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# PHARMACOEPIDEMIOLOGY AND HEALTH ECONOMICS OF ADHERENCE TO PHARMACEUTICAL FRACTURE PREVENTION

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# Pharmacoepidemiology and Health Economics of Adherence to Pharmaceutical Fracture Prevention

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# ABSTRACT

**Background:** Osteoporosis is a disease characterized by weak bone, affecting hundreds of millions of people worldwide, predominantly postmenopausal women. The main clinical consequence of the disease is bone fractures and the lifetime risk of any fracture has been estimated at ~55% in Norwegian women. Hip and vertebral fractures are the two most serious fracture types, associated with substantial pain, disability, and even death. Even though there is consensus that patients at high risk of fracture should be treated, there is still a troubling treatment gap that shows few signs of closing. Only 6.6% of untreated patients receive treatment after their first fracture and there are ~225,000 untreated individuals with a bone mineral density indicative of osteoporosis in Sweden. An equally noteworthy aspect of undertreatment is poor adherence (*compliance* and *persistence*) to treatment, i.e. how patients and physicians adhere to dosing instructions and treatment regimens. Many patients stop filling prescriptions at pharmacies prematurely (*refill non-persistence*) and this is a cause for concern with respect to effective fracture prevention. There are also reports that dispensings at pharmacies are too few and far between to provide adequate drug exposure (measured as *refill compliance*). Oral alendronate, a bisphosphonate, constitutes ~80% of all osteoporosis treatments and is generally recommended for 3-5 years. Treating osteoporosis have in most industrialized countries been estimated to be cost-effective (compared with no treatment) but this depends on several factors, such as the risk of the patient population, drug costs, treatment effectiveness, and the treatment alternatives being compared. Treatment adherence is often not factored into such cost-effectiveness analyses.

**Objectives:** This thesis aims at addressing pharmacoepidemiologic and health economic aspects of poor compliance and persistence to osteoporosis treatment by both establishing the extent of the problem and consequences for fracture risk in a Swedish setting, as well as investigating how it can be incorporated into the health economic framework to inform reimbursement decisions and regional priorities for recommended prescription standards.

The topics of health-economic value or treatment persistence are by no means specific to the Swedish setting. Therefore, even though the included publications are based on Swedish data, the background and findings are also often put in an international context, or entirely without reference to geography.

**Methods & papers:** Three of the articles used Swedish register data on pharmacy dispensings, diagnosis codes, and mortality. Repeat dispensings at pharmacies by 57,000 individuals were used to estimate *refill persistence* and *refill compliance* as an approximation of true drug exposure. **Paper I** investigated the proportion of patients starting an osteoporosis treatment that stopped their treatment prematurely

at different time points, as well as the implications on the risk of fracture in groups stratified by refill persistence. **Paper II** addressed how automatic generic substitution (for off-patent medication) influence persistence to treatment of oral bisphosphonates. A natural experiment was devised for the years 2006-2009 where an off-patent medication was compared to an on-patent medication to isolate the effect of generic substitution. The effect on persistence for patients getting their first medication refill substituted at the pharmacy was also investigated. **Paper III**, amended with a new analysis in a larger dataset, investigated the residual effect after treatment with bisphosphonates on fracture risk and explored whether a *healthy adherer effect* (i.e. that patients with an inherently lower fracture risk stay longer on treatment) confounds the association between refill persistence and residual anti-fracture effect. **Paper IV** proposes a health economic simulation model framework for incorporating adherence and studying the important drivers of cost-effectiveness in this context.

**Main conclusions:**

- Refill persistence to typical oral osteoporosis medication estimated from pharmacy dispensing in Sweden is poor, with ~50% stopping treatment within 12 months. Prescription refill gaps among persistent patients appears to be a margnial problem, with 96% of patients having access to >80% of intended doses.
- Poor refill persistence to osteoporosis treatments is associated with an increased fracture risk in an exposure-dependant manner.
- Automatic generic substitution of alendronate tablets at pharmacies was likely causing reduced treatment persistence to treatment during 2006-2009. Patients who had their alendronate product substituted at the first prescription refill had 25% higher risk of stopping their treatment. This topic should be revisited in more recent data and for other therapeutic areas.
- It is likely that treatments shorter than 6 months with oral bishposphonates has little effect on fracture risk.
- Oral bisphophonates taken for at least 12 months may confer a residual effect of 20-35% on the risk of any fracture for up to 5 years after stopping treatment. It is not clear if and how such a residual effect wanes with time after stopping treatment. The health economic implications of residual effect can be considerable, depending on the context.
- There is a statistically significant inverse relationship between time on bisphosphonate treatment and post-treatment fracture risk. This finding supports an assumption that the magnitude of a residual effect depends on the preceding time on treatment with bisphophonates in health-economic evaluations.

- Incorporating treatment adherence into a health economic evaluation in osteoporosis can have a substantial impact, but is context specific. The choice of accounting for or disregarding adherence to treatment may have an impact on both treatment recommendations, priorities, reimbursement, and prices of treatments for osteoporosis.

Poor persistence to osteoporosis treatments causes increased morbidity and mortality. Improving persistence to osteoporosis treatments would confer substantial health benefit for both patients and society. The clinical and health-economic consequences of persistence to osteoporosis treatments should not be disregarded when setting priorities and drug prices.

# LIST OF SCIENTIFIC PAPERS

I. Adherence to treatment of primary osteoporosis and its association to fractures - the Swedish Adherence Register Analysis (SARA). Landfeldt E, Ström O, Robbins S, Borgström F. Osteoporos Int. 2012 Feb;23(2):433-43.

II. The association between automatic generic substitution and treatment persistence with oral bisphosphonates. Ström O, Landfeldt E. Osteoporos Int. 2012 Aug;23(8):2201-9.

III. Residual effect after oral bisphosphonate treatment and healthy adherer effects--the Swedish Adherence Register Analysis (SARA). Ström O, Landfeldt E, Garellick G. Osteoporos Int. 2015 Jan;26(1):315-25.

IV. Incorporating adherence into health economic modelling of osteoporosis. Ström O, Borgström F, Kanis JA, Jönsson B. Osteoporos Int. 2009 Jan;20(1):23-34.

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AIC | Akaike Information Criterion |
| ARR | Absolute Risk Reduction |
| ATC | Anatomical Therapeutic Chemical classification system |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| CEA | Cost-Effectiveness Analysis |
| CUA | Cost-Utility Analysis |
| DDD | Defined Daily Doses |
| DXA | Dual X-ray Absorptiometry |
| FOB | Fraction Of Benefit |
| GSE | Generis Substitution Event |
| HR | Hazard Ratio |
| HRQOL | Health Related Quality Of Life |
| HRT | Hormone Replacement Therapy |
| HTA | Health Technology Assessment |
| HUI | Health Utility Index |
| ICD-10 | International Classification of Diseases - 10th revision |
| ICER | Incremental Cost-effectiveness Ratio |
| IOF | International Osteoporosis Foundation |
| LS | Lumbar Spine |
| MPA | Swedish Medical Products Agency |
| MPR | Medication Possession Ratio |
| NHANES | National Health And Nutrition Examination Survey |
| NPR | National Patient Register |
| OBPs | Oral Bisphosphonates |
| PDC | Proportion of Days Covered |
| PDR | Prescribed Drugs Register |
| PPIs | Proton Pump Inhibitors |
| PTH | Parathyroid Hormone |
| QALY | Quality Adjusted Life Year |
| RCT | Randomized Controlled Trial |
| RR | Relative Risk |
| RRR | Relative Risk Reduction |
| SARA | Swedish Adherence Register Analysis |
| SMR | Standardized Mortality Ratio |
| TH | Total Hip |
| TLV | Dental and pharmaceutical benefits agency |
| VDE | Variable Dependent Elasticity |
| WHO | World Health Organization |

# 1 INTRODUCTION

Osteoporosis, literally “porous bone”, is a disease characterized by weak bone. It is a major public health problem, affecting hundreds of millions of people worldwide, predominantly postmenopausal women. The main clinical consequence of the disease is bone fractures. It has been estimated in Norwegian data that 55% of women and 25% of men over the age of fifty will sustain an osteoporotic fracture in their lifetime [1]. Approximately 70,000 fragility fractures occur every year in Sweden [2]. Hip and spine fractures are the two most serious fracture types, associated with substantial pain and suffering, disability, and even death. As a result, osteoporosis imposes a significant burden on both the individual and society. During the past two decades, a range of effective medications has become available for the treatment and prevention of osteoporosis. The aim of pharmacological therapy is to reduce the risk of osteoporotic fractures.

The diagnostic definitions of osteoporosis have historically been based on low Bone Mineral Density (BMD) and the presence of fractures, which both are risk factors associated with increased fracture risk. A commonly used threshold is that a BMD 2.5 standard deviations below that of a young healthy individual indicates osteoporosis and the added presence of a previous fragility fracture indicates established osteoporosis. There are several other known risk factors, such as age, sex, fall risk, use of glucocorticoids, type of previous fracture, parental fracture history, smoking, alcohol consumption, comorbidity, and BMI that influence risk assessment and treatment decisions. [3]

A majority of the most influential risk factors are associated with the individual’s age, which may be one of the reasons why the disease suffers from a highly problematic undertreatment. In a Swedish context, ~8.5% of untreated women and 2.3% of untreated men are treated within a year after a fragility fracture [4], and about 30% of all women 70-79 years have a BMD indicating osteoporosis. ~15% of women 75-85 years old have been estimated to have a previously diagnosed hip or vertebral fracture [5].

An equally noteworthy aspect of undertreatment is poor persistence with treatment. ~50% of oral treatments are discontinued within 12 months [6] even though treatment often is recommended for at least 3-5 years. injections or infusions with longer dosing intervals (annually or every 6 months) appear to be associated with higher levels of persistence. Generic alendronate tablets, the mainstay treatment, is affordable (<500 SEK/year) and cost-effective compared with no treatment, but its clinical utility is likely diminished by poor treatment persistence. It is therefore of relevance to consider how more costly treatment options with a possibly better

persistence profile should be regarded, not only with respect to efficacy derived from clinical trials, but also considering that treatments likely will be longer.

In its 2003 report on medication adherence in general, the World Health Organization (WHO) quoted the statement by Haynes et al that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Poor adherence to medication leads to increased morbidity and death and has been reported to incur costs of approximately $100 billion per year in only in the United States [7].

This thesis aims at addressing pharmacoepidemiologic and health economic aspects of poor persistence to osteoporosis treatment by both establishing the extent of the problem as well as investigating how it can be incorporated into the health economic framework that commonly is used to inform reimbursement of new treatments as well as regional priorities for recommended prescription standards.

The topics of health-economic value or treatment persistence are by no means specific to the Swedish setting. Therefore, even though the included publications are based on Swedish data, the background and findings are also often put in an international context, or entirely without reference to geography.

# 2 BACKROUND

## 2.1 Osteoporosis

### 2.1.1 Brief historical outlook

In the 1830s the French pathologist Jean Georges Chretien Frederic Martin Lobstein noticed that some patients' bones were riddled with larger than normal holes, and he coined the term osteoporosis (porous bone) to describe such deteriorated human bone. Somewhere around 1940 postmenopausal osteoporosis was defined in the US and hospitals began treating women with the condition with estrogen. In the 1960s Herbert Fleisch discovered compounds known as bisphosphonates that inhibit bone resorption. However, the seriousness of the condition was not well recognized or acknowledged. In 1984, the National Institutes of Health publicized this disease, citing it as a significant threat to health and emphasizing that bone loss could be reduced by estrogen therapy, calcium, good nutrition and exercise. Such acknowledgements and inventions led to that the bisphosphonates alendronate and risedronate were launched as anti-osteoporosis drugs. [8]

Although the disease has been documented for many years, osteoporosis and the associated fractures have often been viewed as inevitable consequences of aging. The description of osteoporosis that is now widely accepted was formulated less than 20 years ago. The World Health Organization (WHO) published a report in 1994 that provided diagnostic criteria for osteoporosis based on the measurement of bone mineral density (BMD) and recognized osteoporosis as an established and well-defined disease that affected more than 75 million people in the United States, Europe and Japan [9].

### 2.1.2 Pathophysiology

Osteoporosis is a chronic condition typically found in older adults and is caused by an imbalance of bone resorption in excess of bone formation. This bone remodeling typically increases approximately two-fold in women after menopause, and in the 5 to 7 years surrounding menopause, women lose approximately 12% of their bone mass. In this process the repairing of microdamage is slowed and calcium content is released from the estrogen-deprived bone into the blood stream [10].

Osteoporosis in men is most commonly due to secondary disorders or causes, with use of glucocorticoids being the most common reason for secondary osteoporosis. Male primary Osteoporosis also exists, primarily in older men. The traditional view has been that testosterone is the primary sex hormone regulating bone metabolism in males, but during the last two decades it has been proposed that estrogen deficiency in either sex is the primary precipitant of primary osteoporosis. [11]

### 2.1.3 The measurements and definitions of osteoporosis

*2.1.3.1 BMD*

Low bone mass is an important component of the risk of fracture and the measurement of bone mineral density has thus come to form the cornerstone of diagnosis, as well as risk fracture prediction, treatment choice and monitoring of a patient's treatment [12].

Bone mineral density (BMD) is the amount of bone mass per unit volume (volumetric density, g/cm3), or per unit area (areal density, g/cm2), and both can be measured by densitometric techniques. A large variety of techniques is available but the most widely used technique is dual-energy x-ray absorptiometry (DXA), which measures the areal density. The absorption of x-rays is sensitive to the calcium content of tissue, of which bone is the most important source. DXA can be used to assess bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fracture [13]. Commonly measured sites are the lumbar spine, femoral neck, and total hip.

The use of DXA is further supported by the strong association between low BMD and increased fracture risk. A meta-analysis by Marshall and colleagues [14] reported a relative risk of hip fracture of 2.6 for each standard deviation decrease in BMD at the femoral neck. Strong associations between BMD and risk are also present for many of the other skeletal sites (Table 1). It is generally the case that the BMD at a particular site better explains fracture risk at the same site. For example, a standard deviation lower BMD at the lumbar spine is associated with a 2.3-fold increase in the risk vertebral fractures, whereas the risk of a forearm fracture (distal radius) only is increased by a factor 1.7.

**Table 1.** Relative risk (RR) of fracture per standard deviation (SD) in BMD (adapted from Marshall et al. [14])

| Site of measurement | Outcome fracture | | | |
|---|---|---|---|---|
| | **Forearm** | **Hip** | **Spine** | **All fractures** |
| **Distal Radius** | 1.7 | 1.8 | 1.7 | 1.4 |
| **Femoral neck** | 1.4 | 2.6 | 1.8 | 1.6 |
| **Lumbar spine** | 1.5 | 1.6 | 2.3 | 1.5 |

#### *2.1.3.2 T-score and Z-score*

Per the WHO's recommendation, the measured BMD is related to the BMD of a young healthy woman (25-30 years) and the T-score is calculated as the number of standard deviations from the reference population. For example, an individual with a lumbar spine (LS) BMD one standard deviation below that of healthy young woman will have a LS T-score of -1.0 SD. The Z-score is calculated in a similar fashion but where an age matched population is used for reference. Thus, if the example individual with a LS T-score of – 1.0 SD is 75 years old, the corresponding Z-score will instead be positive, because her BMD will be higher than the mean LS BMD among 75-year old women in the general population.

### 2.1.4 Diagnosing osteoporosis

In 1994, the WHO published diagnostic criteria for osteoporosis in postmenopausal women based on the T-score, intended primarily for descriptive epidemiology (Table 2) [9]. These criteria are still widely used, often in combination with other risk factors, to define diagnosis and guide treatment decisions. The term "severe osteoporosis" is commonly also referred to as "established osteoporosis".

**Table 2** Diagnostic thresholds based on BMD and fracture (adapted from WHO report [9]

| Diagnosis | BMD T-score (SD) |
|---|---|
| *Normal* | ≥ -1.0 |
| *Low bone mass (osteopenia)* | < -1.0 but > -2.5 |
| *Osteoporosis* | ≤ -2.5 |
| *Severe Osteoporosis* | ≤ -2.5 + one or more fragility fractures |

These thresholds were developed for BMD at the spine, hip and forearm. It has been suggested that the femoral neck should be the standard measurement site due to its high predictive value for hip fracture [15], whereas in Swedish clinical practice the lowest BMD T-score measured at the spine, total hip, or femoral neck is typically considered. Approximately 21% of all women 50-84 years, and around 50% in women older than 80 years, have a T-score indicating osteoporosis if the refence ranges at the femoral neck is used [16] (Table 3) The commonly used reference BMD and SD are derived from the US NHANES III data [17]. There are local reference data available for several countries (France, Germany, UK, Sweden etc.) which would yield slightly different T-scores. Local differences are relatively small and NHANES III reference data can therefore be used for consistency [5].

**Table 3.** Prevalence of osteoporosis estimated in year 2000 for Sweden , reference ranges at the femoral neck (adapted from Kanis et al [16])

| | Men | | Women | |
|---|---|---|---|---|
| Age (years) | % of population | Number (000) | % of population | Number (000) |
| 50-54 | 2.5 | 7 | 6.3 | 17 |
| 55-59 | 3.5 | 7.6 | 9.6 | 21.1 |
| 60-64 | 5.8 | 11.4 | 14.3 | 30 |
| 65-69 | 7.4 | 14.2 | 20.2 | 43.7 |
| 70-74 | 7.8 | 14.6 | 27.9 | 63 |
| 75-79 | 10.3 | 13.7 | 37.5 | 68.3 |
| 80-84 | 16.6 | 14.7 | 47.2 | 67.8 |
| 50-84 | 6.3 | 83.2 | 21.2 | 310.9 |

### 2.1.5 Fracture risk assessment and the incorporation of additional risk factors

Even though the formal diagnosis of osteoporosis is based on T-score and the existence of prior fractures it should be noted that it is the estimated fracture risk that to a large extent will guide treatment decisions and disease management. A low BMD is associated with a relative risk of fracture of approximately 1.5-3.0 per standard deviation but there are several other risk factors that independently are also associated with the risk of fracture. A patient with a relatively benign BMD not consistent with osteoporosis can thus still be at higher risk of fracture than a patient with confirmed osteoporosis. An interesting note in this context is that the ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke, but significantly better than serum cholesterol to predict myocardial infarction [9].

Most notable of these other risk factors is age, which has a strong impact on fracture risk that is independent from that of BMD and prior fracture [18]. Johnell et al. [19] exemplified this relationship clearly by estimating the 10-year probability of hip fracture at given T-score values. For example, a 50-year old woman with a T-score of -2.0 SD has a 10-year probability of hip fracture of 1%, whereas an 80-year old woman with the same T-score has a probability of 10%. Even though two thirds of all fragility fractures occur in women, the risk at a given age and T-score is similar in women and men, indicating that sex should be regarded more as an important cause of low BMD than an independent risk factor.

Other clinical risk factors to be considered in risk assessment are [3, 20]:

- Low body mass index
- Parental history of hip fracture
- History of fragility fracture
- Glucocorticoid treatment
- Current smoking
- Alcohol intake 3 or more units daily
- Rheumatoid arthritis
- Other secondary causes of osteoporosis
    - Untreated hypogonadism in men and women, e.g. premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism
    - Inflammatory bowel disease, e.g., Crohn's disease and ulcerative colitis.
    - Prolonged immobility
    - Organ transplantation
    - Type I diabetes
    - Thyroid disorders
    - Chronic obstructive pulmonary disease
    - Use of proton pump inhibitors

#### *2.1.5.1 FRAX – A tool for fracture risk assessment*

Along with age, sex, and femoral neck BMD, a number of these risk factors have been included in an algorithm (FRAX) estimating the 10-year probabilities of major osteoporotic fracture (hip, vertebral, wrist, and humerus) and hip fracture. The FRAX models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. [21, 22]

An advantage of the FRAX tool is that it combines several risk factors into one single metric that can be used to support treatment decisions and recommendations. Because the algorithms can provide fracture probabilities both with and without adding information about the patient's BMD, the tool can also be used for simple screening in primary care, which is the setting where it may be most useful. This

to support the decision of whether a BMD measurement (DXA) is warranted, or if the patient should be treated directly, or reassured that no further action is necessary. Other advantages of the algorithm include easily determined risk factors, global validation, application in specific regions or nations, and scores that pertain to both men and women. FRAX estimates the 10-year probability for men and women aged 40 years and older; however, it does not provide recommendations for how to use that information.

Consequently, several countries have incorporated FRAX in treatment guidelines to provide recommendations for how the risk estimates should inform treatment decisions. The Swedish guidelines have also incorporated the FRAX score, but still in combination with T-score and the presence of an existing fracture.

### 2.1.6 Defining an osteoporotic fracture

Fractures are the main clinical symptom of osteoporosis, but the definition of an osteoporotic fracture is not distinct. Opinions differ regarding the exclusion of different sites of fracture both in epidemiological studies, clinical trials, and health economic analyses. A common definition is to consider fractures from low energy trauma as being osteoporotic, or fragility fractures. “Low energy” is often described as being equivalent to fall from a standing height or less, or trauma that in a healthy individual would not give rise to fracture [23]. This implies that a majority of hip and forearm fractures are fragility fractures. At the age of 50 years, approximately 75% of people hospitalized for vertebral fractures have fractures that are attributable to low energy injuries, increasing to 100% by the age of 90 years [24]. A lack of increasing incidence with age or low BMD would indicate that a fracture type is unlikely to be osteoporosis related. Examples of this are fractures to the face, skull, fingers, hands, feet and ankles, of which many therefore often are disregarded in clinical trials and epidemiological studies [25].

Using appropriate definitions of fragility fractures is important to correctly estimate relative risks in clinical trials, avoid introducing statistical noise in the estimation of risk factures, characterizing the burden of disease, and estimating the health economic value of providing fracture preventing interventions.

### 2.1.7 Health consequences of fractures

#### *2.1.7.1 Health related quality of life (HRQOL)*

Loss of HRQOL can be a result of fracture consequences in several health domains, such as pain with loss of physical functioning as well as social and mental consequences. It is considered to be a subjective assessment of the impact of the fracture. HRQOL can measured both with disease specific instruments and with generic instruments, which are designed to be applicable across a wide range of

populations. Disease specific instruments in osteoporosis include Quality of Life Questionnaire (QUALEFFO-41), questionnaire QoL in Osteoporosis (QUALIOST), osteoporosis assessment questionnaire (OPAQ), osteoporosis QoL questionnaire (OQLQ), osteoporosis functional disability questionnaire (OFDQ), and osteoporosis-targeted QoL questionnaire (OPTQoL). [26]

The advantage of disease specific instruments is that they are designed for a specific population and thereby can be more sensitive for detecting differences between groups or subtle effects of a specific condition. A disadvantage is that the results not easily can be compared to other populations or other diseases [26].

Short form 36 questionnaire (SF-36) and the Euroqol five item questionnaire (EQ-5D) are two of the most popular generic instruments for studying quality of life in patients with musculoskeletal disorders.

#### *2.1.7.2 HRQOL estimated as quality weights and QALYs*

If data describing HRQOL are captured using instruments or tariffs based in utility theory, such as EQ-5D, or Health Utility Index (HUI), a quality weight can be derived. EQ-5D is available in versions with three (EQ-5D-3L) and five levels (EQ-5D-5L) of each of five dimensions of quality of life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and there is an increasing number of valuation tariffs for translating the results into quality weights [27]. EQ-5D-3L combined with the Dolan tariff [28] has most commonly been used in osteoporosis. A quality weight is based on the respondents' choices balancing preferences for length of life (Time-trade-off (TTO)), or risk of death (Standard Gamble) on one side, and a hypothetical or experienced health state on the other side. For example, using TTO Dolan et al. [28] asked respondents recruited from the UK general population to consider hypothetical health states as defined in EQ-5D-3L. The respondents provided the length of time (years) in a state of full health that they regarded as equivalent to 10 years in each described target state. Negative values were estimated if a health state was deemed worse than being dead by the respondent. The collected responses were then analyzed in a regression model to attach quality weights that balances length of life and quality of life to each possible health state in EQ-5D-3L.

Such quality weights can be used to estimate quality adjusted life-years (QALY's), which often are used in cost-effectiveness analysis. A QALY is equivalent to a year of life at full health (weight=1.0) or several years with a reduced health, where the number of years depend on the quality weight of the health state of interest. The main advantage of the QALY is that it can be compared between groups and diseases, irrespective of whether mortality or reduced HRQOL is the consequence of the condition.

The quality weight multipliers during the first year after hip, clinical vertebral and forearm fracture relative to the pre-fracture level has been estimated at 0.70, 0.59 and 0.96, respectively [29]. The health effects of major fractures likely extend beyond the first year after fracture. For example, hip [30] and vertebral [31] fractures have been shown to confer long-lasting impact on HRQOL.

#### *2.1.7.3 Mortality*

Post-fracture mortality has been reported to be higher than for non-fractured controls or age and sex-matched mortality in the general population [32]. Mortality is generally increased for all ages and for all fractures, except for minor fractures. Absolute post-fracture mortality increases with age. But relative to the age and sex-matched general population or matched controls it decreases with increased age and time from the fracture. Standardized Mortality Ratios (SMRs) in women were reported by Bliuc et al. [32] in the range of 2.0-3.0 and 1.5-2.5 after hip and vertebral fractures, respectively. It is however not entirely clear how much of the excess mortality after a fracture that can be attributed to the fracture itself, rather than to comorbidity or other unobserved confounders [33, 34]. A relatively common assumption in health economic modeling of osteoporosis treatments is that 30% of the excess mortality is caused by the fracture itself [35-38] whereas others have computed absolute attributable mortality in different age groups [39].

### 2.1.8 Societal burden of disease

It is often reported that approximately 70,000 fragility fractures occur each year in Sweden [2], and this number is closer to 110,000 if a broader spectrum of fracture types is considered [5]. There are several studies addressing the burden of disease, both in terms health and costs. The most comprehensive literature-based summaries and models from a European perspective [5, 40] reports annual monetary costs in Sweden of €1.4 billion and €37 billion if the EU27 countries are considered. Incident fractures represented 66% of this cost, long-term fracture costs 29%, and pharmacological prevention 5%. About 70% of the total costs were incurred in individuals older than 74 years. Hip fractures were estimated to account for 54% of the costs, other fractures 40%, vertebral fractures 5%, and wrist fractures only 1%. The annual number of QALYs lost ranged from about 250,000 in Germany to 39,000 in Sweden, with a total of 1.2 million for the EU27.

The estimated cost of osteoporosis and fractures (€37 billion) may be compared to the cost of other diseases. From a European perspective annual costs have been estimated at €105 billion for dementia, €43.5 billion for headache, €14.6 billion for multiple sclerosis, and €13.9 billion for Parkinson's disease. The cost of coronary heart disease and cerebrovascular disease in the European Union (25 countries) has been estimated at approximately €45 billion and €34 billion, respectively

[40]. The societal burden of disease per capita in both Sweden and Europe can be expected to increase over time, mainly due to demographic changes with a growing elderly population.

### 2.1.9 Treatments for osteoporosis

There are both pharmacological and non-pharmacological interventions for the treatment of osteoporosis and prevention of fractures. Nonpharmacologic interventions include calcium and vitamin D supplementation, weight-bearing exercise, muscle strengthening, and fall prevention [41]. Some randomized trials have shown that wearing hip protectors can reduce hip fracture risk, particularly in the elderly living in nursing homes. A meta-analysis of well-conducted randomized controlled trials has, however, cast some doubt about the anti-fracture efficacy of this intervention [42, 43].

The major pharmacological interventions used in Sweden are the bisphosphonates (alendronate, risedronate, and zoledronate), denosumab, and parathyroid hormone. All of these are approved both for the treatment of osteoporosis and for preventive treatment of increased risk of fracture from use of glucocorticoids. Treatments should be given in combination with calcium and vitamin-D, which also is the standard in RCTs. The available range and relative use of treatments is roughly similar in Europe and the US, with alendronate weekly tablets being the most commonly prescribed drug. In 2018, alendronate accounted for 70-80% of prescribed DDDs in Sweden, followed by Denosumab (~8-10%), a 6 monthly subcutaneous injection, which have been increasingly used since its launch in 2010. Zoledronate (12-month intravenous infusion) is also frequently used but is increasingly sold over the hospital channel, which precludes the study of its market shares in publicly available data. Table 4 shows the different treatments introduced in Europe going back to 1980.

**Table 4.** Year of EMA approval for osteoporosis treatments.

| Treatment | Year |
|---|---|
| ***Bisphosphonates*** | |
| Alendronate | 1995 |
| Etidronate | 1980 |
| Ibandronate | 2005 |
| Risedronate | 2000 |
| Zoledronate | 2005 |
| ***SERMs*** | |
| Raloxifene | 1998 |
| ***Parathyroid hormones*** | |
| Teriparatide | 2003 |
| PTH (1-84) | 2006 |
| ***Strontium Ranelate*** | 2004 |
| ***Antibodies*** | |
| Denosumab | 2010 |
| Romosozumab | 2019 |

The effectiveness (within drug) of the available compounds varies across studies, which likely can be attributed to differences in the studied populations and normal statistical variation. Several meta-analyses comparing treatments to each other and to placebo has been published [44-47]. Results vary depending on the selection of RCTs for inclusion and types of meta-analytical methods used, but the general impression is that bisphosphonates reduce the risk of vertebral fractures by ~50-60 % and non-vertebral fractures by ~20-30% when compared to placebo + calcium and vitamin-D. The injectable non-bisphosphonates (denosumab, teriparatide, Romosozumab) may be even more effective, particularly for vertebral fractures (RRR 70-75%), but possibly also for hip and non-vertebral fractures [48].

#### *2.1.9.1 Generic medicines in osteoporosis*

A generic drug is a medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics. However, a generic medicine's inactive ingredients, name, appearance and packaging can be different. A company can only develop a generic medicine for marketing once the period of exclusivity on the reference medicine has expired. This is usually 10 years from the date of first authorization [49].

The reduction in upfront research costs and market competition brings that generic medicines are typically sold at substantially lower costs. Generic alternatives to brand alendronate (Fosamax™) entered the Swedish market in 2006. This brought price reductions from ~€400/year to ~€225/year in 2007 and the price of generic alendronate had reached ~€25/year in 2011. The period of market exclusivity for branded risedronate ended later but the price is currently also ~€25/year.

The Swedish system uses automatic generic substitution where the pharmacist is obliged to substitute the prescribed medication with the cheapest available alternative. The patient can choose to pay the difference if she wishes to instead receive the prescribed product. The potential downsides of generic substitution will not be extensively covered here but include confusion with changing product names, pill shape, and packaging [50], patient perceptions of inferior effectiveness [51], and physician skepticism [52].

### 2.1.10 Who should be treated according to guideline thresholds?

Who should be treated for osteoporosis is a question that is continuously revisited and reassessed by both the scientific community and treatment guideline groups, representing health authorities and osteoporosis societies. There is a robust consensus that patients at high risk of fracture should be treated but the approaches for defining and assessing the intervention thresholds varies. Thresholds are generally based on prior fracture status, BMD T-score at the hip or spine, 10-year FRAX probability of hip or major osteoporotic fracture, and/or combinations of the individual risk factors described previously (section 2.1.5).

The Swedish guidelines were released in 2012, with a preliminary version in 2010. The national guidelines compile the best available evidence and are intended to be used in the development of regional guidelines. An update is currently underway, with planned release in 2020. The guidelines advocate treatment without information on BMD in presence of a fragility fracture at the hip or vertebrae. For patients with other fracture types, a T score < -2.0 SD and a FRAX-probability of major fracture >15% is required. Patients without prior fractures should have a T-score < -2.5 SD and a FRAX-probability >20% to be considered for treatment.

The Swedish national guidelines can be perceived as convoluted, which possibly could lead to that locally developed guidelines may differ more across the country than ideal. Nevertheless, if the typical risk factors are considered it should be noted that approximately 460,000 individuals have been estimated to have a BMD femoral neck T-score <-2.5 SD [53], approximately 70,000 fragility fractures occur every year , and ~250,000 women and ~30,000 men have been estimated to have a 10-year FRAX-probability of major osteoporotic fracture >30 % [5].

The International Osteoporosis Foundation (IOF) has issued a general guidance [54] recommending that "Women aged over 65 years with a prior fragility fracture can be considered for treatment without the need for further assessment; BMD measurement may be felt more appropriate in younger postmenopausal women" and also advocated treatment "at a FRAX probability equivalent to that associated with a prevalent fragility fracture". The later recommendation is thus implicitly aligned with the traditional view of the fracture as an important risk factor that confers an absolute risk of fracture that increases with the patient's age. This could be contrasted to the Swedish guidelines' FRAX and T-score thresholds that are kept constant and separate from the patient's age.

It is safe to say that both international recommendations and the Swedish national guidelines allow treatment for a large number of individuals, but the translation to regional treatment recommendations, and lastly implementation into clinical practice, may require additional tools and reforms.

### 2.1.11 Undertreatment in Sweden

Even though there is a wide range of treatments available and a robust consensus that patients at high risk of fracture should be treated, there is still a troubling treatment gap that shows few signs of closing. The most commonly cited indicator has been the proportion treated 6-12 months or 0-12 months after a first fragility fracture". This indicator has not been reported since 2014 but has historically been estimated in the range of 12-15% during the last decade. This indicator also includes patients that may have been on treatment before the fracture. The guidelines provide a target a level of 30% for the indicator. A more recent study by Spångeus and colleagues [4] of only untreated patients, using otherwise largely similar definitions, provides a more granular picture. 6.6% of patients received treatment after their first fracture. There was however a clear difference between fracture types with estimates of 5.2% after hip fracture, 5.8% after non-hip-non-vertebral fractures, and 21.2% after clinical vertebral fracture. The discrepancy between treatment after hip and vertebral fracture provides a stark contrast to the national guidelines, which recommends treatment, even without information of BMD, after both fracture types. There is also clear variability between health care regions in the treatment provision on the population level. Figure 1 shows the number of patients/1,000 inhabitants (70-79 years) that filled at least one prescription for alendronate during 2019.

If a broader perspective is adopted, where penetration of osteoporosis treatment is put in relationship to the population at high risk, rather than just post-fracture treatment, an even more disheartening picture is painted. Jonsson et al. [53] estimated a "treatment gap" of 59-64% in women,

depending on age, when the number of individuals with a BMD T-score <-2.5 SD was put in relation to the number of individuals filling prescriptions for osteoporosis medication at Swedish pharmacies. Corresponding estimates for men were 74-81%, indicating an even worse treatment provision in relation to the group level risk. In total ~225,000 untreated individuals with a BMD indicative of osteoporosis. The same study also assessed medication use in relation to the intervention threshold recommended by IOF of a FRAX probability equivalent to that of woman with a prior fracture and unknown BMD. Using the FRAX based threshold resulted in larger treatment gaps for the population 50-64 years (80% and 67% for women and men) and smaller treatment gaps for the population 65-79 years (50% and 23% for women and men). The approach based on absolute FRAX probability does not equally favor treatment in men when compared to the analysis based on BMD T-score.

Undertreatment in Sweden is considerable when adopting any of the commonly used definitions of high risk of fracture. However, other factors such as cost-effectiveness of available treatments, unmet need, priority relative to other diseases, and investment needed to find the patients at high risk must also be considered when assessing this issue.

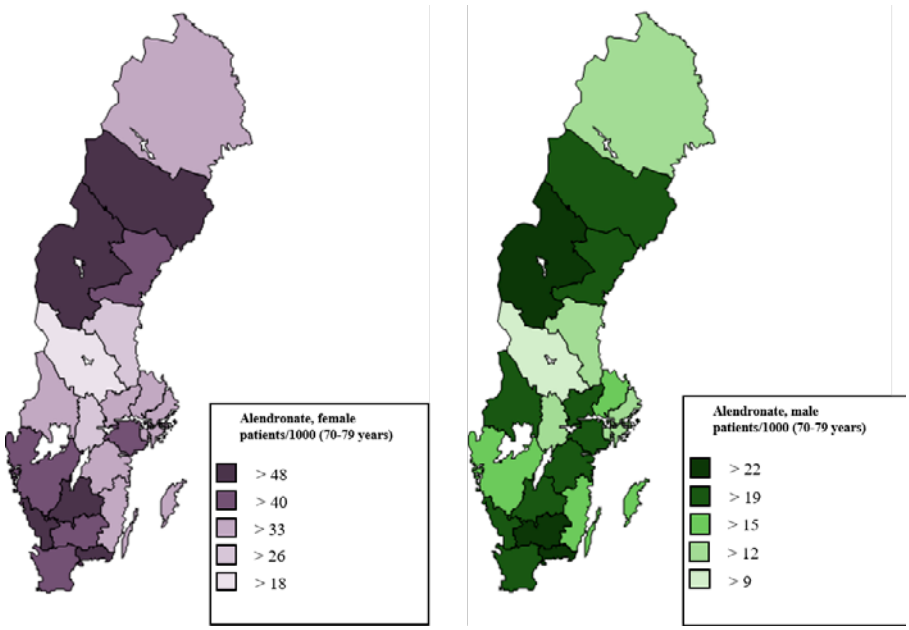


**Figure 1.** Patients/1000 inh. (70-79 years) filling at least one prescription of alendronate during 2019 [55]

## 2.2 Treatment compliance and persistence

Equally important to starting treatment in patients at high risk of fracture is to ensure that patients take the medication as prescribed and recommended. That the health care system and patients are failing to do so can be viewed as an additional component to be added to the undertreatment situation described above.

### 2.2.1 Terminology

There is a wide variety of terminology for drug taking behavior in the literature. The term compliance is widely used, but it has been argued that the term implies "obedience to doctors" and that it should be termed in a way that also includes the active choice of the patient [56]. In line with this view, a number of alternative terms have been proposed: adherence, patient cooperation, therapeutic alliance, or concordance, referring to the agreement between patient and physician.

In this thesis and it's included publications terms "compliance" and "persistence" were used to define the following of dosing instructions and the time on treatment, respectively. The term "adherence" is also often used in the literature to describe different permutations of compliance and persistence but is henceforth used as a general umbrella term for all these concepts. The prefix *refill* is added when explicitly referring to data based on prescriptions or pharmacy dispensing.

### 2.2.2 Measuring adherence

The methods available for measuring medication taking behaviour can be broken down into direct and indirect methods of measurement. Each method has advantages and disadvantages, and no method is considered the gold standard [57]. Examples of direct methods of measures of adherence include directly observed therapy, measurement of concentrations of a drug or its metabolite in blood or urine, and detection or measurement in blood of a biological marker added to the drug formulation. Indirect methods of measurement include asking the patient how easy it was to take the prescribed medication, performing pill counts, ascertaining rates of refilling prescriptions, collecting patient questionnaires, using medication event monitoring systems or asking the patient to keep a medication diary. A commonly used methodology is to study medication taking behavior in registers and claims databases where large samples based on prescriptions or pharmacy dispensings efficiently can be identified. Such databases are often used to produce two types of estimates:

1. Refill persistence, defined as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g., 30, 60, or 90 days).

2. Refill compliance, defined as *medication possession ratio* (MPR) or *propotion of days covered* (PDC). MPR is usually calculated as the number of days of medication available to the patient, divided by the number of days of observation. MPR could in theory > 100% but is often capped at 100%. PDC is instead defined as the proportion of the days of observation during which the patient has medication available, and cannot be estimated > 100%.

These definitions and terminology are in close agreement with those proposed by Cramer et al. [58] with the exception that they instead proposed that *adherence* should synonymous with *compliance*, whereas it in this thesis is used as a general term encompassing both compliance and persistence.

### 2.2.3 Refill persistence

With the support of sufficient computational power and digitalized databases, studies of persistence and compliance to osteoporosis medication based on refill patterns started to appear during the first decade of the 21st century [59]. A number of studies using such data have been published since then, using data from different countries, varying methods, and definitions. The most complete and recent review of the literature by Karlsson et al. [60] identified 40 studies reporting the proportion still on treatment at 12 or 24 months after oral bisphosphonate treatment start (Figure 2) . Pooled estimates were estimated at 45% and 30% after 12 and 24 months respectively. Refill persistence was clearly higher with weekly dosing compared to daily but there was considerable heterogeneity in the results, possibly due to methodological differences between studies.

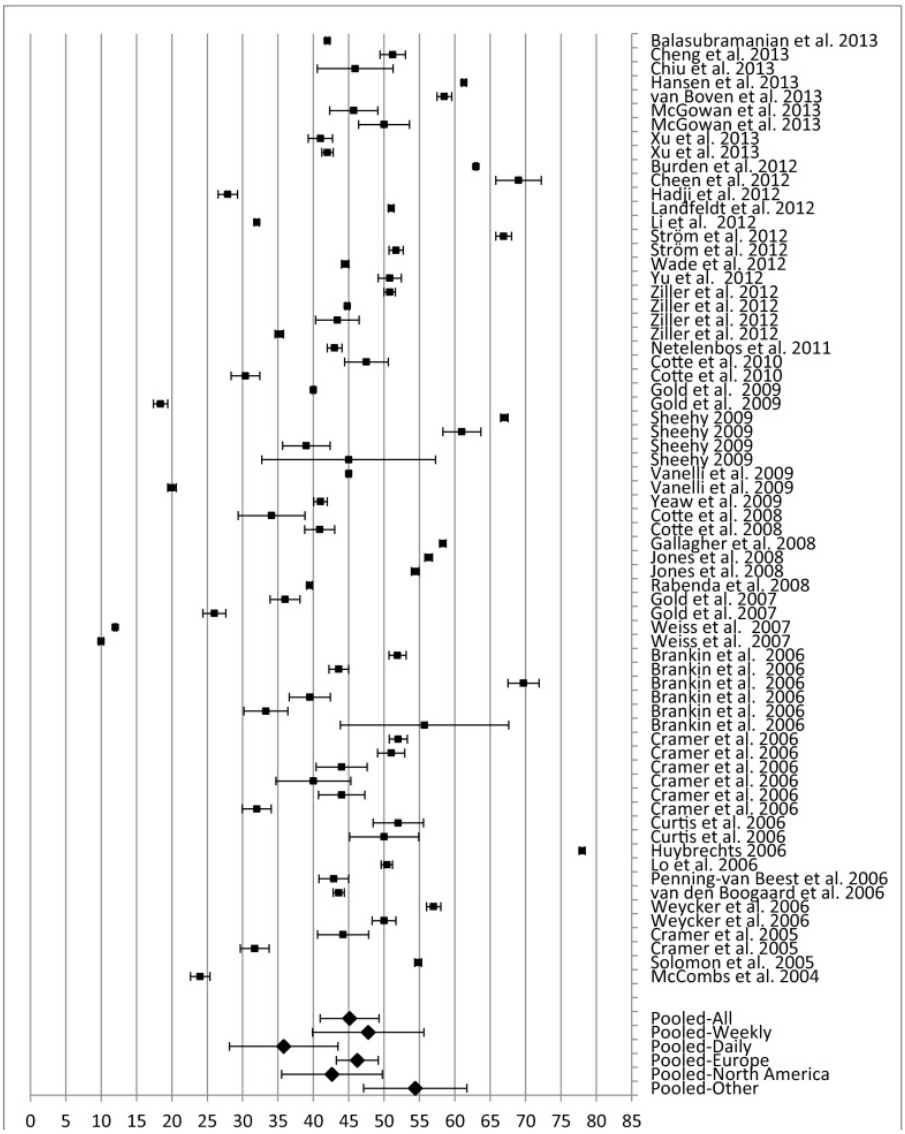


**Figure 2.** Meta-analysis of 12-month refill persistence to oral bisphosphonate treatment (Reproduction from Karlsson et al. [60] via Open Access (http://creativecommons.org/licenses/by-nc/4.0/)

There are also studies of persistence to denosumab (6-monthly subcutaneous injection) [60, 61] and zoledronate (12 monthly infusion) [62] which both have been reported to be associated with higher levels of refill persistence that what typically is seen with oral bisphosphonates.

### 2.2.4 Refill compliance

Medication Possession Ratio (MPR) is another approach to describing refill behavior in prescription data. MPR, expressed in percent, summarizes the number and length of gaps in a treatment regimen but will be highly dependent on the methods used for defining the period of observation, and whether patients are required to be defined as persistent during follow-up. There are several studies of refill compliance [63] that report MPRs of 60-70%, which however generally should be interpreted as a composite of refill gaps and discontinuation. MPR is largely similar to a measure called Proportion of Days Covered (PDC).

### 2.2.5 Refill compliance and fracture risk

Studies have reported that a lower refill compliance measured as MPR is associated with increased fracture risk [64]. But, as stated above, most of these studies make no standardized distinction between refill compliance and refill persistence, meaning that the studied follow-up will influence the estimated level of non-adherence, and that it is implicitly assumed that prescription refill gaps and complete discontinuation have the same impact on fracture risk. Poor refill compliance (MPR <50%) with bisphosphonates is associated with a clear and important increased risk of fractures of approximately 30–40% compared to refill compliant patients (MPR >80%). An MPR >80% is often used as a threshold for high adherence, where improved clinical outcomes can be observed. However, this threshold originates from a blood pressure control study and has been criticized for being arbitrary when extrapolated to other diseases [65].

### 2.2.6 Refill persistence and fracture risk

Whereas clinical trials remain the gold standard for measuring fracture reduction, the high internal validity required to demonstrate efficacy comes at the expense of external validity. The results of such trials may therefore generalize poorly to clinical practice, and the benefits obtained in practice might fall short of the anticipated benefits indicated by clinical trials. However, it is clear that also in randomized trials persistence with therapy declines over time [66]. Thus, any reduced effectiveness caused by sub-optimal adherence is to some extent already captured in clinical trials.

A Dutch study using the Pharmo database [67] reported fracture risk reductions of 12% and 46% in patients remaining adherent (MPR>80%) for 1-2 years and 3-4 years, when compared to patients discontinuing treatment within 1 year. Lindsay et al. [68] reported in 2013 reductions of non-vertebral fractures of 30-45% in patients remaining on oral bisphosphonates for 2 years compared to those only filling a single prescription.

It has been argued that a lower fracture risk in patients remaining longer on treatment partly could be due to a "healthy adherer effect" [69, 70] where patients who persist with therapy are generally of better health compared with patients who discontinue therapy early, irrespective of the reason for stopping treatment.

## 2.3 Health economic evaluation and models in osteoporosis

### 2.3.1 General principles

The basic principles of health economic evaluation have been extensively described and discussed elsewhere [71] and is only briefly summarized here. With increasing health care expenditures, limited resources, and a constantly increasing availability of options it is important for decision makers to consider the economic impact of priorities. Healthcare systems are faced with a largely fixed funding envelope and there are limited resources available to meet all needs and demands. Therefore, one important objective of any healthcare system should be to maximize health given the limited resources. Resources should be used to ensure efficiency in the choices made, so that that resources are allocated in a way that implies that health is maximized. Economic evaluations are comparative analysis of alternative choices or interventions in terms of both their associated costs and consequences, irrespective of when in time they occur. Their purpose is to assist decisions aimed at improving efficiency. When two or more alternatives are compared, the alternative, or combination of alternatives, that confer the highest benefit should be chosen if the net marginal cost per unit of benefit is lower than the "willingness-to-pay" per additional unit of marginal benefit.

Discounting is applied to estimate the present value of costs and health benefits considered in the interpretation of the analysis. This is performed to adjust for differences in the timing of costs and health benefits. The rationale is the "positive time preference," meaning that society or an individual prefers benefits sooner rather than later. Costs should also be given in constant prices in a specific year, where price changes can be adjusted by using the consumer price index.

The typical economic evaluation approaches in health care are:

- **Cost-Minimization Analysis** comparers only the cost associated with the evaluated alternatives. A basic assumption is that the health effects are presumed to be equal.
- **Cost-Benefit Analysis** also incorporates the health effects of the alternatives but transforms the health effects to a monetary value. This generates a single positive or negative net present value in monetary terms of one

alternative compared to another. The economic value put on health will thus decide the acceptable level of investment.

- **Cost-Effectiveness Analysis** (CEA) estimate the incremental cost and effectiveness of the evaluated alternatives. An Incremental Cost-Effectiveness Ratio (ICER) between two alternatives is then calculated. The effectiveness side of the ratio in a CEA can be any type of effectiveness measure (e.g. avoided events, mmHg blood pressure, or life years). **Cost-Utility Analysis** (CUA) can be viewed as a special case of CEA where QALYs (see section 2.1.7.2) are used as the health outcome measure. CUA is commonly used because it allows for comparisons between different populations, diseases, and interventions.

### 2.3.2 Evaluations of fracture prevention in osteoporosis

Cost-effectiveness evaluations of osteoporosis treatments started to emerge in the 1980s and early 1990s but were limited by scarcity of data necessary to describe the natural history of the disease and the consequences of fractures [72]. The early models were developed in the pre-bisphosphate era and consequently evaluated hormone replacement therapy, also factoring in side-effects such as breast cancer, endometrial cancer, and endometrial hyperplasia. Since then numerous models have been published with ever increasing granularity of data and methods [38]. Besides their role in academic research they are also widely used in drug reimbursement decisions where a drug's predicted health benefits and associated cost savings are weighed against the new intervention cost, which typically is higher for newer more innovative interventions. The end result, i.e. the reimbursed drug price will, among other things, depend on the price and effectiveness of already available treatment alternatives, the severity and cost of the disease, the available epidemiological data, the model design, the target population, and most importantly, the effectiveness and other properties of the new interventions.

Osteoporosis models are often designed as *Markov Cohort Models* or *individual state transition models* [71, 73]. Other model techniques, such as Decision Tree and Discrete Event Simulation (DES) are also available but are not described in detail in this thesis since they are rarely used and, in the case of DES, are sometimes impractical for the assessment of decision problems in both osteoporosis, as well as other diseases. Decision Tree models cannot easily incorporate the passing of time, which is a fundamental characteristic of the progression of the disease. DES handles a population as a discrete sequence of events in time. Each event occurs at a particular time-point and marks a change of state in the model. No change is assumed to occur between events and the simulation can "jump" to the next event

(DES modeling in discrete cycles is also possible). DES can allow more flexible and granular modeling and can be useful especially when the individual patient history is a key driver of future events, or if there are resource constraints [74]. However, DES models are less transparent, often more complex, and more challenging to validate and review [75].

In a *Markov cohort model* a hypothetical cohort of patients are distributed over a set of mutually exclusive health states and where that distribution changes over a pre-set number of discrete cycles, representing the passage of time. An important assumption of the Markov cohort model is the "no memory assumption of the Markovian Property", i.e. future events only depend on the current state of the patient, and not on prior events. The distribution over the available health states is handled by transition probabilities that defines the proportion of the cohort at risk that should transition into a different state.

The cohort distribution is then combined with a set of cycle and state dependent costs and effects. By summarising costs and effects over states and cycles, the average total cost and effect per patient is obtained.

An advantage of the Markov Cohort Model is that it actually is a calculation rather than a simulation. This confers both the advantage of efficient testing of the model and instantaneous calculation of results. The major limitation is that it is inflexible with regards to modeling probabilities or costs that are dependent on the passing of time after a specific event (e.g. after a fracture) or when it is necessary to keep track of a patient's history as she transitions to a different health state.

In an Individual State Transition Model, or Markov chain model, iterations of a hypothetical subject travel through the model one by one, instead of as a cohort. Each simulation will thus generate its own path through the model, generating distributions of outcomes, called first-order uncertainty. The approach will thus require enough iterations to reach stable means of the outcomes of interest (e.g. events, costs, and QALYs). An important feature is that the model can continuously store the history of each iteration, allowing future events to depend on historical events. For example, the occurrence of a fracture can be allowed to influence the probability of a future fracture in a time dependent manner. This "memory" allows the hypothetical patients to freely transition between health states without losing the information about the past.

Alendronate, which has been the mainstay option for patients with osteoporosis, has generally been estimated to be cost-effective compared to no treatment [37, 76, 77], but such results are dependent on drug costs at the time, the available alternatives, and the risk level of the evaluated population. Willingness-to-pay for health care interventions, drug costs, and fracture risk are dependent on the

country or even regional setting, so whether a drug should be regarded as cost-effective becomes a local matter. Also, value-based pricing and cost-effectiveness are used differently by health care systems in developed countries, resulting in regional variance in its impact and relevance. When new treatment alternatives are introduced, they have typically been more costly and sometimes more effective, creating the need for detailed analysis of cost-effectiveness to support development of priorities and recommendations.

### 2.3.3 Typical cost-effectiveness models in osteoporosis

A typical cost-effectiveness model [35, 78-80] for the evaluation of fracture preventing medication in osteoporosis is designed around different fracture types or categories of fracture types, such as fractures to the hip, vertebrae, wrist, non-hip, non-hip-non-vertebrae. The types and categories used are often based on the endpoints used in the randomized clinical trials used to feed the model.

The models typically use age dependent fracture risks for the general population that are modified by applying relative risks from risk factors that defines the population of interest and risk reductions reported in clinical trials.

The outcome of an economic evaluation in osteoporosis will depend on a range of data types, assumptions, and properties of the decision problem:

- Intervention and management costs of the alternatives
- Differences in fracture risk and adverse events between the compared alternatives
- Risk profile of the population of interest
- Health care costs and HRQOL effects of events associated with the evaluated alternatives.
- Intended and actual treatment length. Many treatment regimens should last for 3-5 years, but this can vary for different drugs, local treatment recommendations, or other factors sepcific to the evaluation being performed.
- Model properties (structure, cycle length, discounting, assumptions)

### 2.3.4 Residual effect after treatment in cost-effectiveness models

An important aspect of the modeling of fracture risk is what happens with it after a treatment is stopped, prematurely, or as intended [81]. It is unlikely that the effect on the bone disappears immediately when a treatment is stopped, and perhaps equally unlikely that it would confer fracture protection indefinitely. This period

with post-treatment effect is often called “offset time” or “residual effect”. The residual effect has somewhat arbitrarily often been assumed to last for a number of years equal to length of treatment (e.g. 5+5 years) but then linearly decline back to the risk of an untreated patient [35, 77, 81]. This aspect may seem to be a minor detail but can have large implications for the estimated cost-effectiveness, because it confers treatment effect for no cost [81]. An analogous example is how progression free survival or overall survival is handled in oncology modeling, where assumptions regarding what happens after the time period studied in clinical trials can have substantial impact on the estimated health gains [82].

Residual effect has been studied in extensions of clinical trials where post-treatment protective effect on fractures has been observed for up to 30 months after PTH [83], and up to 15 years on BMD in small sample of women treated with HRT in early menopause [84]. In a small sample extension of the HORIZON trial studying zoledronate, a residual effect on BMD was observed when a 6 year regimen was compared to a 3 year regimen [85]. Increases in the risk of morphometric vertebral fractures have been observed after stopping treatment with both alendronate and zoledronate [85, 86]. Neither extension trial showed an overall reduction in nonvertebral fractures from continuing treatment beyond the treatment period in the original trials.

In a 1-year follow-up of subjects who had completed 3 years of risedronate or placebo, BMD decreased in the former risedronate users but remained higher than in the former placebo subjects [87]. Despite the resolution of treatment effect on BMD, the risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo subjects.

It is not clear how large or long the residual effect on BMD and fracture risk is, if it applies to all fracture types, how it varies across different treatments, how long a treatment must be to confer a residual effect, or how and if the residual effect varies with the time on treatment.

# 3 AIMS OF THESIS

Considerable effort and funds are committed to develop and provide pharmaceutical fracture prevention in industrialized countries, and several safe and effective treatments are available to prescribers and patients. However, less effort is invested in ensuring that medication is used to prevent as many fractures as possible. This thesis aims at addressing pharmacoepidemiologic and health economic aspects of poor refill persistence to osteoporosis treatment by both establishing the extent of the problem as well as investigating how it can be incorporated into the health economic framework that commonly is used to inform reimbursement of new treatments as well as regional priorities for recommended prescription standards. Three of the articles in this thesis are based on Swedish register data to study pharmacoepidemiological aspects of refill persistence to treatment and the fourth used a simulation model to assess the health economic implications. The specific objective(s) of the included articles were to:

I. Estimate refill persistence and refill compliance to treatment of primary osteoporosis in Sweden. A second aim was to investigate the determinants of non-persistence and the association between adherence and fracture incidence.

II. Investigate the association between automated generic substitution and refill persistence with alendronate treatment of primary osteoporosis in Sweden.

III. Investigate the residual effect of alendronate and risedronate on fracture risk and assess whether a healthy adherer effect confounds the association between refill persistence and residual anti-fracture effect.

IV. To develop a health economic model that could incorporate adherence and identify the important drivers of cost-effectiveness in this context.

# 4 PARTICIPANTS AND METHODS

## 4.1 Introduction

For the three research articles addressing the pharmacoepidemiology of osteoporosis included in this thesis, we used patient-level data from national registries. Linking of data was performed on patient level to enable analysis of outcomes on individual level and in relation to how and when pharmaceutical treatments were used. As the data sources cover essentially all patients with a fracture or an osteoporosis treatment in Sweden the results are representative for the whole population. The fourth article was based on a simulation model that synthesized secondary data from several other published studies. This section will summarize and discuss study design, data sources and other methodological aspects of the included articles. Papers I-III are all based on the same research dataset and will therefore in many cases be addressed together, whereas the modeling study will be described separately. Table 5 provides an overview of the four articles.

**Table 5.** Study overview of research papers I-IV

| Study | I | II | III | IV |
|---|---|---|---|---|
| **Publication year** | **2011** | **2011** | **2014** | **2008** |
| **Topic** | Persistence to osteoporosis treatment and relation to fractures | Persistence and generic substitution | Residual effect after osteoporosis treatment | Incorporation of treatment adherence in health economic models |
| **Methods** | Retrospective cohort, survival analysis, hazard models | Retrospective cohort, survival analysis, hazard models | Retrospective cohort, survival analysis, hazard models | Health-economic modeling study |
| **Data sources** | Patient register, Swedish prescribed drug register | Patient register, Swedish prescribed drug register | Patient register, Swedish prescribed drug register | Literature data |
| **Patients** | Patients starting alendronate, risedronate, strontium ranelate, raloxifene, parathyroid hormone (PTH). Secondary osteoporosis and tumors excluded | Patients starting alendronate or risedronate | Patients stopping alendronate or risedronate | Typical osteoporosis patients starting treatment |
| **Main outcomes** | Treatment discontinuation, Medical Possession Ratio, fractures | Generic substitution, treatment discontinuation | Fractures, mortality | Incremental cost-effectiveness ratio, fractures, QALYs, Life years, costs |
| **Number of patients** | 56,586 | 43,056 | 17,249 | N/A |

## 4.2 Papers I-III

### 4.2.1 Data sources

All three register studies used the national patient register and the prescribed drugs register. The different research datasets originate from the same data extraction, called the SARA (Swedish Adherence Register Analysis) study.

#### *4.2.1.1 The National Patient Register*

The National Patient Register (NPR) maintained by the National Board of Health and Welfare has collected data on in-patient care back to the 1960's. Initially it contained information about all patients treated in psychiatric care and approximately 16 percent of patients in somatic care. The register at that time covered 6 of the 26 county councils in Sweden. From 1987 NPR includes all in-patient care in Sweden. Since 2001 the register also covers outpatient doctor visits including day surgery and psychiatric care from both private and public caregivers. NPR contains a host of variables with the most important being ICD-10 codes for diagnosis and procedure codes for identifying inpatient and outpatient procedures. The NPR is updated annually creating some delay in the possibility to study recent events.

NPR was linked to the Swedish Prescribed Drug Register and Cause of Death Register when creating the SARA study extraction. The quality and accuracy of the national registers is high. 98.6% of all inclusions in National Patient Register, Prescribed Drug Register, and the Causes of Death Register are entered correctly, and the frequency of missing values is very low [88, 89].

#### *4.2.1.2 The Swedish Prescribed Drug Register*

All prescriptions dispensed at Swedish outpatient pharmacies are captured in the Swedish Prescribed Drug Register (PDR) going back to June 2005. PDR is also maintained by the National Board of Health and Welfare and contains a range of variables. The most important variables for these studies were dispensing date, ATC codes, product ID, package strength, size and count, and return of medication. Being a newer register, collecting its data in a harmonized manner from the pharmacy IT-systems, data from PDR can be extracted with dispensing records close in time to the date of extraction.

#### *4.2.1.3 The Cause of death register*

The Swedish cause of death register is a high quality virtually complete register of all deaths in Sweden since 1952. Although originally created for official statistics, it is a highly important data source for medical research since it can be linked to other registers. For the purposes of these studies only the date of death was used to be able to censor follow-up and estimate mortality.

### 4.2.2 Patient selection

The PDR and NPR were linked together using the research subject's social security number and pseudonymized by the National Board of Health and Welfare before extraction. Patients were included by either having at least one ICD-10 code in NPR for a fracture from 1998 and onwards (Dec 31st 2008) or by having been dispensed at least one osteoporosis medication in the PDR from June 2005 and onwards (Dec 31st 2009). Dates of death were linked to the sample (Figure 3).

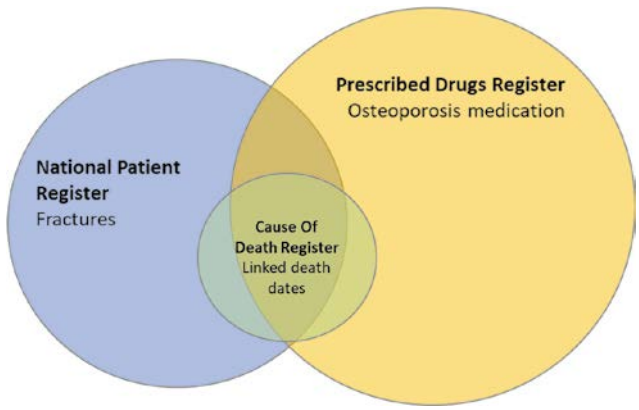


**Figure 3.** Conceptual venn diagram of the included subjects and data sources

The inclusion and exclusion criteria used in each study was based on the research questions investigated but also by considering how the patient sample could be defined to minimize the risk of bias:

- Paper I, which investigated refill persistence and compliance in Swedish osteoporosis care and its association to fracture risk, included all patients that were likely to have started a new treatment for osteoporosis. Patients with malignancies, diagnoses or treatments indicating secondary osteoporosis were excluded to only capture primary osteoporosis.
- Paper II investigated refill persistence and its relation to generic substitution in patients using oral bisphosphonates and was therefore designed to only include such individuals. Besides excluding malignancies and secondary osteoporosis we also excluded patients exclusively using brand-name alendronate (Fosamax®) because these patients were not considered to be representative for the typical patient at that time.
- In paper III we were mainly interested in the period after stopping treatment and excluded therefore also patients that had not stopped their treatment by July 1st, 2008 to be able to require at least six months of follow-up for all subjects.

### 4.2.3 Study outcomes and definitions

The register-based studies, Papers I-III, focused on four types of outcomes; persistence and compliance measures, generic substitution events, fractures, and mortality. Below are specifications and definitions of the outcomes that were used:

*4.2.3.1 Persistence and compliance measures:*

1. Refill persistence (Papers I-III)
   Refill persistence was operationalized as days on treatment without gaps longer than 8 weeks, often called "permissible gap", or "grace period". Thus, a patient was defined as non-persistent if she did not receive a dispensing within 8 weeks from the day that the preceding dispensing should have been fully consumed. If patients had accumulated larger amounts of medication the definition permitted patients to consume their accumulated medication, as long as he/she afterwards filled a new prescription within the grace period.

2. Medication Possession Ratio (Paper I)
   Medication refill compliance was quantified using Medication Possession Ratio (MPR), defined as the number of days of medication available to the patient, divided by the number of days on treatment. For example, a patient who persisted with therapy for 365 days but only filled prescriptions with medication covering 325 days would have had an estimated MPR of (325/365) × 100≈89%. To avoid making MPR a composite of persistence and compliance we only estimated MPR while the patient was persistent. This approach is different from how it has been handled in many other published studies but has the advantage of separating two problems that may be of different magnitude, associate differently to outcomes, and may have different solutions.

*4.2.3.2 Generic substitution events (Paper II)*

The term Generic Substitution Event (GSE) was devised to describe pharmacy dispensings of prescriptions for the same medication to the same patient but that was of a different brand than the previous dispensing.

*4.2.3.3 Fractures (Papers I & III)*

Fractures were identified using ICD-10 diagnosis codes. The study included the broad range of fracture types listed in Table 6. Only the primary diagnosis was used to avoid capturing historical fractures as new events. Information regarding the causes of the fractures (W-codes determined by the physician) that could have

been used to only capture low-energy trauma was available, but the coverage was incomplete, and all fractures were therefore included in all main analyses. It is not entirely clear whether the risk of cervical spine fractures and ankle fractures is affected by osteoporosis, but they were both included in the analyses as a conservative measure.

**Table 6.** Included fracture types

| Description | ICD-10 codes |
|---|---|
| Neck | S12.x |
| Rib, Sternum, and Thoracic spine | S22.x |
| Lumbar spine and pelvis | S32.x |
| Shoulder and upper arm | S42.x |
| Forearm | S52.x |
| Femur (including hip) | S72.x |
| Lower leg (including ankle) | S82.x |
| Osteoporosis with fracture | M80.0, M80.2, M80.8, M80.9 |

### 4.2.4 Statistical methods and covariates

When retrospective cohorts are created from registers or other data sources it is often necessary to create an "index time point". The index time point is the start of observation ($t_0$) of a specific analysis and must be defined in a way so that it can be distinguished from other similar time points in an individual's available follow-up. Examples could be the first prescription of *X* between dates *Z* and *Y,* or *X* days before an inpatient stay with a specific ICD-10 code. Each individual will have a certain amount of available follow-up that will be limited by the extracted time period, or lack of follow-up for other reasons that is defined by the study definitions. Throughout the three publications using retrospective data, analyses have included descriptive statistics measured at an index time point or as averages or proportions during a defined period preceding the index time point (e.g. 2 years). The nature of the data and research question were well suited to survival analysis and hazard modeling, which was use in papers I-III. This since the extracted research subjects do not have a common index date (start of observation) because they are included retrospectively, and they also have different amounts of available follow-up, which necessitates right-censoring. Patients were typically censored at death or when reaching the date limit of the extraction, and treatment termination, fracture, or death was used as failure events depending on the context of the analysis. Unadjusted non-parametric survival analyses were reported as Kaplan-Meier curves, life tables, and median time on treatment. Proportional

hazard models were developed for estimating adjusted hazard ratios and choice of distribution was made by minimizing the Akaike Information Criterion (AIC) and maximizing the log-likelihood. The proportional hazards assumption was investigated using graphical inspection and by including time dependent covariates and exploring if the estimated coefficients of these regressors significantly varied with observation time.

Covariates were used both to study risk factors for poor persistence but also to adjust for observed confounders when estimating the relationship between persistence and fracture incidence. Selection of covariates (Table 7) was based on factors that were deemed relevant for the context rather than whether they were statistically significant.

**Table 7.** Summary of included variables in Papers I-III

| Variable | Time frame | Paper I | Paper II | Paper III | Note |
|---|---|---|---|---|---|
| Age | At index | √ | √ | √ | |
| Sex | At index | √ | √ | √ | |
| Urban/rural region | At index | √ | √ | √ | Definition from Statistics Sweden combined with pharmacy location |
| ApoDos | During follow-up | √ | √ | √ | Pre-packaged medication, indicative of special living or assistance needs |
| Weekly dosing regimen | During follow-up | √ | √ | √ | vs. daily regimen |
| Treatment type | During follow-up | √ | √ | √ | |
| Low level glucocorticoid exposure | 1 year | √ | √ | √ | Less than 2,000 mg |
| Gastroprotective treatment | 1st 6m of OP-treatment | √ | √ | √ | PPIs, H2-antagonist, sucralfate, alginic acid |
| Prevalent fracture | 5 years | √ | √ | √ | Excluding skull, fingers, metacarpals, face, and feet |
| Prevalent co-morbidities | 5 years | √ | √ | √ | As defined by Quan et al [90] |
| Switcher | During follow-up | √ | | | |
| Time on treatment | before discontinuation | | | √ | Limited by start of register in 2005 |
| Calendar year at treatment start | | | √ | | |

### 4.2.5 Overview of study design of papers I-III

*4.2.5.1 Paper I: Adherence to treatment of primary osteoporosis and its association to fractures-the Swedish Adherence Register Analysis (SARA)*

Persistence to treatment was estimated in 56,586 patients who were defined to have started a new treatment for primary osteoporosis based on filling prescriptions for osteoporosis medications. Exclusions were based on diagnoses or medication patterns indicative of secondary osteoporosis or malignant tumors. Treatment refill persistence and refill compliance were measured for up to 4 years using the methods described in section 4.2.3.1. Switching between the included treatments was allowed without being defined as non-persistent. Patient characteristics associated with treatment discontinuation was studied using a parametric multivariate proportional hazards model reporting hazard ratios. The parametric models were specified to include age, sex, urban/rural living, weekly/daily dosing regimen, prevalent hospitalized fracture, individual comorbidities, pre-packaged medication ("ApoDos"), low-level exposure to glucocorticoid medication ($\leq 2$ g of accumulated glucocorticoid medication 12 months prior to index prescription), and filled prescription for gastroprotective agent (proton pump inhibitor, H2-receptor antagonist, sucralfate, and/or alginic acid) during the first 6 months of osteoporosis treatment. The association between persistence and fracture at any skeletal site was estimated in a multiple failure model to avoid censoring patients at the time of first fracture and controlled for the above listed covariates. Patients were right censored at time of death or end of data availability.

*4.2.5.2 The association between automatic generic substitution and treatment persistence with oral bisphosphonates*

Given the marked increase in generic substitution of alendronate it was deemed relevant to refine the analyses in paper I by investigating if persistence patterns were linked to automated replacement of brand drugs with less costly generic alternatives. Data on product ID was used to separate otherwise identical prescriptions and thereby facilitating the definition of Generic Substitution Events (GSE). Given that patients with long treatments statistically would experience more GSEs the methods were designed to avoid capturing this expected pattern:

- The proportion of dispensings constituting a GSEs and the number of available alendronate products during 2006 to 2009 were calculated to provide a backdrop for the other analyses.
- Persistence to generic alendronate was estimated for patients starting their treatment in 2006, 2007, 2008, or 2009.
- A parametric multivariate proportional hazards model (Weibull) to analyse whether the occurrence of a GSE between the first and second prescription

was associated with persistence. The analysis was conducted in patients who had filled at least two prescriptions (i.e., being at risk of a GSE). A dummy variable indicating whether a patient's first re-fill was a GSE was included in the model, as well as interaction terms to investigate if the patient's age or sex had an impact on the association between GSEs and persistence.

- Lastly, a comparison vs. risedronate was performed. Only one risedronate product was available during the study period and was therefore used to design a natural experiment where risedronate was used as a reference group not at risk of GSEs. By contrast, patients prescribed alendronate were at an increasing risk of experiencing a GSE between 2006 and 2009. Both treatments were analysed in the Weibull model described above with calendar year of starting treatment as dummy variables.

#### *4.2.5.3 Residual effect after oral bisphosphonate treatment and healthy adherer effects*

To study the residual effect after stopping bisphosphonate treatment patients who had discontinued a regimen of oral bisphosphonates (OBPs) between December 2005 and July 2008 were selected for analysis. Patients were followed from the time point of stopping their treatment until death or end of data availability. Patients were divided by time on the preceding regimen and time periods after stopping treatments in 12 groups, as depicted in Figure 4 below:

| | **Time after stopping treatment** | | |
|---|---|---|---|
| **Time on preceding treatment** | 0-6 months | 7-12 months | 12-18 months |
| < 1 month | reference | reference | reference |
| 1-6 months | | | |
| 7-12 months | | | |
| > 12 months | | | |

**Figure 4.** Schematic description of patient stratification in paper III

- Fracture incidence was measured in these strata in an adjusted proportional hazards model, using the groups with less than one month of pre-index treatment as references to estimate hazard ratios.
- Time on treatment was used a continuous variable to test if it was statistically associated with post-treatment fracture incidence.
- Patient characteristics were compared across persistence groups and mortality after stopping treatment was measured to assess if persistence was associated with the health status of the patient.

#### *4.2.5.4 Revisiting residual effect in paper III in a new analysis*

The analysis in paper III was performed on a register extraction that covered fracture diagnoses from 1998 until Dec 31st 2008 and prescription data from mid-2005 until the end of 2009. It could be argued that this time window of linked data (~3.5 years) was too short given the objectives and the restrictions that were put on the data. A new analysis with a similar design is therefore presented in this thesis, based on a preliminary design and thus preliminary results not yet published in a peer reviewed manuscript.

The research questions that paper III only partly could address were:

- How long is the residual effect after stopping treatment with OBPs?
- Does it attenuate differently depending on the length of treatment?
- Are there other factors (unobserved confounders) that are associated with both treatment persistence and fracture incidence after stopping treatment?

The new analysis was performed on a larger and more recently extracted data set of a similar nature that covered June 2005 to December 2015 (10.5 years). Another difference was that the extraction included patients that either had received an osteoporosis medication OR had filled prescriptions for 45 Defined Daily Doses (DDD) of glucocorticoids (ATC H02AB). Fractures diagnosed in both the outpatient and inpatient settings were included as outcomes whereas only hospitalized fractures were used as outcome event in research paper III.

Similarly to the design of paper III the patients were stratified by time on treatment and time after stopping treatment, but longer follow-up time was now available. Time on treatment was divided into <1 month, 2-6 months, 7-12 months, 13-24 months, and 25+ months, and time after stopping treatment into year 1, year 2-3, year 4-5, and years 6+. Beyond adjusting for patient characteristics, the analysis

was also contrasted to a patient sample stratified by their time on statins (ATC C10AA.x), instead of OBPs. Statins are cholesterol-lowering drugs and were chosen because:

- It is a long-term preventive treatment where treatment desicions are based on risk factors and refill persistence is sub-optimal (analogous to fracture prevention in osteoporosis).
- They are commonly used in the general population.
- There is no reason to suspect that statins would have a protective or adverse effects on fracture risk. Wang et al. reported a pooled HR of 1.00 when studying the association between statin use and fracture risk in a meta-analysis of 27,900 randomized participants [91].

An alternative design would have been to instead measure the risk of cardiovascular events in relation to refill persistence in the OBP sample. The reason for instead selecting a population using statins followed on fractures was that the potential unobserved confounding investigated should influence fracture risk, rather than cardiovascular outcomes.

Both cohorts were followed from stopping treatment (OBPs or statins) and fracture incidence was measured in the specified time windows. When considering the representativeness of the statin sample it should be noted that the data material was drawn from patients that had filled at least one osteoporosis prescription or 45 DDD worth of glucocorticoids.

The rationale for performing the statin analysis was to investigate if there are unobserved confounders that are associated both with the exposure (pre-index time on treatment) and the outcome (fracture risk). Examples of such unobserved confounders could be propensity of falling, risk taking behavior, diet, bone mineral density, mobility, smoking, etc. The interpretation of an association between pre-index persistence to OBPs and post-index fracture risk would be strengthened by the absence of such an association when instead considering pre-index persistence to statins.

The two samples were run in nearly identical adjusted single failure proportional hazards models with interaction terms between time windows and drug exposure strata. Adjustment was made for age, sex, use of glucocorticoids, prior fracture, and Charlson Quan comorbidity index. The statin model was also adjusted for how patients had been included in the research data; filled prescriptions of osteoporosis medication or glucocorticoid medication. Results were reported as patient characteristics, hazard ratios and cumulative hazard functions.

### 4.2.6 Paper IV – Health economic model

Paper IV was based on the development of health economic simulation with the purpose of exploring how the different concepts relating to adherence could be included in a health economic framework and analyzing how the different aspects of adherence would influence the health economic assessment of an intervention conferring an improved adherence profile in osteoporosis.

#### *4.2.6.1 Model design and incorporated aspects of adherence*

Health economic model analyses of pharmaceutical interventions in the osteoporosis space can often be handled in a Markov cohort model framework, where a "memory" of past events not is necessary or can be approximated by introducing health states that represents the passage of time after an important event, such as a fracture. In a more complex context where there are several types of time points that contain important information, the number of states necessary in the model can become unpractical to handle, and other modeling techniques are therefore better suited. In this model design we wanted to use an individual's time point of treatment discontinuation as well as the timing of different fracture events, why fore an individual state transition model instead was used.

The model was designed to be able to handle and separate concepts/features that potentially could be of importance when incorporating medication taking behavior in a health economic assessment of pharmaceuticals in fracture prevention:

- Separation of persistence (time on treatment) and compliance/adherence (proximity to instructions), which not necessarily would impact outcomes equally. The input data for these could theoretically be derived from any type of study and register-based refill patterns is only one method for linking patterns to outcomes.
    - Persistence was incorporated to allow each individual model iteration (patient) to stop treatment in 6-month intervals.
    - Compliance was defined as a multiplicative factor (FOB=Fraction Of Benefit) that only should reflect sub-optimal drug-taking behaviour not captured by persistence. The FOB was meant as a reduction of the treatment effectiveness derived from a randomized trial, but the model did not address the likely magnitude of the FOB or how it should be derived.
- Possibility to allow persistence to influence the modelled residual effect after stopping treatment. The model could accommodate different lengths of a linearly declining effect. We used a base-case assumption that the time period with residual effect was the same as the time on treatment. I.e. a

patient stopping treatment after 12 months received a residual effect that linearly approached the effect in the comparator arm during 12 months. It was also possible to model fixed length that was independent from the time on treatment.

- A situation where the patient had been prescribed a treatment but never filled any prescriptions at a pharmacy was called primary non-adherence. Only costs for physician visits and DXA-scan was assumed.

#### *4.2.6.2 Model Structure, perspective, and data*

The employed model structure was largely similar to what has been used in several other publications evaluating interventions in osteoporosis [35, 36, 79, 92, 93]. In general, an individual state transition approach lends flexibility to the structure design where several health states and time effects can be combined, limiting the number of health states necessary. In this case the time-dependent post-event consequences after vertebral fractures and hip fractures were combined into a "post-fracture state" where different HRQOL-weights, mortalities, and costs was applied depending on a patient's simulated fracture history.

The analysis was done from a societal perspective, including health-care costs, costs of informal care, and loss of productivity. Mortality costs were not included in the analysis. A yearly discount rate of 3% was used for both costs and effects.

Appropriate data on risks, effects, costs, mortality and HRQOL were collected from the literature. Data were taken from Swedish sources as far as possible but data on real world persistence to standard of care treatments were not available and was therefore taken from a US source [94].

#### *4.2.6.3 Analytical scope*

The model was used to compare different adherence profiles to assess the health economic implications of different levels of refill persistence and compliance and these aspects interacted with other factors such as drug prices, underlying fracture risk, and assumptions regarding residual effect after stopping treatment.

The base-case population was specified as a 70-year old woman without a prior fracture and a BMD T-score of -2.5 SD.

Three treatment scenarios were compared to each other; "full adherence", "partial adherence", and "no treatment":

- In the **full adherence** scenario patients received the full treatment effect as estimated in randomized trials and stayed on treatment for a duration of 5 years. The drug cost in the full adherence arm was set at €600/year to emulate a newer more expensive treatment option.
- With **partial adherence** patients were at risk of discontinuing treatment during the treatment period (based on US claims data) and only received 80% of the treatment effect (Fraction Of Benefit) based on a theoretically sub-optimal refill compliance. Patients were also at risk of primary non-adherence, where the treatment was not started at all. The drug cost in the partial adherence arm was set at €400/year.
- Patients receiving **no treatment** had the same underlying fracture risks but no intervention costs or treatment effects.

Model results were reported as number of fractures, costs, QALYs, Life years, Number Needed to Treat (NNT), and the incremental cost-effectiveness ratios (ICER).

A separate measure called Variable Dependent Elasticity" (VDE) was also estimated. We defined VDE as the percentage change in the ICER that occurred in response to a percentage change in a given variable. For example, if, in response to a 20% increase in the price of the high adherence drug, the ICER increased by 30%, the VDE would be 30/20 = 0.5. i.e. a 1% increase in drug price influenced the ICER by +1.5%. 1,000 different model simulations were run where 10 different model variables were allowed to freely vary ±50% in a uniform distribution. The 1,000 model results were then log-transformed and analysed with multivariate linear regression to estimate the independent average impact of each variable on the ICER.

## 4.3 Research ethics & funding

The studies using sensitive data have been approved by the regional ethical committee board at Karolinska Institutet, Stockholm (dnr 2008/1265-31/2, dnr 2013/1543-31/4, dnr 2016/464-32). Registry based studies contain sensitive data on patients' health and well-being. In these studies, only pseudo-anonymized data (no personal numbers) were accessible and the data were kept in a secure setting. Furthermore, data is only presented on aggregated level to ensure that patients are not identifiable in the presented results. The potential harm on patient's lives is deemed to be minor whereas the increased knowledge of pharmacoepidemiological and health economic aspects of osteoporosis may serve as a knowledgebase

for better and more cost-effective use of health care resources in the future which will benefit patients and society at large.

Swedish research is regulated both by international conventions and international and national laws. The regulations aim to not damage or expose people to unnecessary risks when an individual's data is used in research. For register-based research any caution mainly concerns the risk that information recorded and used in research can be wrongfully disclosed. Therefore, it is essential that the data is de-identified or anonymized and that there are strict rules on confidentiality and other aspects of personal data protection. However, it is important to note that individuals can also be damaged indirectly by laws and regulations that hampers research. Progress in terms of improved methods for patient identification, prevention and treatment may be delayed or hindered.

Papers I, III, and IV were executed using funds provided by Amgen inc. Amgen was at the time in the process of launching denosumab, which is a monoclonal antibody injected subcutaneously every 6 months and that has been shown to reduce the risk of fracture in patients with low bone mineral density. The bi-annual administration of denosumab confers a possibly beneficial adherence profile which could add health-economic value linked to avoided fractures. All sponsored manuscripts have been reviewed by Amgen according Amgen's process for sponsored outcomes research and have been planned, executed, and interpreted with scientific integrity. Authorship has followed the guidelines of the International Committee of Medical Journal Editors (ICMJE).

This project has also been part of the Forte research programme "Increasing value and choice in health and social care" (Grant Nr 2012-1688), and the support is greatly acknowledged.

# 5 RESULTS

Below is a summary of the results from each of the research papers included in the thesis, as well as the new analysis related to paper III.

## 5.1 Paper I: Persistence to osteoporosis treatments is poor and associated with fracture risk

We analyzed persistence to treatment with common medications indicated for prevention of fractures and its association to fracture incidence and patient characteristics.

The study describes adherence behavior of 57,000 Swedish patients. Refill persistence to treatment of osteoporosis in Sweden is low and approximately 50% of treatment-naïve patients discontinue their treatment within 1 year from starting it. A total of 51%, 35%, 25%, and 14% were still on treatment (switching allowed) after 1, 2, 3, and 4 years, respectively. When instead adherence was measured as prescription refill gaps in patients still on treatment the Medication Possession Ratio (MPR) was estimated at 94%, indicating that persistence may be a better approach to characterizing the adherence challenges in the Swedish setting. When the sample was stratified, we could show that there were differences between different medications and between weekly and daily dosing. The oral bisphosphonates, alendronate and risedronate were comparable, whilst persistence to Raloxifene (a Selective Estrogen Receptor Modulator) and strontium ranelate (no longer used in Sweden) showed higher rates of discontinuation. PTH (Parathyroid hormone) which is much more costly and used in more severe patients showed better persistence (75% after 12 months) but with a sharp drop around 18 months, which was aligned with reimbursement restrictions at the time. Risk of stopping treatment was markedly lower (HR 0.56) for patients filling prescriptions for weekly alendronate or risedronate when compared to daily dosing formulations. All results were generally stable when the "grace period" (or permissible gap) was varied between 4 and 12 weeks.

The association between time on treatment and fracture risk is shown in Figure 5. Compared with <1 month of therapy, treatment for 1 month to 1 year, 1 to 2 years, and 2 to 3 years was associated with a lower 3-year fracture incidence (HR 0.86, $p = 0.091$; HR 0.67, $p < 0.001$; and HR 0.59, $p < 0.001$, respectively). No significant relationship was identified between MPR and fracture risk.

The following patient characteristics was associated with reduced risk of stopping treatment; Weekly dosing regimen, undergoing a treatment switch, receiving prepackaged medication, female sex, and any prevalent fracture during the last 5 years.

Living in an urban region, concomitant gastroprotective treatment, any prevalent comorbidity and low-level glucocorticoid exposure were all associated with increased risk of stopping treatment. The patient's age did not impact the risk of stopping treatment.

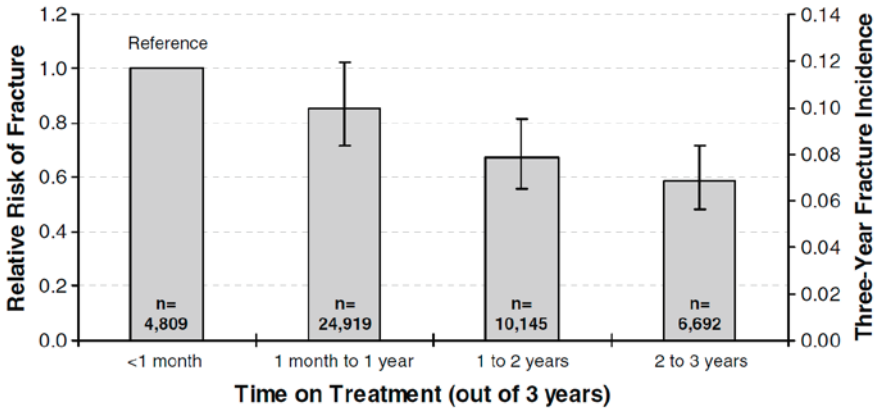


**Figure 5.** Relative and absolute risk of any fracture for different levels of persistence. Patients with <1 month treatment as reference. (re-use from paper II with permission from Springer Nature)

## 5.2 Paper II: Automatic generic substitution of oral bisphosphonates likely reduces treatment persistence

In a cohort of women and men (n=36,433) identified in the Swedish Prescribed Drug Register through filled prescriptions for alendronate or risedronate between 2005 and 2009 the possible impact of automatic generic substitution was studied.

Generic alendronate appeared on the market already in 2005 but the Swedish Prescribed Drug Register was not available until mid-2005 which made an analysis of likely treatment naïve patients before 2006 unfeasible. Between 2006 and 2009, the number of alendronate products increased from 15 to 25, the proportion of prescriptions constituting a substitution event increased from 10.8% to 45.2%, and the proportion of patients persisting with alendronate treatment for 12 months fell from 66.9% to 51.7%. Patients starting alendronate treatment in 2006 had lower risk of stopping treatment compared with those starting in 2007 (HR 1.34, 95% CI 1.29–1.39), 2008 (HR 1.49, 95% CI 1.43–1.55), and 2009 (HR 1.50, 95% CI 1.40–1.60).

Irrespective of calendar year, individuals who had their alendronate product substituted at the first prescription refill had significantly higher probability of discontinuation (HR 1.25, 95% CI 1.20–1.30). No difference over time was observed in persistence with proprietary risedronate during the same period (Figure 6). The analysis of both patient groups was adjusted for available covariates.

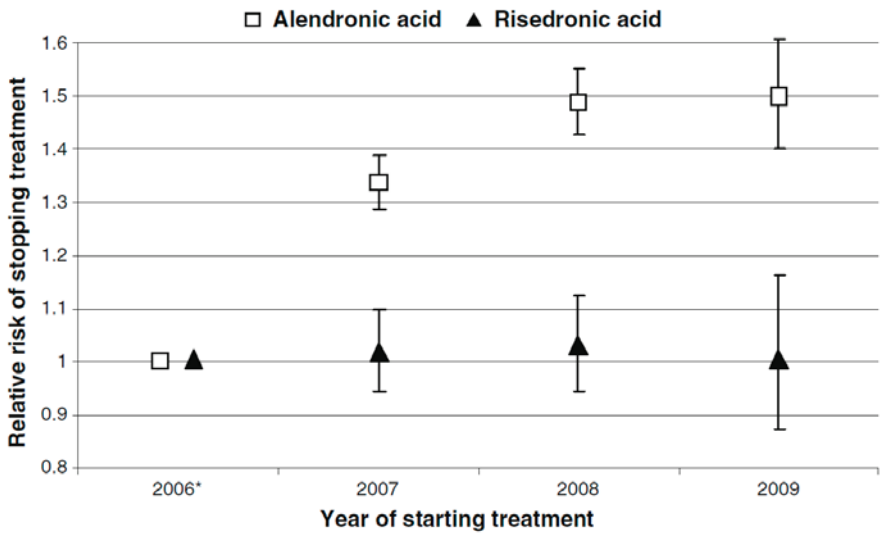


**Figure 6.** Hazard Ratios of stopping treatment for weekly alendronate and risedronate between 2006 and 2009. 2006 used as reference year (*), (re-use from paper II with permission from Springer Nature)

## 5.3 Paper III: There is likely a residual effect after treatment with oral bisphosphonates, and that also is associated with the preceding time on treatment

Patients were followed from the time point of stopping their treatment with oral bisphosphonates and stratified by the preceding time on treatment.

A total of 867 hospitalized fractures were sustained during the follow-up after treatment discontinuation (Table 2). Hip and femur fractures were most common (34%), followed by forearm fractures (9%) and vertebral fractures (8%). The composite group “other fractures” constituted 49% of all fractures.

Time on treatment was found to be significantly inversely associated with incidence of hospitalized fractures after treatment termination when adjusting for available

covariates, indicating that longer treatments may confer a better post-treatment residual effect. When the follow-up was divided into three time-windows (0-6 months, 7-12 months, and 13-18 months) there was a marked difference in fracture incidence during the first 0-6 months depending on the preceding time on treatment. Whether this difference persisted or attenuated over time was not possible to estimate with certainty given the limited sample and length of follow-up. Nonetheless, there was a trend that the effect from the preceding time on treatment decreased with time.

Mortality was elevated during the first 6 months after stopping treatment in patients with preceding treatments longer than 12 months. The reason for this could not be assessed but it is possible that serious illness and deteriorating health is a more common reason for discontinuing longer treatments (>1 year), than is the case for shorter treatments. Mortality was similar across all treatment duration groups beyond 6 months after stopping treatment.

Patient characteristics, including prevalent fractures and co-morbidities, and post-treatment mortality were comparable across persistence durations, and we found no evidence of a healthy adherer effect.

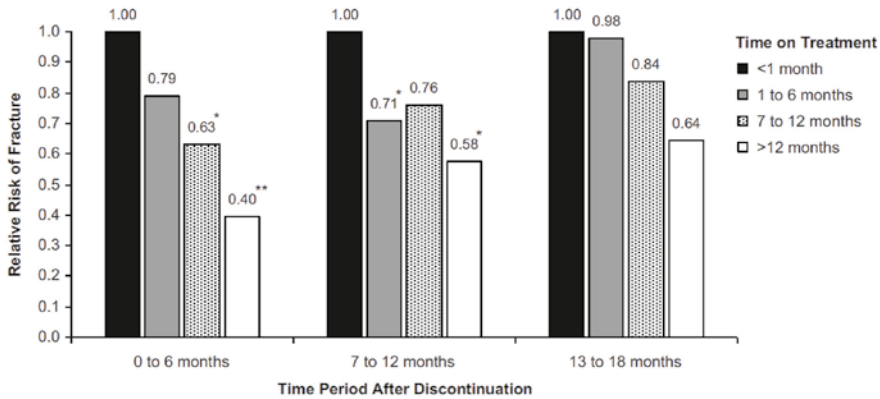


**Figure 7.** Hazard Ratios of fracture after stopping treatment with alendronate or risedronate, stratified by preceding time on treatment and time after treatment. Preceding treatment <1 month used as reference in each follow-up time window. (re-use from paper III with permission from Springer Nature)

## 5.4 Revisiting residual effect in a new analysis with new data

Using the methods described in section 4.2.5.4 a new analysis of residual effect was performed in a considerably larger dataset with longer follow-up. Results are preliminary and have not been published or peer reviewed elsewhere.

### 5.4.1 Patient characteristics

Patient characteristics were generally comparable across different levels of persistence. Prior fractures were more frequent and glucocorticoid use less frequent in patients with treatments longer than 24 months. T-score data for the Total Hip and Lumbar spine were only available for a subset of patients (n = 6,190) but were reported as means where available. Mean and maximum follow-up was 3.4 and 9.5 years, respectively.

Patient characteristics for statin users (n = 132,725) are not reported here but were also largely comparable across different levels of persistence to statins.

**Table 8.** Patient characteristics

| | Pre-index treatment length with bisphosphonates | | | | | |
|---|---|---|---|---|---|---|
| | **<1 month** | **2-6 months** | **7-12 months** | **13-24 months** | **25+ months** | **All patients** |
| n | 6,285 | 33,821 | 18,815 | 17,463 | 19,886 | 96,270 |
| Female | 85% | 80% | 79% | 81% | 86% | 82% |
| age (mean, years) | 73,0 | 72,0 | 72,7 | 73,0 | 74,9 | 73,0 |
| Prior fracture (any)[1] | 46% | 48% | 47% | 50% | 61% | 51% |
| Prior fracture (hip)[1] | 8,8% | 9,0% | 8,8% | 9,2% | 11,0% | 9,4% |
| Glucocorticoid use[2] | 35,5% | 39,4% | 42,7% | 39,2% | 26,0% | 37,0% |
| Secondary osteoporosis | 13,4% | 14,1% | 13,3% | 11,5% | 11,0% | 12,8% |
| T-score (Total hip, mean SD)[3] | -2,04 | -1,96 | -1,90 | -1,97 | -1,98 | -1,96 |
| T-score (Lumbar spine, mean SD)[3] | -2,19 | -1,94 | -1,96 | -2,05 | -1,99 | -1,99 |

[1]Going back to 2001

[2]Equivalent to prednisolone 5mg/day for 3 months during 12 months before index

[3]T-score data only available for 6,190 patients (6.4%)

### 5.4.2 Cumulative incidence of any fracture

Cumulative incidence of any fracture was plotted for men and women for up to 8 years after stopping treatment in Figure 8. The cumulative incidence during this period was estimated at 23% and 38% for men and women, respectively.

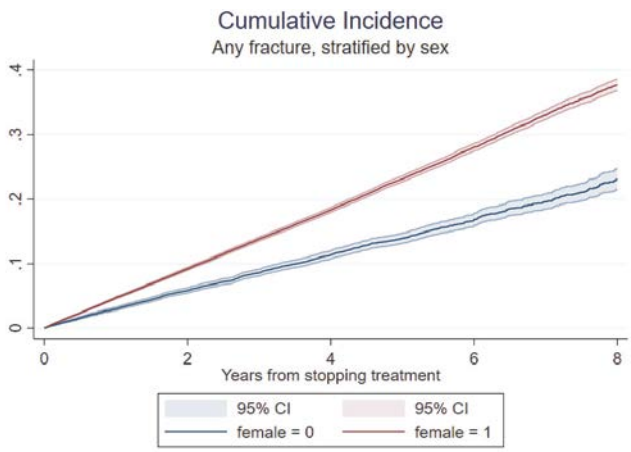


**Figure 8.** Cumulative incidence with $CI_{95}$ of any fracture after stopping treatment in women (female=1) and men (female=0) from the selected sample

### 5.4.3 Residual effect stratified by pre-index persistence and follow-up time

Figure 9 shows hazard ratios of any fracture over time and stratified by preceding time on treatment with oral bisphosphonates. HRs are reported relative to patients treated for <1 month in each time period. There were little or no residual protective effect after treatments shorter than 6 months while treatments longer than 6 months appeared to confer risk reductions in the range of 20-35% during the first five years after stopping treatment. Hazard ratios were not statistically different form the refence group beyond five years. This does not preclude that there are long-term protective effects beyond five years after stopping treatment, but the available sample did not contain enough patients with sufficiently long follow-up to draw such conclusions.

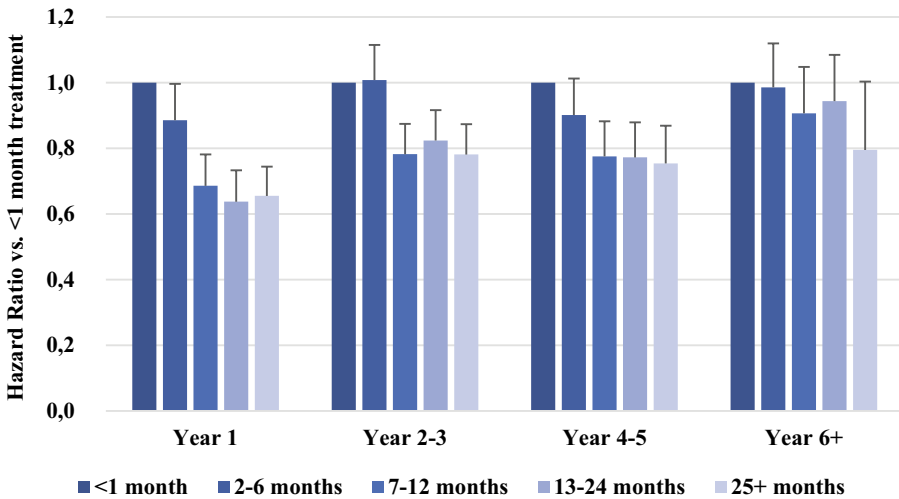


**Figure 9.** Adjusted HR of any fracture after stopping OBP treatment, stratified by time on OBPs before stopping treatment. The group with <1 month of treatment was used as reference in each follow-up time window.

The reference analysis (Figure 10) of the relationship between persistence to statins and fracture risk showed no tendency that persistence to statins was associated with an increased or decreased risk of fracture during follow-up.

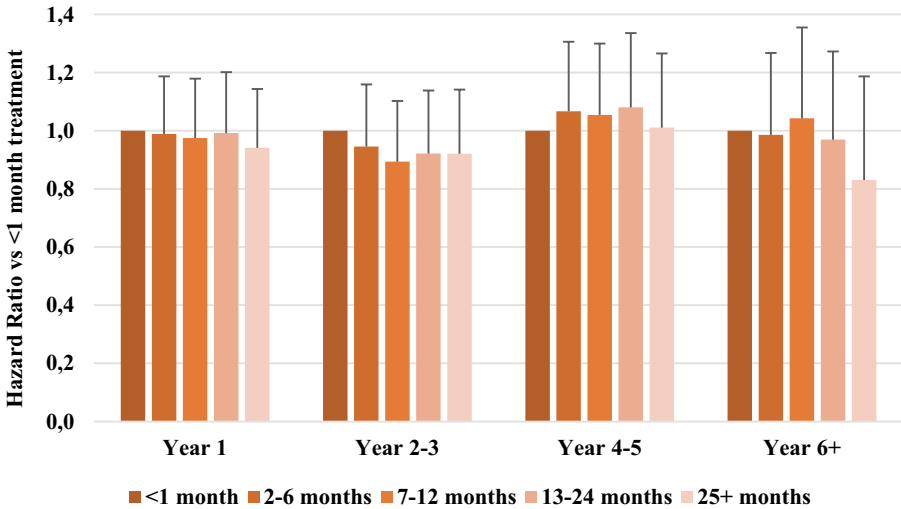


**Figure 10.** Adjusted HR of any fracture after stopping statin treatment, stratified by time on statins before stopping treatment (n= 132,725). The group with <1 month of treatment was used as reference in each follow-up time window.

## 5.5 Paper IV: Health economic modeling indicates that adherence could have implications for cost-effectiveness but that it is dependent on the analysed scenario, assumptions, and data.

The model was used to compare a hypothetical "fully adherent" patient group with a "partially adherent" group, as well as a "no treatment" option. The "partial adherence" alternative was designed to approximate how treatments are used in clinical practice, as opposed to a clinical trial setting.

In the base-case scenario, which simulated and intended 5-year treatment, the partial adherence group incurred lower drug costs (-68%), higher fracture costs (+13%), more fractures, and fewer Life years and QALYs gained when compared to the "full adherence alternative". When estimating the net differences in this hypothetical analysis, full adherence over 5 years costed more (+ €712), resulted in more Life Years and QALYs gained (+0.021/patient and +0.038/patient). The resulting Incremental Cost-Effectiveness Ratio (ICER) was estimated at €18,809/ QALY gained. However, the exact ICER of "full vs. partial adherence" was not necessarily the most relevant outcome of this article, as it mainly was used to relate different aspects of cost-effectiveness to each other.

The model was used to analyse the impact of different variables, input data, and assumptions. The potentially important drivers of cost-effectiveness in this context include (in no particular order);

- Magnitude of reduced drug effectiveness due to poor compliance
- Assumptions and data regarding offset time (residual effect after stopping treatment)
- The underlying fracture risk in the treated population
- The anti-fracture drug effect of the analysed interventions
- Drug prices
- Fracture related health care costs

Other seemingly unrelated factors such as discount rates and the intended treatment length for a fully adherent patient also impacted results. The level of suboptimal treatment persistence, which is the main reason addressing this in the first place, was estimated to have a smaller independent impact on the model results. This emphasizes that all the aspects that should be taken into account when incorporating adherence into an osteoporosis model are interlinked. For example, increasing persistence to a very expensive but moderately effective treatment may be cost-ineffective, depending the treatment alternative, the level of risk in the population, and so forth.

Model analysis of optimal adherence was associated with fewer osteoporotic fractures, and the impact was more evident among those with prior fractures. The health benefits of adherence were often partially offset by increased intervention costs associated with the improved drug-taking behavior.

# 6 DISCUSSION AND CONCLUSIONS

There is and has been considerable effort invested in finding and developing new chemical entities and formulations for the prevention of osteoporotic fractures. This is naturally a good thing since the patient population in question is large and the consequences of fractures in terms mortality, quality of life and costs are considerable. This effort is in many ways driven by actors on free markets whose intrinsic purpose is to develop new pharmaceutical products, often improving on what already is available, or providing treatments options for a diverse patient population. Nonetheless, the emergence of new treatments options may, in the case of osteoporosis, confer smaller potential improvements in outcomes than would improvements in drug delivery and case-finding. The Swedish government agencies that primarily are tasked with regulating and assessing osteoporosis treatments in terms of effectiveness and safety (MPA[1]) [95], and cost-effectiveness (TLV) [96] focus mainly on the properties of the drug itself and less so on factors such as practicality of administration, convenience, or other factors that may influence how the drug is used.

This thesis aimed at addressing pharmacoepidemiologic and health economic aspects of poor adherence to osteoporosis treatment by both establishing the extent of the problem as well as investigating how it can be incorporated into the health economic framework that commonly is used to inform reimbursement of new treatments as well as regional priorities for recommended prescription standards.

All three register studies (papers I-III) used the national patient register and the prescribed drugs register. The different research datasets originate from the same data extraction, called the SARA study (Swedish Adherence Register Analysis). Studying drug taking behaviour in register data is associated with some inherent limitations. For example, it is difficult to ascertain why a patient has stopped her treatment. It could be due to side-effects, low perceived risk due to an asymptomatic disease, insufficient follow-up by the care giver, or a conscious decision by the physician to stop treatment. It is also not possible to know if a pharmacy dispensing always means that the patient has consumed the medication as intended.

[1] *Benefits are defined on the basis of the indication sought and should generally be direct and concrete, such as prolonged survival, cured infection, prevented / delayed stroke / heart attack or reduced pain.*

## 6.1 Refill persistence and the relationship to fracture risk

This thesis illustrates that relative risk reduction estimated in clinical trials is too blunt an instrument when assessing whether a treatment is effective in a real-world setting. Generic alendronate has been the mainstay of pharmaceutical fracture prevention in Sweden for some time and results from this thesis showed that ~50% of Swedish patients have stopped their treatment within 12 months after starting it. Treatment is generally recommended to persist for 3-5 years. The type of register data used here can however not address why treatment has been stopped prematurely. It could be due to experiencing adverse drug reactions, lack of follow-up and encouragement from the treating physician, or lack of motivation due to an asymptomatic disease in combination with concomitant medication for other conditions perceived to be more important. The results from paper III studying residual effect suggested that treatment discontinuation may coincide with the contraction of conditions associated with increased mortality, which may be a justified course of action. Nonetheless, a study by Jonsson et al. [53] comparing osteoporosis care in Swedish regions showed that there were large differences across regions in the proportion of patients that was switched over to another option after discontinuation of alendronate treatment within 12 months. Results ranged from 3-4% in Kronoberg and Västernorrland to 16% in Jönköping, indicating that health care organization and policy have substantial roles to play in improving persistence to osteoporosis treatment in general.

Irrespective of the underlying reasons for stopping treatment it appears to be associated with reduced treatment effectiveness due to insufficient drug exposure. Patients filling osteoporosis medication prescriptions for 2-3 years had ~40% lower incidence of fractures than those who had only filled prescriptions for <30 days of medication during the same time frame. Absolute risk reduction (ARR) was ~5.0% over three years, meaning that one fracture could be avoided for every 20 early dropouts that instead could be kept on treatment for 2-3 years. The analyses in paper III and the new analysis contrasting the results to refill persistence to statins and its association to fractures did not indicate the association between fractures and refill persistence was confounded by a “healthy adherer effect” (i.e. unobserved confounding).

## 6.2 Refill compliance

Medication Possession Ratio (MPR) and its methodological sibling, Proportion of Days Covered (PDC), have been used extensively for studying adherence in retrospective pharmacy and prescription data [63]. The version of MPR used in paper I of this thesis was actually closer to the definition of PDC, given that accumulation of drugs was counted for in a way that prohibited MPR from being >100%.

However, the main difference from other osteoporosis adherence research was that MPR only was measured in persistent patients, avoiding the variable to be a composite of refill persistence and refill compliance. MPR in persistent patients was estimated at 95%, which suggests that refill persistence should be the adherence metric of choice in osteoporosis. This appears to be true in the Swedish context but studies in other health care systems are warranted. Moreover, the relationship to fracture risk is not necessarily the same for gaps in an ongoing treatment and completely stopping treatment for a longer period.

## 6.3 Generic substitution

The generic substitution reform from 2005 has been estimated to have led to savings of approximately 8 billion Swedish kronor annually during 2007–2010. Such cost-savings can be an important contribution when increasing treatment uptake and access to new more expensive treatments that are protected by market exclusivity for ~10 years after their authorization. The findings in this thesis do however identify a possible risk related to automatic generic substitution (AGS) of osteoporosis at the pharmacies, namely reduced treatment persistence. If the estimated relative difference over time compared to proprietary risedronate are combined with the fracture risk results in Paper I it is plausible that AGS is the cause of unwanted excess risk of fractures in the osteoporotic population.

Only osteoporosis medication (oral bisphosphonates) was studied and additional research would be necessary to ascertain if similar patterns exist for other therapy areas and other types of patient populations. Neither treatment persistence studied in Paper I or its association to automatic generic substitution were influenced by age in adjusted hazard models. At least the latter finding is unexpected since cognitive impairment and polypharmacy are more common among the elderly, and such characteristics could be suspected to interact negatively with an automatic replacement of the package of medicines expected by the patient.

The study period included cohorts of patients that started their treatments in 2006-2009, which was only 2-5 years after the reform. It cannot be excluded that some form of habituation has occurred since then, where patients are more accustomed to automatic generic substitution.

If a negative association between AGS and persistence to preventive long-term treatments in general were to be established, it would highlight the need to amend the reform with measures to improve the situation. Possible alternatives could be generic prescribing, where brand names not are used in prescriber communication and electronic prescriptions, stricter regulations for how medicine packages should be labeled or shaped, or simply an evidence-based strategy for how prescribers and pharmacists should communicate with patients with respect to generic substitution.

## 6.4 Residual effect

The unique properties of bisphosphonates (binding to bone mineral and long retention in the skeleton) provide opportunities as well as challenges for both clinicians [97], guidelines, and health economic evaluations. The effects on remodeling of the bone persist after stopping treatment, and this has led to interest in RCT extensions where residual effect on BMD and fractures could be studied [85-87]. However, RCTs typically run for 3-5 years and patients will therefore have been treated considerably longer than what is the case for many patients in the real-world setting.

The question of residual effect after osteoporosis treatments is important in different ways depending on the perspective adopted. One aspect is that of necessary length of treatment and the implications of "treatment holidays", where a patient stops treatment for a longer period and then returns [98]. Reasons for considering such holidays are related to unnecessary costs of treatment and management and an increased risk of the rare but very serious atypical femur fractures after long exposure to bisphosphonates [99]. The FDA have suggested that a drug holiday may not be advisable in high-risk patients, but for patients discontinuing treatment, there were no concrete recommendations on what should be done [100].

The results in this thesis from paper III complemented with a new preliminary analysis in a larger sample indicate that at least 12 months of treatment with oral bisphosphonates (OBPs) is necessary to achieve a residual effect post-treatment. However, the analysis in paper III only followed patients after stopping treatment, but not those staying on treatment, which precludes any conclusions regarding the appropriateness of treatment holidays. Conversely, the findings in paper I associating poor refill persistence to increased fracture risk indicate that remaining on treatment is the better option for patients at high risk of fracture.

### 6.4.1 The new complementary analysis of residual effect

The new analysis in this thesis was designed to fill some of the gaps left by the limited sample and follow-up in paper III. A refence analysis of patients with different levels of persistence to statins was also performed to investigate if a general "healthy adherer effect" could invalidate any interpretations of the relationship between persistence and fracture risk. An alternative design would have been to instead measure the risk of cardiovascular events after bisphosphonate use. The reason for instead selecting a statin population followed on fractures was that the potential unobserved confounding investigated should influence fracture risk, rather than cardiovascular outcomes. For example, propensity of falling or risk-taking behavior would not necessarily increase the risk of myocardial infarction or stroke.

The new complementing analysis generally supported the results from paper III but also suggests that a residual effect of 20-35% on any fracture after OBPs may be maintained for up to 5 years. Whether such a long residual effect also is present after treatment with other therapeutic options, such as denosumab, zoledronic acid, PTH, and the forthcoming romosozumab, is unclear but should be factored into the treatment choice. The reference analysis of persistence to statins showed no pattern that a general "adherence behavior" would be associated with lower fracture risk. A limitation of the new preliminary analysis is that it only was performed on single failure data, meaning the patients could incur a maximum of one fracture during follow-up. It is possible that the estimated magnitude of the residual effect would increase if multiple failures were allowed, and it would also increase statistical power.

The RCT extensions of patients stopping zoledronate [85] and alendronate [86] had limited samples but showed a statistically significant increase vs. controls in the risk of vertebral fractures, but not for non-vertebral fractures. These findings suggest that it could be appropriate to also investigate different fracture types separately in this larger register based sample.

### 6.4.2 Health economic implications of residual effect

The health economic implications of residual effect can be considerable, since it concerns drug effect for no additional drug cost [81]. This would be especially true if residual effect were shown to be different across treatments. A post-hoc analysis of the FREEDOM trial indicates that stopping denosumab may cause an increased risk of multiple vertebral fractures [101] and the effect of risedronate on Total Hip BMD has been reported decrease within a year from stopping risedronate [87]. New effective treatments may be deemed less cost-effective if there are reasons to believe that post-treatment fracture risk more rapidly will return to pre-treatment levels. Another alternative is that post-reimbursement follow-up of residual effect data would be required by Health Technology Assessment (HTA) bodies.

Paper III and its complementary analysis showed that refill persistence had a clear impact on the post-treatment fracture risk, at least for treatments longer than 12 months and during the first year after stopping treatment. How treatment persistence interacts with residual effect over longer time is still unclear, and it was not specifically analyzed in the complementary analysis in this thesis. From an HTA perspective such a relationship could mean that persistence to treatment would be even more important for decisions regarding pricing and reimbursement of new therapies.

## 6.5 Health economic modeling and adherence

Since persistence to osteoporosis treatments is sub-optimal and actual treatment durations for most patients are considerably shorter than what is studied in clinical trials it raises the question of how it should be handled in health economic evaluations. When comparing a treatment to "no treatment" it is tempting to conclude that poor persistence will result in losing a part of the effectiveness and an equally large part of the intervention cost. This notion is only true if all relationships are proportional and independent of time, so that half of the drug exposure confers half the effect and that the costs, risks and consequences of disease are the same at the beginning and end of the evaluated time period. In the case of osteoporosis this is not the case. Risk of fracture increases steeply with age, and so does fracture related costs and mortality. Moreover, as was concluded in paper III of this thesis and its complementary analysis, persistence also influences the fracture risk after treatment. The impact of persistence can be even larger when several treatments with different intervention costs and effectiveness profiles are compared.

Paper IV suggests a framework for combining the pieces of this puzzle without introducing double counting of costs or effects and that also is reasonably aligned with how data realistically can be collected. Nonetheless, incorporating adherence in osteoporosis models requires substantial amounts of additional data that may not always be available. For example, it is not possible to collect refill persistence data in the real-world setting for a new treatment before it enters the market.

The modeling framework proposed in paper IV was based on a specific scenario that was chosen to reflect a typical osteoporosis population, but what drives cost-effectiveness in one scenario can be of less importance in another. We therefore attempted to identify more universally important factors by letting model variables vary independently in a large number of model simulations. Results suggested that underlying risk of the population, residual effect, and drug costs all had considerably impact on the influence of persistence for cost-effectiveness. But that all variables are interlinked and modulate each other's impact is also the main limitation of an attempt generalize what drives the importance of persistence in health economic evaluation of osteoporosis treatments.

It is advisable that those who perform or assess the incorporation of adherence in health economic osteoporosis models carefully consider what an assumption or technical solution means, not only in the direct sense, but also how it will interact with other aspects of the decision problem. The choice of accounting for or disregarding adherence may have an impact on both treatment recommendations, priorities, reimbursement, and prices of treatments for osteoporosis.

## 6.6 Main Conclusions

- Refill persistence to typical oral osteoporosis medication estimated from pharmacy dispensing in Sweden is poor, with ~50% stopping treatment within 12 months. Prescription refill gaps among persistent patients appears to be a margnial problem, with 96% of patients having access to >80% of intended doses.
- Poor refill persistence to osteoporosis treatments is associated with an increased fracture risk in an exposure-dependant manner.
- Automatic generic substitution of alendronate tablets at pharmacies was likely causing reduced treatment persistence to treatment during 2006-2009. Patients who had their alendronate product substituted at the first prescription refill had 25% higher risk of discontinuation their treatment. This topic should be revisited in more recent data and for other theraputic areas.
- It is likely that treatments shorter than 6 months with oral bishposphonates has little effect on fracture risk.
- There is a statistically significant inverse relationship between time on bisphosphonate treatment and post-treatment fracture risk. This finding supports an assumption that the magnitude of a residual effect depends on the preceding time on treatment with bisphophonates in health-economic evaluations.
- Oral bisphophonates taken for at least 12 months may confer a residual effect of 20-35% on the risk of any fracture for up to 5 years after stopping treatment. It is not clear if and how such a residual effect wanes with time after stopping treatment. The health economic implications of residual effect can be considerable, depending on the context.
- Incorporating treatment adherence into a health economic evaluation in osteoporosis can have a substantial impact, but is context specific. The choice of accounting for or disregarding adherence to treatment may have an impact on both treatment recommendations, priorities, reimbursement, and prices of treatments for osteoporosis.

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