Persistence and Compliance to Treatment of Osteoporosis in Sweden

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Abstract

Prescribed treatment regimens are seldom followed correctly. Patients do not take their medication for the prescribed duration (referred to as persistence) or according to treatment instructions (referred to as compliance). The purpose of this study was to estimate persistence and compliance to treatment of osteoporosis in Sweden, assess the societal burden of real-world patient behaviour, and estimate the monetary net benefit of five hypothetical interventions improving persistence. The study was based on a historical cohort extracted from the Swedish Prescription Register. Persistence was operationalized as the number of days on treatment and compliance as Medication Possession Ratio. The burden and intervention assessments were analyzed using a microsimulation model for all patients who started treatment during 2008. Persistence to treatment of osteoporosis was found to be poor. One in four patients discontinued treatment immediately after the first prescription and less than half of the cohort persisted with therapy for one year. Compliance was close to perfect. The burden of actual persistence (measured in terms of discounted lifetime costs and quality-adjusted life-years) was estimated at MSEK 368. However, interventions aimed at increasing persistence should not be implemented unless specific patients groups are targeted and large improvements in patient behaviour expected.

Keywords: *persistence, compliance, osteoporosis, cost-benefit analysis, health policy*

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Glossary

Alendronate	The primary treatment option of osteoporosis in Sweden.
ATC	The Anatomical Therapeutic Chemical (ATC) Classification System, used for the classification of drugs.
CBA	Cost-Benefit Analysis, a method of economic evaluation.
Co-morbidity	The presence of one or more diseases in addition to a primary disease.
Compliance	The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.
Grace period	The maximum allowed gap (time off treatment) between filled prescriptions by a persistent patient. Also known as "permissible gap".
HRT	Hormone Replacement Therapy, a secondary treatment option of osteoporosis in Sweden.
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).
Index prescription	A patient's first filled prescription during the study period.
MPR	Medication Possession Ratio, commonly used to quantify compliance i retrospective studies.
NB	Monetary Net Benefit (NB), the outcome measure of CBA.
Persistence	The accumulation of time from treatment initiation to discontinuation of therapy.
QALY	Quality-Adjusted Life-Year, a frequently used effectiveness measure in health economic evaluations, incorporates both the quality and quantity of life.
Raloxifene	A treatment of osteoporosis in Sweden, only prescribed to females.
RCT	Randomized controlled trial, performed to test e.g. the efficacy of pharmaceutical treatments.
Residual effect	The effect from the drug after treatment termination.
Risedronate	A treatment of osteoporosis in Sweden.
Strontium ranelate	A treatment of osteoporosis in Sweden.
TLV	The Dental and Pharmaceutical Benefits Agency (*Tandvårds- och läkemedelsförmånsverket*), the governmental institution that determines reimbursement status for all medications in Sweden.
WTP	Willingness-to-pay, often in relation to the outcome effect measure in health economic evaluation, e.g. the WTP for a life-year or QALY.

1 Introduction

Drugs only work if patients take them, and ever since the days of Hippocrates, physicians have been concerned whether the treatment regimens they prescribe are being followed correctly [1]. In modern times, these issues are still a world-wide problem of striking magnitude. It has been estimated that only 50% of all patients with chronic diseases take their drugs as prescribed [2], and that between 30% and 50% of all prescriptions fail to produce the desired result [3]. Thus, poor patient behaviour is an important reason behind unsuccessful pharmacotherapy, with increased morbidity, mortality and health care utilization as a result. This is especially true for chronic diseases requiring long-term therapy, such as osteoporosis [2].

Osteoporosis is a progressive skeletal disease characterized by porous and weak bone. It is a major public health problem, affecting hundreds of millions of people worldwide [4], predominantly postmenopausal females [5]. The main clinical consequence of osteoporosis is bone fractures. Hip fractures, the most serious fracture type, are associated with substantial pain and suffering, prolonged or permanent disability, and even death[1] [6]. As a result, osteoporosis places a significant burden on both the individual and the society [9, 10].

During the past two decades, numerous self-administered medications have been made available for the treatment and prevention of osteoporosis [11]. The primary aim of pharmaceutical therapy is to reduce the risk of osteoporotic fractures [5]. Currently prescribed treatments reduce the overall fracture risk by as much as 50% [9]. However, patients need to take the medication for the prescribed duration (referred to as persistence) and according to treatment instructions (referred to as compliance) in order to receive the intended clinical benefit [2]. Patients who discontinue therapy prematurely, or ignore dosing requirements, will have a higher fracture risk compared to patients who remain on therapy in accordance with the treatment regimen. A higher fracture risk results in a larger incidence of fractures, reduced quality of life and increased mortality for the patient, and larger health care costs. Thus, persistence and compliance are crucial in the medical management of osteoporosis, both for individual patients and from a societal perspective [12, 13].

Several studies have investigated persistence and compliance to treatment of osteoporosis. The results suggest that a significant proportion of osteoporotic patients do not to take their medication as prescribed [14–25]. However, disease patterns and treatment practices differ considerably between countries and regions and previous findings are only valid for the population and setting studied. It is therefore necessary to attain country-specific estimates, and to date, persistence and compliance to treatment of osteoporosis in Sweden are unknown.

Estimates of treatment pattern characteristics such as persistence and compliance are useful for descriptive purposes. However, in order to provide information of value for health policy decision-makers, it is not sufficient to merely describe to what degree patients follow their treatment regimens. Public health interventions targeting persistence and compliance in the medical management of any disease require financial resources and the taxpayers' money may be better spent elsewhere. Thus, it is necessary to assess the societal consequences (i.e. the societal value of what is forgone in terms of financial resources and health) of persistence and compliance in order to determine whether or not public funds should be used to improve potentially aberrant patient behaviour in Sweden.

This master's thesis presents a health economic study of real-world patient behaviour in the pharmaceutical treatment of osteoporosis in Sweden, and an assessment of its consequences for the society. Specifically, medication persistence and compliance were estimated, and the total societal loss, or burden, of current patient behaviour assessed. The study also investigated the societal value of different hypothetical health policy interventions targeting persistence and

[1] It has been estimated that between 20% and 30% of all patients who sustain a hip fracture die within one year of the fracture [6], and approximately 30% of the excess mortality is directly related to the fracture event [7, 8].

compliance to treatment of osteoporosis. The purpose of the study was to (i) describe to what extent osteoporotic patients in Sweden take their medication as prescribed, (ii) estimate the consequences for the society in terms of health and health care resource utilization, and (iii) provide guidance to health policy decision-makers by producing estimates of the amount of resources that should be allocated to improve persistence and compliance to treatment of osteoporosis in Sweden given current cost-effectiveness guidelines.

The thesis is structured as follows. Section 2 provides a brief background to osteoporosis and the field of health economics and explains important terms and concepts. Section 3 states the study objectives. Section 4 contains the methods and Section 5 the results. Discussion and conclusions are located in Section 6.

2 Background

2.1 Osteoporosis

Osteoporosis is a chronic progressive skeletal disease characterized by low bone mineral density (BMD) and bone structure deterioration. The diagnostic criterion of osteoporosis is BMD less than or equal to 2.5 standard deviations below the average BMD of a young adult female [26]. The condition is primarily a consequence of bone loss due to insufficient levels of estrogen, particularly in menopausal and postmenopausal females [5], albeit many additional clinical risk factors exist[2] [27]. Current research is almost exclusively directed towards the prevention and treatment of osteoporosis in females [11].

The primary clinical complication of osteoporosis is fractures due to fragile skeletal bone. Osteoporotic fractures are generally sustained in relation to low-energy trauma. The majority of all fractures associated with the disease occur at the hip, spine, and wrist [28]. Most attention has been paid to hip fractures, the most serious fracture type, which contributes substantially to morbidity and mortality and is associated with large health care costs [6].

Osteoporosis is a major and growing health problem worldwide [9]. In 2005, it was estimated that over 200 million people globally suffer from the condition [4]. The estimated general prevalence of osteoporosis in Sweden increases with age and rises from approximately 6% of females aged 50 years to 50% of females aged 84 years. The comparable figures for males in Sweden are 2.4% and 20% [29]. The cumulative lifetime risk for Swedish females at the age of 45 years of sustaining a hip, vertebral and wrist fracture has been estimated at 23.3%, 15.4% and 21.5%, respectively. Corresponding values for males at the age of 45 years are 11.2%, 8.6% and 5.2%. The risk of sustaining any of these fractures has been estimated to be 47.3% and 23.8% for females and males, respectively [30]. Approximately 70,000 fractures related to osteoporosis occur annually in Sweden [31].

The economic burden of osteoporosis is substantial. In Sweden, the total annual cost of fractures related to the disease has been estimated at MSEK 5,639, which is about 3% of the total national health care expenditure [10]. Costs in Europe have been estimated at MSEK 30,700, and are expected to increase to MSEK 76,700 in 2050 due to a higher incidence of fractures because of an aging population [32].

2.1.1 Treatment of Osteoporosis

There are several therapies available for the prevention and treatment of osteoporosis, including bisphosphonates, selective estrogen-receptor modulators (SERMs), and strontium ranelate (henceforth strontium) [11]. The drugs decrease bone resorption and/or increase bone formation and have in numerous randomized controlled trials (RCTs) demonstrated a reduction in the overall risk of bone fractures by as much as 50% [9]. A fracture increases the risk of further fractures and the goal of interventions should therefore be to prevent the first fracture [5]. However, in spite of the availability of efficacious treatments, a large share of individuals with osteoporosis is not treated [9, 33–37]. One important reason why the disease is not optimally diagnosed is because osteoporosis is an asymptomatic[3] condition [14, 38]. Osteoporosis is in this sense a "silent disease"[39] and patients are as a result often first recognized and commenced on treatment after their first fracture.

The primary treatment option of osteoporosis in Sweden is bisphosphonates. Four types of bisphosphonates are currently recommended by the Swedish Medical Products Agency [40] to be prescribed for the indication osteoporosis: alendronate, risedronate, etidronate, and zoledronate. Alendronate is the first-choice treatment.

[2] Well-known risk factors associated with osteoporosis include lack of physical exercise, excessive alcohol consumption, low body weight, and cigarette smoking [27].

[3] An **asymptomatic** condition is an illness or condition that is present without any recognizable symptoms.

Other treatments of osteoporosis in Sweden include strontium and raloxifene, a SERM. Both treatments are generally only prescribed to patients who do not tolerate bisphosphonates. Treatment with hormone replacement therapy (HRT) is no longer recommended in Sweden for fracture prevention except under special circumstances [40].

New medications, including treatments of osteoporosis, need to be evaluated to ensure that they are cost-effective in relation to already existing therapies. Such assessments, and similar health economic analyses, are performed by health economists.

2.2 Health Economics

Health economics can be defined as the application of economic theories, methods, and concepts to the topics of health and health care. In this field, researchers study how health is produced and allocated within society and the health care system. The general importance of effective resource allocation, growing health care costs due to an aging population, and a continuous stream of new pharmaceutical drugs, emphasize the need to assess how to make the best use of the money spent on health and health care. Health economics is concerned with these issues and various health economic evaluations are performed to aid decision-makers in maximizing welfare from a limited budget [41].

It is the responsibility of the Dental and Pharmaceutical Benefits Agency (*Tandvårds- och läkemedelsförmånsverket*, TLV) to determine whether or not the Swedish government should use public funds to subsidize a specific treatment. TLV makes decisions on the grounds of health economic assessments and in order to be eligible for subsidization, pharmaceutical companies are required to provide evidence that their products are cost-effective. Cost-effectiveness analysis has as a consequence become one of the more prominent tools within health economics in general and health care policy decision-making in particular.

2.2.1 Cost-Benefit Analysis

Cost-benefit analysis (CBA) is a method of economic evaluation that incorporates costs (measured as opportunity costs[4]) and benefits (e.g. life years gained) in monetary terms, discounted to present values. In a hypothetical evaluation of treatment A and treatment B, denote the average per-patient cost difference $\bar{C}^A - \bar{C}^B = \Delta\bar{C}$, the average per-patient effect difference $\bar{E}^A - \bar{E}^B = \Delta\bar{E}$, society's willingness-to-pay (WTP) per unit of effectiveness λ, and the total number of patients N. The total monetary net benefit (NB) is then defined as:

$$\mathrm{NB}(\lambda) = \Delta\bar{E} \cdot N \cdot \lambda - \Delta\bar{C} \cdot N \tag{1}$$

where $\Delta\bar{C} \cdot N$ is the total cost difference, $\Delta\bar{E} \cdot N$ the total effect difference, and $\Delta\bar{E} \cdot N \cdot \lambda$ the monetary value of the total effect difference. Based on the calculated NB, project A should be implemented in place of project B if $\mathrm{NB}(\lambda)>0$ [43].

Quality-adjusted life-year (QALY) is a common outcome effect measure used in health economic evaluation, including CBA. It incorporates both the quality and quantity of life and is constructed by multiplying every life year with a weight, measured in utilities, reflecting quality of life [44]. The utility value normally ranges between 0 (reflecting dead) and 1 (reflecting full health). As an example, if a person lives for ten years and assigns a quality weight of 0.8 to each of those years, her total number of QALYs would be 8 (10×0.8).

In Sweden, there is no official general WTP threshold for a QALY. In practice, TLV uses different cost-effectiveness thresholds depending on for example the severity of the disease. However, the National Board of Health and Welfare (*Socialstyrelsen*) has suggested that the WTP

[4] **Opportunity cost** is the value of the best alternative use of a resource, taking both explicit costs (direct costs such as out-of-pocket payments) and indirect costs (such as the value of time) into account [42].

for a QALY in the prevention and treatment of cardiovascular diseases lies in the range of SEK 500,000 and SEK 1,000,000, although no explicit roof is placed on the threshold [45]. Another estimate, based on calculations of the value of a statistical life in Sweden, states that the WTP for a QALY is SEK 655,000 [46].

2.2.2 Burden of Illness Studies

Unlike cost-benefit analysis, burden of illness (BOI) studies are performed to assess the monetary implications of a specific disease. Cost items are included based on the perspective of the study (e.g. patient, institution, society). The societal perspective takes all relevant costs into account and resources are valued according to their opportunity cost. The purpose is to convey the true cost to the society. The impact on health (e.g. the quantity and quality of life) is occasionally included in BOI studies (in contrast to cost of illness studies that only incorporate costs).

Regarding choice of population, the total burden can in broad terms be derived using two approaches. The first method, based on prevalence, estimates a patient-specific burden, neglecting the moment of disease onset, during a specific timeframe. The estimate is then multiplied by the prevalence during the timeframe to obtain the total burden for the sample population. Incidence-based evaluation, on the other hand, estimates discounted lifetime costs (and sometimes health effects) from diagnosis to cure, or death in the case of chronic diseases such as osteoporosis. Compared with the prevalence based approach, incidence-based studies require substantially more data, such as estimates of the disease progression during each stage of life and the concomitant use of health care resources [41]. The burden assessment in the present study, described in Section 4.2, was an incidence-based evaluation.

2.3 Terminology

The concepts persistence and compliance have generated some confusion in the medical science literature [47]. It is therefore important to provide clear definitions and carefully present the methods and assumptions used for quantifying the terms.

Persistence
Persistence, in a medical context, is defined as the "accumulation of time from treatment initiation to discontinuation of therapy" [48]. In this study, the term was operationalized as the number of days on treatment.

Compliance
Medication compliance generally refers to the extent to which a patient acts according to medical or health advice [49]. In the context of the medical treatment of osteoporosis, compliance reflects "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [48]. In retrospective studies, compliance is commonly quantified using Medication Possession Ratio (MPR) [50]. In this study, MPR was used to measure compliance and was defined as the number of days of medication available to the patient, divided by the number of days on treatment (i.e. persistence).

2.4 Medication Persistence

Low persistence with prescribed medication regimens is regarded as a major problem in the treatment of many illnesses [2, 48], especially chronic diseases including osteoporosis [51–55]. The consequence of low persistence is increased morbidity and mortality, since patients who terminate treatment fail to receive the intended drug benefit [55]. Previous studies have shown that between approximately 20% and 90% of all patients drop out of treatment of osteoporosis during the first year [14–25]. The variability in results can to some extent be attributed different assumptions

regarding persistence, different statistical methods employed and different populations studied, and the estimates are therefore not necessarily comparable. To date, medication persistence to treatment of osteoporosis in Sweden is unknown.

Persistence can be measured in either prospective or retrospective studies. Prospective assessments verify clinically if a patient is still on treatment. This approach is expensive and labour-intensive, but precise. However, the high internal validity[5] of prospective studies comes at the expense of external validity[6], as patient behaviour is likely to change with the knowledge of being observed. Retrospective investigations of persistence, on the other hand, utilize historical prescription records. These studies are therefore less expensive and not troubled by bias due to unnatural participant behaviour, but also less accurate because there is no information available as to whether the patient actually has consumed the medication collected from the pharmacy [54]. However, it is reasonable to assume that patients would not continue to refill prescriptions without the intention to take their medication [57].

The determinants of low persistence to treatment of osteoporosis are not very well understood. Studies suggest that several factors are important, including complex dosing requirements[7], cost of medication, drug-related side effects, the patient-physician relationship, and patient inability to detect improvements in an asymptomatic disease [59–65].

The optimal duration of treatment of osteoporosis remains to be defined [66, 67]. It has been shown that the therapeutic effects of continuous treatment with alendronate sustain over a 10-year period [68]. However, there are concerns that long-term suppression of bone remodelling may eventually lead to reduced bone strength [66, 69]. A frequently used treatment length in RCTs evaluating the effect of osteoporosis drugs, as well as in health economic models of osteoporosis, is five years [70–72].

Numerous interventions with the aim to improve persistence and compliance to treatment of conditions other than osteoporosis have been attempted and investigated [73]. Results from these studies indicate that improvement is difficult and that successful interventions generally only produce a modest positive change in patient behaviour. Improving persistence and compliance to treatment of osteoporosis may be even more problematic. Osteoporotic patients have been shown to lack knowledge of prevention, treatment, and consequences [74–76], and the asymptomatic nature of the condition may further reduce interest and motivation. Previously studied interventions to improve persistence and compliance to treatment of osteoporosis have mainly focused on information and education, monitoring, counselling, and support programs for the patient [77–83]. Few interventions have proved to be successful. One exception is a study by Cook *et al.* [82], where intervention subjects received telephone counselling, consistent with motivation interviewing principles, from nurses. The study reported a statistically significant improvement in persistence (the proportion on treatment after three and six months) of 19%.

Whilst improving persistence is achievable, it does not immediately follow that interventions targeting persistence are cost-effective. Ultimately, the cost of the intervention must be weighted against the effects. Furthermore, it may be inefficient to allocate resources to enhance persistence for all patient groups. Improved persistence implies larger drug costs due to additional filled prescriptions, as well as lower morbidity costs and improved quantity and quality of life due to a longer exposure to the medication. The costs and effects are therefore likely to differ between for example females and males and different age groups because of sex and age-specific differences in e.g. fracture risk and mortality. A purpose of the present study was to investigate the cost-effectiveness of hypothetical interventions improving persistence.

[5]**Internal validity**: When inferences and conclusions about causal effects in a study are valid for the population being studied [56].

[6]**External validity**: When inferences and conclusions from a study can be generalized from the population and setting studied to other populations and settings [56].

[7]As an example, alendronate should be taken after fasting overnight, with at least 200 ml of water and no other food or beverages, while remaining upright for at least 30 minutes [58].

2.5 Medication Compliance

It has been argued that poor compliance is the weakest link in the treatment of osteoporosis [13]. The average level of compliance, measured as MPR, has been estimated to lie between 50% and 80% [15, 17, 21, 84–86]. As in the case of medication persistence, the exact reasons behind poor compliance are not clear. Compliance to treatment of osteoporosis in Sweden is not known.

Investigating compliance is not an easy task [54]. RCTs are not likely to generate reliable results given that patients may be much more inclined to follow treatment recommendations during the trial period [55, 78]. In retrospective studies, compliance is commonly quantified as MPR [48]. This measure is not ideal, since it fails to incorporate whether or not the patient takes the medication correctly according to medical recommendations, or even if the patient takes the medication at all. What is measured is if the patient has medication available, which is a measure of compliance, but obviously far from perfect. Nonetheless, in the absence of a more accurate measure, and to maintain consistency and comparability between previous studies, MPR was used in the present study to quantify compliance.

Intuitively, poor compliance is related to reduced treatment efficacy, since some (or even all) of the clinical benefits from the medication are lost if the patient fails to follow treatment instructions [55]. Numerous studies [15, 25, 87, 88] have investigated the relationship between MPR and fracture risk. The results suggest that low MPR is associated with an increased risk of fractures. However, many of the studies have followed patients beyond their last filled prescription (i.e. during their non-persistent follow-up) and the estimated risk increase could therefore be a consequence of both suboptimal persistence and/or compliance. In addition, the estimates are seldom controlled for known clinical risk factors, such as smoking, lack of physical exercise, and excess alcohol intake [89].

Moreover, several studies [13, 15, 87] indicate that patients with poor compliance share certain characteristics. For example, in the prevention of coronary heart disease, patients with poor compliance to placebo have been proved to have worse health outcomes compared to their compliant counterparts [90, 91]. Fracture rates have also been shown to be higher in non-compliant patients taking placebo [61]. These findings suggest that the casual relationship between compliance and e.g. fracture risk may be difficult to estimate.

To conclude, the association between medication compliance and a relevant clinical outcome measure (e.g. fracture risk) is to date largely unknown.

3 Study Objectives

The objectives of this study were to:

I. Estimate medication persistence and compliance to treatment of osteoporosis in Sweden between December 1, 2005 and December 31, 2008.

II. Assess the total societal burden (the total societal loss in terms of a monetary net benefit) of actual compared to perfect persistence for all treatment-naïve[8] patients starting therapy between January 1, 2008 and December 31, 2008. Medication compliance was omitted from the analysis because of the difficulty to link MPR to a relevant outcome measure, e.g. fracture risk (see Section 2.5).

III. Estimate the monetary net benefit of five hypothetical interventions improving persistence by specific percentual levels. Compliance was omitted also from this analysis.

[8] A **treatment-naïve** patient refers to an individual who has not previously been treated.

4 Methods

4.1 Methods I: Estimating Medication Persistence and Compliance

The analysis of persistence and compliance, the first study objective, was based on a historical cohort extracted from the Swedish Prescription Register. The study period was June 1, 2005 through December 31, 2008. Estimates of persistence and compliance, based on records of filled prescriptions and death dates, were derived using nonparametric survival analysis[9] (since patients entered and exited the cohort at different points in time). Patient-level comorbidity data was obtained from the National Patient Register. Data management was performed in a SQL environment using Microsoft SQL Server Management Studio 2005, Microsoft Corporation. The statistical analyses were executed in Stata 9.1, StataCorp LP, Collage Station, TX.

The study design and procedures were approved by the Ethical Vetting Board in Stockholm.

4.1.1 Data Sources

The Swedish Prescription Register
The Swedish Prescription Register was established in June 2005 and contains information on all filled prescriptions of the Swedish population. Specifically, the register contains information regarding:

- The pharmacy (e.g. regional code for the pharmacy)
- The patient (e.g. gender and age)
- The prescription (e.g. date, dose and ATC-code)

The register is managed by the Centre for Epidemiology (EpC) at the Swedish National Board of Health and Welfare. Data was extracted from June 1, 2005 through December 31, 2008 (the latest data entry available).

The Causes of Death Register
The Causes of Death Register is under the responsibility of the Swedish National Board of Health and Welfare and contains specific information on many different aspects of deaths. Only the date of death was obtained for the purpose of this study. Data was extracted from June 1, 2005 through December 31, 2006 (the latest data entry available).

The National Patient Register
EpC at the Swedish National Board of Health and Welfare is responsible for the National Patient Register, an in-patient care registration system containing a wide variety of data items, such as:

- Data on the patient (e.g. sex and age)
- Administrative data (e.g. date of admission and length of stay)
- Medical data (e.g. main diagnosis)

Patient-level data on co-morbidities, used to exclude individuals with secondary caused osteoporosis, was extracted from January 1, 1998 through December 31, 2007 (the latest data entry available).

4.1.2 Patient Selection

The population used to estimate medication persistence and compliance was derived from the Swedish Prescription Register and the National Patient Register by the following inclusion and exclusion criteria:

[9]The interested reader is referred to [92], and similar texts, for an introduction to survival analysis.

Inclusion criteria

- Older than 50 years of age.
- Records of filled prescriptions for one or several of the following osteoporosis treatments:
  - alendronate
  - risedronate
  - strontium
  - raloxifene
- Washout period: No records of filled prescriptions for alendronate, risedronate, strontium and/or raloxifene five months prior to index prescription[10]. (The length of the washout was chosen to cover the base case grace period (see Section 4.1.3) and a standard three-month prescription.)

Exclusion criterion

- Secondary caused osteoporosis (identified via ICD-10 diagnosis codes from the National Patient Register).

Patients with records of filled prescriptions for etidronate were not included in the final cohort because in Sweden the treatment is administered in cycles with calcium (two weeks of medication with etidronate, followed by 76 days of treatment with calcium). Including etidronate would therefore skew the estimates of persistence and compliance since patients would appear to have discontinued treatment when switching to calcium. Moreover, zoledronate was not included in the study because the treatment received indication for osteoporosis in October 2007 [93] (and consequently has an unsatisfactory follow-up).

4.1.3 Prescription Record Analysis: Measuring Persistence and Compliance

This section describes the methodology and assumptions used when interpreting the prescription records from the Swedish Prescription Register. Patients receiving inpatient care during the study period were assumed to be fully persistent and compliant to treatment while hospitalized.

Measuring Persistence

Persistence was operationalized as the number of days on treatment. It was measured from index prescription until the end of the duration of the last prescription. Patients were allowed to have gaps between filled prescriptions, but were defined non-persistent (to have terminated treatment) if they had a gap exceeding a pre-specified length of time, known as grace period[11] or permissible gap. Put differently, persistent patients were not allowed to be off treatment longer than the specified grace period. Ideally, the grace period should equal the maximum length of time a patient can be off treatment and still receive the intended drug effect [48]. However, this time period (where the residual effect from the osteoporosis treatment equals the full treatment effect) is not known [66]. In previous studies of persistence and compliance to treatment of osteoporosis, the chosen grace period typically lies in the range of between one and three months. In the present study, the base case grace period was set to two months. Grace periods of one and three months were explored in a sensitivity analysis.

Patients were permitted to accumulate medication from overlapping prescriptions (sometimes referred to as drug stockpiling [94]) and use the stock to cover future gaps between filled prescriptions. However, once the patients were without medication for a period exceeding the grace period, or when they reached their last prescription, the duration of the accumulated

[10] **Index prescription**: The patient's first filled prescription during the study period (December 1, 2005 through December 31, 2008).

[11] More generally, a **grace period** is a specified period of time after the due date before a penalty is charged.

medication was not taken into account. The drop point was instead determined by the end of the duration of the last filled prescription. A patient with several overlapping prescriptions would otherwise be considered persistent long after the duration of her last filled prescription. It was in other words assumed that a patient who stopped to fill her prescriptions would not be inclined to consume her stock (if any) of accumulated medication.

Switching between the included treatments was allowed when establishing persistence status. A patient switching (within the grace period) from alendronate to strontium was consequently considered to be persistent to treatment, but not if the same patient switched from alendronate to HRT (because HRT was not included in the study). Figure 1 illustrates how persistence was calculated for three examples of treatment patterns.

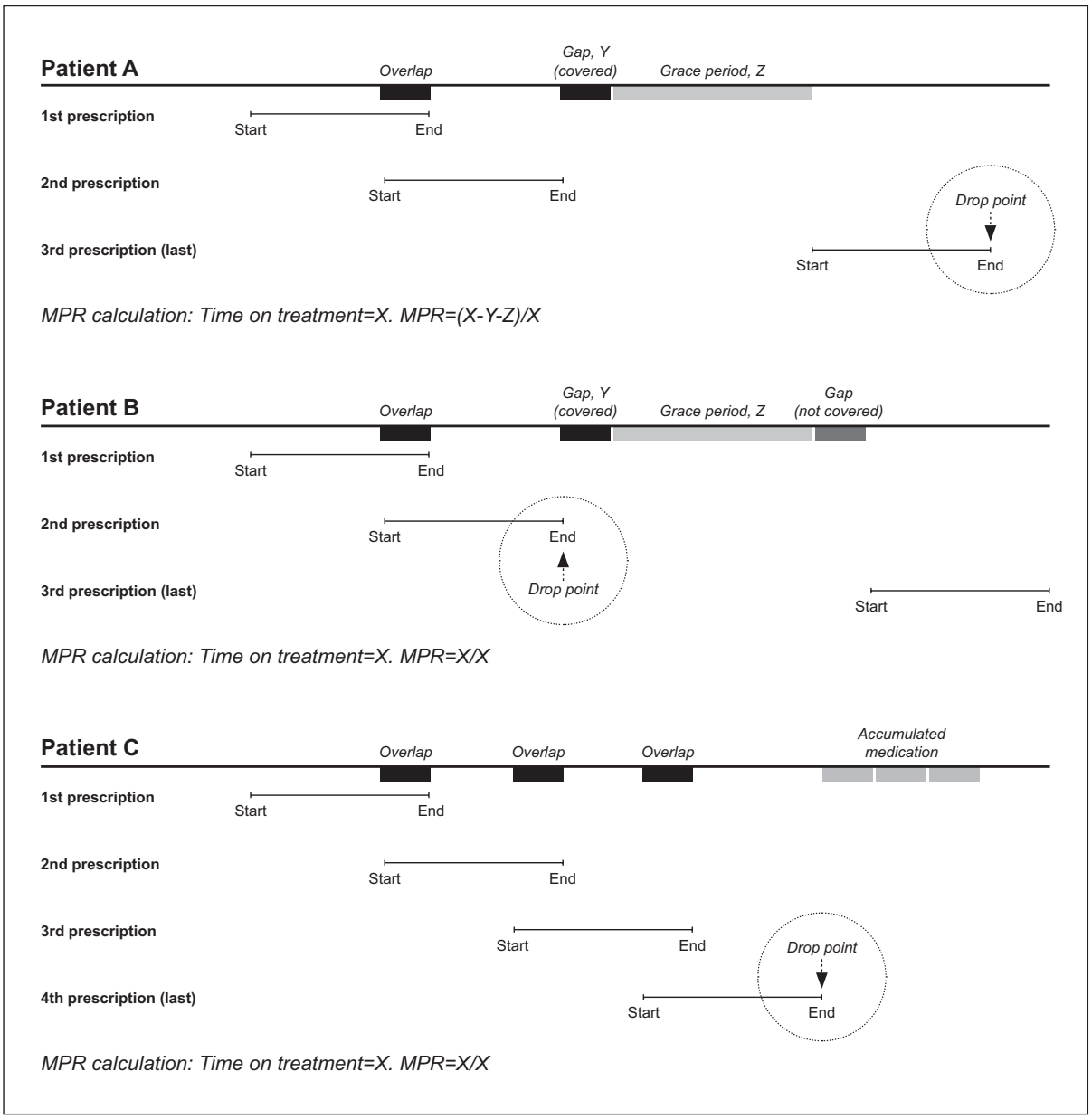


Figure 1: *Treatment Pattern Analysis (Persistence and Compliance)*

As shown in Figure 1, *Patient A* filled a total of three prescriptions. The first two prescriptions overlapped (illustrated as a solid black box labelled "Overlap") since the second prescription was filled before the end of the duration of the first prescription. The overlap implies that *Patient A* accumulated a stock of medication. As mentioned earlier, patients were permitted to use such drug stocks to cover future gaps between filled prescriptions. In the example, *Patient A* used her entire stock to cover the gap (the solid black box labelled "Gap (covered)") between the end of the duration of the second prescription and the start of the grace period. After the covered gap, *Patient A* was off treatment for an additional two months. However, since *Patient A* filled her third prescription within the grace period, she was regarded persistent to therapy until the end of the duration of her last prescription (the encircled drop point).

On the other hand, if *Patient A* would have had a break between the second and third prescription exceeding both the duration of her accumulated medication and the grace period, she would have been considered non-persistent after the duration of her second prescription. This was the case for *Patient B*, who was not allowed to consume her accumulated stock of medication and therefore terminated treatment at the end of the duration of her second prescription.

Patient C filled a total of four prescriptions and had three overlaps. Still, she was not allowed to consume her accumulated stock of medication after the end of the duration of her last prescription.

Measuring Compliance

Medication compliance was operationalized as MPR (see Section 2.3). Let ϕ denote the number of days with medication available to the patient, and Φ the number of days the patient was on treatment. MPR was then defined as:

$$\text{MPR} = \frac{\phi}{\Phi} \tag{2}$$

where ϕ was obtained by adding the duration of all prescriptions filled during time on treatment (i.e. while the patient was persistent). The total duration of all filled prescriptions was not allowed to exceed the number of days on treatment. Thus, MPR $\in$ [0,1].

Moreover, in the calculation of MPR, patients were not allowed to accumulate medication to fill future gaps between prescriptions. Drug stockpiling was not permitted to avoid overestimating MPR in patients with many overlaps and gaps between filled prescriptions. MPR, as the term was quantified in this study, was in other words a measure of gaps between filled prescriptions (and, if applicable, the length of the grace period).

Figure 1 shows how compliance was calculated for three examples of treatment patterns. *Patient A* had a break between her second and third filled prescription. The break consisted of a gap, *Y*, and the grace period, *Z*. Let *X* denote time on treatment. Using Equation 2, the MPR for *Patient A* was then calculated as: MPR=$\frac{X-Y-Z}{X}$.

Neither *Patient B* or *Patient C* had any gaps during their time on treatment and therefore had an MPR of 100%.

4.2 Methods II: Estimating the Societal Burden of Actual Persistence

As mentioned in the introduction, the therapeutic goal of osteoporosis treatment is to reduce the risk of bone fractures. However, in order to receive the intended clinical benefit (i.e. fracture risk reduction), patients must take their medication. Poor persistence to treatment of osteoporosis is therefore associated with an increased fracture risk and, as a consequence, increased morbidity, mortality, and health care costs.

The second objective of this study was to assess the total societal burden of actual compared to perfect persistence to treatment of osteoporosis in Sweden. The analysis was carried out on the historical cohort described in Section 4.1.2, but included only treatment-naïve patients who

started therapy between January 1, 2008 and December 31, 2008. The assessment was performed using a microsimulation model (see Section 4.2.1). Actual persistence rates for females and males were obtained from Section 5.1.3. The burden was calculated from a societal perspective, in relation to perfect persistence, and measured in terms of incremental discounted lifetime costs ($C^{Perfect} - C^{Actual} = \Delta C$) and QALYs ($E^{Perfect} - E^{Actual} = \Delta E$). Patients were stratified into $2 \times 4 \times 4 = 32$ groups according to sex (female/male), age (50-60 years, 60-70 years, 70-80 years, and 80+ years), and treatment type (alendronate, risedronate, strontium, and raloxifene). Simulations were performed for the mean patient of each stratum. The stratum-specific results were then multiplied by the number of patients in each stratum to obtain the total difference in discounted lifetime cost and QALYs between perfect and actual persistence. The total burden was derived using a cost-benefit approach (see Equation 1):

$$\text{Total burden} = \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \Delta\bar{E}_{ijk} \cdot n_{ijk} \cdot \lambda - \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \Delta\bar{C}_{ijk} \cdot n_{ijk} \tag{3}$$

where $\Delta\bar{E}_{ijk}$ was the average per-patient effect difference, $\Delta\bar{C}_{ijk}$ the average per-patient cost difference, and n_{ijk} the number of patients of sex i, in age group j, on treatment k. The burden was in other words measured as a loss to society in terms of a NB.

4.2.1 The Microsimulation Model

This section describes the microsimulation model constructed to estimate the burden of actual persistence to treatment of osteoporosis in Sweden. The model structure was based on previously published models evaluating osteoporosis treatments [71, 95–97]. Model data is presented in Appendix B. Model validation results are located in Appendix B.7. The model was constructed using TreeAge Pro 2008, TreeAge Software, Inc., Williamstown, MA.

Markov Cohort and Monte Carlo Simulation Models
Markov cohort models are a specific type of discrete state-transition simulation models. A hypothetical cohort is divided between a finite set of predetermined states and transitions between the states take place over a series of discrete time periods (cycles). The states are mutually exclusive and collectively exhaustive. Costs and effects are allocated as a mean value per state and cycle, in contrast to for example decision tree models that lack the time dimension. Moreover, future events are only dependent on the current state, and not on prior events. This crucial assumption of the Markov model is known as the Markovian property. It implies that all patients within each state are treated the same irrespectively of their history within the model [98].

Monte Carlo simulation models, or microsimulation models, are similar to Markov cohort models with the exception of per-patient variation in model outcomes. In a microsimulation model, patients populate the model individually and it is therefore possible to retain a patient-specific record or memory of e.g. previous states. Consequently, there will be random variation in individual results. The possibility to simulate patients individually is sometimes important in models that incorporate complex treatment and disease patterns, where for example future transition probabilities are directly dependent on past events. To achieve stable results (estimates), a sufficient number of trials (individuals populating model) must be executed.

Markov cohort and microsimulation models are two commonly used approaches in health economic decision analysis [98]. These model structures are particularly suitable for modelling osteoporosis because a fracture is an easily definable event, based on continuous risk over time [71, 99]. Moreover, regarding the discrepancy between Markov cohort and microsimulation models, it has recently been argued that the latter "have a better ability to represent the complexity and the heterogeneity of pathology such as osteoporosis"[70].

Model Structure
The model cycle length was six months (chosen to accommodate bi-annual persistence estimates) and all patients were individually followed from the age of treatment initiation to time of death or an age of 100 years. The structure of the model is shown in Figure 2 below.

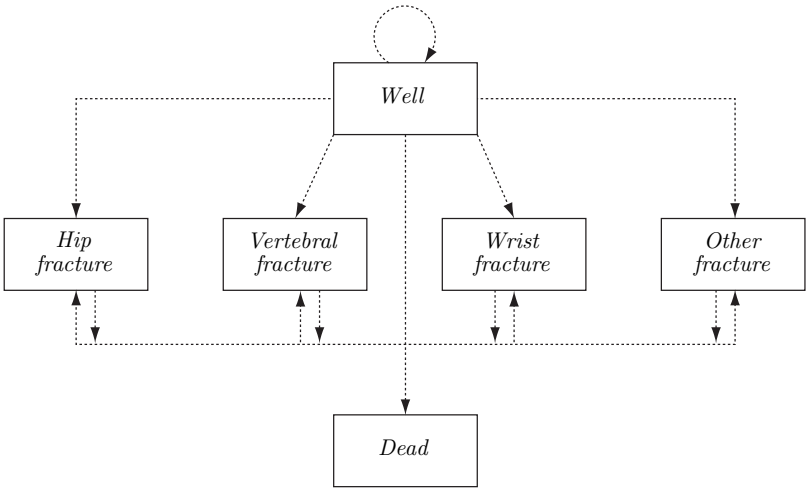


Figure 2: *State Transition Diagram*

The model consisted of six health states: *well*, *hip fracture*, *vertebral fracture*, *wrist fracture*, *other osteoporotic fracture*[12], and *dead*. All patients began in the *well* health state. In each cycle (i.e. every six months) the patient had a probability of sustaining a fracture, remaining healthy or dying. If a patient died, she moved to the *dead* health state and remained there for the rest of the simulation. If a patient incurred a fracture, she moved, depending on fracture type, to the *hip fracture*, *spine fracture*, *wrist fracture* or *other osteoporotic fracture* health state. A living patient was always at risk of experiencing a new fracture, but was only allowed to sustain one fracture (or stay *well* or move to the *dead* health state) in a given cycle. The reason for not allowing multiple events was the lack of relevant epidemiological data.

Allocation of Costs and Utilities
The model simulated patients individually and evaluated their costs and effects (utilities) every six months (i.e. in each cycle). Each fracture event was associated with a fracture-specific, age-differentiated cost and reduction in utility. Hip and vertebral fractures were assumed to have both short-term (first year after fracture) and long-term (beyond the first year) implications. Wrist and other osteoporotic fractures were assumed to have an impact on costs and quality of life only during the first year after the event. At the end of the simulation, each patient's discounted lifetime cost and number of QALYs (the number of years each patient was alive multiplied by the quality weight associated with each of those life years) was calculated.

Included Costs
The burden assessment was made from a societal perspective and both direct and indirect costs were therefore included. The list below contains all costs that were taken into account.

- **Direct Costs**
  - Inpatient care (hospitalization) costs
  - Outpatient care costs
  - Nursing home costs

[12]**Other osteoporotic fractures**: pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures.

  - Drug costs
  - Treatment management costs
  - Cost of informal care

- **Indirect Costs**
  - Productivity costs[13]

- **Cost in added life-years**[14]

Modelling Persistence
The microsimulation model incorporated a five-year treatment duration. All patients initiated treatment at the start of the simulation (i.e. when they entered the model). While on treatment, patients received the clinical benefit (i.e. fracture risk reduction) from their respective treatment. The societal burden of actual persistence was measured in relation to perfect persistence, and two different persistence scenarios were therefore evaluated for the cohort.

In the first scenario, patients were assumed to be perfectly persistent to therapy and received the clinical benefit from their respective medication in each cycle during the treatment duration. In the second scenario, patients terminated treatment in line with actual persistence rates in Sweden (the results from Section 5.1.3). Specifically, patients had a predefined probability of discontinuing treatment in each cycle (i.e. every six months) during the five-year treatment duration. Patients who dropped out of treatment did not receive any drug effect for the remainder of the treatment duration.

In previous health economic evaluations of osteoporosis treatments, a fixed, linearly decreasing residual effect (known as offset time) of five years has been a commonly employed assumption [101–104]. However, when incorporating a treatment pattern characteristic such as persistence, this assumption must be modified to better reflect the actual exposure of the medication; otherwise, a patient on treatment for six months would receive the same residual effect as a patient on treatment for five years (the full treatment duration). A dynamic offset algorithm, where the linearly decreasing residual effect equalled the patient-specific time spent on treatment, was therefore implemented. Let X denote the current cycle, Y the cycle in which the patient terminated treatment, and Z the full treatment effect. Note that $X \geq Y$; the residual effect starts after treatment termination. The residual effect R in cycle X was then defined:

$$R_X = [1 - \frac{(X - Y)}{Y}] \cdot Z \tag{4}$$

A patient perfectly persistent to treatment would consequently receive five years of linearly decreasing residual effect, in addition to five years of full treatment effect. The dynamic offset assumption is illustrated in Figure 3 on the next page.

4.2.2 Simulation Procedure

This section contains a brief review of the different steps included in the estimation of the societal burden of actual compared to perfect persistence.

1. The total cohort, consisting of all treatment-naïve patients who started therapy in Sweden during 2008, was extracted.

[13] **Productivity costs**: Costs related to the loss of production because the individual is being less productive or absent from work, following of illness or death [41].

[14] **Cost in added life-years** is the difference between total production and total consumption during life years gained. It has been argued that such costs should be taken into account when performing health economic analyses from a societal perspective [100].

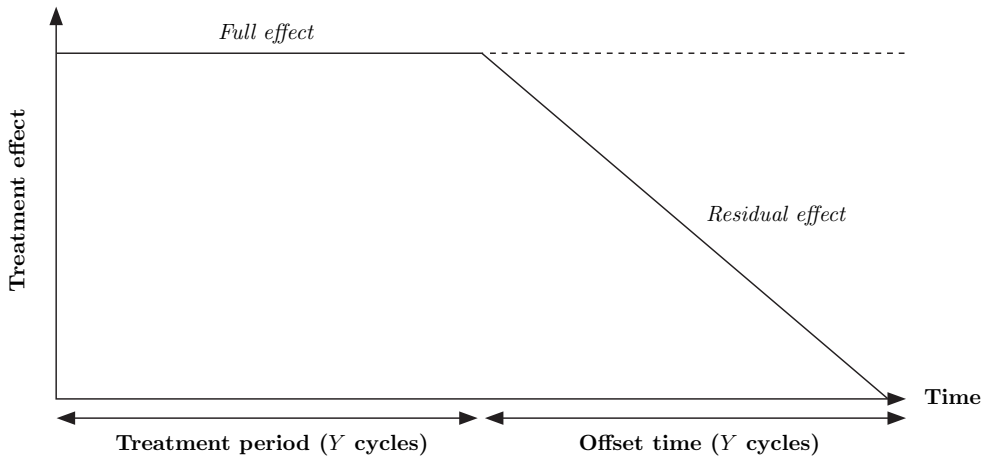


Figure 3: *The Dynamic Offset*

2. The cohort was stratified into 32 groups (according to sex, age, and treatment type).
3. The microsimulation model was synchronized in line with the characteristics of the mean patient of the first stratum (i.e. female, 55 years of age, taking alendronate).
4. A total of 500,000 trials (identical patients with the characteristics of the mean patient of the first stratum) were simulated. The patients were specified to be perfectly persistent to the five-year treatment duration.
5. The average discounted lifetime cost and QALYs were extracted from the model results.
6. The model was modified to incorporate actual persistence rates. A second round of simulations was executed based on the mean patient of the first stratum.
7. The average lifetime cost and QALYs from the second simulation were obtained.
8. The per-patient strata-specific difference in average discounted lifetime cost and QALYs between perfect and actual persistence was calculated.
9. The per-patient strata-specific difference was multiplied by the number of patients in the first stratum to obtain the total stratum-specific difference in discounted lifetime cost and QALYs.
10. Step 3 to 9 was repeated for each stratum.
11. The total societal burden was calculated by adding the total stratum-specific differences in discounted lifetime cost and QALYs together.

4.3 Methods III: Estimating the Net Benefit of Improved Persistence

The third, and last, objective of this study was to estimate the NB of interventions improving actual persistence (the result from Section 5.1.3). The analysis was carried out on the historical cohort described in Section 4.2 and performed using the microsimulation model described in Section 4.2.1. Five hypothetical interventions were simulated, with improvement in persistence (the estimated survival function) to the five year treatment duration of 10%, 20%, ..., 50%. Larger improvements were omitted due to the modest persistence improvements reported in previous studies (see Section 2.4). The exact content of the interventions is outside the scope

of this study, but could potentially contain different types of reminders, personal counselling, monthly physician visits, *et cetera*.

The NB of the five investigated interventions was calculated by relating the simulated average per-patient discounted lifetime cost and QALYs with actual persistence, $\bar{C}^{Actual}$ and $\bar{E}^{Actual}$, to the corresponding estimates obtained with adjusted persistence rates, $\bar{C}^{\Psi}$ and $\bar{E}^{\Psi}$, for intervention $\Psi = 1, 2, \ldots, 5$. The total cost difference of adjusted compared to actual persistence was then calculated as:

$$\Delta C_{Total}^{\Psi-Actual} = \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \bar{C}_{ijk}^{\Psi} \cdot n_{ijk} - \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \bar{C}_{ijk}^{Actual} \cdot n_{ijk} \tag{5}$$

where n_{ijk} was the number of patients of sex i, in age group j, on treatment k. The total effect difference was calculated analogously as:

$$\Delta E_{Total}^{\Psi-Actual} = \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \bar{E}_{ijk}^{\Psi} \cdot n_{ijk} - \sum_{i=1}^{2}\sum_{j=1}^{4}\sum_{k=1}^{4} \bar{E}_{ijk}^{Actual} \cdot n_{ijk} \tag{6}$$

The total NB, $NB_{Total}^{\Psi-Actual}$, was calculated using Equation 1. The per-patient NB was defined:

$$NB_{Per\text{-}patient}^{\Psi-Actual} = \frac{NB_{Total}^{\Psi-Actual}}{N} \tag{7}$$

As explained in Section 2.2.1, a NB greater than zero implies that the monetary value of the benefits exceeds the costs. The estimated NBs should therefore be interpreted as the amount of financial resources (in total or per patient) that cost-effectively could be allocated to implement the different interventions, given the chosen societal WTP for a QALY.

5 Results

5.1 Results I: Estimates of Medication Persistence and Compliance

The first study objective was to estimate medication persistence and compliance to treatment of osteoporosis in Sweden. The results are presented in this section.

5.1.1 Final Study Population

Below is a patient selection flowchart of the final cohort.

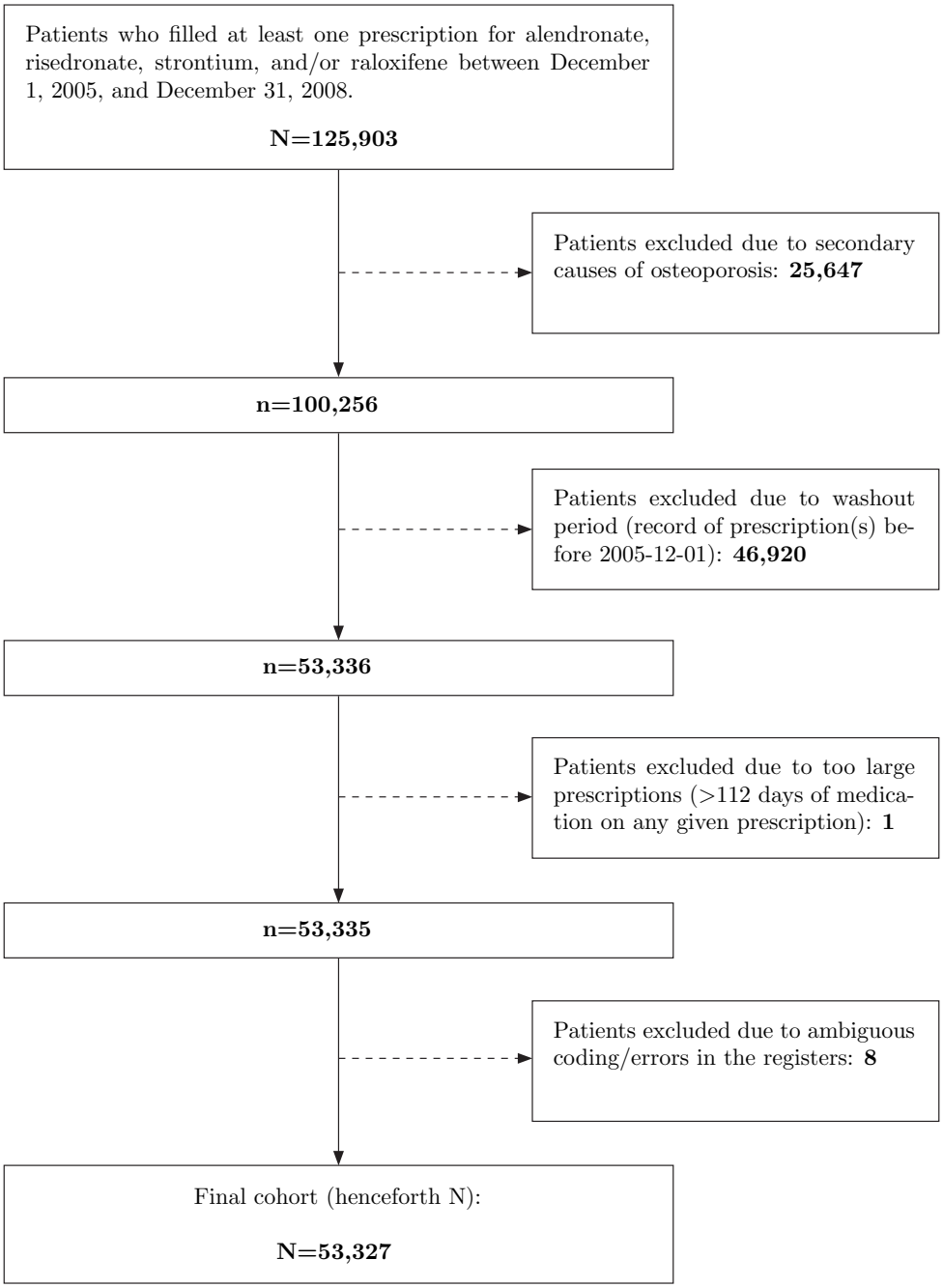


Figure 4: *Patient Selection Flowchart*

The final cohort consisted of a total of N=53,327 individuals. Patients with secondary caused osteoporosis, identified via ICD-10 diagnosis codes (see Appendix A) from the National Patient Register, were excluded. Moreover, patients filling prescriptions of medications lasting more than 112 days[15], indicating coding error and/or secondary caused osteoporosis, were also removed from the cohort. A washout-period of five months (equal to a three-month prescription and the base case grace period of two months) was used to capture treatment-naïve patients.

5.1.2 Descriptive Statistics

Table 1 below contains summary descriptive data for all patients included in the final cohort.

Table 1: Descriptive Statistics of the Final Cohort

	Females				Males			
Variable	**Mean**	**Min.**	**Max.**	**95% CI**	**Mean**	**Min.**	**Max.**	**95% CI**
Follow-up (days)	321.66	1	1,126	313.38 - 318.28	283.16	1	1,126	277.46 - 288.86
Age	70.96	51	100	70.78 - 70.95	70.33	51	97	70.11 - 70.55
Weekly regimen	0.9363	0	1	0.9341 - 0.9386	0.9531	0	1	0.9485 - 0.9577

Approximately 85% of the cohort were females. Only 6% of all patients were on a daily dosing regimen (the rest were on a weekly regimen). The maximum follow-up (days on treatment) was 1,126 days (December 1, 2005 through December 31, 2008). Individual age was measured at the start of the follow-up. Figure 5 shows the distribution of age and observation time.

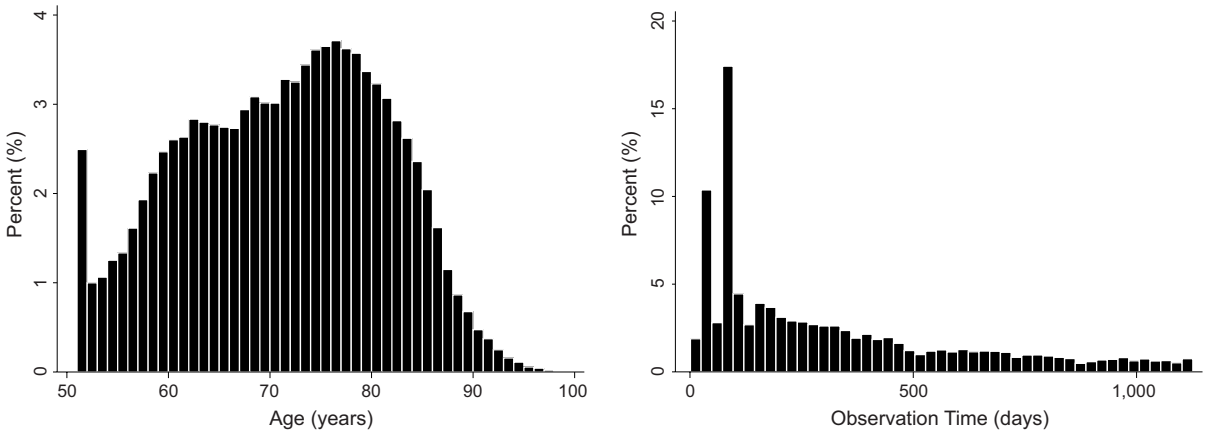


Figure 5: *Distribution of Age and Observation Time*

A notable share of the cohort was 51 years of age. The reason for this discrepancy is unknown, but could be related to structural treatment practices dependent on age. Approximately 25% of all included patients terminated treatment after 28 or 84 days (i.e. after their index prescription).

Moreover, the final cohort filled a total of 296,304 prescriptions between December 1, 2005 and December 31, 2008. Table 2 on the next page presents the distribution (by treatment type). Of all prescription records, 76% were for alendronate (the first-choice treatment of osteoporosis in Sweden). Risedronate had a share of 20% of all prescriptions, while strontium and raloxifene had 1% and 2%, respectively. Note that raloxifene is only prescribed to females.

[15]In Sweden, patients are not permitted to collect medication lasting more than three months from a single prescription refill. The cut-off point of 112 days was chosen to equal a standard one-month package (28 daily tablets) and a three-month package (consisting of twelve once-weekly tablets, 7×12=84 days of medication). Since three months is larger than 84 days, the cut-off point was extended to not exclude osteoporotic patients who received a small amount (i.e. a one-month package) of extra medication in addition to a three-month package.

Table 2: Distribution of Filled Prescriptions (By Treatment Type)

	alendronate	risedronate	strontium	raloxifene	Total
Frequency	225,980	60,167	3,167	6,990	**296,304**
Proportion of all prescriptions	0.7627	0.2031	0.0107	0.0236	**1.00**

5.1.3 Statistical Analysis of Persistence

Nonparametric survival analysis was used to produce estimates of persistence in the form of Kaplan-Meier survival functions. The grace period was set to two months.

Kaplan-Meier Survival Estimates
The estimated survival function, $\hat{S}(t)$, for females and males combined, with treatment termination as failure event, is presented below. Patients were right censored for death (date of deaths available up until December 31, 2006) and register limit (December 31, 2008).

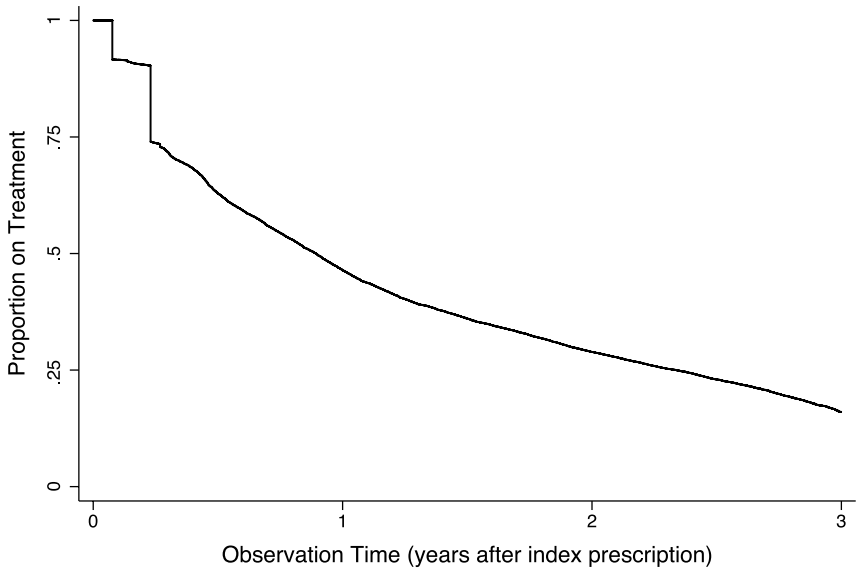


Figure 6: *The Estimated Kaplan-Meier Survival Curve (Females and Males Combined)*

In accordance with the histogram of observation time (Figure 5), the estimated survival function shows that a substantial proportion of all patients terminated treatment after their index prescription (illustrated as two vertical drops in the beginning of the curve). The estimated number of failures and the proportion of the cohort still on treatment at specific time periods are presented in Table 3 below.

Table 3: Life-Table (Failure: Treatment Termination)

Time point	Fail (at)	Survivor Function	Std. Error	95% CI
28 days	4,392	0.9158	0.0012	0.9134 - 0.9182
84 days	8,738	0.7398	0.0020	0.7359 - 0.7436
6 months	5,292	0.6280	0.0022	0.6237 - 0.6322
12 months	6,897	0.4640	0.0023	0.4594 - 0.4686
18 months	3,603	0.3602	0.0024	0.3555 - 0.3649
2 years	1,907	0.2888	0.0024	0.2840 - 0.2935
2.5 years	1,051	0.2296	0.0025	0.2247 - 0.2346
3 years	574.0	0.1600	0.0033	0.1536 - 0.1666

As previously noted, a large share of the cohort terminated treatment immediately after the duration of their first filled prescription: 4,392 patients, 8% of the cohort, discontinued treatment after 28 days (92% remained persistent) and 8,738 after 84 days (74% were considered persistent). A total of 63%, 46%, 29%, and 16% were still on treatment after 6 months, 1 year, 2 years, and 3 years, respectively. The median survival time (i.e. the median number of days on treatment), defined as the earliest time at which half of the study participants have experienced the event [92] (i.e. terminated their treatment), was estimated at 326 days.

Separate survival curves for females and males are shown in Figure 7 below, and in the corresponding life table (Table 4). The estimated survival functions were significantly different (log-rank test, $p<0.001$).

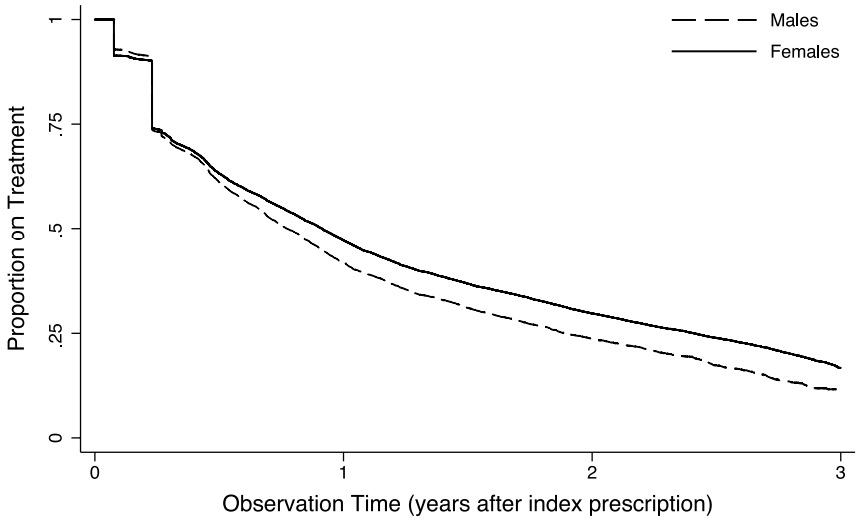


Figure 7: *The Estimated Kaplan-Meier Survival Curve (By Sex)*

The 2,611 males that started treatment with alendronate, risedronate, or strontium (raloxifene is only prescribed to females) between December 1, 2005 and December 31, 2008, were significantly less persistent to therapy compared to their female counterparts, although the trend was similar.

Table 4: Life-Table, By Sex (Failure: Treatment Termination)

	Females		Males	
Time point	**Survivor Function**	**95% CI**	**Survivor Function**	**95% CI**
28 days	0.9136	0.9109 - 0.9162	0.9284	0.9225 - 0.9339
84 days	0.7405	0.7363 - 0.7447	0.7353	0.7252 - 0.7451
6 months	0.6312	0.6265 - 0.6358	0.6097	0.5984 - 0.6208
12 months	0.4719	0.4669 - 0.4769	0.4175	0.4055 - 0.4295
18 months	0.3686	0.3635 - 0.3736	0.3108	0.2989 - 0.3227
2 years	0.2975	0.2923 - 0.3026	0.2365	0.2247 - 0.2486
2.5 years	0.2387	0.2334 - 0.2442	0.1733	0.1608 - 0.1861
3 years	0.1671	0.1601 - 0.1743	0.1163	0.1015 - 0.1321

Females were found to be more persistent to therapy across most studied time points compared to the included male patients. The estimated difference in persistence between the sexes was fairly small, but increased over time. Similar proportions, approximately 25% of both the female and male patient group, terminated treatment after the duration of their first filled prescription, and less than 12% of the males remained persistent after three years of therapy, compared to approximately 16% of all females. The median number of days on treatment was estimated at 333 and 281 for females and males, respectively.

Persistence Grace Period Sensitivity Analyses
The length of the grace period (permissible gap between filled prescriptions) obviously has an impact on the estimated levels of persistence. Figure 8 below contains estimates of persistence based on two other grace periods (one month and three months), in addition to the base case grace period of two months.

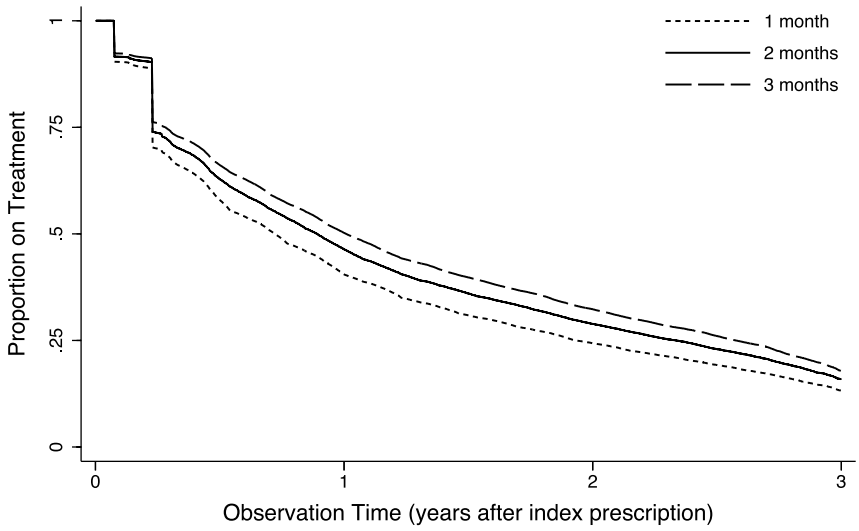


Figure 8: *Kaplan-Meier Survival Curves (For Three Different Grace Periods)*

The length of the grace period was of relatively small importance for the estimated levels of persistence. The reason is that patients in Sweden had overlapping prescriptions and few gaps and therefore mainly terminated treatment in relation to their last prescription (and not because they had a break between filled prescriptions exceeding the grace period).

5.1.4 Statistical Analysis of Compliance

Compliance was quantified with MPR and calculated (using Equation 2) while the patients were persistent (i.e. on treatment). The results, shown in Table 5 below, were based on the base case grace period of two months.

Table 5: Descriptive Statistics: MPR Analysis (Females and Males Combined)

Variable	Mean	Std. Dev.	Min.	Max.	95% CI
Follow-up (days)	315.83	289.63	1	1,126	313.38 - 318.28
Days with medication	290.71	260.90	1	1,114	288.49 - 292.92
MPR	0.9467	0.0728	0.2791	1	0.9461 - 0.9473

The average time on treatment was 316 days (out of a maximum of 1,126). The average number of days with medication was lower, indicating gaps between filled prescriptions, but the difference was small (291 days compared to 316). Average MPR was estimated at 94.7%. Figure 9 on the next page displays the distribution of MPR for the total cohort. Surprisingly, nearly 50% of all patients had a MPR of 100% (i.e. no gaps between prescriptions).

MPR was not significantly different between females and males (Student's unpaired t-test (two-tailed), p=0.1422).

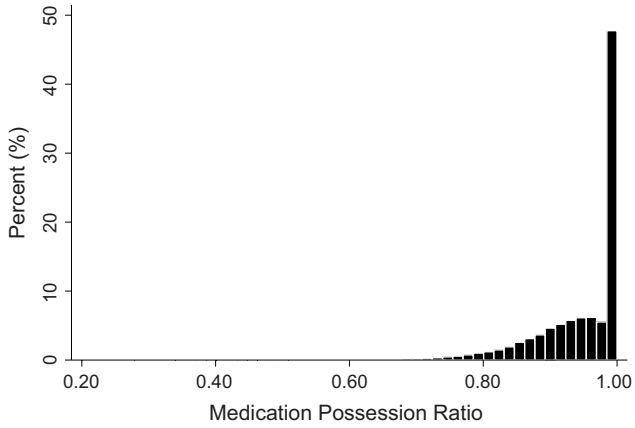


Figure 9: *Histogram of Medication Possession Ratio*

Compliance Grace Period Sensitivity Analysis
Estimates of average MPR based on two other grace periods (one month and three months) are presented below in Table 6.

Table 6: Sensitivity Analysis of MPR

Grace period	Mean MPR	Std. Dev.	Min.	Max.	95% CI
1 month	0.9597	0.0579	0.2791	1	0.9592 - 0.9602
2 months	0.9467	0.0728	0.2791	1	0.9461 - 0.9473
3 months	0.9348	0.0883	0.2544	1	0.9340 - 0.9355

5.2 Results II: Assessment of the Societal Burden of Actual Persistence

The second objective of this study was to assess the total societal burden of actual compared to perfect persistence. The analysis was performed on all treatment-naïve patients who started treatment with alendronate, risedronate, strontium, or raloxifene between January 1, 2008 and December 31, 2008.

5.2.1 Descriptive Statistics

The final cohort consisted of N=15,414 subjects. Table 7 below shows the total number of patients stratified by sex, age, and treatment type.

Table 7: Number of Patients (By Each Stratum)

	Age (females)				Age (males)				
Treatment	**50-60**	**60-70**	**70-80**	**80+**	**50-60**	**60-70**	**70-80**	**80+**	**Total**
alendronate	1,729	3,140	3,780	1,989	380	619	771	433	**12,841**
risedronate	394	579	542	276	78	134	118	66	**2,187**
strontium	23	45	95	84	2	1	3	6	**259**
raloxifene	49	50	11	17	0	0	0	0	**127**
Total	**2,195**	**3,814**	**4,428**	**2,366**	**460**	**754**	**892**	**505**	**15,414**

5.2.2 Simulation Results

The microsimulation model was populated with the real-world persistence rates for females and males from Section 5.1.3. The estimates were extrapolated to five years assuming that no patients discontinued treatment during year four and five. All results were based on 500,000 simulated trials. A discount rate of 3% was used for costs and effects, as suggested by TLV [105].

Incidence of Fractures
The average per-patient fracture incidence, $\bar{F}_{ijk}$, was estimated during the first ten years following treatment initiation for each of the 32 patient groups. The total number of fractures was calculated with actual persistence to therapy during the five-year treatment duration, and with perfect persistence, respectively. Denote the per-patient average fracture incidence difference (perfect compared to actual persistence) $\Delta\bar{F}_{ijk} = \bar{F}_{ijk}^{Perfect} - \bar{F}_{ijk}^{Actual}$. The difference in the estimated total number of fractures for treatment k (shown in Table 8) was then calculated as $F_k = \sum_{i=1}^{2}\sum_{j=1}^{4}\Delta\bar{F}_{ijk} \cdot n_{ijk}$.

Table 8: Difference in Estimated 10-Year Fracture Incidence (Perfect-Actual)

Fracture type	**alendronate**	**risedronate**	**strontium**	**raloxifene**
Hip fracture	-330	-35	-3	±0
Vertebral fracture	-342	-43	-7	-2
Wrist fracture	-54	-26	±0	±0
Other fracture	-211	-43	-4	±0

With actual compared to perfect persistence to treatment, a total of 330 additional hip fractures were estimated for the 12,841 patients starting treatment with alendronate during 2008. Put differently, improving persistence from the actual to a perfect level would avoid 330 hip fractures in ten years for this patient group. There was no difference in the estimated incidence of wrist fractures for patients on strontium, or hip, wrist, and other fractures for patients on raloxifene, because the treatments do not have effect on these respective fracture types. The larger estimated incidence of fractures for patients with actual persistence implies larger morbidity costs and reduced quality and quantity of life compared to patients perfectly persistent to therapy.

Incremental Costs
Table 9 contains simulated discounted lifetime costs with actual and perfect persistence, stratified by sex and treatment type: $C_{ik} = \sum_{j=1}^{4}\bar{C}_{ijk} \cdot n_{ijk}$, for sex i and treatment k.

Table 9: Estimated Total Discounted Lifetime Cost (MSEK)

	$C^{Perfect}$		C^{Actual}		$\Delta C^{Perfect-Actual}$	
Treatment	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
alendronate	26,689	4,538	26,699	4,529	-10	9
risedronate	4,501	831	4,484	826	17	5
strontium	599	22.73	596	22.57	3	0.15
raloxifene	309	0	307	0	2	0
Total	**32,098**	**5,391**	**32,086**	**5,377**	**11.86**	**14.13**

Perfect compared to actual persistence was associated with overall larger costs. The total cost difference, $\Delta C^{Perfect-Actual}$, was estimated at MSEK 11.86 and 14.13 for females and males, respectively.

The relatively large difference for the small male patient group can be explained by the fact that males (at most ages) have a lower risk of fractures compared to females. As a consequence, males received a smaller absolute benefit from the additional drug exposure following perfect

persistence, while the increase in per-patient drug cost (from the additional filled prescriptions) was identical for both sexes.

Surprisingly, for females on alendronate, the estimated cost difference was negative, indicating that the medication cost increase was smaller than the cost decrease due to reduced morbidity associated with the additional time on treatment. For males on alendronate, however, the cost difference was positive.

For patients on risedronate, the total cost difference was estimated at MSEK 22. The result was caused by the relatively high average annual drug cost of that particular treatment (397% higher than alendronate, the least expensive treatment option).

Table 10 below contains the difference in the estimated total discounted lifetime cost between perfect and actual persistence, stratified by sex and the included cost items.

Table 10: Incremental Total Discounted Lifetime Cost of Perfect Persistence (MSEK)

	Females		**Males**	
Cost item	$\Delta C^{Perfect-Actual}$	Percent (%)	$\Delta C^{Perfect-Actual}$	Percent (%)
Inpatient care cost	-62	-524	-8	-59
Outpatient care cost	-8	-65	-1	-7
Nursing home cost	-99	-836	-10	-69
Drug cost	46	392	9	63
Treatment management	68	576	14	96
Net consumption	66	559	11	77
Total	**11.86**	**100**	**14.13**	**100**

Note: Inpatient and outpatient care costs include indirect costs.

The increase in the estimated lifetime cost of perfect compared to actual persistence was primarily driven by increased drug costs and costs related to treatment management (since perfectly persistent patients filled prescriptions for the entire treatment duration). Perfect persistence was also associated with lower mortality and an increased cost to society from the added life years (given that consumption on average is larger than production at ages above 65 years). However, these cost increases were to a large degree offset by a substantial reduction in both nursing home costs and inpatient care cost (due to the additional drug exposure).

Incremental Effects

Table 11 contains the estimated discounted number of QALYs with actual and perfect persistence, stratified by sex and treatment type: $E_{ik} = \sum_{j=1}^{4} \bar{E}_{ijk} \cdot n_{ijk}$, for sex i and treatment k. Patients with actual persistence to treatment had lower quality of life compared to perfectly persistent patients, since the former failed to receive the full drug benefit for the entire treatment duration. The incremental health effect, $\Delta E^{Perfect-Actual}$, was estimated at 581 QALYs for females and 75 QALYs for males.

Table 11: Estimated Total Discounted QALYs

	$E^{Perfect}$		E^{Actual}		$\Delta E^{Perfect-Actual}$	
Treatment	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
alendronate	96,806	18,451	96,302	18,385	504	65
risedronate	17,334	3,484	17,267	3,475	67	10
strontium	1,909	81.16	1,901	80.93	8	0.23
raloxifene	1,409	0	1,407	0	2.35	0
Total	**117,458**	**22,016**	**116,877**	**21,941**	**581**	**75**

The Total Burden
Table 12 contains the total cost difference, $\Delta C_k = \sum_{i=1}^{2}\sum_{j=1}^{4}\Delta\bar{C}_{ijk}\cdot n_{ijk}$, and total effect difference, $\Delta E_k = \sum_{i=1}^{2}\sum_{j=1}^{4}\Delta\bar{E}_{ijk}\cdot n_{ijk}$, for treatment k and with λ=SEK 600,000. The total burden was calculated using a NB approach according to Equation 3.

Table 12: The Total Estimated Burden of Actual Persistence (MSEK)

Treatment	ΔC	ΔE (QALYs)	$\Delta E \cdot \lambda$	Burden
alendronate	-1	570	342	343
raloxifene	2	2	1	-1
risedronate	22	76	46	24
stronitum	3	8	5	2
Total	**26**	**656**	**394**	**368**

The total burden of actual compared to perfect persistence to treatment of osteoporosis, assessed for all treatment-naïve patients who started therapy with alendronate, risedronate, strontium, or raloxifene during 2008 in Sweden, was estimated at MSEK 368.

The burden of perfect compared to actual persistence for patients on raloxifene was estimated at MSEK -1, indicating that a heavier burden would be placed on the society following an improvement in persistence for patients on that particular treatment. The reason for this result is that raloxifene was modelled without taking the treatment risk reduction of invasive breast cancer into account (see Appendix B.3), thereby underestimating its cost-effectiveness.

5.3 Results III: Estimates of the Net Benefit of Improved Persistence

The third, and last, objective of this study was to estimate the NB of improved persistence in Sweden. Five hypothetical interventions were simulated, with improvement in persistence (the estimated survival function) to the five year treatment duration of 10%, 20%, ..., 50%. Figure 10 and Table 13 display the estimated survival function and the median survival time (median number of days on treatment) for the included females after adjustment by the hypothetical interventions. It was assumed that no patients discontinued treatment during year four or five.

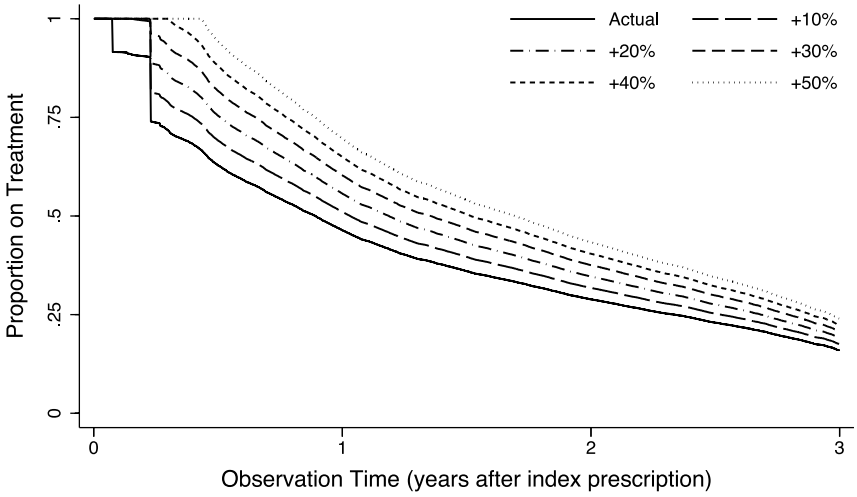


Figure 10: *Estimated Survival Functions (For Females, After Adjustment)*

Table 13: Estimated Median Survival Time (For Females, After Adjustment)

	Persistence Improvement					
	+0%	**+10%**	**+20%**	**+30%**	**+40%**	**+50%**
Median survival time (days)	333	386	445	512	577	639

An increase in persistence for females with 10%, 20%, 30%, 40%, and 50% would result in an increase in the median number of days on treatment of 16%, 34%, 54%, 73%, and 92%, respectively. The corresponding estimates for males were 17%, 31%, 47%, 61%, and 79%.

5.3.1 Simulation Results

The total estimated cost and effect difference between persistence adjusted for the five interventions and actual persistence, $\Delta C_{Total}^{\Psi-Actual}$ and $\Delta E_{Total}^{\Psi-Actual}$, was calculated using Equation 5 and Equation 6. The total NB was calculated using Equation 1, and the per-patient NB using Equation 7. All results were based on 500,000 trials. As before, a discount rate of 3% was used for both costs and effects. Table 14 below contains the estimated total and per-patient NB of the five interventions for females and males combined, with λ=SEK 600,000.

Table 14: Estimated Total and Per-Patient NB (Females and Males Combined) (MSEK)

Intervention (Ψ)	$\Delta C^{\Psi-Actual}$	$\Delta E^{\Psi-Actual}$ (QALYs)	$\Delta E^{\Psi-Actual} \cdot \lambda$	$NB_{Total}^{\Psi-Actual}$	$NB_{Per\text{-}patient}^{\Psi-Actual}$
+10%	1.92	27	16	14	915
+20%	3.83	53	32	28	1,832
+30%	4.72	77	46	42	2,695
+40%	7.65	107	64	57	3,671
+50%	9.55	126	76	66	4,288

The results suggest that it would be cost-effective to allocate between approximately SEK 900 and SEK 4,300 per patient to increase persistence rates for the included females and males, depending on the level of improvement. The average per-patient NB per percentual unit of increase in persistence (from the actual level) was estimated at approximately SEK 100.

Tables 15 and 16 below show the simulation results for females and males, respectively.

Table 15: Estimated Total and Per-Patient NB (Females)

	Age				
Females (*N*=12,803)	**55**	**65**	**75**	**84**	**Total**
Intervention: +10%					
Total NB (MSEK)	0.35	2.91	6.30	3.36	**13**
Per-patient NB (SEK)	160	763	1,423	1,421	**1,009**
Intervention: +20%					
Total NB (MSEK)	0.70	5.82	12.61	6.73	**26**
Per-patient NB (SEK)	320	1,527	2,848	2,846	**2,021**
Intervention: +30%					
Total NB (MSEK)	1.15	8.56	18.44	9.84	**38**
Per-patient NB (SEK)	524	2,244	4,164	4,161	**2,967**
Intervention: +40%					
Total NB (MSEK)	1.41	11.66	25.27	13.50	**52**
Per-patient NB (SEK)	641	3,058	5,706	5,706	**4,049**
Intervention: +50%					
Total NB (MSEK)	1.44	13.62	29.51	15.72	**60**
Per-patient NB (SEK)	657	3,571	6,665	6,645	**4,710**

Table 16: Estimated Total and Per-Patient NB (Males)

	Age				
Males (*N*=2,611)	**55**	**65**	**75**	**84**	**Total**
Intervention: +10%					
Total NB (MSEK)	0.10	0.24	0.51	0.33	**1.18**
Per-patient NB (SEK)	211	324	576	649	**453**
Intervention: +20%					
Total NB (MSEK)	0.19	0.49	1.03	0.66	**2.37**
Per-patient NB (SEK)	423	649	1,154	1,300	**907**
Intervention: +30%					
Total NB (MSEK)	0.29	0.73	1.54	0.99	**3.56**
Per-patient NB (SEK)	634	974	1,732	1,952	**1,362**
Intervention: +40%					
Total NB (MSEK)	0.39	0.98	2.06	1.32	**4.75**
Per-patient NB (SEK)	846	1,299	2,311	2,605	**1,817**
Intervention: +50%					
Total NB (MSEK)	0.46	1.21	2.53	1.59	**5.80**
Per-patient NB (SEK)	1,004	1,605	2,840	3,157	**2,221**

For females, it would be cost-effective to spend between SEK 900 and SEK 4,300 per-patient to implement the simulated interventions, depending on the expected level of increase in persistence. The corresponding estimated range for males was SEK 450 and SEK 2,200. The average per-patient NB per percentual unit of increase in persistence (from the actual level) for females and males was estimated at approximately SEK 100 and SEK 50, respectively. The average per-patient NB per extra day of median survival time (see Table 13) was estimated at SEK 15 for females and SEK 10 for males.

5.3.2 Sensitivity Analysis

The results above were based on a societal WTP for a QALY of λ=SEK 600,000. Table 17 contains the simulated total and per-patient NB estimated with λ=SEK 400,000, SEK 800,000 and SEK 1000,000.

Table 17: Sensitivity Analysis: Total and Per-Patient NB (Females and Males Combined)

λ (SEK)	Intervention (Ψ)	$NB_{Total}^{\Psi-Actual}$ (MSEK)	$NB_{Per\text{-}patient}^{\Psi-Actual}$ (SEK)
400,000	+10%	9	569
	+20%	18	1,139
	+30%	26	1,695
	+40%	35	2,282
	+50%	41	2,652
800,000	+10%	19	1,262
	+20%	39	2,526
	+30%	57	3,696
	+40%	78	5,060
	+50%	91	5,924
1000,000	+10%	25	1,608
	+20%	50	3,219
	+30%	72	4,697
	+40%	99	6,449
	+50%	117	7,560

6 Discussion and Conclusion

This was a retrospective register study of actual treatment behaviour in the pharmaceutical management of osteoporosis in Sweden and an assessment of its clinical and monetary implications from a societal perspective. The analyses were performed using patient-level data from three Swedish registers: the National Prescription Register, the National Patient Register, and the Causes of Death Register.

The first objective was to estimate persistence and compliance to treatment of osteoporosis in Sweden. The analysis was performed on all treatment-naïve patients who started treatment with alendronate, risedronate, strontium, or raloxifene between December 1, 2005 and December 31, 2008. In line with results from previous studies, real-world persistence was found to be poor. One in four patients terminated treatment immediately after their index prescription, less than half of the cohort persisted with therapy for more than one year, and only 16% was still on treatment after three years. Females were found to be significantly more persistent to therapy compared to males, although the difference was fairly small.

Compliance to treatment, on the other hand, was found to be close to perfect. Average MPR (for females and males combined) was estimated at 94.67% (95% CI: 0.9461-0.9473). This was noticeably higher compared to findings from preceding research, which lies in the range of 50% and 80%. A possible reason for this variation in results, in addition to actual discrepancies in medication possession, is methodological differences in the quantification of MPR. In the present study, MPR was measured while the patients were still on treatment. Other studies, for example Siris *et al.* [88], have measured MPR across the patients' entire observation time irrespectively of their persistence status, and Cramer and colleagues [17] measured MPR during a fixed time frame. Thus, the estimates are not necessarily comparable.

Neither the estimated persistence nor compliance rates were sensitive to the length of the grace period. The estimated Kaplan-Meier survival function varied with a maximum of ± 5 percentage units when changing the length of the grace period from two months (base case) to one and three months. The estimated average MPR varied with a maximum of ± 2 percentage units following the same variation in grace period. These results, together with the estimated high average MPR, indicates that patients in Sweden generally had few and short gaps (if any) between filled prescriptions and therefore discontinued treatment in relation to their last filled prescription (and not because they had a break in treatment exceeding the grace period).

The analysis of persistence and compliance was based on a population of patients filling prescriptions for four different treatment types. However, it should be noted that actual treatment behaviour may differ substantially among these medications (e.g. because different types of patients are for various reasons prescribed different osteoporosis drugs). The estimated persistence and compliance rates may therefore not be valid for each of the four treatments separately. On the other hand, producing estimates for each specific drug type is not straightforward because a share of all patients (about 5%) switched between the included treatments. Additionally, an unknown share switched between an included osteoporosis treatment to another medication not studied, e.g. from alendronate to HRT. Thus, in a subgroup analysis by treatment type, a switching patient would appear to have terminated treatment when she merely switched to another osteoporosis drug. Separate estimates for each of the four treatments were, for this reason, excluded from the present study. Analyses of switching patterns in Sweden, and the relationship between switching and persistence and compliance, should be two topics of interest for future research.

Moreover, the present study of persistence and compliance was based on a cohort of patients who were supposed to be new to treatment (i.e. treatment-naïve). A washout period, or drug-free period, of five months was used to capture individuals who had not previously been treated with any of the four included osteoporosis medications. The purpose was to avoid analyzing patients who previously had terminated treatment, i.e. to measure persistence in an already

non-persistent population. The washout was set to five months (equal to the base case grace period of two months and a standard three-month prescription) and was not extended due to data limitations (start and end date of the National Prescription Register). However, it may be the case that the five-month washout period was insufficient and that a proportion of the included subjects already had been on treatment. This would imply that persistence was slightly overestimated.

The second objective of the present study was to assess the total societal burden of actual compared to perfect persistence to treatment of osteoporosis in Sweden. The analysis was performed with a microsimulation model and carried out on all treatment-naïve patients who started therapy during 2008. The total burden was evaluated from a societal perspective and measured in terms of discounted lifetime costs and quality-adjusted life-years (QALYs).

As expected, perfect compared to actual persistence was associated with a lower incidence of fractures. With actual persistence to treatment, the studied cohort was estimated to sustain 1,100 additional fractures (hip, vertebral, wrist, and other osteoporotic fractures) the first ten years following treatment initiation, compared with perfect persistence. The estimated higher fracture incidence was related to larger morbidity costs and reduced quantity and quality of life.

In spite of decreased morbidity, the total estimated incremental lifetime cost of perfect compared to actual persistence was positive for the four included treatments. This cost increase was driven by additional drug costs, caused by the fact that perfectly persistent patients fill more prescriptions compared to patients who discontinue treatment prematurely. Thus, the total monetary burden (neglecting the value of health effects) of actual persistence was negative. Conversely, for females who started treatment with alendronate during 2008, perfect persistence was associated with on average lower discounted lifetime costs (i.e. was cost saving). For this patient group, the increased drug cost following perfect persistence was lower than the reduction in costs related to lower morbidity from the additional drug exposure. For males on alendronate, however, the incremental lifetime cost of perfect persistence was positive because of the smaller absolute benefit males receive from the extra drug exposure (due to a lower relative risk of fracture compared to females).

The estimated total discounted lifetime QALYs lost due to actual compared to perfect persistence was estimated at 656 (581 QALYs for the included females and 75 QALYs for the male share of the studied cohort). This is equivalent to 656 life years at full health. The monetary value of this health burden, using societal WTP for a QALY of SEK 600,000, was estimated at MSEK 394.

In total, the societal burden of actual compared to perfect persistence, incorporating both costs and health effects, was estimated at MSEK 368. This constituted about 0.13% of the annual health care expenditure in Sweden during 2007 (latest data available).

It should be emphasized that although the burden evaluation was based on lifetime consequences for the included patients, the studied population was an annual cohort of treatment-naïve individuals. Each subsequent year, a similar patient group will initiate therapy in Sweden, with patient-specific lifetime costs and QALYs depending on, among many factors, persistence to treatment. The estimated burden in the present study can therefore be interpreted as a yearly loss to society. However, 2008 may not necessarily be a representative year in the treatment of osteoporosis in Sweden, especially not in the future. New treatment practices and other changes in the medical management of osteoporosis will naturally affect the total annual clinical and economic consequences of real-world persistence, and perhaps even persistence rates *per se*. Thus, the results from this study should perhaps be rescaled and extrapolated with some caution.

It should also be noted that no currently prescribed treatment of osteoporosis, even in combination with supporting interventions, is likely to induce perfect persistence for large patient groups. The burden assessment in the present study was, in this sense, purely theoretical. Future osteoporosis medications, on the other hand, may be able to enhance treatment behaviour with

extended effect durations. Already available bi-annual and annual infusions, such as zoledronate, would be expected to induce better persistence compared to for example daily or weekly oral bisphosphonates, since patients only have the possibility to discontinue therapy between the infusions. Thus, although perfect persistence at the moment may be an unrealistic comparator in a burden assessment, new pharmaceuticals may be able to reduce the problem of persistence in the future, especially in combination with supporting interventions.

Moreover, it is important to keep in mind that the present burden assessment was based on a five-year treatment duration (a common treatment length in both RCTs as well as in health economic models of osteoporosis). Other durations would have generated different burden assessments. The dynamic offset (where time on treatment was assumed to be closely related to the length of the residual effect) was also of importance for the estimated results. A fixed offset time, frequently used in previous models of osteoporosis, would have reduced the consequence of suboptimal persistence, because patients would receive the same residual drug effect irrespective of drug exposure. Ideally, the actual drug-specific residual effects should have been implemented in the model. However, little research has been conducted in this area and the treatment-specific length, scale, and shape of the residual effect is to date largely unknown. This should be a subject of interest for future research.

In this study, persistence rates were estimated up to three years following treatment initiation (the maximum study period). The burden assessment was based on a five-year treatment duration and an assumption of constant persistence beyond year three. However, a proportion of all patients who were persistent after three years would be expected to discontinue treatment at a later time point (i.e. during year four and five). This would imply that the employed assumption of constant persistence during the last two years of the modelled treatment duration caused the burden assessment to be underestimated (since the difference between perfect and actual persistence was underestimated). The extent of the bias is unknown and updated persistence and burden estimates should be produced when prescription record data for 2009 and 2010 is made available.

The relative risk (RR) of fracture for individuals with osteoporosis compared to the general population was modelled using a method based on, among other factors, BMD (see Appendix B.2). Specifically, age-dependent RRs were derived assuming the WHO diagnostic criterion of osteoporosis (BMD less than or equal to 2.5 standard deviations below the average BMD of a young adult female). However, a proportion of the studied cohort would be expected to have an even lower BMD (following the natural progression of the disease), and as a consequence, a higher RR of fracture. The burden assessment was, for this reason, underestimated.

An important assumption underlying the burden assessment in the present study was that patients do not return to treatment once they have discontinued therapy. Still, a proportion of the included subjects would be expected to temporarily stop to fill their prescriptions. The burden of actual persistence was therefore overestimated (since some patients would have received the drug benefit in later cycles when they re-started therapy). The extent of this patient behaviour (to temporarily discontinue therapy for longer durations) in the treatment of osteoporosis in Sweden is unknown and should be of interest for future research.

The third, and last, objective of this study was to estimate the monetary net benefit (NB) of improved persistence. Five hypothetical interventions were analyzed, with improvement in persistence (the estimated survival function) to the modelled five-year treatment duration of 10%, 20%, ..., 50%.

The estimated per-patient NB of improved persistence was larger for females and for older individuals, following a larger absolute benefit from the additional drug exposure. The study results suggest that it on average would be cost-effective (given a societal WTP for a QALY of SEK 600,000) to allocate between approximately SEK 900 and SEK 4,300 per patient to increase persistence rates depending on the level of improvement (approximately SEK 300 per-patient

per percentual unit of increase in persistence). For females at older ages (75+), the comparable figures were SEK 1,400 and SEK 6,600.

As a comparison to these estimates, a nursing visit in Sweden is priced at SEK 540 and a physician visit at SEK 1,208. Hence, the hypothetical interventions would have to be restricted to a limited number of traditional medical management activities, such as one or two nursing visits per patient and year during the five year treatment duration. There is also the possibility to implement one or several projects at a total fixed cost between MSEK 14 and MSEK 66 (depending on the anticipated persistence increase) and a low per-patient marginal cost. One example of such an intervention would be a cell phone text messaging program, reminding patients on a daily or weekly basis (depending on dosing regimen) to take their medication as prescribed. However, in the light of previous research it seems reasonable to assume that perhaps more extensive and proactive activities are required in order to increase persistence by any non-trivial amount.

Thus, although there is substantial room for improvement, interventions targeting persistence to treatment of osteoporosis are likely to be an inefficient use of health care resources unless substantial improvements are expected and patients at older ages are targeted specifically.

A limitation of the present study concerns censoring for death. In Sweden, the Causes of Death Register contains dates of death, but the data is first made available approximately two years after it is registered (after the death). In the present study, the information was therefore missing for the last two years of the study period (January 1, 2007 through December 1, 2008). Thus, given that the persistence survival estimates were produced for the entire study period (December 1, 2005 through December 31, 2008), it was not possible to censor for death after December 31, 2006. Instead, after that date, death was incorrectly interpreted as a failure (since diseased individuals cannot fill prescriptions and therefore would appear to have discontinued treatment). The estimated persistence rates were, for this reason, underestimated. However, the impact on the overall results was limited since only a small percentage of all patients died during the relevant time frame and only a fraction of those were still on treatment (i.e. persistent).

Another study limitation concerns what is known in the literature as primary non-adherence. It refers to patients who receive a prescription but not collect the drugs at the pharmacy (i.e. never fills the prescription). This aspect of persistence was naturally not included in the study, since the analysis was based on pharmacy records of filled prescriptions, not records of prescriptions from physicians or other health practitioners. Persistence was therefore overestimated, but the extent of the bias is difficult to assess. The scope and implications of the problem of primary non-adherence to treatment of osteoporosis in Sweden remains unknown and the issue should be devoted attention in future research.

To conclude, this study has shown that persistence to treatment is a serious problem in the medical management of osteoporosis in Sweden. Compliance (operationalized as MPR) was found to be close to perfect. The total burden of actual compared to perfect persistence, assessed for all treatment-naïve patients who started therapy during 2008, was estimated at MSEK 368 (WTP for a QALY: SEK 600,000). However, interventions aimed at increasing persistence should be implemented with caution unless specific patient groups are targeted and large improvements in treatment behaviour expected.

A Secondary Causes of Osteoporosis

Secondary osteoporosis is a condition of osteoporosis caused by an underlying disease, disorder, deficiency, or drug. Patients suspected to have secondary caused osteoporosis were excluded from the present study since these patients usually receive a different type of medical management (e.g. multiple osteoporosis medications, extreme doses, *et cetera*). Table 18 below contains the ICD-10 diagnosis codes [106] used to exclude patients suspected to have secondary caused osteoporosis.

Table 18: Secondary Causes of Osteoporosis

Disease/Condition/Disorder	**ICD-10 Code**
Addison's disease	E27.1
Anorexia nervosa	F50.0
Cushing's syndrome	E24.0, E24.2, E24.3, E24.4, E24.8, E24.9
Ehlers-Danlos syndrome	Q79.6
Epilepsy	G40
Hemiparesis	G81.9
Hemochromatosis	E83.1
Homocystinuria	E72.1
Hyperparathyroidism	D35.1, E21.0
Hypothyroidism	E03.9
Kallmann syndrome	E23.0
Klinefelter's syndrome	Q98.0, Q98.1, Q98.2, Q98.3, Q98.4
Liver failure	K72
Renal failure	N17, N18, N19
Malabsorption	K90
Cancer (malignacy)	C, D
Mastocytosis	Q82.2
Paget's disease	M88
Myelom	C90
Osteomalacia	M83
Prolactinoma	D35.2
Rheumatoid arthritis	M05, M06
Turner syndrome	Q96
Hyperthyroidism	E05
Osteoporosis in endocrine disorders	M82.1
Drug-induced osteoporosis	M81.4
Idiopathic osteoporosis	M81.5

Note: All sub-codes were included for the listed ICD-10 codes.

B The Microsimulation Model

B.1 Risk Conversion

The risks that were used in the microsimulation model were specified as annual. The following conversion [107] to six-month risks was used for absorbing states (i.e. *dead*):

$$Risk_{Annual} = 1 - \sqrt{1 - Risk_{Annual}} \tag{8}$$

For non-absorbing states, i.e. all fracture states, risks were converted as follows:

$$Risk_{Annual} = \frac{1}{2} \cdot Risk_{Annual} \tag{9}$$

B.2 Fracture Risk

In the model, the age-differentiated risk of fracture depended on three elements: (i) the fracture risk of an individual in the general population, (ii) the increased fracture risk associated with osteoporosis, and (iii) the risk reduction, if any, attributed to the treatment. Thus, the risk of experiencing a fracture event in the model was defined as:

(general population fracture risk) · (relative fracture risk) · (risk reduction from treatment)

B.2.1 General Population Fracture Risk

The population fracture incidence was taken from Kanis *et al.* [30]. The data was linearly interpolated between available data points and linearly extrapolated to an age of 100 years.

Table 19: Population Fracture Incidence (Rate/10,000)

	Females				Males			
Age	**Hip**	**Vertebral**	**Wrist**	**Other**	**Hip**	**Vertebral**	**Wrist**	**Other**
50	6	16	40	30	9	23	8	39
55	6	16	44	44	9	15	13	80
60	14	25	52	65	8	18	14	75
65	26	38	64	96	18	24	25	108
70	46	64	82	141	26	40	17	133
75	101	98	98	209	50	57	14	132
80	182	114	114	308	116	81	23	309
85	308	145	132	455	162	109	30	470
90	462	193	149	455	179	135	36	534

B.2.2 Relative Fracture Risk

The fracture incidence in the general population was adjusted to reflect the risk in patients with osteoporosis. The relative risk (RR) was derived using a method, described in Kanis *et al.* [29], incorporating data on bone mineral density (BMD) and the prevalence of fractures.

B.2.3 Treatment Efficiency Data

Efficacy data for the four treatments was obtained from meta-analyses conducted for the National Institute for Health and Clinical Excellence (NICE) [108].

Table 20: Treatment Efficacy Data (Relative Risk of Fracture)

	Hip fracture	**CI 95%**	**Vertebral fracture**	**CI 95%**	**Wrist fracture**	**CI 95%**	**Other fractures**	**CI 95%**
alendronate	0.62	0.40-0.98	0.56	0.46-0.67	0.85	0.67-1.09	0.82	0.73-0.93
risedronate	0.74	0.59-0.93	0.58	0.46-0.72	0.68	0.43-1.07	0.80	0.72-0.90
strontium ranelate	0.85	0.61-1.19	0.62	0.55-0.71	-	-	0.86	0.74-0.99
raloxifene	-	-	0.64	0.54-0.78	-	-	-	-

B.3 Treatment Side Effects

Treatment with alendronate and risedronate was assumed to be associated with an increased risk of upper gastrointestinal adverse events (GIAEs) that require a general practitioner (GP) consultation. The rate was assumed to be 23.5 GP consultations per 1,000 patients during the initial treatment month, and 3.5 GP consultations per 1,000 patients during subsequent months. Each GP consultation was assumed to incur a course of H2 receptor antagonists, or equivalent. The utility loss associated with GIAEs was set to 0.91 [109]. The symptoms were assumed to last a full month. The assumptions were similar to those employed by NICE [110].

Raloxifene has been shown to have a significant treatment risk reduction of invasive breast cancer. The positive side effect has sometimes been included in cost-effectiveness analyses of the treatment, but was omitted in the present study because raloxifene is not prescribed for the indication breast cancer in Sweden. The cost-effectiveness of the treatment was therefore underestimated compared to other evaluations. However, the impact from this simplification on the overall study result was limited since negative side effects (i.e. the increased risk of venous thrombosis) associated with raloxifene was also excluded from the analysis and because only 128 patients (0.83% of the total cohort) started treatment with raloxifene during 2008.

No side effects were included for treatment with strontium.

B.4 Mortality

B.4.1 Population Mortality

The age-specific mortality rates for females and males in the general population in Sweden for 2008 were obtained from Statistics Sweden [111].

B.4.2 Mortality Related to Fractures

Age-differentiated mortality after hip and vertebral fractures were derived from Oden *et al.* [112] and Johnell *et al.* [113], respectively. Wrist fracture was assumed not to be associated with any excess mortality in accordance with clinical findings [114, 115].

Data describing the relative risk of death after other osteoporotic fractures have been published by Barrett *et al.* [116] Since all other osteoporotic fractures were combined into a single model health state, a weighted average was produced via the incidence distribution of different types of other osteoporotic fractures in Sweden, obtained from Kanis *et al.* [117]

It was conservatively assumed that 30% of the excess mortality (compared to general population mortality) after hip, vertebral and other fractures were associated with the fracture event [7, 8, 118–120]. Mortality related to fractures was not differentiated by sex [113]. The RR of dying (compared to the general population) after hip, vertebral, wrist, and other osteoporotic fractures is shown in Table 21.

Table 21: Relative Risk of Dying (Compared to the General Population)

Age	Hip (1st year)	Vertebral (1st year)	Hip (2nd year and following)	Wrist	Other
50	13.2	14.9	6.0	9.8	1.22
55	10.4	12.5	4.7	8.2	1.22
60	8.0	10.3	3.7	6.8	1.22
65	5.8	7.9	2.9	5.2	1.22
70	5.3	6.2	2.7	4.1	1.22
75	4.4	4.5	2.2	3.0	1.22
80	3.2	2.9	1.6	1.9	1.22
85	2.4	2.0	1.3	1.3	1.22
90	1.9	1.4	1.0	1.0	1.22

B.5 Cost Data

All costs are in Swedish kronor (SEK), 2008 values.

B.5.1 Unit Costs

Table 22: Unit Costs

Cost item	Unit cost (SEK)	Source
Daily cost of nursing home	1,604	[31]
Cost of a BMD measurement	1,412	[31]
Cost of a physician visit	1,208	[31]
Price of a course of H2-antagonist	40	[58]
Cost of an IV infusion	2,811	[121, 122]
Cost of a nurse visit*	540	[122]

* Average of prices for Sahlgrenska, Akademiska and Stockholm/Gotland region.

B.5.2 Cost of Fractures

Costs of hip, vertebral and wrist fractures were taken from the Swedish KOFOR study [31, 123]. Other fractures consisted of pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures. In terms of fracture related costs, it was assumed that femur and pelvis fractures were equivalent to hip fractures, humerus fractures to be equivalent to vertebral fractures, and fractures to the rib, clavicle, scapula, and sternum to be equivalent to wrist fractures. The costs were weighted to represent the age distribution.

Table 23: Short-Term (First Year After Fracture) Fracture Costs (SEK)

Age	Hip fracture	Vertebral fracture	Wrist fracture	Other fracture
50-54	113,090	17,997	21,097	36,382
55-59	113,090	17,997	21,097	39,207
60-64	116,539	119,886	21,097	46,671
65-69	116,539	119,886	21,097	77,686
70-74	130,080	124,103	21,097	79,626
75-79	130,080	124,103	21,097	75,169
80-84	172,814	124,945	21,097	70,810
85+	172,814	124,945	21,097	76,771

Costs for the second and subsequent years following hip fracture were based on the probability of needing nursing home care after the fracture [124]. Patients residing in a nursing home were assumed to remain there for the rest of their lives. The daily cost of a nursing home is shown in Table 22. Vertebral, wrist, and other osteoporotic fractures were not assumed to be associated with any long-term costs.

B.5.3 Average Annual Drug Cost

The average yearly drug cost for alendronate, risedronate, strontium, and raloxifene was based on all records of filled prescriptions for the cohort of treatment-naïve patients starting treatment during 2008. Price, package size and dose information were taken from FASS [58] and TLV [93]. The distribution of filled prescription for each of the included treatments is shown in Table 24, 25, 26, and 27, below.

Table 24: Filled Prescriptions for alendronate During 2008

ID	Product Name	Price (SEK)	Cost/Year (SEK)	Freq.	Prop.
23026	Alenat Veckotablett	300	1,198	6,884	0.193
51868	Alendronat Mylan Veckotablett	110	438	5,597	0.157
24993	Alendronat ratiopharm Veckotablett	299	1,196	5,521	0.155
25243	Alendronat Teva Veckotablett	46	184	4,889	0.137
143141	Alendronat Sandoz Veckotablett	99	396	2,843	0.080
23015	Alenat Veckotablett	146	1,752	2,170	0.061
24780	Alendronat ratiopharm Veckotablett	118	1,410	1,535	0.043
25232	Alendronat Teva Veckotablett	43	516	1,479	0.041
51859	Alendronat Mylan Veckotablett	79	942	928	0.026
5565	Fosamax Veckotablett	352	1,406	864	0.024
112641	Alendronat Ranbaxy Veckotablett	118	470	769	0.022
112632	Alendronat Ranbaxy Veckotablett	44	522	611	0.017
5507	Fosamax Veckotablett	46	552	464	0.013
372607	Fosamax	337	1,348	254	0.007
143130	Alendronat Sandoz Veckotablett	38	456	242	0.007
23090	Alenat	297	1,186	151	0.004
372623	Fosamax	571	3,426	147	0.004
21236	Alendronat Teva	145	578	103	0.003
372615	Fosamax	762	3,046	102	0.003
37706	Alendronat Mylan	291	1,164	94	0.003
45352	Alendronat Orifarm Veckotablett	67	266	54	0.002
45361	Alendronat Orifarm Veckotablett	88	350	7	0.000
40760	Fosamax Veckotablett	618	2,472	1	0.000

Table 25: Filled Prescriptions for risedronate During 2008

ID	Product Name	Price (SEK)	Cost/Year (SEK)	Freq.	Prop.
10746	Optinate Septimum	792	3,168	3,049	0.484
68823	Optinate Septimum	853	3,412	2,026	0.322
10591	Optinate Septimum	337	4,044	1,077	0.171
52942	Optinate	785	3,138	86	0.014
548784	Optinate	787	3,148	59	0.009
548792	Optinate	2,108	25,290	5	0.001

Table 26: Filled Prescriptions for strontium During 2008

ID	Product Name	Price (SEK)	Cost/Year (SEK)	Freq.	Prop.
20533	Protelos	1,012	4,048	357	0.577
20456	Protelos	369	4,422	262	0.423

Table 27: Filled Prescriptions for raloxifene During 2008

ID	Product Name	Price (SEK)	Cost/Year (SEK)	Freq.	Prop.
480897	Evista	776	3,102	399	0.800
480863	Evista	289	3,468	73	0.146
10987	Evista	280	3,360	20	0.040
11991	Evista	767	3,068	7	0.014

The average annual treatment cost, shown in Table 28 below, was obtained by multiplying each product proportion with the respective cost/year.

Table 28: Average Annual Drug Cost

	alendronate	risedronate	strontium	raloxifene
Average Price/Year (SEK)	860	3,413	4,206	3,165

B.5.4 Cost of Intervention

The standard assumption of the monitoring of osteoporosis therapies has been one yearly physician visit (SEK 1,208/visit) and a bone mineral density measurement (SEK 1,412/measurement) every second year [103, 125–127]. This assumption was incorporated in the model.

B.5.5 Indirect Costs

Indirect costs of osteoporotic fractures were included in the total cost of fractures in this study.

B.5.6 Cost in Added Life Years

Data on cost in added life years was obtained from M. Ekman [128].

Table 29: Difference Between Consumption and Production

Age	Net Consumption
60	-74,969
70	174,912
80	205,285
90	323,943

B.6 Quality of Life

The impact on quality of life the first year after a hip, vertebral and wrist fracture, as well as subsequent years after a hip fracture, was based on a meta-analysis by Peasgood *et al.* [129] The disutility after other osteoporotic fractures were based on expert opinions [130]. Wrist fractures and other osteoporotic fractures were assumed to only affect quality of life during the first year.

The reduction in quality of life during the second and subsequent years following a vertebral fracture was conservatively assumed to be 0.05 [131]. It was equal to a utility multiplier of 0.929 [63]. Population utility values for Sweden was derived from Lundberg *et al.* [132]

Table 30: Utility Multipliers

Time frame/Fracture type	Utility multiplier
First year after fracture	
Hip fracture	0.700
Vertebral fracture	0.590
Wrist fracture	0.956
Other fractures	0.902
Second and subsequent years after fracture	
Hip fracture	0.800
Vertebral fracture	0.929

B.7 Model Validation

B.7.1 Internal Validation

The predicted ten-year fracture incidence in the general population (calculated using general population fracture risks and mortality rates) was compared to the corresponding estimates produced by the microsimulation model. The aim was to validate that the model calculated fracture probabilities and mortality correctly. The results are shown in Table 31.

Table 31: Internal Validation: Predicted Ten-Year Fracture Incidence

	Hip fracture	Vertebral fracture	Wrist fracture	Other fracture
Population prediction	0.067	0.057	0.062	0.013
Model output	0.067	0.057	0.062	0.013

B.7.2 External Validation

The ten-year hip fracture incidence generated by the microsimulation model was compared to the corresponding estimates of the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX) [27, 89]. FRAX produces a ten-year probability of fracture based on numerous patient characteristics, including clinical risk factors, such as smoking. The microsimulation model, on the other hand, generates a ten-year fracture incidence based on the general population. Risks are therefore expected to be higher in the microsimulation model, since a proportion of individuals in the general population have some risk factors. Furthermore, the incidence will also be higher in the microsimulation model because FRAX estimates the probability of the first fracture, while the microsimulation model estimates all fractures, including multiple fractures sustained by a single patient. The risks, shown in Table 32, were derived for a 75 year old female, with a T-score between -1 to -2.5.

Table 32: External Validation: Predicted Ten-Year Fracture Incidence

T-score	Model output	FRAX	FRAX (with one clinical risk factor)
-2.5	0.1589	0.094	0.150
-2	0.9760	0.060	0.980
-1.5	0.0599	0.040	0.065
-1	0.0368	0.026	0.043

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