identify the relevant patients at risk of fracture to treat. In an ongoing project, an individual fracture prediction model is being developed by a WHO working group [9, 85, 153-156] and can be used in combination with intervention thresholds. It is important, however, that the estimated thresholds are relevant for the region in question when making decisions of whether to treat based on cost-effectiveness thresholds.

The analyses in paper IV showed there to be differences between countries in the ten-year risk at which intervention becomes cost-effective. The most important variables for explaining these country differences were fracture related costs, intervention costs and the WTP for a QALY gained. These are variables that are likely to continue to differ internationally, thus making it relevant to estimate country-specific intervention thresholds.

For the important variables, information about treatment costs and the WTP for a QALY (if based on the GDP per capita approach as in this study) is available for most countries. However, data on fracture related costs is scarce and only available for a few countries. Even the fracture cost data used in this study differs quite markedly in quality, which contributes to some uncertainty in the results. Therefore it will be important to make reassessments of the intervention thresholds when new information becomes available. Moreover, it will be relevant to conduct re-estimations of the underlying equivalent indexes (i.e. morbidity and cost), which are used to convert the consequences of all fracture types into one single fracture risk, since a great deal of the information concerning fracture types besides at the hip ,vertebral and the wrist is quite weak.

6 CONCLUSIONS

The main conclusions that can be drawn from this thesis are that:

- Hip fracture is related to the highest costs followed by vertebral and wrist fracture and vertebral fracture is indicated to have the largest loss in health related quality of life the year after the fracture event.

- Treatment with strontium ranelate compared to no treatment in elderly women at increased risk of fracture is indicated to be cost-effective.

- Treatment with raloxifene compared to no treatment in elderly women at increased risk of fracture is indicated to be cost-effective.

- Intervention thresholds could be an important tool for finding patients eligible for treatment according to cost-effectiveness criteria.

- The cost-effectiveness for a given patient group differs between countries, which is mainly explained by differences in fracture risk and costs.

- Because of differences in WTP per QALY gained, fracture related costs and intervention costs, estimating country-specific interventions thresholds are relevant.

- When new information becomes available it is relevant to make re-assessments of the cost-effectiveness of treatments estimated in previous analyses.

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