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Department of Traumatology and Orthopedics, University of Tartu, Tartu, Estonia

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ABBREVIATIONS

APC	Annual Percent Change
ATC	Anatomical Therapeutic Chemical classification
BMD	Bone Mineral Density
BMI	Body Mass Index
DDD	Defined Daily Dose
DID	Defined Daily Doses per 1,000 Inhabitants per Day
EHIF	Estonian Health Insurance Fund
GP	General Practitioner
ICD-10	International Classification of Diseases 10th edition
IOF	the International Osteoporosis Foundation
MEMS	Medication Event Monitoring System
MPR	Medication Possession Ratio
OP	Osteoporosis
PDD	Prescribed Daily Dose
PMN	Primary Medication Non-adherence
QALY	Quality Adjusted Life-Year
SAM	State Agency of Medicines
SERM	Selective Estrogen-Receptor Modulator
WHO	World Health Organization

1. INTRODUCTION

A medicine is a substance or combination of substances intended to prevent, diagnose or cure a disease or its symptoms, to relieve a disease condition in a human or animal, or to restore or alter vital functions in a human or animal through pharmacological, immunological or metabolic effect (1). However, a medicine is only effective if the patient takes it and in terms of a chronic condition, does so for a sufficient period of time (2).

The concept of patients taking medicines as prescribed by their healthcare provider is termed medication adherence (3). Compliance or concordance are sometimes used to describe the same concept, but recently it has been agreed that medication adherence is the preferred term. This is mainly because compliance implies the patient must obey their doctor's order, but in reality the medication process requires cooperation between the prescriber and patient. Concordance is actually a different concept that refers to the discussion between physician and patient during which agreement is reached regarding a suitable treatment plan (4).

Medication adherence can be divided into primary and secondary adherence. Primary adherence describes whether the patient purchases the medicines from the pharmacy after the initial prescription and starts the treatment in the first place. Secondary adherence follows the behaviour of the patient after the first dispensing from the pharmacy until the discontinuation of treatment (5). Secondary adherence can in turn be divided into three different concepts: the initiation of treatment, implementation of the dosing regimen and discontinuation of therapy, while persistence is the length of time between initiation and discontinuation of therapy (4).

Medication non-adherence is the most important reason why the efficacy medicines show in clinical trials are not reached in real life clinical practice (6). It has been assessed that on average only 50% of patients sufficiently adhere to treatment plans (7). When a patient does not take the medicines as agreed upon with a physician, they do not meet the clinical endpoints aimed at, and often put additional pressure on healthcare services via the need to treat complications that were not prevented because of the patient's poor adherence to the initial treatment (8).

Osteoporosis is a chronic disease characterized by the loss of bone tissue and as a consequence bone fragility (9). If bones are fragile fractures may occur following a low force trauma. Osteoporosis is often asymptomatic until a fracture but after a fracture in a major site (e.g. the hip or spine) the quality of life of the patient is significantly reduced (10). There are effective treatment options available that decrease the risk of fractures but the asymptomatic nature of the disease makes adherence to these medicines is suboptimal (11).

In Estonia the preconditions for quantitative and qualitative drug utilization research are very high. The State Agency of Medicines (SAM) collects package level consumption data from medicine wholesalers that covers 100% of drug

use in Estonia (ambulatory care and hospital care, prescription medicines and over-the-counter medicines). This data dates back to 1994 and enables long-term quantitative research. The Estonian Health Insurance Fund (EHIF) collects patient level prescription and dispensing data and also data on healthcare services that are provided to a patient. All EHIF insured patients are included in this database, providing data on more than 95% of ambulatory prescription drugs in Estonia. Dispensing data is available from 2004 onwards and enables qualitative utilization research. In 2010 ePrescribing was implemented in Estonia, which enabled primary adherence to be calculated by comparing prescription data with dispensing data. Estonia's ePrescription system is one of the most comprehensive in Europe, with only Denmark and Sweden reported to have a digital prescribing system that covers all prescriptions and pharmacies in the country (12).

The aim of the current thesis was to use Estonian data to establish the general utilization of osteoporosis medicines in Estonia and explore the possible connection between trends in osteoporosis related fractures and the consumption of medicines. Furthermore to ascertain primary and secondary adherence to osteoporosis medicines, including which patient characteristics influence adherence.

2. REVIEW OF LITERATURE

2.1. Osteoporosis

Osteoporosis (OP) is a major health problem (13) and cause of morbidity and mortality in the Western world (14,15). OP is a growing chronic health condition that is putting a significant load on both patients and society (16). OP alters bone quality and architecture, making bones more fragile and susceptible to fractures (9). The annual number of fractures in Europe is expected to increase around 30% during the period from 2010 to 2025, with a total cost related to OP induced fractures of approximately 120 billion EUR in 2025 (17). It has been demonstrated that the estimated number of fractures per a certain population is most sensitive to assumptions made using rate of fracture incidence trends (18), thus if the trend in fractures is reduced, the estimated numbers are not reached. One way to reduce the trend in OP induced fractures is effective pharmacotherapy (19).

OP is characterized by reduced bone mineral density (BMD) and disruption of bone microarchitecture, resulting in increased bone fragility and increased fracture risk (9,20). Bone is a living tissue that is constantly being renewed. Two activities maintain bone homeostasis: bone formation by osteoblasts; and bone resorption by osteoclasts (21). Under pathologic conditions, this balance is disrupted. High osteoclast activity or low osteoblast activity leads to low bone mass (osteoporosis), while low osteoclast activity or high osteoblast activity leads to high bone mass (osteopetrosis) (22). Loss of bone mass *per se* and OP are usually asymptomatic until a fracture occurs (2). The disease has clinical and public health importance only because of the fractures (23), which cause pain, degrade people's quality of life, and are often disabling (10). Clinically, osteoporosis is recognized by the occurrence of characteristic fractures after low-energy trauma; usually these are fractures of the hip, vertebrae, or distal forearm (24).

Fracture incidence trends have been shown to differ in different parts of the world (25). This indicates a need for local research on possible changes in the incidence rate of OP induced fractures. The potential drivers of negative changes to fracture rates are urbanization and a general aging of the population. Conversely osteoporosis medication use, birth cohort effects such as maternal and offspring nutrition, an increase in BMI, and lifestyle interventions such as smoking cessation and fall prevention, can result in a more positive trend (26,27). Increasing the consumption of osteoporosis medicines per a population has been shown to be one of the main factors that could positively influence fracture incidence trends (28,29). However, it has also been acknowledged that these results need to be verified among local populations and countries (30).

To alleviate the public and private burden of osteoporosis related fractures, risk assessments and a reduction in individuals' risk of fractures are critical (31). Key steps highlighted to tackle osteoporosis are: awareness raising campaigns; preventive lifestyle strategies; evidence-based guidelines; fracture

care; post-fracture rehabilitation and prevention of falls; economic data and an European fracture database (32). However, the exact loss of quality adjusted life years (QALY) following a fracture is difficult to assess, as various research has reported different utility (33).

Losing bone mass and quality is a normal part of the ageing process, but some people lose bone density at a higher than average rate and this can lead to the development of OP and fractures. Postmenopausal women are most affected by bone loss, due to changes in levels of reproductive hormones (34,35). Although men are less disposed to osteoporosis, they have been shown to be undertreated, thus also cannot go unrecognised when interventions to improve the quality of treatment are planned (36). There are many other diseases and factors that can increase bone loss and the risk of developing of OP, including: diabetes; several hormone-related conditions (hyperthyroidism, hyperparathyroidism, Cushing's disease); rheumatoid arthritis; malabsorption problems; long term use of high dose glucocorticoids; insufficient calcium and vitamin D intake; low physical activity; increased alcohol consumption; low body mass index (BMI); family history of fracture or OP; genetic predisposition. All these factors should be taken into account when assessing risk of fracture to determine which patients require further assessment and or treatment (37,38).

OP develops slowly over several years. It is a chronic and progressive disease and is the most common metabolic bone disease. An understanding of bone metabolism and OP mechanisms is crucial in terms of effective disease prevention, diagnosis, and therapy. OP diagnosis and fracture risk estimation is based mostly on T-scores on BMD scale. T-score is the difference between a measured BMD and the average BMD in healthy young adults (39). Osteoporosis in postmenopausal women is defined as a T-score $\leq$2.5 SD (40); however, OP fractures might also occur among those at a moderate risk (41–43).

2.2. Treatment of osteoporosis

Treatment for osteoporosis is based on using medicines that strengthen bones. As a chronic and progressive bone disease, long-term treatment is needed to control bone metabolic disruption, and patients need to adhere to treatment if it is to be effective and cost-effective (44,45).

The efficacy of osteoporosis drugs ultimately depends on whether they reduce the risk of fractures (46). The medicines used to ameliorate osteoporosis are the bisphosphonates (ATC group M05BA), peptides of the parathyroid hormone family (ATC group H05AA), selective estrogen-receptor modulators (SERMs) (ATC group G03XC), and other drugs that affect bone structure and mineralization (strontium ranelate and denosumab) (ATC group M05BX) (47).

The drugs used against OP have all been shown to reduce the risk of vertebral fractures, some have also been shown to reduce the risk of non-vertebral fractures and those of the hip (48,49). The effects of the different

agents used to treat osteoporosis are summarized in Table 1, which is modified from Kanis et al. (47). To date no single agent has been shown to be significantly superior in preventing fractures (50,51). The safety profile of the existing osteoporosis medicines have also been shown as favourable (52). There are several novel antiosteoporotic compounds in development with many of the new drugs combining efficacy with convenient administration that might translate into better adherence (53).

The bisphosphonates group is the first-line OP treatment option in most countries and comprises orally administered alendronic acid, ibandronic acid, and risedronic acid, and parenterally administered pamidronic acid and zolendronic acid. Bisphosphonates combinations group consists of combination preparations of bisphosphonates with added calcium, colecalciferol, or both.

Not all active substances classified in the WHO ATC are used in Estonia. In Estonia, the active substances used to treat osteoporosis are alendronic acid, ibandronic acid, risedronic acid, zolendronic acid, alendronic acid combined with colecalciferol, strontium ranelate, and denosumab (54).

As can be seen from Table 1, regardless of the active ingredient, all the trials that ascertained the efficacy of an osteoporosis medicine to ameliorate the risk of vertebral fractures lasted at least three years and patients' medicine intake was monitored to assure sufficient adherence. These trials indicated that the optimal treatment duration using osteoporosis medicines is at least three years, and sufficient adherence is necessary to obtain the results hoped for. Although some studies have shown self-reported improvement in patients' quality of life after only one year of treatment with bisphosphonates (55), this should be considered a surrogate endpoint.

The maximum required duration of treatment with bisphosphonates has recently been the subject of debate. Some authors recommend a drug holiday to prevent side effects from long-term use after 5 to 10 years of bisphosphonate treatment. Because bisphosphonates accumulate in bones and continue to provide some residual antifracture risk reduction it does not pose a risk. The duration of treatment and length of the holiday should be based on individuals' fracture risk, although patients at a mild risk might stop treatment after 5 years and remain on holiday as long as their bone mineral density is stable and no fractures occur; higher risk patients should be treated for 10 years and have a holiday of no more than a year or two (63). Other research has shown long-term bisphosphonate use does not influence bone material properties, but is associated with adverse effects (64).

Table 1. Anti-fracture efficacy of the most frequently used treatments of postmenopausal osteoporosis, when given with calcium and vitamin D, as derived from randomised controlled trials (modified from Kanis et al. (47)).

Active substance	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk		Duration of treatment
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]	
Alendronate	+	+	NA	+ (including hip)	3 years (56)
Risedronate	+	+	NA	+ (including hip)	3 years (57)
Ibandronate	NA	+	NA	+[b]	3 years (58)
Zolendronate	+	+	NA	+[c]	3 years (59)
Raloxifene	+	+	NA	NA	3 years (60)
Strontium ranelate	+	+	+ (including hip[b])	+ (including hip[b])	3 years (61)
Denosumab	+	+[c]	+ (including hip)	+[c]	3 years (62)

NA no evidence available, + effective drug

[a]Women with a prior vertebral fracture

[b]In subsets of patients (post-hoc analysis)

[c]Mixed group of patients with or without prevalent vertebral fractures

Monitoring the efficacy of anti-osteoporotic drugs in a real-life setting is part of successful osteoporosis management, as it can help identify poor-adherent from non-responder patients (65). Although a connection between increases in medicine consumption and the decrease in price of drugs has been suggested for other drug classes (66), specific data concerning changes in the consumption of osteoporosis medicines and the price of drugs is scarce.

2.3. Drug utilization research

2.3.1. Definition

Drug utilization research was defined by the WHO in 1977, as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (67). The discipline can be seen as a bridge between pharmacoepidemiology and health services research, and is closely connected to clinical pharmacology that aims to promote the safe and effective use of medicines (3).

The ultimate goal of drug utilization research must be to assess whether using a drug therapy is rational or not. To reach this goal, methods of auditing drug therapy are necessary (67).

Drug utilization can be measured in costs; the weight of active ingredients used; the number of packets or tablets; the number of prescriptions; and defined daily doses. It is valuable to use more than one type of measurement, as it provides researchers other aspects to investigate that might help them better understand drug use (3).

2.3.2. Methods and data collection

Drug utilization studies can be quantitative or qualitative (68). Quantitative studies report on the present state, developmental trends, and time course of drug usage; qualitative studies assess the appropriateness of drug utilization by linking prescription data to the reasons for prescribing (68).

The data sources used in drug utilization research can be primary or secondary. Primary data is collected by an investigator specifically for research purposes; secondary data sources (patient files, medical records) have not been generated for research purposes, but can be used in the analysis of a research question (69).

Data used in drug utilization research can be obtained from sales registries, procurement records, drug warehouse records, prescriptions, medical records, dispensing records, pharmacy stock accounts, health professionals, and patients themselves (3).

2.3.3. Units of measurement in drug utilization research

Use of the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) as the measuring unit are the recommended methods in quantitative drug utilization studies. This system is widely used internationally, which makes cross-national comparisons possible (70). If one wants to perform valid and comprehensive cross-national utilization research, it is necessary to implement and validate ATC/DDD systems across all the countries in order to make the data comparable (71).

In the ATC classification system, the active substances are divided into different groups according to the organ or system upon which they act, and their therapeutic, pharmacological, and chemical properties. Drugs are classified at five different levels. Drugs are first divided into fourteen main groups based on organ systems they affect (1st level), then pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/ therapeutic subgroups, and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than dividing them into therapeutic or chemical subgroups (70).

DDD is the assumed average maintenance dose of a drug per its main use in adults. Defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose (PDD). Doses per individual patients and patient groups often differ from the DDD. Drug consumption data presented in DDD only gives a rough estimate of consumption, but not an exact record of the actual number of patients (70).

Drug consumption figures should preferably be presented as DDD/1000 inhabitants/day (DID), or when in-hospital drug use is considered, as DDD per 100 bed days. Sales or prescription data presented in DID may provide a rough estimate of the proportion of the population within a defined area treated with certain drugs. For example, the figure 10 DID indicates that 1% of the population receives a certain treatment. This is only correct however if the prescribed dose corresponds to the DDD (70).

2.4. Medication adherence

2.4.1. General aspects

Adherence to medicines refers to whether a patient takes their medicines as prescribed (day-to-day treatment with respect to timing, dosage, and frequency). Following the regimen to a sufficient extent is critical to achieving a drug's therapeutic effect (72). Medication non-adherence is the number one reason that the efficacy of medication shown in clinical trials is not achieved in real-life settings, and is associated with adverse treatment outcomes (6,73). Suboptimal medication adherence is universal across different classes of medicines (74). When facing a clinical situation where targets have not been reached, despite

substantial efforts to prescribe the most adequate therapy, non-adherence should be considered (75). Optimal adherence to treatment has been shown to substantially decrease health care costs compared to suboptimal adherence or almost non-existent adherence (76).

In real-life, the majority of patients' adherence to medicines is suboptimal (77), thus the cost-effectiveness of interventions is questionable as the efficacy of medicines is different than during clinical trials (78,79). It has been suggested that adherence to medicines should be taken into account when evaluating the cost-effectiveness of medicines, but this is currently not done in the majority of cases (80). If adherence can be improved, it would help achieve the optimal effect of medicines and reduce the outcomes of diseases the medicines are meant to prevent (81). Several factors, such as age, comorbidities, and polypharmacy, may affect adherence and influence the outcome of treatments. Even a change to the appearance of medicine packaging has been shown to create confusion and reduce patients' adherence (82).

2.4.2. Primary and secondary adherence

Adherence to medicines can be divided into primary and secondary adherence (83). Primary medication non-adherence (PMN) occurs when a new treatment is indicated, but the patient does not obtain the initial medicine prescription within an acceptable period of time. Secondary non-adherence measures prescription dispensing amongst patients who collected their first prescription (5). Secondary adherence to chronic disease medicines comprises three aspects: whether the treatment was initiated by the patient; if medicines are taken as prescribed; and whether the patient persists with the treatment for a sufficient time period (4). The adherence stages described have different drivers and thus the reasons patients become non-adherent are different, and possible solutions to non-adherence therefore must be multidisciplinary to cover all the different aspects of non-adherence (84).

2.4.3. Research methods

Aspects of secondary non-adherence to medicines have been studied quite thoroughly in other countries, but not in Estonia. Pre-initiation or primary non-adherence however has not been the subject of a lot of research, due primarily to resource related issues. Most adherence related research is done based on medicine claims databases, which effectively capture dispensing data, but often lack information regarding how often a medicine was prescribed (85). The increasing use of ePrescribing systems around the world (86) enhances the possibilities to study PMN, as the acts of prescribing and dispensing medicines are recorded in the same database, or can be easily collated from two different databases (87).

Medication adherence can be approached using direct methods (e.g. measuring drug concentrations in blood) or indirect methods (e.g. interviewing patients about their intake of medicines) (3). Direct methods require a clinical visit and bodily fluid to be collected, and are therefore costly and impractical in terms of every day adherence assessments. Direct methods are also subject to so called white coat adherence, meaning sampling is sparse and a patient can escalate their adherence before an appointment with a doctor (88). Indirect methods of adherence assessment can be self-reported scales or diaries, pill counts, prescription and dispensing databases, and electronic monitoring of drug intake (3). A critical review of self-reported measurements found them to be insufficiently precise, and in general unreliable in comparison with more objective tools (89). Pill counts were one of the earliest methods of adherence research, but these tend to overestimate the number of doses actually taken, as patients can easily reduce the number of tablets left in stock before checked upon (77). A medication event monitoring system (MEMS) is a smart medication package that records the time and date of every opening of the package. Adherence data resulting from the use of such packages are reliable and detailed. MEMS are too costly and labour intensive to use in every day practice, but are considered the gold standard of medication adherence measurement in clinical trials (90). Using prescription or dispensing databases are the gold standard to measure adherence in a community setting. Although they have their limitations, they have proved to be a valid proxy to establish patients' medication adherence (91). As using a prescriptions database requires the researcher to assume the prescription was also dispensed and done so on the same day as it was prescribed, data from a dispensing database is a better estimate of actual patient behaviour (3).

2.4.4. Adherence to osteoporosis medicines

Osteoporosis consists of chronic and progressive metabolic bone failure that requires long-term treatment. Previous research has shown that even a small decrease in the medication possession ratio (MPR), increases the risk of a hip fracture and the relative risk reduction of a hip fracture can be up to 60% per persistent patients compared to non-persistent ones (27,92), these results emphasize the importance of adherence to treatment to achieve optimal antifracture efficacy (8). The number of patients to receive treatment within a year after an OP-related fracture has been shown to be less than 20% (93), indicating there is a significant gap between the need for osteoporosis treatment and the actual prescribing of medicines (94). About half of the patients who do receive treatment adhere to it sufficiently, and only 35% persist with the treatment for at least a year (7,11). Although once weekly or monthly, rather than daily administered medicines are associated with improved adherence, uptake is still suboptimal (95). The number of fractures prevented and the QALY gain

obtained at real-world adherence levels are only 38% and 41% respectively of those expected with full adherence (96).

PMN rates vary substantially between different drug classes (97) and osteoporosis medicines have been shown to have some of the highest (98). This could be because osteoporosis does not usually cause pain or other symptoms until a disease induced fracture occurs, and patients tend to underestimate the severity of the disease, which leads to lower adherence (99).

Improvement in adherence to osteoporosis medicines is imperative, as it would effectively prevent more fractures (100) and help save healthcare resources from being spent on the treatment of bone fragility fractures (72). There are several factors that have been shown to affect patients' medication adherence, but most important seem to be the doctor–patient relationship, patient awareness about the medicine and the disease, and also the co-payment of medicines (101,102). The efficacy and safety of medicines are important determinants of patient preferences and informed patient decision making can have a beneficial impact on adherence to treatment of osteoporosis (103). Although there is a need to stress the favourable benefit–risk ratio of osteoporosis medicines among patients who need pharmacological therapy, quoting relevant statistics to patients is not usually sufficient to allay their concerns and improve adherence (104). Each patient's reasons for non-adherence tend to be different, and depend on individual beliefs or circumstances. Thus strategies to improve adherence to medicines should be individualized accordingly (105). Understanding patients' preferences and incorporating them in clinical decision-making could lead to improved care (106). The International Osteoporosis Foundation (IOF) has declared that there is an increasing need for strategies to be implemented in an appropriate health economic setting for the management of non-adherence for guideline development and for better reimbursement regulations (17,107).

The widespread non-adherence indicates the need for policies to ensure safer, more effective, and cost-effective use of medication (108). While adherence research dates back several decades, there is still a considerable amount to be learned about adherence with regard to chronic disorders. For example, about the predictors of adherence to more precisely target subgroups at a higher risk of suboptimal adherence, and also possible interventions to improve adherence (109).

2.5. Electronic prescribing

ePrescribing is a system that facilitates the interaction between physicians and pharmacies, by enabling physicians to create and pass-on prescriptions electronically to pharmacies (110). ePrescribing in general has several benefits: social; health; and economic (111). ePrescribing service users have perceived it as easy to use and beneficial in managing their medication (112). In addition to the aforementioned benefits, the increase in the use of electronic prescribing

systems (86) enhances the possibilities to carry-out primary medication non-adherence studies (87).

Although it has been shown that initially primary medication non-adherence can increase after the implementation of e-prescribing (113), this issue was resolved after patients became acquainted with the system and PMN rates improved compared to the baseline.

E-prescribing was introduced at the beginning of 2010 in Estonia, and it is one component of the Estonian eHealth system (114) that also combines the Electronic Health Record, Digital Registration, Digital Image, and Digital Prescription projects. All health care institutions, private professionals, and pharmacies are required to use this system, and all medical records and prescriptions in Estonia are centrally stored in the eHealth system (115). The Estonian ePrescribing system is currently one of the most comprehensive in Europe (12). The system is maintained and developed by the EHIF. All ePrescriptions are recorded at the Prescription Centre. The prescribing and dispensing of ambulatory medicines is done using the Prescription Centre. Health care professionals and pharmacies use third-party software as their interfaces, but they are connected to the central Prescription Centre and all activities concerning prescribing are saved in the central system. When an ePrescription is issued to a patient, they can go to any pharmacy in Estonia and get the medicine dispensed there. More than 99% of ambulatory medicines are prescribed digitally in Estonia and 100% of dispensings are saved by the Prescription Centre, because (the few) paper prescriptions are also inserted into the electronic system during dispensing (114).

As known to author the ePrescription system saves data on: date of prescribing; prescription number; patient's identifier, age, and gender; diagnosis code; medicine's active substance(s), strength(s), and dosage; instructions for administration; rate of reimbursement; the doctor's name and speciality. If an ePrescription or paper prescription is dispensed from a pharmacy, the date of dispensing, package details, number of packages, name of the pharmacist and pharmacy, amount paid by the EHIF, patient, and the total, and comments by the pharmacist – if there are any – are added to the already saved data of the prescription.

2.6. Summary of the literature

The efficacy of osteoporosis medicines have been established in numerous clinical trials, as has the loss of health utility following an osteoporosis induced fracture. However, the efficacy of medicines is impaired by less than optimal medication adherence, which stops patients receiving the maximum effect from medicines.

Worldwide, it has been established that on average only half of patients sufficiently adhere to prescribed medication therapy, meaning the other half might not gain the full benefits of a medicine, but are still susceptible to adverse

side-effects. Thus, assessing medication adherence is important, as interventions to improve adherence can be developed only if the nature and magnitude of the problem is measured.

Estonia is in a rather unique position in Europe and worldwide in terms of medication adherence research and qualitative drug utilization research in general, due to the ePrescribing system that has universal coverage of doctors and pharmacies. This allows a very thorough assessment of patients' behaviour in terms of the ambulatory consumption of prescription only medicines.

Despite the extensive opportunities of the ePrescribing system, it has not been utilized much in medication adherence research in general, and adherence to osteoporosis medicines has never previously been studied in Estonia. The trend in osteoporosis induced fractures has been described by Jürisson et al. (27), but has not been collated to the utilization of medicines.

3. AIMS OF THE RESEARCH

The present thesis is an epidemiologic study with an overall aim to analyse the utilization of osteoporosis medicines in Estonia and whether it correlates with hip fracture incidence trends. The aspects of utilization studied are to be the overall consumption of osteoporosis medicines, the rate of medication adherence in Estonia and whether specific patient populations with low adherence could be identified.

The specific aims were:

1. To analyse the consumption of osteoporosis medicines in Estonia and compare it to the consumption of the other Baltic countries;
2. To analyse possible relationships between the consumption of osteoporosis medicines and the trends in osteoporosis related hip fractures;
3. To establish primary and secondary adherence to osteoporosis medicines in Estonia, and explore the factors that influence adherence;
4. To establish the average time from prescribing to dispensing of osteoporosis medicines, and calculate the expenditure of inefficacious treatment courses.

4. PATIENTS AND METHODS

4.1. Summary of the studies

A summary of the patients and methods included in the four studies upon which this thesis is based is presented in Table 2.

Table 2. Overview of the study subjects and designs in studies I–IV

Study characteristic	Timing	Population/study material	Primary aim	Publication
Baltic comparison study	2010–2014	Consumption of osteoporosis medicines in the Baltic countries based on wholesalers' data	Comparison and analysis of consumption in Estonia compared to other Baltic countries	I
Drug utilization and fractures study	2004–2015	Hip fractures recorded in the EHIF database and consumption of medicines according to wholesalers' data	Medicine consumption and its possible relationship with the trend in osteoporosis related fractures	II
Primary adherence study	2012–2015	8,404 patients (>18 years old) who started osteoporosis treatment	Primary adherence to osteoporosis medicines and the factors influencing it	III
Secondary adherence study	2001–2015	24,652 patients (>50 years old) who started osteoporosis treatment	Secondary adherence to osteoporosis medicines and the factors influencing it	IV

4.2. Ethics

The studies included in this thesis did not produce ethical concerns, as the patients were not identifiable to the researchers.

4.3. Databases

4.3.1. Medicine wholesales database

In the Baltic comparison study and the drug utilization and fractures study Estonian State Agency of Medicines' (SAM) database was used to establish the total consumption of osteoporosis medicines in Estonia. SAM collects drug utilization data from medicine wholesalers. Every wholesaler holding an activity license in Estonia must submit quarterly reports to the SAM stating the amounts of every medicine sold. The reports cover 100% of Estonian drug sales. SAM compiles overall drug consumption reports using the WHO's ATC/DDD classification.

4.3.2. Health services database

Treatment invoices are submitted to the EHIF by health care providers. The number of invoices submitted for hip fractures diagnosed according to ICD-10 (S72.0–S72.2) was used to identify the number of fractures per annum in Estonia in the drug utilization and fractures study. Hip fractures were used as a proxy for all osteoporotic fractures, because a hip fracture is considered the most serious consequence of osteoporosis (116). Worldwide 1-year mortality following a hip fracture is estimated at 20–25% (117). Data was retrieved on the incidence of hip fractures from the health services database of the EHIF. To avoid duplication, only one invoice per patient per year was considered, as sequential fractures in one year are very uncommon.

4.3.3. Population data

Estonian population data was used in the drug utilization and fractures study to calculate hip fracture incidence. Population data in age groups for any given year was obtained from Statistics Estonia. Statistics Estonia publishes among other data the official population of Estonia (118).

4.3.4. Prescriptions database

In the primary and secondary adherence studies the Estonian Health Insurance Fund's prescriptions database was used. The EHIF can extract data per patient using a unique identifier. The actual identity of the patient was concealed from the researchers. For every prescription, the patient's identifier, age, gender, diagnosis code, prescribing doctor and their speciality, medicine and the number of packages dispensed, and the amount paid for the medicine by the EHIF and in total is stored in the database. Since 2010, with the introduction of ePrescribing, the database includes prescribing data in addition to dispensing

data. Until 2010 only dispensed prescriptions can be extracted from the database. Only prescriptions reimbursed by the EHIF are included in the database. Valid health insurance is needed in Estonia to get osteoporosis medicines reimbursed. Around 95% of the population in Estonia is insured, including all retired persons, so the EHIF prescriptions database covers the vast majority of ambulatory drug consumption in Estonia (114).

In the primary adherence study, data from the EHIF Prescription Centre on all prescriptions that were issued for osteoporosis medicines in Estonia from 2012 to 2015 was extracted, with information on each patient regarding whether they had a prescription for an osteoporosis medicine in the prior year. Medicine dispensing data was extracted from the 1st of January 2012 to the 1st of March 2016.

In the secondary adherence study, prescriptions that were dispensed from Estonian general pharmacies during the years 2001 to 2015 were used to establish secondary adherence to osteoporosis medicines in Estonia.

4.4. Patients

In the drug utilization and fractures study, hip fracture incidence in Estonia was standardized using age distribution (5-year age groups) based on 2009 data. This was done because the study covered a total of 11 years and the population in Estonia is ageing. Men and women of all age-groups were included in the study, as the consumption data gathered by SAM also includes total consumption of medicines.

In the primary adherence study, all patients older than 18 years of age who were prescribed an osteoporosis medicine were included, regardless of 10th edition of the International Classification of Diseases (ICD-10) codes. Only patients over 18 were analysed because children probably do not make the decision to purchase or not purchase a medicine by themselves. Patients who died shortly after (≤60 days) their first prescription were excluded from the study.

In the secondary adherence study, all patients aged 50+ years old who were dispensed at least one prescription with an ICD-10 diagnosis code referring to osteoporosis (M80, M81, M82, M83, M84, M85 or Q78) were included. Patients above 50 were included in order to be sure they were osteoporosis patients and not misclassified while prescribing. M80 refers to osteoporosis with an existing pathological fracture, M81 refers to osteoporosis but without an existing pathological fracture, M82 refers to osteoporosis in diseases classified elsewhere, M83 refers to adult osteomalacia, M84 refers to disorders of continuity of bone, M85 refers to other disorders of bone density and structure, and Q78 refers to other congenital bone fragility. If the patient had prescriptions with different diagnosis codes, then the aforementioned codes had to be present at least once for the patient to be included in the study (number of patients given in Table 2).

Only patients who started osteoporosis treatment were included in the secondary adherence study. Patients could not have osteoporosis medicines dispensed to them for at least a year to be defined as a new user. Data on death was linked to patients' identifiers and following-up patients who died during the study was stopped, but other patients were followed for new prescriptions until the completion of the study at the end of 2015.

4.5. Defining adherence

4.5.1. Primary medication adherence

Primary adherence describes whether the patient purchases the medicines from the pharmacy after the initial prescription and starts the treatment in the first place. Primary medication non-adherence (PMN) occurs when a patient does not purchase a medicine the first time it is prescribed. PMN was defined in the study as an initial prescription not being dispensed within 60 days. Prescriptions are generally valid for 60 days in Estonia, and the amount of any newly prescribed medicine should not exceed 60 days. If the doctor and patient see that a medicine is effective and tolerated, refill prescriptions can be prescribed that cover medicine for up to 180 days and are also valid for 180 days.

4.5.2. Secondary medication adherence

Secondary adherence follows the behaviour of the patient after the first dispensing from the pharmacy until the discontinuation of treatment. The term adherence was used to describe the initiation of treatment, implementation of treatment, and persistence with treatment. This could also be referred to as secondary adherence because all these aspects can be monitored after a patient has purchased their first prescription. In our study, each aspect of secondary adherence was analysed separately and provided results on all of them. Sufficient implementation was considered to be the theoretical medicines possession rate (MPR) of 80% or more doses taken over the course of treatment. The minimal time to take osteoporosis medicines for them to be effective is 1-year (119). This was considered a conservative estimate of sufficient persistence. Most of the clinical trials upon which osteoporosis medicines were granted marketing authorizations lasted three years (56,120,121). Sufficient medication adherence was thus defined in the context of this study as a patient taking 80% or more medicine doses and persisting with such implementation for one to three years.

4.5.3. Time to purchase

In the primary adherence study, the time between prescribing and dispensing was also analysed, and compared the average time of purchasing initial prescriptions to that of all prescriptions of osteoporosis medicines. As secondary prescriptions can be prescribed three refills at a time, it was calculated when the initial amount of medicine dispensed ran out, and set a potential dispensing date for the next prescription accordingly. In reality however, patients can purchase all three refill prescriptions at once, which means that their actual dispensing time is negative compared to what would be expected, as they are dispensed before the previous amount of purchased medicine is depleted.

4.5.4. Treatment gaps

In the secondary adherence study, gaps in treatment or so called "drug holidays" were also analysed. A gap was considered to be 90 to 180 days after the amount of medicine already dispensed to the patient should have been used up and no refill prescription was given. A gap that lasted longer than 180 days was considered the end of treatment and if the same patient started treatment again later in the study, it was considered a new treatment course.

4.6. Data analysis

In the drug utilization and fractures study and the secondary adherence study the Joinpoint Regression Program, Version 4.3.1.0 was used for trend analysis. Joinpoint is statistical software used to analyse trends. It uses joinpoint models to test if a trend change is statistically significant. Results of these tests are presented as the average annual percent change (APC) over a year. The tests of significance use a Monte Carlo Permutation method (122). In both studies, p-values less than 0.05 were considered statistically significant.

Potential relationships between the consumption of osteoporosis medicines and the average price of a daily dose was assessed using Spearman's correlation coefficient in the drug utilization and fractures study, as both potential indicators were non-normally distributed.

In the Baltic comparison study, regression lines were compared with STATGRAPHICS Centurion XVII Version 17.1.12. This was done to establish whether there were differences in the trends of osteoporosis medicines consumption between the Baltic countries.

In the primary and the secondary adherence studies, multiple logistic regression analyses were performed using Stata v12 and v13 (StataCorp LP), respectively. Multiple logistic regression analysis was used to compare primary and secondary adherent or non-adherent patients per socio-demographic background variable. Statistical significance was set at p-values less than 0.05.

Microsoft Excel was used as the main tool for data management, descriptive analysis and graph design (other than specified above) in all the studies.

5. RESULTS

5.1. Trends in the utilization of osteoporosis medicines and hip fractures

5.1.1. Utilization of osteoporosis medicines in Estonia and in the Baltic and Nordic countries

The trend in the consumption of osteoporosis medicines from 2004 to 2015 in Estonia can be divided into two different periods (Figure 1). From 2004 to 2009 the increase was very steep, with an annual average of 41.2% ($p<0.05$). During this period consumption increased from 0.8 DID to 3.9 DID, an almost 5-fold increase. From 2009 to 2015 consumption plateaued, with a statistically non-significant positive trend.

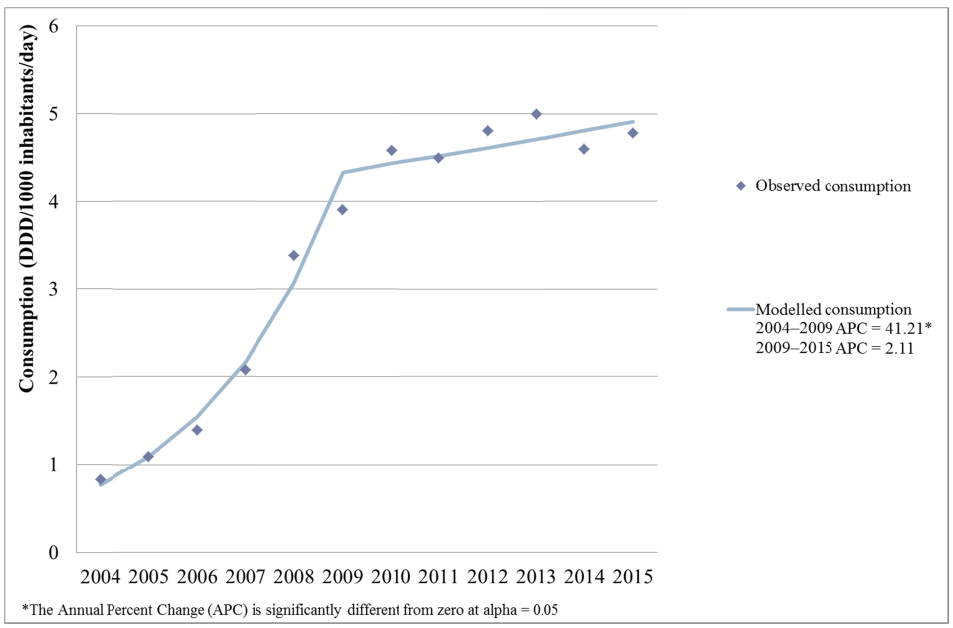

Figure 1. The actual and modelled trend of consumption of osteoporosis medicines in terms of the number of defined daily doses per 1000 inhabitants per day in Estonia from 2004 to 2015.

The consumption of all osteoporosis medicines was 4.8 DID in Estonia in 2015. This means that 4.8 of every 1,000 Estonian inhabitants consumed an average dose of an osteoporosis medicine every day. Considering that the population of Estonia was approximately 1,315,000 in 2015, this would translate to an estimated 6,300 patients.

When comparing Estonian consumption with that of the other Baltic countries, then can be seen that the consumption of osteoporosis medicines was rather similar in the Baltic countries in 2014: 5.2 DID in Latvia, 3.3 DID in Lithuania, and 4.6 DID in Estonia. The trends in consumption were also rather similar in the Baltic countries from 2010 to 2014 (Figure 2). Consumption increased from 2010 to 2013 and was then followed by a small decrease in 2014. An overall increase only occurred in Latvia, with consumption increasing from 4.2 DID to 5.2 DID. In Estonia, consumption stayed at the same level of 4.6 DID and there was a slight decrease in Lithuania from 3.4 DID to 3.3 DID. The average annual changes were +0.3% in Estonia, +5.9% in Latvia, and -0.8% in Lithuania. The slight differences in trends between countries were statistically non-significant, with a p-value of 0.41 between Estonia and Latvia, 0.46 between Estonia and Lithuania, and 0.24 between Latvia and Lithuania.

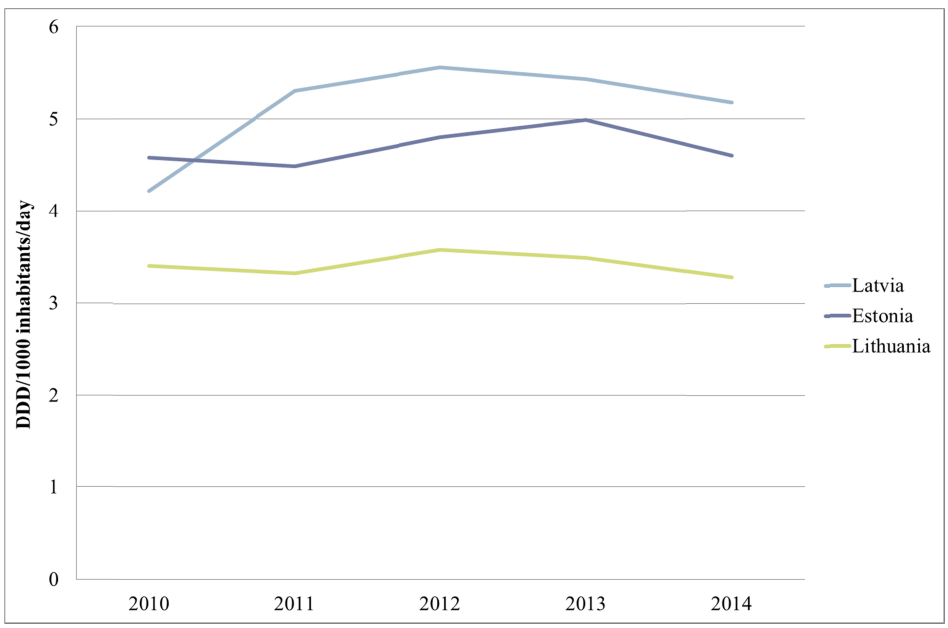

Figure 2. The consumption of osteoporosis drugs (ATC group code M05B) in the Baltic countries from 2010 to 2014, in terms of the amount of defined daily doses per 1000 inhabitants per day.

In the Baltic countries, the choice of active substances per each country did not change much from 2010 to 2014 (Figure 3). Only the consumption of denosumab and its share of the total consumption of osteoporosis medicines increased in all the countries. This was highest in Lithuania, with denosumab consumption increasing from 0.0 DID in 2010 to 0.8 DID in 2014. In Estonia the consumption of denosumab was 0.4 DID by 2014, which is approximately

500 patients. In Latvia the consumption of denosumab was lowest, with 0.2 DID in 2014. The consumption of bisphosphonates remained stable in all the countries. The consumption of strontium ranelate decreased in Lithuania and Estonia, and stayed the same as in 2010 in Latvia, following the restriction in its use by the European Medicines Agency in April 2013.

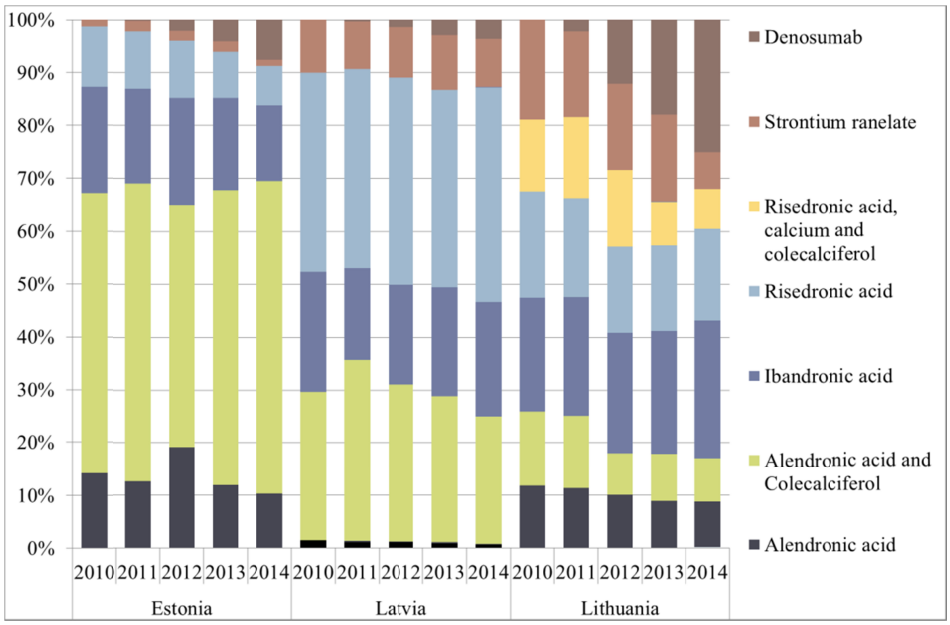

Figure 3. The consumption of drugs against osteoporosis (ATC group M05B) in the Baltic countries from 2010 to 2014 expressed as the proportion of the different active substances.

When comparing the share of different active substances used in the Baltic countries, Estonia stands out with its high use of the combination of alendronic acid and colecalciferol, which constituted almost 60% of total consumption of drugs against osteoporosis in 2014. Other active substances that were comparatively more used were ibandronic acid and plain alendronic acid, which consisted of 14% and 10% of the market share, respectively. In Latvia, the most used active substance was risedronic acid, which accounted for 40% of the total. The combination of alendronic acid and colecalciferol and plain ibandronic acid amounted to 1.3 DID and 1.1 DID, respectively. The most used active substance in Lithuania in 2014 was ibandronic acid, with 26% of the total (0.9 DID). The second most used was denosumab, with 25% of the total (0.8 DID).

When comparing the consumption of osteoporosis drugs in Estonia to that of the Nordic countries (Denmark, Finland, Norway, and Sweden), the average consumption in the Nordic countries was 2.5-fold higher than in Estonia (12.0

DID and 4.6 DID, respectively) in 2015 (Figure 4). The highest consumption was in Denmark, with 18.4 DID.

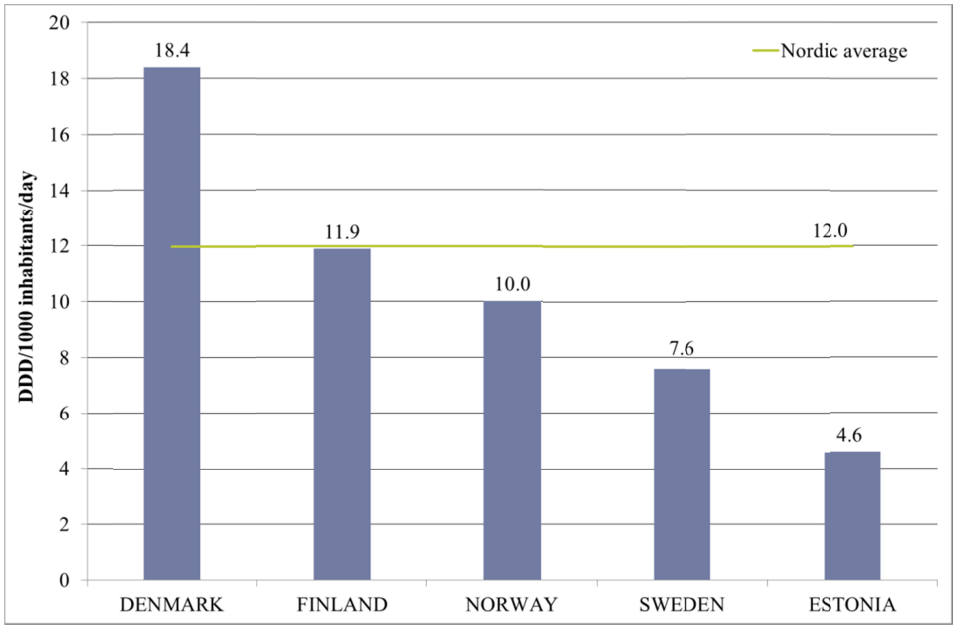

Figure 4. The total consumption of osteoporosis medicines in Estonia and the Nordic countries in 2015, expressed in defined daily doses per 1000 inhabitants per day and the average consumption of the Nordic countries.

5.1.2. The price of osteoporosis medicines

The average price of a daily dose of osteoporosis medicine moved in the opposite direction to consumption from 2004 to 2015 (Figure 5). The average price decreased by 16.9% ($p<0.05$) on average every year from 2004 to 2009. From 2009 to 2015 the decrease was 4.7% and the trend non-statistically significant.

The correlation between the consumption of osteoporosis medicines and the average price of a daily dose was -0.94 ($p<0.001$) from 2004 to 2015. The correlation for the period 2004 to 2010 was -0.95 and for the period 2011 to 2015 it was -0,26.

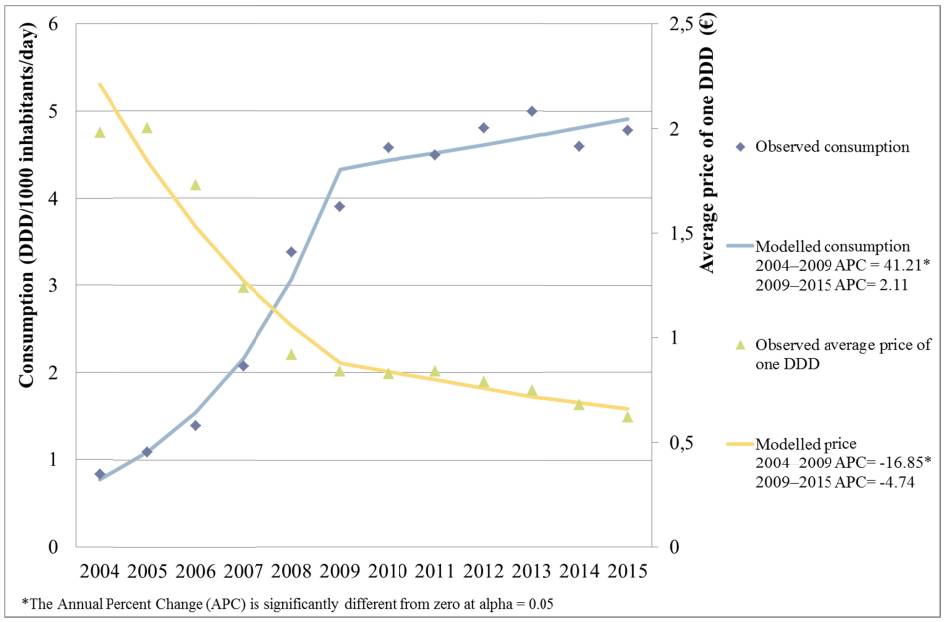

Figure 5. The actual and modelled trends in consumption of osteoporosis medicines, in terms of the number of defined daily doses per 1000 inhabitants per day (DID) and the average price of an osteoporosis medicine (ATC group M05B) daily dose in euros in Estonia from 2004 to 2015.

5.1.3. Trend in hip fractures in Estonia

There were around 1,500 hip fractures every year in Estonia from 2004 to 2015. Table 3 presents the standardized rate of hip fractures in 5-year age groups of patients over 50 years old for the years 2004 to 2015.

Table 3. Estonian 2009-standardized hip fracture incidence rates per 100,000 persons in the years 2004 to 2015

Age group	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
50–54	45.4	43.2	42.0	48.6	44.1	42.9	47.2	38.6	52.5	33.5	36.2	37.2
55–59	61.0	73.2	68.5	64.2	54.9	72.3	65.1	68.1	75.9	58.7	61.7	60.7
60–64	102.0	141.8	98.6	123.9	106.9	112.4	126.4	119.3	84.3	101.0	106.1	91.9
65–69	178.2	173.9	184.3	154.3	132.8	180.9	190.1	178.5	140.8	129.6	122.3	152.1
70–74	256.5	318.6	278.3	250.2	284.0	278.8	297.5	287.3	231.1	256.8	237.8	219.3
75–79	507.5	452.2	500.9	453.3	530.4	570.3	490.6	518.5	430.5	454.3	378.2	442.9
80–84	929.1	947.9	939.8	881.5	1,103.9	1,066.8	1,021.5	951.5	827.6	871.3	836.3	848.3
85+	1,960.3	2,055.4	1,939.1	1,986.6	2,017.9	2,259.3	2,116.7	2,130.1	2,123.9	1,926.3	1,836.4	1,924.2
Total	**109.9**	**116.8**	**112.0**	**106.4**	**116.1**	**123.2**	**118.1**	**117.4**	**103.0**	**102.5**	**94.4**	**99.7**

The trend in standardized hip fracture incidence rates from 2004 to 2015 can be divided into two periods. From 2004 to 2010 the rate of hip fractures increased on average 1.2% every year. The highest fracture rate was in 2009, with 123.2 fractures per 100,000 persons. The trend was not statistically significant. From 2010 to 2015 there was a statistically significant 4.5% ($p<0.05$) average annual decrease in standardized incidence rates of hip fractures (Figure 6). The results of table 3 are discussed in detail under point 6.3.

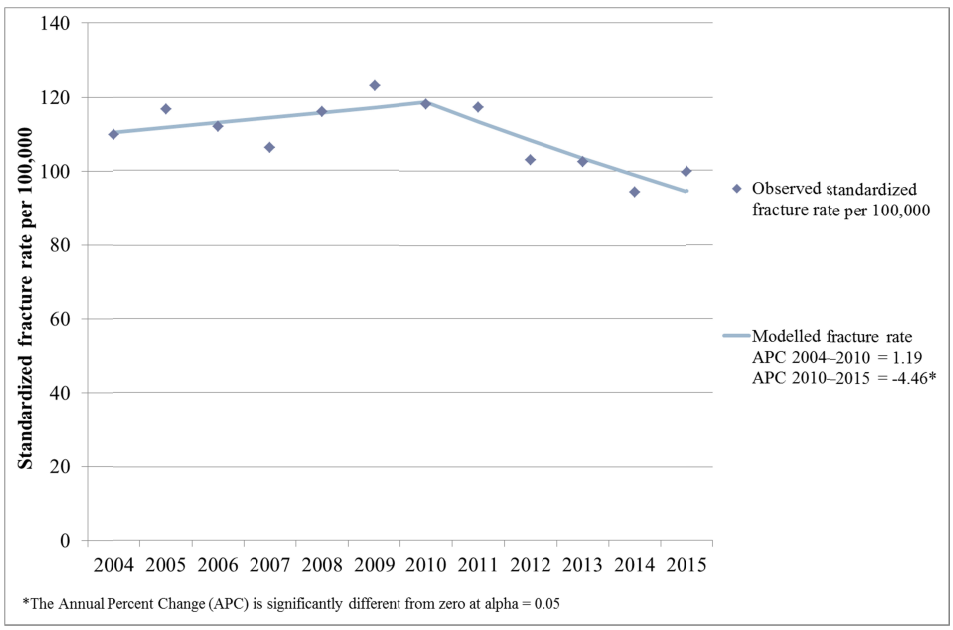

Figure 6. The standardized incidence rate and modelled trend of hip fractures (ICD-10 codes S72.0–S72.2) per 100,000 persons in Estonia from 2004 to 2015.

5.2. Medication adherence

5.2.1. Primary Adherence

5.2.1.1. Patients

8,404 patients were prescribed osteoporosis medicines for the first time in Estonia from 2012 to 2015, and were included in our study (Figure 7). 7,834 (93.2%) of the patients were female and 570 (6.8%) male.

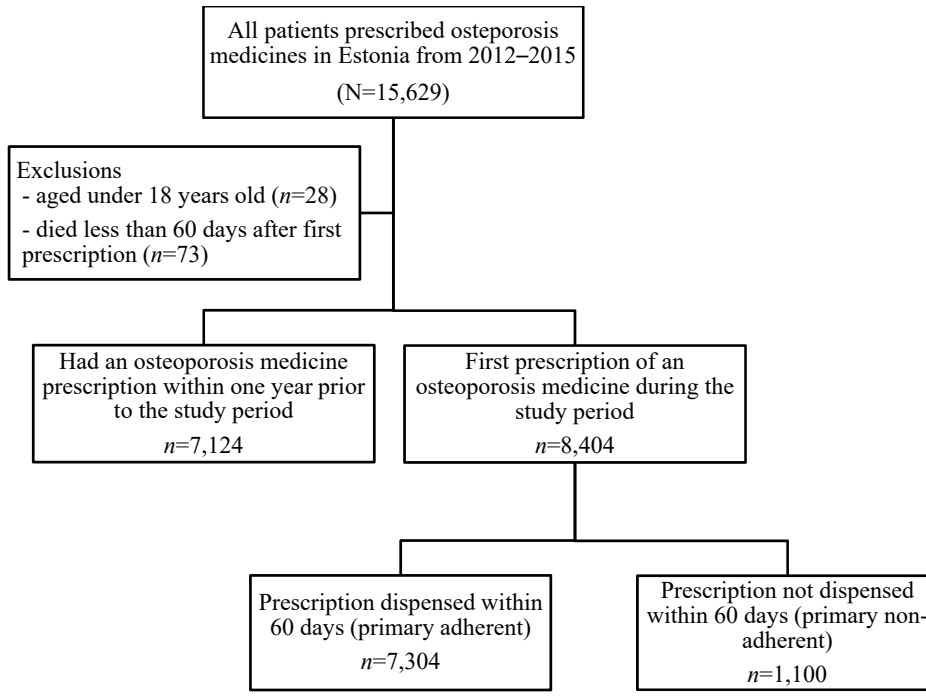

Figure 7. Identification of the primary medication adherence study cohort.

5.2.1.2. Primary medication non-adherence

1,100 (13.1%) patients out of the 8,404 did not purchase their first prescription within 60 days of prescribing. 462 patients (42.0% of the PMN patients, or 5.5% of the total number of patients) failed to purchase the first prescription, but did purchase a subsequent prescription. The median time for these patients between the first prescription and an actual dispensing was 92 days. 638 patients (7.6%) never purchased medication. Some of those patients (*n*=82) had more than one prescription that was not dispensed. For example, 3 patients had 5 prescriptions but did not purchase any of them. 4 patients had 4 prescriptions that all expired without being dispensed and 18 patients had 3 expired prescriptions with no dispensing.

5.2.1.3. Patient characteristics associated with primary medication non-adherence

The characteristics of patients who were primary adherent or primary non-adherent are presented in Table 4. Gender did not influence the probability of a patient being primary adherent or non-adherent ($p = 0.813$). Patients who had a prior fracture (M80) were more likely to purchase their first prescription than

patients with osteoporosis but no fracture (M81) or patients with other diagnoses. Initial prescriptions by orthopaedists or rheumatologists were more frequently dispensed than those issued by general practitioners. Differences in the purchase proportion of prescriptions by other specialists were non-significant compared to GPs'. Patients started on strontium ranelate or denosumab were more likely to be primary non-adherent compared to patients started on plain alendronic acid. There were no significant differences between the other active substances. Younger patients were more likely to be primary non-adherent than older patients, with the odds to be adherent increasing 7% (95% CI 3-10, p-value<0.001) with every 5 years of age.

Table 4. Characteristics of primary adherent and primary non-adherent patients

	Primary adherent (*n*=7,304)	**%**	**Primary non-adherent (*n*=1,100)**	**%**	**Adjusted OR**	**95% CI**		**p-value**
Gender								
Male	488	85.8	81	14.2	1 (ref)			
Female	6,816	87.0	1,019	13.0	0.97	0.75	1.25	0.813
Diagnosis								
M80	4,527	88.9	568	11.2	1 (ref)			
M81	2,395	85.2	415	14.8	0.78	0.68	0.90	0.001
Other	382	76.6	117	23.5	0.46	0.36	0.59	<0.001
Doctor's speciality								
Orthopaedic surgeon	1,000	88.4	132	11.7	1.69	1.35	2.12	<0.001
GP	1,768	83.9	340	16.1	1 (ref)			
Rheumatologist	3,500	88.5	453	11.5	1.47	1.25	1.71	<0.001
Other	1,036	85.6	175	14.5	1.19	0.97	1.46	0.093
Active substance								
alendronic acid	990	85.0	175	15.0	1 (ref)			
ibandronic acid	835	85.8	138	14.2	1.04	0.81	1.33	0.751
risedronic acid	324	86.6	50	13.4	1.08	0.77	1.52	0.663
zoledronic acid	32	72.7	12	27.3	0.58	0.29	1.18	0.133
alendronic acid and colecalciferol	4,676	88.2	625	11.8	1.13	0.93	1.36	0.215
risedronic acid, calcium and colecalciferol, sequential	0	0.0	1	100.0	-			
eptotermin alfa	0	0.0	1	100.0	-			
strontium ranelate	177	80.5	43	19.6	0.67	0.46	0.98	0.037
denosumab	270	83.1	55	16.9	0.71	0.50	1.00	0.050
Age								
mean (sd)	70.3 (10.3)		68.4 (12.2)		1.07*	1.03	1.10	<0.001

** Odds ratio presented per every 5-year change in age*

5.2.1.4. Time to dispensing

3,340 (45.7%) of the 7,304 primary adherent patients purchased their first prescription on the same day it was prescribed. 5,873 (80.4%) purchased it within a week, 89.0% within two weeks, and 95.0% less than 25 days from the date of the prescription (Figure 8). After 25 days the dispensing of medicines was occasional with no peaks near the end of prescription expiration date.

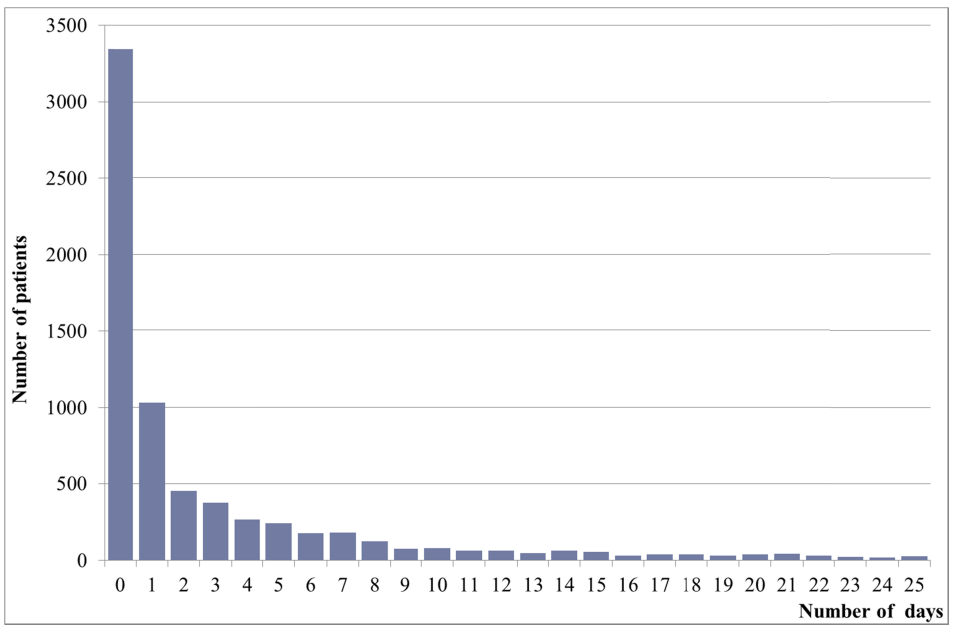

Figure 8. The number of days between prescribing and dispensing of first prescriptions to patients who started osteoporosis treatment in Estonia during 2012 to 2015.

Of all osteoporosis prescriptions purchased in Estonia from 2012 to 2015 (148,263 prescriptions), 14.7% were dispensed on the day of prescribing and 66.3% before the prior prescription was depleted or within a week after a new prescription was issued (Figure 9).

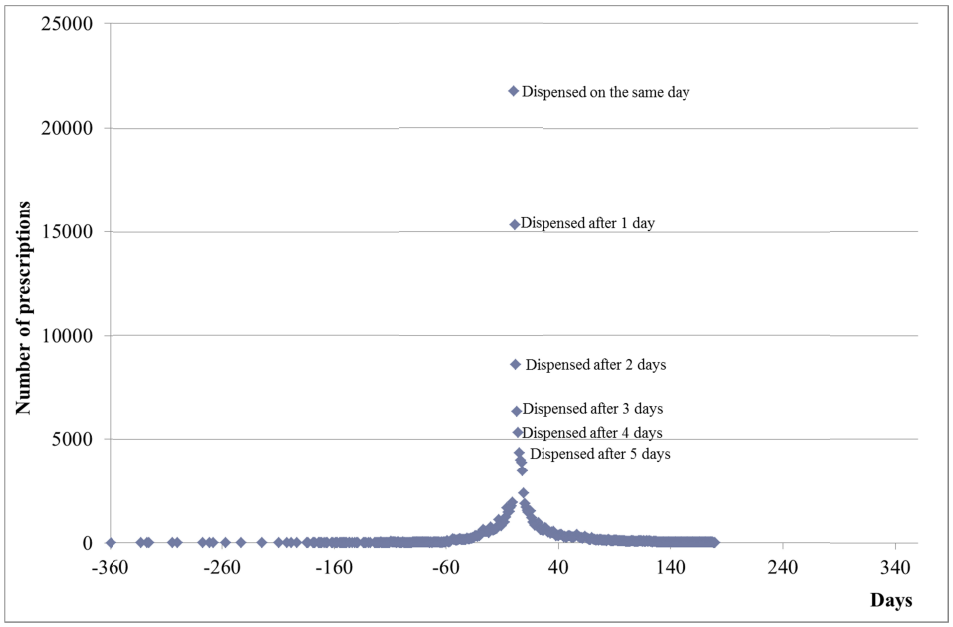

Figure 9. Number of days from prescribing to dispensing of all osteoporosis medicine prescriptions issued in Estonia from 2012 to 2015.

5.2.2. Secondary adherence

5.2.2.1. Patients

In total, 25,480 new patients received osteoporosis medicines – at least one prescription – in Estonia from 2001 to 2015. 825 were under 50 and left out of the study. 3 patients were dispensed their first prescription after the patient had died and these patients were also left out of the study. Of the 24,652 patients included, 23,091 were female (93.7%) and 1,564 male (6.3%). The patients' age distribution is presented in Figure 10.

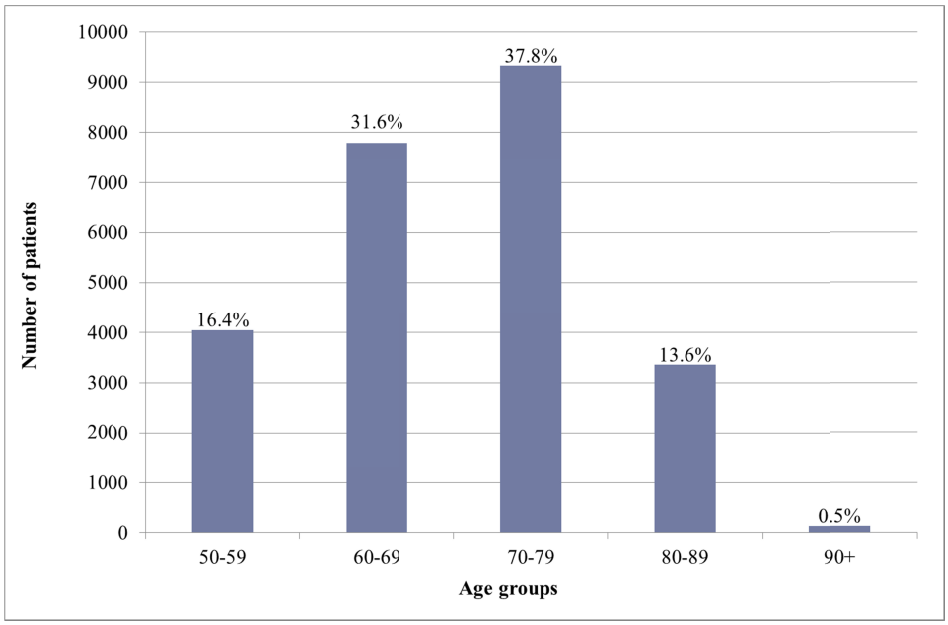

Figure 10. Age distribution of patients aged 50+ years old who started treatment using osteoporosis medicines (ATC group M05B) in Estonia from 2001 to 2015.

5.2.2.2. Initiation of treatment

4,636 (18.8%) of the 24,652 patients who started treatment with osteoporosis medicines were dispensed only one prescription. The number of patients starting treatment per year increased steadily from 2001 to 2009, and declined from 2010 to 2015. The percentage of patients who were dispensed only one prescription and not more, showed a 2.4% annual increase throughout the study, which was statistically significant (Figure 11).

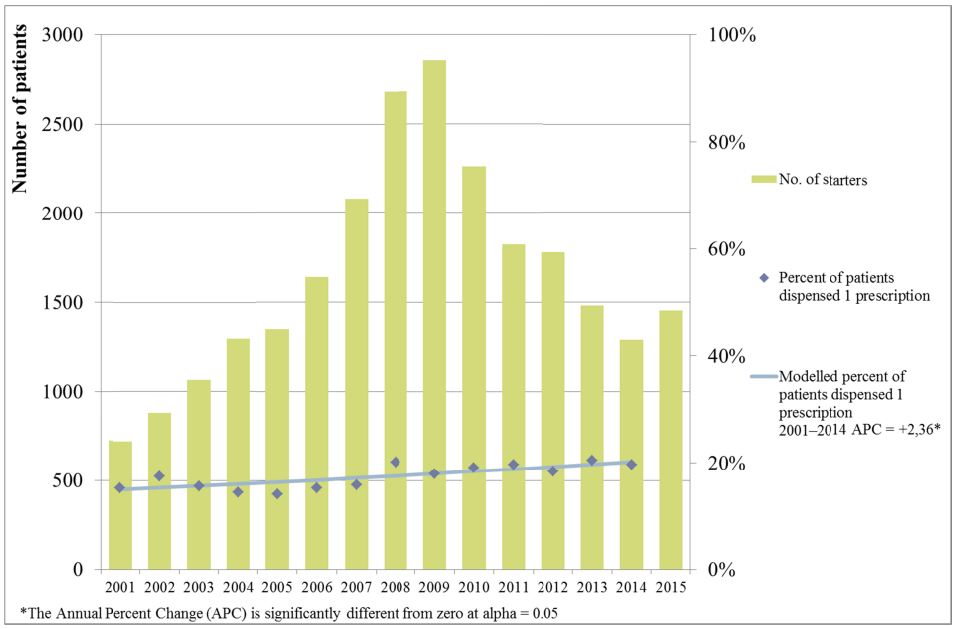

Figure 11. The yearly number of patients who started treatment with osteoporosis medicines and the modelled trend of patients who were dispensed only one prescription.

5.2.2.3. Implementation of treatment

44.2% of patients had a MPR ≥80% throughout their follow-up period. 18.8% of patients purchased only one prescription and 37.0% of patients had a MPR less than 80%. The share of patients with a MPR over 80% increased from 2001 to 2014. At the beginning of the 2000s, 60–70% of patients were not implementing their treatment sufficiently, but this decreased to approximately 20% by 2014 (Figure 12). The increase in the number of patients with sufficient implementation can be divided into two periods: from 2001 to 2005, and 2005 to 2014. During the first period, the annual increase was 29% and during the second 5%.

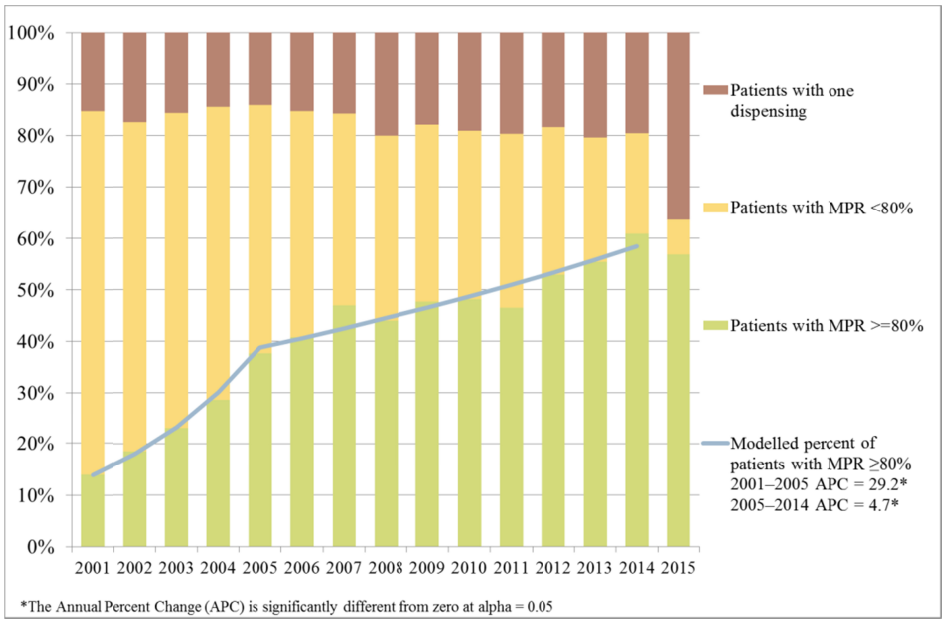

Figure 12. Implementation of osteoporosis treatment in Estonia according to the year the treatment was initiated. Data presented as the percentage of patients who had a medication possession ratio (MPR) ≥80%, <80%, and those who were dispensed only one prescription, and the modelled annual change in the percentage of patients with a MPR ≥80%.

5.2.2.4. Persistence with treatment

8,922 (36.2%) patients had sufficient implementation (MPR ≥80%) and persisted with treatment for at least 1 year. 19.8% of patients had a continuous treatment course that lasted for at least 3 years and had a MPR ≥80% over the course. 299 patients persisted with osteoporosis treatment for longer than 10 years with good implementation (Figure 13).

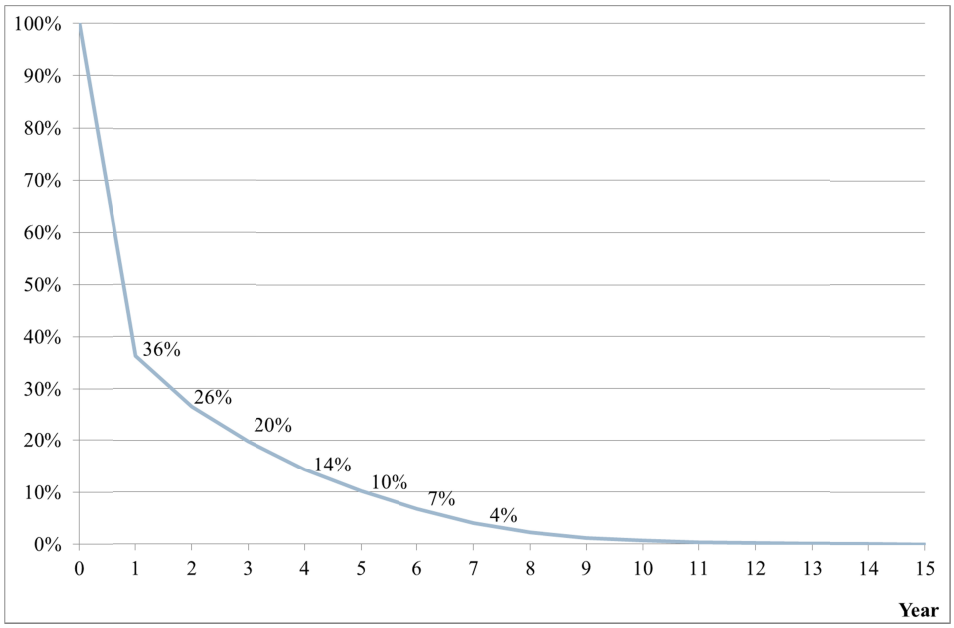

Figure 13. The percentage of patients with a MPR ≥80% who persisted with treatment over a given number of years.

5.2.2.5. Gaps and restarters

2,483 patients took short "drug holidays" during their treatment. 4,555 patients restarted treatment after stopping for a longer period of time, and 2,360 patients had both types of gap: drug holidays and restarted treatment. 47.0% of the patients who purchased at least 2 prescriptions had short or long gaps in their treatment. 17,737 patients (72.0% of the total number of patients) had only one treatment course and 4,636 (26.1%) were dispensed only one prescription. 19.5% of patients started treatment twice and 8.5% had 3 or more initiations of treatment. 2 patients started treatment 9 times during the 15-year time period.

5.2.2.6. What drives secondary adherence

Patient characteristics that relate to medication adherence are presented in Table 5. Females were 2.4-times more likely ($p<0.001$) than men to have a treatment course longer than one year with good implementation. Age also seemed to be a factor that influenced adherence. When patients aged 50–59 were taken as the baseline, the probability to be adherent increased for the age group 60–69 by 20% ($p<0.001$) and for 70–79 by 12% ($p=0.004$), but decreased for patients 80+. The results were similar when we calculated statistical differences at 3-year persistence. Patients who had a fracture when they were first prescribed osteoporosis medicines (ICD-code M80) were more likely to be adherent to

treatment than those who did not initially have a fracture (ICD-code M81). When treatment was initiated by a general practitioner, the probability of the patient being adherent was lower than when treatment was started by a specialist. The number of different medicinal products or active substances used from ATC group M05B increased the probability of being adherent with every additional product and active substance.

Table 5. Factors related to the probability of having a MPR ≥80% for at least 1 or 3 years.

		MPR ≥80% for at least 1 year (OR, CI 95%, p-value)	MPR ≥80% for at least 3 years (OR, CI 95%, p-value)
Gender	**Male**	1	1
	Female	2.37 (2.09–2.69) p<0.001	2.72 (2.28–3.25) p<0.001
Age in years	**50–59**	1	1
	60–69	1.20 (1.11–1.30) p<0.001	1.29 (1.18–1.43) p<0.001
	70–79	1.12 (1.04–1.21) p=0.004	1.18 (1.07–1.30) p=0.001
	80–89	0.89 (0.80–0.98) p=0.014	0.77 (0.69–0.88) p<0.001
	90+	0.45 (0.29–0.70) p<0.001	0.18 (0.07–0.44) p<0.001
Diagnosis	**M80**	1	1
	M81	0.87 (0.83–0.92) p<0.001	0.86 (0.81–0.92) p<0.001
Doctor's speciality	**General Practitioner**	1	1
	Orthopedic surgeon	1.13 (1.02–1.26) p=0.018	0.97 (0.86–1.11) p=0.696
	Rheumatologist	1.47 (1.38–1.56) p<0.001	1.33 (1.24–1.43) p<0.001
	Other	0.88 (0.80–0.96) p=0.003	0.87 (0.78–0.96) p=0.009
Number of different preparations dispensed	**For every additional medicinal product**	1.91 (1.86–1.97) p<0.001	2.24 (2.17–2.31) p<0.001
Number of different active substances dispensed	**For every additional active substance**	2.05 (1.97–2.13) p<0.001	2.46 (2.36–2.57) p<0.001

5.2.2.7. Expenditure on medicines

From 2001 to 2015, a total of €14,172,142 was spent on osteoporosis medicines per patients who started treatment in Estonia. €8,247,370 was paid by the EHIF and €6,647,697 by the patients. Of the 14 million, €8,471,773 (59.8%) was spent on medicines per patients who were adherent for at least one year. €5,700,369 (40.2%) was spent on the treatment of patients who did not have sufficient implementation, did not persist long enough, or who purchased only one prescription. The study period was also divided into two periods: before 2007 when osteoporosis medicines did not have higher reimbursement and after 2007 and these periods were analysed separately. The percentage of expenditure on possibly ineffective treatment during the pre-reimbursement period was 70.1% in total. 72.1% of money spent by EHIF was for ineffective treatment and 69.0% spent by patients. The amount paid by the patients was 1,939,517€ (66.4%) and by EHIF 982,737€ (33.6%). During the period after 2007 32.5% of the expenditure was for ineffective treatment. During this period 30.2% of expenditure by EHIF was for ineffective treatment and 36.6% of the patients' expenditure. The amount paid by the patients from 2007 onward was 3,984,510€ (35.4%) and by EHIF 7,264,632€ (64.6%).

6. DISCUSSION

6.1. Utilization of osteoporosis medicines

People at risk from osteoporosis in Estonia is estimated at 5.8% of the total population (17). This translates to approximately 75,000 to 80,000 people whose bone quality might be affected by osteoporosis and are therefore at risk of bone fractures (107). According to our studies, osteoporosis ameliorating drugs were received daily by approximately 6,300 patients in Estonia in 2015. This is less than 10% of the total number of patients at risk of osteoporosis. In addition, comparison with the Nordic countries suggests the consumption of osteoporosis medicines in Estonia should be higher, as Estonian consumption was 2.5-fold lower in 2015 than the Nordic average. Similar conclusions are reported in an EU osteoporosis report, which also suggested that changes in healthcare policy concerning osteoporosis is warranted (107).

During the 1990s, no medicine with evidenced efficacy against osteoporosis was used in Estonia; the consumption of bisphosphonates started at the beginning of the 2000s (123). Owing to the high price of these medicines and no higher reimbursement by the EHIF, consumption was still very low during the first half of the 2000s. Consumption derived from the wholesale statistics does not reflect all the patients who received treatment against osteoporosis, as there were several clinical trials of medicines in Estonia during the first half of the 2000s. This helped patients get access to medicines they would not otherwise be able to afford. The number of trials that included patients from Estonia was around 20. Probably the impact of clinical trials was also greater than just the patients who got the study drug, as patients in the placebo arm were put on vitamin D and calcium supplements, and knowledge of osteoporosis and the possible preventive measures was increased amongst both doctors and patients.

The consumption of osteoporosis medicines in Estonia more than doubled in just two years after 2007. The reasons for this were the EHIF providing a 75% reimbursement (90% if the patient was older than 63) for patients with a prior fracture and DXA T-score ≤ -2.5SD, and the first generic medicines coming to market, which brought down the cost of some medicines. Before 2007, bisphosphonates were reimbursed at 50%, but to a limit of €12.8 per prescription. The price of bisphosphonates exceeded this limit considerably. As the 75% reimbursement class does not have an upper limit that the EHIF will pay for a prescription, the medicines got much cheaper for patients.

From the beginning of the 2000s until 2015 there was a general increasing trend of consumption of all types of medicines in Estonia (54). This was due to changes in people's lifestyles and the aging of the population (124), which made an increase in the consumption of medicines imperative. The consumption of osteoporosis drugs also increased rapidly in the 2000s, but remained stable from 2010 to 2015. This is supported by the opinion of Estonian GPs and pharmacists that the knowledge of patients about osteoporosis increased during

the same period, which increased adherence to medicines, and thereby the consumption of medicines (125). As the price of medicines, which is also an important factor that influences consumption, did not decrease from 2010, the increase in consumption stopped. Regarding chronic conditions, increased drug utilization can reduce expenditure on related healthcare services when it is driven by improved adherence to guidelines-based therapy (126). Studies carried out in Europe investigating the consumption of osteoporosis drugs have shown continual increases (127). In the US however, the consumption of osteoporosis drugs seems to be decreasing (128).

The most used preparation in Estonia during 2014 was the combination of alendronic acid and vitamin D, which constituted 59% of total antiosteoporotic medicine consumption. Although the cheapest orally administered product was ibandronic acid at €0.25 per DDD, its market share was still only 14% in 2014. The combination of alendronic acid and vitamin D was the most expensive of the oral bisphosphonates at €0.51 per DDD, meaning it cost twice as much as the cheapest bisphosphonate ibandronate. As the combination product is subsidised and the plain vitamin D products are not, then out-of-pocket payment is lower for the patient per the combination product than buying plain bisphosphonate and vitamin D separately. This explains the high use of the combination product as a proportion of the total of osteoporosis drugs. Although a combination product of calcium and vitamin D is also reimbursed to osteoporosis patients the patients for some reason still preferred to take the combination preparation and probably added calcium separately.

Overall wealth in Estonia is substantially lower than the EU average and expenditure on healthcare out of the GDP is less than optimal. As a result, the co-payment for patients is higher in Estonia and many patients cannot afford to pay for their medicines. Also, the reimbursement regulations for osteoporosis ameliorating drugs have not changed in Estonia and only patients with a fragility fracture and DXA T-score under –2.5SD get medicines reimbursed at a rate of 75% or 90% if they are older than 63. This translates into generally low consumption of osteoporosis medicines in Estonia.

6.2. The price of medicines

The trends of overall consumption of osteoporosis medicines and the average daily dose price of medicines moving in opposite directions suggests that offering reimbursement to patients at risk of a fracture because of decreased bone mass, but without an actual fracture, might help to further increase the use of osteoporosis medicines in Estonia. As discussed before the number of patients taking osteoporosis medicines in Estonia cannot be regarded as sufficient, as the number of patients at risk of a fracture is substantially higher than the number of patients using medicines that help to reduce that risk.

6.3. Trend in hip fractures

Urbanization, lack of physical exercise, an unhealthy diet, and smoking are the most important factors increasing fracture risk, and thus fracture trends were expected to increase in developed countries (17). An increase in the standardized incidence rate of hip fractures was observed in our study from 2004 to 2009, similar to what was reported before by Jürisson et al. (27). From 2010 the rate started to decrease. This is similar to what has been reported in most countries where standardized incidence of fractures has been studied (25). The change in the trend occurred earlier in western and northern European countries compared to Estonia. For instance, in Scandinavia the decrease started in the 1990s (26). The unexpected declines in fractures are speculated to be the result of several different factors. One important aspect is the increasing use of osteoporosis drugs, but also is the growth in average BMI – as body weight increases, so does the weight of bones – in reducing incidence of fractures. Improvement of general health, the declining numbers of smokers, and campaigns to prevent falls are also named as reasons for the declining trends in osteoporosis induced fractures (129,130). If these aspects are put into an Estonian context, then the percentage of women with a BMI over 25 was 70.0 in the 1990s and 71.5 in the 2000s, thus a substantial rise in the percentage is not seen (131). The number of smokers amongst women over 55 has increased in Estonia, as in the 1990s 19% stated themselves to smoke and 34% did so in the 2000s (131). It seems that in Estonia the possible explanations per the decreasing trend are more likely to be the increased use of osteoporosis medicines and improvement in general health, as we have not had specific nationwide fall prevention campaigns. Jürisson et al. (27) also hypothesized that the decrease in the osteoporosis related fracture rate is due to increased use of bisphosphonates, a reduction in falls-related comorbidity which in turn is the result of improved general health, and prevention and better treatment of other chronic diseases. The claim of better general health in Estonia can be supported by the life expectancy of a 65 year old woman in Estonia increasing from 17.9 to 20.3 years (2.4 years in total) between 2004 and 2015 (131).

The quick increase in consumption of osteoporosis medicines in Estonia was followed by a decrease in the standardized incidence of hip fractures rate. An increase in consumption and decrease in fractures has been demonstrated in earlier studies (28,116). A declining trend in fractures has been shown to be reversible with a reduction in the consumption of osteoporosis drugs (30). Since 2010 the consumption of osteoporosis drugs levelled-off in Estonia. Utilization of osteoporosis medicines is only one driver of changes in the incidence of hip fractures (129), but if the stop in the increase of the utilization of osteoporosis drugs in Estonia will have an effect on the trend in fractures remains to be seen. Our study indicates that the utilization of osteoporosis medicines has an effect on the rate of osteoporosis related fractures and consumption of medicines is strongly influenced by the price of medicines.

6.4. Primary adherence

6.4.1. Primary medication non-adherence

The introduction of electronic prescribing has made it easier to assess primary adherence to medicines, which was difficult before because of a lack of data (83). The percentage of patients who are prescribed but never purchase their medicines varies in studies from 2.4 to 30.7%, depending on how primary non-adherence is defined and which drug classes are included in the study (132). Primary non-adherence was defined as a patient not being dispensed their initial prescription within 60 days after prescribing. As a prescription is valid in Estonia for 60 days, this meant that if the initial prescription expired without being dispensed, the patient was considered primary non-adherent. In the study osteoporosis medicine primary non-adherence was found to be 13.1%. This is an average result when all medicine classes are compared (133). However, rates of primary non-adherence per osteoporosis medicines have been shown to be one of the highest. The rates for osteoporosis medicines have been reported to be from 22.4–37.0% (98,134–136). Our result suggests a substantially lower rate of PMN than found before. The most recent and largest study to date by Reynolds et al. reported primary non-adherence to bisphosphonates to be almost 30% (136). The number of patients included in our study was similar to Reynolds et al.'s study and a 60-day window was used in both studies to establish primary non-adherence. In Reynolds et al.'s study, only women over 55 were included, but in the current study all patients over 18 years old were included. Owing to the nature of the disease, the number of men (6.8%) and patients under 55 (3.1%) was small in our study. Therefore, the different patient selection criteria are probably not the cause for the difference in results. The Estonian electronic prescribing system is one of a few in Europe and globally where there is one central prescriptions system in a country and all doctors and pharmacies are connected to that system. After a prescription is issued the patient can purchase the drug from any pharmacy of their choice in Estonia. There are digital prescribing systems where a patient can use some or name certain pharmacies from where they can purchase their medicine with a digital prescription (12). In Reynolds et al.'s study, patients could only use certain pharmacies from where they could buy their medicine and if they used other pharmacies they would be misclassified as primary non-adherent. The fact that pharmacies are very easily accessible in Estonia (there is a pharmacy in most healthcare and shopping centres), could be one of the reasons for the low rate of primary non-adherence.

Setting the rule that a prescription must be dispensed within 60-days for a patient to be considered primary adherent is arbitrary. A patient could start treatment even if they fail to purchase the initial prescription. In our study, 462 (42.0%) of the 1,100 primary non-adherent patients started treatment with a subsequent prescription, and half of those patients did it less than 3 months after the first prescription was issued. As patients probably receive further coun-

selling and motivation from their doctor with the next prescription, that 40% of patients initiated treatment after this additional visit, suggests that patient behaviour can be turned in the right direction with further information and support. Our result also indicates that concentrating only on whether the initial prescription is dispensed overestimates the proportion of patients who fail to initiate treatment.

6.4.2. Characteristics influencing primary adherence

Older patients were found to be more primary adherent than younger patients in Estonia. This result is opposite to that found by Reynolds et al. (136). As patients older than 63 get medicines reimbursed at a higher rate (90%) than patients under 63 (75%) in Estonia, this could be one of the reasons that older patients have better primary adherence. Treatment initiation has been shown to be influenced by the price of medicines (137). Denosumab is administered once every six months and has been shown to result in better secondary adherence than oral bisphosphonates (138), but it is also more expensive and our study showed that primary medication adherence is lower with denosumab than with alendronic acid. This means potential PMN issues must be addressed by the doctor when initiating treatment with denosumab. The diagnosis code and prescribing doctor's speciality where also factors that influenced PMN. Patients with a prior fracture were more likely to purchase initial prescriptions than patients without a fracture. In addition, patients whose treatment was started by orthopaedists or rheumatologists had better initiation. However, these results are interconnected as patients with fractures are more frequently prescribed by specialists.

6.4.3. Time to dispensing

Previous research has reported that 64% of osteoporosis medicine prescriptions are purchased within a week (136). The dispensing of other drug classes have been shown to be faster, with 65% purchased on the same day and 89% within 30 days (139). Our results showed faster dispensing compared to earlier osteoporosis drug studies and were more similar to the results of other drug classes. 80% of prescriptions were purchased within a week of prescribing and 89% were purchased within two weeks in our study. If all the osteoporosis drug prescriptions of all patients during 2012 to 2015 were investigated, then almost 70% of prescriptions were dispensed before the amount purchased with the prior prescription was depleted or less than a week from the prescribing of a new prescription. When a doctor prescribes or when a pharmacist dispenses medicines, they see which prescriptions are active to the patient in the Prescription Centre. According to our study, if they happen to come across prescriptions that are older than a week and are still active, they should discuss

possible adherence issues with the patient. Proactive interventions by pharmacies have been shown to improve adherence (140).

6.5. Secondary adherence

6.5.1. Initiation

The number of patients who started osteoporosis treatment increased rapidly at the beginning and middle of the 2000s, peaking in 2009. Then the number of new patients started to decrease. The fast increase can possibly be explained by the drugs becoming more affordable to patients, with generic medicines entering the market and the EHIF providing 75% and 90% reimbursement to patients with a prior fracture (114). A crucial factor that influences whether a patient starts treatment and is adherent is how much the patient knows about the disease and the treatment. Estonian doctors and pharmacists have assessed the knowledge of patients to have improved over time (125). The decline in new users following the swift increase is harder to explain. Also, the percentage of patients who purchased medicine with only one prescription increased, which is opposite to what would be expected when medicines become cheaper. This indicates that the affordability of medicines is probably not the main factor hindering treatment initiation in Estonia.

If we add up the percentage of patients who never purchased their medicine from the PMN study and the patients who purchased medicine with only one prescription in the secondary adherence study we get a total of approximately one fourth of patients who do not initiate treatment although a physician has seen it necessary and prescribed a medicine. The study results are not directly comparable though as we used a little bit different inclusion criteria in the studies but it gives us a rough idea of the phenomena.

6.5.2. Implementation

A MPR ≥80% is most often used as the threshold of sufficient implementation of osteoporosis treatment, as it has been shown to be optimal for the treatment to be effective (141). In Estonia, 44.2% of patients had a MPR ≥80% during at least one of their treatment courses. Implementation of osteoporosis treatment has previously been reported to be from 46% (142) to 95% (143). Typically, daily dosing regimens have lower implementation compared to weekly or monthly regimens (144), and higher implementation has been shown when including only persistent patients in the study. Studying persistent patients gives better results, because patients who have already taken medicines for a long period are also usually more careful to take their medicines at the correct dosing interval. All osteoporosis medicines and all starting patients were included in our study, but nonetheless the result that a MPR ≥80% was achieved by only 44.2% of patients is still one of the lowest results seen in osteoporosis medicine

adherence studies. This can probably be explained by our untypically long study period and that new patients were included. Adherence studies lasting a year are already considered long term (81) and patients who are freshly prescribed treatment have poorer adherence (145). Persisting with treatment for 1 to 2.5 years, but not implementing the treatment with a MPR ≥80%, can increase the pooled fracture risk up to 46% (81). This means there are still several patients at a higher risk of a fracture in Estonia despite being prescribed osteoporosis medicines, because they do not take them as prescribed. In the middle of the 2000s, the number of patients taking more than 80% of prescribed medicines increased rapidly. This was probably due to once weekly medicines replacing once daily medicines that have lower adherence (146).

6.5.3. Persistence

Typically in adherence studies, 1-year persistence is used to identify persistent patients. However, persisting with treatment is not enough the patients also must take the medicines at the correct dosing intervals. It was established that in Estonia, 36.2% of patients persisted with osteoporosis treatment for at least one year and 19.8% for three years while maintaining a MPR ≥80% throughout the treatment course. 1-year persistence has been reported in earlier studies (147) over a range of 18%–75%. This wide difference in results is caused by the different methods used to assess persistence (e.g. data-derived, self-reported). Being persistent 3 years reduces fracture risk by 41% compared to being persistent for a month (143). Our results suggest that long-term persistence to osteoporosis medicines might be lower than observed before.

6.5.4. Factors that influence secondary adherence

Some patient characteristics predict poorer adherence (148) and several were found in the current study. Males were less adherent to treatment than females. This is not surprising as males tend to have poorer adherence across studies (149). However, as only 6% of osteoporosis patients were male, tackling them separately to improve their adherence to osteoporosis medicines would probably not result in a population wide health benefit. As males are expected to have poorer adherence than females in terms of taking medicines against other chronic diseases, a general intervention to improve the knowledge of males about the need to take medicines correctly is relevant.

Patients' age, an existent fracture, and the prescribing doctor seemed to significantly influence adherence. However, there is co-variance between these factors, because older people are at a greater risk of a fracture and patients with fractures are more often prescribed by specialist doctors, not their GPs. Taking this into account, it is hard to assess which of these factors has the largest impact on adherence, but as having a fracture has been shown to motivate

patients to take their medicines (150), this might be the key factor that makes patients adherent.

Medicine affordability has also been shown to influence adherence (151). As the reimbursement rate of medicines increases from 75% to 90% at the age of 63 in Estonia, this could explain – at least in part – the higher adherence to treatment in the age groups above 60 compared to the group 50–59.

Substituting products was found not to have a negative outcome on adherence, as the number of different medicinal preparations available containing the same active substance did not decrease adherence. This means that the cheapest alternative can be recommended to the patient in the pharmacy, as foreseen by legislation, without them worrying about using a generic substitution. The decisions taken by the state to increase the use of generic medicines has raised some concerns amongst the general public, but our study establishes that adherence to osteoporosis medicines is not negatively affected by generic substitutions.

6.5.5. Possible interventions

Adherence to medicines is not easy to alter and the results of interventional studies are controversial, with for example phone call based interventions showing some effect in some studies (134,135,152) but having no effect on adherence in others (153–155). The importance of early identification of adherence problems has been stressed lately, with a proposal to base intervention on bone turnover markers (156). If an ePrescriptions database could be used to identify poor adherence early on, it would definitely be less resource demanding and easier to implement than routine biomarker assessment. Prior research has come to the conclusion that when planning any intervention to improve adherence, it cannot address only one aspect of adherence or be oriented at one participant during the prescribing and dispensing process to be effective. It should be multidisciplinary and include patients, doctors, and pharmacists (84). It has also been shown that dispensing data, similar to what is available from the EHIF database, can be used to identify patients that are at risk of having poor adherence later on during the course of treatment based on their dispensing history (157).

6.5.6. Expenditure

Poor adherence to osteoporosis medicines leads to wasted money and the occurrence of avoidable fractures (158). Our study showed that 40% of the total expenditure on osteoporosis medicines was spent on treating patients who did not persist with treatment for at least a year. Spending on these medicines might not have served its purpose as the duration of treatment was suboptimal. If 3-year persistence was used as the proxy for adherence, the percentage would

have been even higher. National health systems are working with constrained budgets and not adhering to treatment influences the cost-effectiveness of medicines. This means we do not spend the limited resources as efficiently as we hope, because the health benefits assumed from clinical trials are not achieved in every day practice. In addition to the lower cost-effectiveness, hospitalization costs and those of other medical services increase when patients do not adhere to treatment (159). These results highlight the importance of improving adherence, because inefficient use of resources and overspending postpones access to newer technologies.

When the study period was divided into pre- and post-reimbursement periods it was seen that during the pre-reimbursement period the percent spent on ineffective treatment was substantially larger with 70.1% and decreased to 32.5% in the post-reimbursement period. This change is in line with the increase seen in the implementation of treatment. While in the middle of the 2000s patients did not take their medicines very orderly but did much more so in the 2010s. This resulted in the decrease of money spent on ineffective treatment. Still, approximately one third of the expenditure during the post-reimbursement period was for ineffective treatment.

6.6. Limitations of the studies

The main limitation of the utilization study was that the consumption data was based on wholesale data, which does not depict the actual amount of drugs that reached patients, but as pharmacies do not hold large stocks of medicines and order them from wholesalers as necessary, wholesale data correlates with pharmacy sales data rather well. ATC/DDD system was used to assess the potential number of patients. DDDs of osteoporosis medicines are very accurate as different dosing regimens are not used. Wholesale data also does not allow patient level analysis to assess prescribing quality or real treatment recommendations for patients.

The main limitation of the standardized hip fracture incidence study was using data from the EHIF database. The EHIF database is a claims database used by healthcare facilities to invoice the EHIF and different cases are not differentiated on the bills. This means the assumption was made that a patient breaks their hip only once a year, thus multiple fractures would go unnoticed. However, the number of patients with multiple fractures in one year is negligible.

The main limitation of the primary adherence study was that the EHIF database does not include data on patients' socio-demographic characteristics (for instance income) and thus the potential impact of these characteristics on primary adherence could not be assessed. In addition, due to technical reasons the use of other medicines by osteoporosis patients could not be analysed and the potential impact of polypharmacy on primary adherence.

The main limitation of the secondary adherence study was that dispensing data was used to assess adherence, but it is unknown whether the patient actually took the medicines they were dispensed. However, the use of MEMS in real life studies with tens of thousands of patients is impractical and prescribing databases have been shown to give a good estimate of the real use of medicines. Another limitation was that whether the prescribing of osteoporosis medicines was justified in every case could not be assessed and the reasons why patients stopped taking their medicines could not be analysed.

7. CONCLUSIONS

I The number of regular users of osteoporosis medicines is less than 10% of patients in risk of osteoporosis in Estonia, approximately 6,300 patients.

II The level of consumption of osteoporosis medicines is rather similar in the Baltic countries, with the consumption trends also following similar patterns.

III The age standardized incidence of hip fractures started decreasing three years after higher reimbursement of osteoporosis medicines was established in 2007 and cheaper generic medicines came to market. The consumption of osteoporosis medicines doubled in two years from 2008 – 2009. The decrease in fractures might in part be due to the increase in osteoporosis medicines consumption.

IV The trends of general consumption of osteoporosis medicines and the average daily dose price of these medicines moved in opposite directions. This suggests that consumption is affected at least in part by the price of medicines, especially when the medicines are expensive for patients.

V The PMN of osteoporosis medicines was found to be 13.1%, which is considerably lower than reported before. 42.0% of the initially PMN patients started treatment with a subsequent prescription. Half of these patients did so within 3 months of the initial prescription.

VI PMN was influenced by patients' gender, age, diagnosis code, prescribing doctor's speciality, and prescribed active substance.

VII Eighty percent of patients purchased their initial osteoporosis medicine prescription within a week of the prescription and 95% did so within 25 days.

VIII 18.8% of patients were dispensed only one prescription. 44.2% of patients had a MPR ≥80% throughout the treatment course. 36.2% of patients persisted with treatment for one year with a MPR ≥80% and 19.8% persisted for three years with good implementation.

IX Secondary adherence was influenced by patients' age, gender, diagnosis code, prescribing doctor's speciality, number of different active substances prescribed, and the number of different preparations dispensed.

X Forty percent of the expenditure on osteoporosis medicines was spent on patients who were non-adherent and did not persist for a year, thus the clinical effect hoped for might not have been achieved.

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9. SUMMARY IN ESTONIAN

Osteoporoosiravimite kasutamine, ravijärgimus ning osteoporoosist tingitud reieluu proksimaalse osa murdude trend Eestis

Osteoporoos on krooniline haigus mida iseloomustab luukoe metabolismi tasakaalu kaldumine luukoe lammutamise poole võrreldes luukoe moodustumisega (21). Sellest tulenevalt muutuvad inimese luud hapraks ning võivad kergesti murduda (9). Lähtuvalt üldisest elanikkonna vananemisest, inimeste elustiili muutusest ja linnastumisest eeldatakse, et osteoporoosist tingitud luumurdude hulk kasvab Euroopa Liidus 30% alates aastast 2010 aastaks 2025 ning sellega seotud kulutused suurenevad 121 miljardi euroni (17).

Osteoporoosi raviks on olemas efektiivsed ravimid, mis tugevdavad patsientide luukudet ning aitavad selle kaudu ära hoida luumurdude teket (49). Enamikes arenenud riikides on osteoporoosi valikravimiteks bisfosfonaadid ning järgmise reana kasutatakse denosumabi ning strontsium ranelaati. Osteoporoosi raviks on kasutusel ka selektiivsed östrogeeni retseptori modulaatorid ning paratüreoidhormoonid, kuid Eestis neid ei kasutata (54). Kõik osteoporoosi raviks kasutusel olevad ravimid on murdude vältimisel sarnase efektiivsusega ning kõigi nende efektiivsus on tõestatud kolm aastat kestnud kliinilistes uuringutes (47). Seega on efektiivseks osteoporoosiennetuseks vajalik kasutada ravimeid vähemalt kolm aastat.

Peamine põhjus, miks ei saavuta patsiendid krooniliste haiguste ravil sarnaseid tulemusi nagu on näidatud kliinilistes uuringutes, on ebapiisav ravijärgimus (6). Ravijärgimus iseloomustab seda kui hästi patsient järgib kokkulepitud raviskeemi (3). Ravijärgimuse võib jagada esmaseks ja teiseseks ravijärgimuseks (83). Esmane ravijärgimus kirjeldab kas patsient ostab välja talle väljastatud esimese retsepti ning teisene ravijärgimus kuidas patsient käitub peale seda kui ta on esmase retsepti välja ostnud (5). Teisest ravijärgimust võib omakorda jagada kolmeks etapiks: ravi alustamine, raviannuste võtmise korralikkus ning ravikestus (4). On oluline eristada millises ravijärgimuse etapis probleeme esineb, sest ebapiisava ravijärgimuse põhjused ning seega ka lahendused on erinevates etappides erinevad. Piisavaks ravijärgimuseks loetakse kui patsient võtab vähemalt 80% talle ettenähtud raviannustest ning osteoporoosiravimite puhul jätkab raviga vähemalt kolme aasta vältel (141).

Kui teisest ravijärgimust on mujal maailmas uuritud juba aastakümneid, siis esmase ravijärgimuse uuringuid on tehtud vähe, sest selleks ei ole piisavalt andmeid. Eesti Haigekassa retseptikeskus pakub hea võimaluse ka esmase ravijärgimuse uurimiseks, sest selles kajastub nii retsepti väljastamise info kui ka ravimi apteegist väljaostmise info. Euroopas on sarnane üleriigiline süsteem, mis hõlmab kõiki retseptide väljastajaid ning kõiki apteeke lisaks Eestile kasutusel veel ainult Taanis ning Rootsis (12).

Uurimistöö eesmärgid

Uurimistööle seati järgnevad konkreetsed eesmärgid:

1) Analüüsida osteoporoosiravimite summaarset kasutamist Eestis ning võrrelda seda teiste Balti riikidega;
2) Analüüsida ravimite kasutamise ning osteoporoosist tingitud luumurdude esinemise omavahelist mõju;
3) Välja selgitada esmase ja teisese ravijärgimuse määr Eestis ning neid mõjutavad patsiendi karakteristikud;
4) Välja selgitada keskmine aeg, mis kulub osteoporoosiravimite retseptide välja kirjutamisest nende ostmiseni ning arvutada välja kulutused, mis tehti mitteefektiivsetele ravikuuridele.

Patsiendid ja metoodika

Ravimite kasutamise uuringutes (1. ja 2. uuring) kasutati andmeid Ravimiameti andmebaasist. Ravimiamet kogub ravimite hulgimüüjatelt 4 korda aastas aruandeid, mis peavad eristama kõiki müüdud pakendeid. Koondstatistika avaldatakse Ravimiameti veebilehel ning eraldi Eesti kasutamist kirjeldava või Läti ja Leedu kolleegidega koostöös ühise Balti ravimite kasutamist kirjeldava raamatuna.

Reieluu proksimaalse osa murdude trende kirjeldavas uuringus (2. uuring) kasutati lisaks Haigekassa tervishoiuteenuste andmebaasi ning Statistikaameti rahvastiku andmebaasi. Eelduseks võeti, et tõenäoliselt ei esine samal patsiendil korduvaid reieluu proksimaalseid murde sama aasta vältel ning arvestati iga patsiendi kohta ühte esmase murruga raviarvet aastas.

Esmase ja teisese ravijärgimuse uuringutes (3. ja 4. uuring) kasutati Haigekassa retseptiandmebaasi. Esmase ravijärgimuse hindamiseks kasutati digiretsepti andmebaasi andmeid ning teisese ravijärgimuse hindamiseks ka varasemate paberretseptide alusel koostatud andmebaasi. Esmane ravijärgimus defineeriti olukorrana kus patsient ostis oma esimese osteoporoosiravimi retsepti välja 60 päeva jooksul alates selle väljastamisest. Teisese ravijärgimuse uuringus analüüsiti kõiki erinevaid ravijärgimuse etappe – ravi alustamist, raviannuste võtmist ning ravikuuri kestust. Piisavaks ravijärgimuseks loeti olukord kui patsient võttis vähemalt 80% ettenähtud annustest ning jätkas ravi vähemalt ühe aasta vältel.

Peamised tulemused

Ravimite kasutamise uuring

Osteoporoosi ravimite kasutamine suurenes 2000ndate aastate keskel ning teises pooles väga kiiresti. Aastatel 2004 kuni 2009 suurenes aastane keskmine kasutamine 41%. Viimastel aastatel nende ravimite kasutamine Eestis enam oluliselt

ei muutunud. 2015.a oli osteoporoosiravimite kasutamine Eestis 4,8 DPD/1000/ööpäevas, mis vastab umbes 6300 igapäevasele kasutajale. Samas hinnatakse osteoporoosi poolt ohustatuks Eestis ligikaudu 80 000 inimest (107), seega ei saa lugeda ravimi kasutamist Eestis piisavaks.

Reieluu proksimaalse osa murdude trend

Eestis esines aastatel 2004–2015 ligikaudu 1500 reieluu proksimaalse osa murdu aastas. Kui aastatel 2004–2010 oli trend pigem tõusev, aga statistiliselt mitteoluline, siis 2010 kuni 2015 vähenes standardiseeritud murrukordaja statistiliselt oluliselt 4,5% aastas. Langustrend algas kolm aastat pärast seda kui osteoporoosiravimitele kinnitati kõrgem soodusmäär ning turule tulid geneerilised ravimid, mis langetas patsientide jaoks oluliselt nende ravimite hinda ning tõstis üldise kasutamise paari aastaga kahekordseks. Ravimite kasutamise trend ja ravimi keskmise päevadoosi hinna trend liikusid üksteisele vastupidises suunas ($r = -0,94$; $p<0,001$).

Esmase ravijärgimuse uuring

Aastatel 2012–2015 väljastati esmakordselt osteoporoosiravi retsept 8404-le uuringukriteeriumitele vastanud patsiendile. 1100 (13,1%) ei ostnud oma esimese retseptiga ravimit välja. Samas 462 patsienti (42,0% esmaselt ravijärgimatutest ning 5,5% kõikidest patsientidest) siiski alustas ravi mõne järgmise retseptiga. Pooled patsientidest alustasid ravi vähem kui kolm kuud pärast esmase retsepti väljastamist. Kolmele patsiendile väljastati uuringuperioodil 5 osteoporoosiravimi retsepti, aga nad ei ostnud neist ühtki välja.

Ligi pool patsientidest (45,7%) ostis oma esimese osteoporoosiravimi retsepti välja samal päeval kui see neile väljastati. Nädala jooksul ostis selle välja 80,4% ning 25 päeva jooksul 95,0% patsientidest. Kui vaadelda kõiki osteoporoosiravimite retsepte, siis 66,3% nendest osteti välja enne kui olemasolev ravimivaru oli lõppenud või nädala jooksul peale uue retsepti väljastamist.

Esmane ravijärgimus ei olnud meeste ja naiste puhul erinev. Luumurruga patisendid ostsid oma esimese retsepti tõenäolisemalt välja kui luumurruta patsiendid. Samuti osteti rohkem välja eriarstide kirjutatud retsepte kui perearstide omi. Toimeainetest osteti vähem välja esmaseid denosumabi ja strontsium ranelaadi retsepte võrreldes alendroonhappe omadega. Bisfosfonaatide vahel erinevusi ei olnud. Vanematel patsientidel oli parem esmane ravijärgimus kui noorematel. Tõenäosus ravijärgimuseks suurenes 7% iga lisanduva viie eluaastaga.

Teisese ravijärgimuse uuring

Aastatel 2001–2015 alustas osteoporoosiravi Eestis 24 652 uuringukriteeriumidele vastavat patsienti. Ainult ühe retseptiga ostis ravimit 18,8% patsientidest. Terve ravikuuri vältel ostis välja vähemalt 80% ettenähtud raviannustest 44,2% patsientidest. Vähemalt ühe aasta vältel ostis välja piisava hulga raviannustest 36,2% patsientidest ja 19,8% patsientidest ostis ravimeid vähemalt kolm aastat piisava ravijärgimusega.

Patsientidest, kes ostsid ravimit vähemalt kahe retseptiga, 47% pidasid ravimi võtmises lühemaid või pikemaid pause.

Naistel oli 2,4 korda suurem tõenäosus läbida vähemalt aastane ravikuur hea ravijärgimusega. Võrreldes 50–59 aastaste patsientidega oli 60–69 aastastel 20% parem ravijärgimus ning 70–79 aastastel 12% parem. Samas üle 80 aastastel patsientidel ravijärgimus vähenes, võrreldes noorematega. Suurema kasutatud ravimite või toimeainete arvu puhul oli patsientide ravijärgimus parem.

Viieteistkümne aasta vältel kulutasid patsiendid omaosalusena ja Eesti Haigekassa kokku osteoporoosiravimite ostmiseks 14 172 142€. Sellest 40% kulus patsientide raviks kes ei võtnud ravimeid piisavalt korralikult või ei jätkanud ravi vähemalt aasta vältel. Jagades uuringuperioodi kaheks osaks: enne 2007.a kui ravimitel ei olnud soodustust ning pärast 2007.a, siis esimesel perioodil maksid patsiendid 66,4% (1 939 517€) ja Haigekassa 33,6% (982 737€) ravimite hinnast ning teisel perioodil patsiendid 35,4% (3 984 510€) ja Haigekassa 64,6% (7 264 632€). Eeldatavalt ebaefektiivsele ravile (alla 80% annustest või lühem kui aastane ravikuur) kulus esimesel perioodil 70,1% rahast ning teisel perioodil 32,5%.

Järeldused

I Igapäevaselt kasutab Eestis osteoporoosiravimeid vähem kui 10% osteoporoosiriskiga patsientidest, orienteeruvalt 6 300 inimest.

II Osteoporoosiravimite kasutamine Balti riikides on küllalt sarnane ning samuti on sarnased trendid, mida ravimite kasutamise muutus järgib ehk viimastel aastatel ei ole kasutamine üheski riigis oluliselt suurenenud.

III Vanusele standardiseeritud reieluu proksimaalse osa murdude arv hakkas Eestis vähenema kolm aastat pärast seda, kui osteoporoosiravimitele kinnitati aastal 2007 kõrgem soodustuse määr ning turule tulnud geneerilised ravimid suurendasid nende ravimite kasutamise aastatel 2008 kuni 2009 kahekordseks. Murdude vähenemise põhjuseks võib osaliselt pidada ka ravimite kasutamise kasvu.

IV Osteoporoosiravimite üldine kasutamine ning keskmine ravimi päevadoosi maksumus muutusid uuringu vältel erisuunaliselt (r = -0,94). Ravimite kasutamine suurenes ning päevadoosi hind vähenes. Korrelatsioon oli tugevam 2000ndatel kui ravimid olid patsientide jaoks suhteliselt kallimad ning nõrgem 2010ndatel kui ravimite hind oli patsientide jaoks odavam,

aga kasutamise kasv siiski pidurdus. See näitab, et ravimite hinna langus võib positiivselt mõjutada ravimite kasutamise üldist taset, eelkõige juhul kui ravimite hind on patsientide jaoks suhteliselt kõrge.

V Oma esimese osteoporoosiravimi retsepti jätab Eestis välja ostmata 13,1% patsientidest, mis on oluliselt vähem kui leitud varasemates rahvusvahelistes uuringutes. Samuti leiti, et 42,0% patsientidest, kes jätsid oma esimese retsepti välja ostmata ostavad siiski ravimeid mõne järgmise retseptiga. Pooled nendest patsientidest ostsid ravimi välja vähem kui 3 kuud pärast esmase retsepti väljastamist.

VI Esmane ravijärgimus oli parem vanematel patsientidel (riskisuhe 1,07; $p<0,001$, iga lisanduva 5 eluaastaga), varasema luumurruga patsientidel (riskisuhe luumurruta patsientidel 0,78, $p=0,001$), patsientidel kellele määras ravimi ortopeed (riskisuhe 1,69 võrreldes perearstiga, $p<0,001$) või reumatoloog (riskisuhe 1,47 võrreldes perearstiga, $p<0,001$) ning kellele määrati bisfosfonaat (riskisuhe strontsium ranelaadil 0,67; $p=0,037$ ja 0,71 denosumabil; $p=0,05$).

VII Kui patsient oma esimese retsepti välja ostab, siis teeb ta seda suhteliselt kiiresti pärast retsepti kirjutamist: kõigist ravimeid kasutanud patsientidest 80,4% patsientidest ostsid oma esmase osteoporoosiravimi retsepti välja nädala jooksul peale retsepti kirjutamist ning 95,0% tegi seda 25 päeva jooksul.

VIII Kõigist osteoporoosiravi alustanud patsientidest 18,8%-le väljastati ravimit ainult ühe retseptiga, 44,2% patsientidest ostsid kogu ravikuuri vältel apteegist välja 80% või rohkem ettenähtud ravimi annustest. Veidi rohkem kui kolmandik (36,2%) patsientidest võttis vähemalt 80% ettenähtud annustest vähemalt aasta jooksul ning 19,8% patsientidest vähemalt 3 aasta vältel.

IX Teisene ravijärgimus oli parem naistel (riskisuhe 2,37 võrreldes meestega, $p<0,001$), varasema luumurruga patsientidel (riskisuhe luumurruta patsientidel 0,87; $p<0,001$), patsientidel kellele väljastas esimese retsepti ortopeed (riskisuhe 1,13 võrreldes perearstiga, $p=0,018$) või reumatoloog (riskisuhe 1,47 võrreldes perearstiga, $p<0,001$) ning kes kasutasid ravikuuri jooksul rohkem erinevaid toimeaineid (riskisuhe 2,05 iga lisanduva toimeainega, $p<0,001$) või erinevaid ravimpreparaate (riskisuhe 1,91 iga lisanduva preparaadiga, $p<0,001$).

X Aastatel 2001–2015 osteoporoosiravimitele kulunud rahast kulus 40% nende patsientide raviks, kellel ei olnud piisavalt hea ravijärgimus ning kes ei tarvitanud ravimeid vähemalt aasta vältel ja võib eeldada, et need patsiendid ei saanud ravimitest loodetavat kasu.

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PUBLICATIONS

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Publikatsioonid

1. Maasalu, Katre; Laius, Ott; Zhytnik, Lidiia; Kõks, Sulev; Prans, Ele; Reimann, Ene; Märtson, Aare (2017). **Transcriptional landscape analysis identifies differently expressed genes involved in follicle-stimulating hormone induced postmenopausal osteoporosis**. Experimental Biology and Medicine, 242 (2), 203−2013.10.1177/1535370216679899.
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4. Laius, O; Maasalu, K; Kõks, S; Märtson, A. (2016). **Use of drugs against osteoporosis in the Baltic countries during 2010-2014**. Medicina (Kaunas), 52 (5), 315−320.DOI:10.1016/j.medici.2016.10.001.
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8. Godman, Brian; Malmstrom, Rickard E.; Diogene, Eduardo; Jayathissa, Sisira; McTaggart, Stuart; Cars, Thomas; Alvarez-Madrazo, Samantha; Baumgaertel, Christoph; Brzezinska, Anna; Bucsics, Anna; Campbell, Stephen; Eriksson, Irene; Finlayson, Alexander; Fuerst, Jurij; Garuoliene, Kristina; Gutierrez-Ibarluzea, Inaki; Hviding, Krystyna; Herholz, Harald; Joppi, Roberta; Kalaba, Marija ... Gustafsson, Lars L. (2014). **Dabigatran – a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs**. Frontiers in Pharmacology, 5, ARTN 109.10.3389/fphar.2014.00109.
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