TITLE

Adherence to Osteoporosis Medicines in Estonia – a Comprehensive 15 Year Retrospective Prescriptions Database Study

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CONFLICT OF INTERESTS

Ott Laius, Heti Pisarev, Katre Maasalu, Sulev Kõks and Aare Märtson declare that they have no conflict of interest.

CONTRIBUTIONS

Ott Laius, Heti Pisarev, Katre Maasalu, Sulev Kõks and Aare Märtson declare that all authors read and approved the manuscript.

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SUMMARY

Some patients do not take medicines as they are supposed to. Our research showed that in Estonia one fifth of patients did not start treatment with osteoporosis medicines and only 20 percent used the medicines for at least three years as they should. This induces unnecessary costs to the healthcare system.

ABSTRACT

Purpose
Medication non-adherence is the number one reason for not obtaining the expected clinical effect of medicines. With osteoporosis treatment it has been shown that both implementation of treatment and persistence influence the risk of fractures significantly. Long-term adherence to medication in Estonia is to be determined with this study.

Methods
A fifteen year retrospective study was carried out in order to establish initiation, implementation and persistence of Estonian patients. All new users of osteoporosis medicines were analyzed for all prescriptions they received during the study period. Sufficient adherence to treatment was defined as a patient being dispensed 80% or more prescribed doses for at least one year.

Results
The study period was from 2001 to 2015. 24,652 patients were included in the study. 93.7% (n=23,091) of the patients were women and 6.3% (n=1,564) were men. 4,636 (18%) patients were dispensed only one prescription. 44.2% of patients included in the study had medication possession ratio (MPR) ≥80% over follow-up period. 8,922 (36.2%) of all patients who were prescribed from 2001 to 2015 persisted for 1 year with MPR≥80% and 19.8% persisted for 3 years. 40% of expenditure on osteoporosis medication was made for treatment courses with unsufficient adherence.

Conclusions
There is room for improvement in Estonia with medication adherence relating to all three aspects that determine adherence - initiation, implementation and persistence. This means further efforts are to be made to educate patients and healthcare professionals on realizing the importance of good adherence.

KEYWORDS

Osteoporosis; adherence; persistence; bisphosphonates; database.

1. INTRODUCTION

Medication non-adherence is the number one reason for not obtaining the expected effect shown in clinical trials in real life [1] and it results in worsening of the disease and increased health care costs [2]. Adherence to medicines of chronic diseases comprises of three aspects: whether the patient initiates treatment, if he or she takes it as prescribed by the doctor and whether he or she persists with the treatment for a sufficient period of time [3].

Osteoporosis is a major health threat [4]. It alters bone architecture leaving them more fragile and more susceptible to fractures [5]. The main negative health outcome of fractures is loss of quality of life due to pain and disability caused by them [6]. Loss of bone mass itself is asymptomatic until a fracture occurs [7] and osteoporosis has clinical and public health relevance only because of the fractures [8]. The aging population and changes in people's lifestyle result in a constant increase in the number of fractures all over the world [9]. Osteoporosis is a growing chronic health state in the Western world and is putting a significant load on both the individual and the society [10].

Effective pharmacological treatment options against osteoporosis are available (e.g. bisphosphonates, denosumab, strontium ranelate) [11]. With no single agent demonstrating superiority over another in preventing fractures [12]. Osteoporosis pharmacotherapy needs to be used for a longer period of time and patients need to adhere to treatment for it to be effective and cost-effective [11]. The number of patients who receive treatment within a year after a fragility fracture has been shown to be less than 20 % [13]. Half of the patients who receive the treatment adhere to it sufficiently and only 35% continue the treatment for at least a year [14].

Improving adherence would effectively prevent more fractures [15] and healthcare resources could be spared by reducing finances spent on fragility fractures' treatment [16]. Several factors have been shown to influence adherence to medication but most important of those seem to be doctor-patient relationship, patient awareness and co-payment of medicines [17, 18].

The aim of our study was to establish adherence to osteoporosis medicines in Estonia and identify patient groups with poorer adherence so that future interventions may be targeted to improve adherence. We studied all three aspects of adherence - initiation, implementation and persistence.

2. METHODS

2.1 Setting and study cohort

We use the term adherence to describe the combination of initiation of treatment, implementation of treatment and persistence with treatment. We studied each element of adherence separately and also provide results for all of them. We considered sufficient theoretical medicines possession rate (MPR) of 80% or more during treatment. Osteoporosis medicines have demonstrated efficacy in clinical trials when taken at least for one year [19]. This could be considered a conservative estimate of sufficient persistence. Most of the efficacy trials have lasted for at least 3-years though [20–22]. Adherence in the context of our study was defined as a patient taking 80% or more of prescribed doses and persisting with treatment for one to three years.

To establish adherence to osteoporosis medicines in Estonia we analyzed prescriptions dispensed from Estonian general pharmacies from 2001 to 2015. Pharmacy dispensing data has been shown to

be a valid proxy to assess patients' medication adherence [23]. Prescription data were obtained from the Estonian Health Insurance Fund (EHIF) that keeps record of every dispensed prescription. Osteoporosis medications are reimbursed to all Estonian citizens with valid health insurance. Approximately 95% of the total population and all retired persons are insured in Estonia, so the study covered the vast majority of ambulatory drug consumption in Estonia [24].

Patients aged 50 or above who were dispensed prescriptions with diagnosis codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), M82 (osteoporosis in diseases classified elsewhere), M83 (adult osteomalacia), M84 (disorders of continuity of bone), M85 (other disorders of bone density and structure) or Q78.8 (other congenital bone fragility) according to the tenth edition of the international classification of diseases (ICD-10) were included in the analysis. At least one of the diagnosis codes had to be present on at least one of the prescriptions for the patient to be included in the study. All prescriptions of one patient were identified by a unique identifier applied to each patient by EHIF. The actual identity of the patient was concealed from the researchers. For every prescription patient's identifier, age, sex, diagnosis, specialty of the prescribing doctor, preparation and amount of packages dispensed was extracted.

New users of osteoporosis medicines were eligible for our study. New users were defined as patients who had not been dispensed an osteoporosis medicines prescription for at least one year prior to the start of the study.

Patients were followed up until they stopped treatment, until death or until the end of the study on the 31st of December 2015.

2.2 Osteoporosis medicines

Osteoporosis medicines used in Estonia are all classified in the anatomical therapeutic chemical (ATC) classification group M05B [25]. WHO defined daily dose (DDD) was used to calculate the number of days that the dispensed medicine would last a patient. For osteoporosis medicines the number of DDDs dispensed is a good predictor of treatment duration because the doses and dosing intervals do not differ between patients. We calculated the medication possession cumulatively meaning that with every prescription the number of DDDs dispensed was added to what the patient would have left from the previous prescriptions.

2.3 Treatment gaps

We also analyzed gaps in treatment or "drug holidays". A period of 90 days or more when the already dispensed amount of medicines should have been depleted and a new prescription had not been dispensed was considered a gap. A gap longer than 180 days was considered an end of treatment course and if the patient was dispensed another prescription later in the study it was considered a new treatment course.

2.4 Data analysis

Analyses were undertaken using Stata v13 (StataCorp LP) and Joinpoint Regression Program, Version 4.3.1.0. Joinpoint is statistical software for the analysis of trends using joinpoint models enabling to test if an apparent change in trend is statistically significant. Results are presented as average annual percent change (APC) over time period. The tests of significance use a Monte Carlo Permutation

method [26]. Comparsion of adherent/non-adherent patients by background variables was done by logistic regression. We considered statistically significant p-values less than 0.05.

3. RESULTS

3.1 Patients

In total 25,480 new patients were identified who received osteoporosis medicines with at least one prescription during our study period. 825 of them were under 50 and were therefore left out of the study. Prescriptions of 3 patients were dispensed after the patient had died and these patients were also left out. 24,652 patients were included in the study. 93.7% (n=23,091) of the patients were women and 6.3% (n=1,564) were men. Age distribution of patients is presented in figure 1.

3.2 Initiation of treatment

Out of the 24,652 patients who started treatment with osteoporosis medicines 4,636 (18%) were dispensed only one prescription. The number of patients starting treatment was growing steadily from 2001 to 2009 and declined from 2010 to 2015. The increase was on average 17.7% per year and the decrease 13.0% per year. Both trends of change are statistically significant. The percent of patients who were dispensed only one prescription showed a statistically significant 2.4% annual increase throughout the study (figure 2).

3.3 Implementation of treatment

Overall 44.2% of patients included in the study had MPR ≥80% throughout their follow-up period. 18.8% of patients were dispensed only one prescription and for these patients we did not calculate MPR. 37.0% of patients had MPR less than 80%. The percent of patients who had MPR over 80% showed an increasing trend during our study period. Out of the patients who initiated treatment in the beginning of 2000s around 60 to 70 percent were not implementing treatment sufficiently but only 20 to 30 percent of patients who started treatment towards the end of the study were not implementing the treatment (figure 3). The increase of patients with MPR≥80% can be divided into two periods - from 2001 to 2005 and from 2005 onward. Initially the annual increase of patients with MPR ≥80% was 29% and later it was 5%.

3.4 Persistence with treatment

Of the 24,652 patients who were included in our study 8,922 (36.2%) had MPR ≥80% and had a treatment course that lasted for at least 1 year. Only 19.8% of the patients persisted with treatment for at least 3 years with MPR≥80%. There were also almost 300 patients (n=299) who persisted with osteoporosis treatment with good implementation for longer than 10 years (figure 4).

3.5 Gaps and restarters

As our study period was very long patients who started treatment early in the study could stop treatment at some point and then start again after a while. They could also take smaller “drug holidays” during treatment. 2,483 patients had such “drug holidays” during their treatment. 4,555 patients restarted treatment after stopping and 2,360 patients had “drug holidays” and they also restarted treatment. 47.0% of the patients who were dispensed medicines with at least 2 prescriptions had shorter or longer gaps in their treatment. 17,737 patients (72.0%) started

treatment only once during the study but 4,636 of these patients were dispensed only one prescription. 19.5% of patients started osteoporosis treatment twice and 8.5% had 3 or more initiations of treatment. 2 patients restarted treatment 9 times during our 15-year study.

3.6 What drives adherence

Patient characteristics that determine medication adherence are presented in table 1. Women are 2.4-times more likely ($p<0.001$) to have a treatment course longer than one year with MPR≥80% than men. The age of patients is statistically related with the probability of one being adherent for at least a year. Compared with patients aged 50-59 the probability increases for the age group 60-69 by 20% ($p<0.001$) and for 70-79 by 12% ($p=0.004$) but decreases with older patients. The results are similar if we look at 3-year persistence. Patients who had a fracture when starting treatment (ICD-code M80) were more likely to have good implementation and persist with treatment than those who did not have a fracture (ICD-code M81). When treatment was started by general practitioner adherence was lower than when treatment was started by specialist doctors. Using more than one different medicinal product or active substance from ATC group M05B increased the probability of having a treatment course with MPR≥80% that lasted at least for one year.

3.7 Expenditure on medication

In total 14,172,142€ was spent on osteoporosis medicines of patients who started treatment during our study period in Estonia. 8,247,370€ was spent by the Estonian Health Insurance Fund and 6,647,697€ out-of-pocket by patients. Of the 14 million 8,471,773€ was spent on treatment of patients who had MPR≥80% and persisted for at least one year. 5,700,369€ was spent on treatment of patients who had MPR<80%, who persisted for less than a year or who were dispensed medicines with only one prescription.

4. DISCUSSION

4.1 Initiation

In the beginning of our study the number of new patients who received osteoporosis therapy for the first time increased very quickly reached its peak in 2009 and then started decreasing. The increase is probably due to the drugs becoming more affordable to patients with EHIF providing bigger reimbursement and generic medicines coming to the market [24]. The major decline of new users is unexplained though, as the number of patients in Estonia receiving osteoporosis treatment cannot be regarded as sufficient [25]. Also the number of patients who were dispensed only one prescription has not decreased as would be expected when medicines become cheaper. It has rather increased indicating that affordability is not the main factor hindering initiation in Estonia. Aspects that do influence initiation need further clarification to plan for effective interventions to enhance initiation.

4.2 Implementation

MPR≥80% is considered optimal for osteoporosis treatment to be effective [27]. Overall 44.2% of patients in our study achieved this for at least one of their treatment courses. This is a rather poor result for osteoporosis treatment as implementation percentages have been reported from 46% [28] to even 94.6% [29]. Lower implementation percentages have been reported when using daily dosing regimens which have been shown to provide lower implementation [30] and on the other hand

higher implementation have been achieved while looking at the implementation of persistent patients which is bound to provide better results as patients who are mindful about taking their medicines for a longer period of time do so probably more orderly than patients overall. 44.2% of patients having MPR≥80% is one of the lowest percentages shown in adherence studies but this is probably because of our very long study period and including every new patient in the study. Other studies usually have shorter durations [31] and new patients typically have poorer adherence [32]. It is shown that during a treatment course of one to two and a half years not implementing the treatment can increase pooled fracture risk by up to 46% [31]. This means that there is a great number of patients in higher risk of fracture in Estonia despite the fact they are prescribed osteoporosis medicines. The quick increase of patients taking more than 80% of their medicines in the beginning of the study might be related to the increasing use of once weekly medicines and decreasing use of once daily medicines in the middle of the 2000s in Estonia. Once weekly medicines have been shown to have better adherence than once daily medicines [33]. Patients taking "drug holidays" also needs to be addressed while improving adherence as almost half of the patients had gaps in their treatment and it has been suggested that focusing on the reduction of gaps might have greater influence on overall adherence than improving MPR of patients who are on treatment [34].

4.3 Persistence

Usually 1-year persistence is used to illustrate the duration of treatment. In our study 36.2% of patients continued treatment for at least a year and 19.8% for three years with MPR≥80%. In earlier studies 1-year persistence has been reported in a wide range of 18%-75%. The variation is driven by the different methods used in the studies (data-derived persistence and self-report etc.) [35]. But as with implementation - analyzing all new patients long-term is bound to give poorer results of adherence. It has been shown that 3-year persistence may reduce the risk of fractures by 41% compared to 1-month persistence [36]. This means that interventions to improve persistence are also needed in Estonia and that long-term persistence to treatment of new patients might be even lower than suggested before in similar studies.

4.4 Factors that influence adherence

Several patient characteristics have been shown before to predict poorer adherence [37] and our study was no different. First of all men tended to have poorer adherence in our study compared to women. This is not unexpected as men have been shown before to be less adherent [38]. As the proportion of men taking osteoporosis medicines is very small (6.3% of men in our study) tackling men separately to improve their adherence would probably not give a population wide health benefit.

There is some co-variance between the effects of patients' age, existent fracture and the prescribing doctor on adherence. All of these factors showed significant influence on adherence but as older people have more fractures and patients with fractures tend to put on treatment by specialist doctors rather than their GP then the patients decision to take ones medicine or not might come down to whether a patient has a fracture or not, as having a prior fracture motivates patients to take their medicines as prescribed [39]. Whether patient can afford their medicines is also a driver for adherence [40]. In Estonia the reimbursement percentage increases at the age of 63 from 75% to 90%. This could explain the higher adherence in the age groups above 60 compared to the group of

50 – 59. Higher reimbursement for osteoporosis medicines was established in the mid-2000s in Estonia. Before 2007 osteoporosis drugs were reimbursed with 50% by EHIF.

A bit unexpected for us was the result that the number of different medical products with the same active substance used by the patient did not have a negative effect on adherence. This could mean that generic substitution can be carried out without concern in Estonia and the patient can have the cheapest alternative offered to them. There has been concern in Estonia amongst the general public about generic substitution with a preparation containing the same active substance but our study indicates that what comes to osteoporosis treatment these concerns do not affect patients' medication adherence.

4.5 Expenditure

Medicines are expensive and national health systems are constantly working with constrained budgets. Poor adherence to osteoporosis medication has been shown to lead to significant waste of money and avoidable fractures [41]. Our study showed that up to 40% of the expenditure on osteoporosis medication might not have served its purpose because patients did not adhere to treatment. This could also influence the cost-effectiveness of medicines as the health benefits we assume from clinical trials are most likely not achieved in every day practice. In addition costs of hospitalization and other medical services have been shown to increase with poor adherence [42].This is also underpinning the importance of improving adherence as otherwise we are putting an even bigger pressure on the health system and the money spent in vain might restrict access to newer medicines.

4.6 Strengths

The studies of patient behavior are important for the development of medicines' policies and reimbursement systems but also as feedback to doctors and patients. The main strength of our study is the duration of the study. Fifteen year adherence studies have hardly ever done before [31] and studies lasting one to two years are already considered long-term. All osteoporosis medicines are prescription only and our study covers over 95% of Estonian population making it a representative study of our actual adherence situation because of full coverage.

4.7 Limitations

Our study also has some limitations. Most and foremost as we looked at dispensing data we cannot know whether the patient actually consumed the medicines they bought from the pharmacy. We make the assumption that every pill that is dispensed from the pharmacy is also consumed but this surely is not the actual case. This is a common issue with adherence assessment though as medication event monitoring systems are seldom used in real life adherence studies. We also could not assess whether the prescribing of osteoporosis medicines was justified in every single case and if the patients where in fact in need for long-term therapy. The reasons why patients stop taking their medication cannot be analyzed using databases but the actual reasons could provide us with the most valuable information on how to approve adherence.

5. CONCLUSIONS

There is room for improvement in Estonia with medication adherence relating to all three aspects that determine adherence. 18% of patients were dispensed only one prescription, 44.2% of patients had MPR≥80%, 36.2% of patients persisted with treatment for a year and only 19.8% three years or more with good implementation. Around 40% of the expenditure on osteoporosis medication probably would not result in the clinical effect aimed for as it was spent on non-adherent treatment courses.

This means further efforts are to be made to educate patients and healthcare professionals on the importance of good adherence to antiosteoporotic treatment in order to gain the clinical effectiveness offered by these drugs but that is not achieved with poor adherence to treatment.

Further research should be done to pin point the reasons for not initiating, implementing or persisting with medication and evaluate the potential regional differences of adherence in Estonia to better target interventions.

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7. TABLES

Table 1. Factors relating to the probability of having MPR≥ 80% for at least 1 year or 3 years

		MPR ≥ 80% for at least 1 year (OR, CI95%, p-value)	**MPR ≥ 80% for at least 3 years (OR, CI95%, p-value)**
Sex	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**
Doctors' speciality	General Practitioner	1	1
	Orthopedist	**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**

8. FIGURES

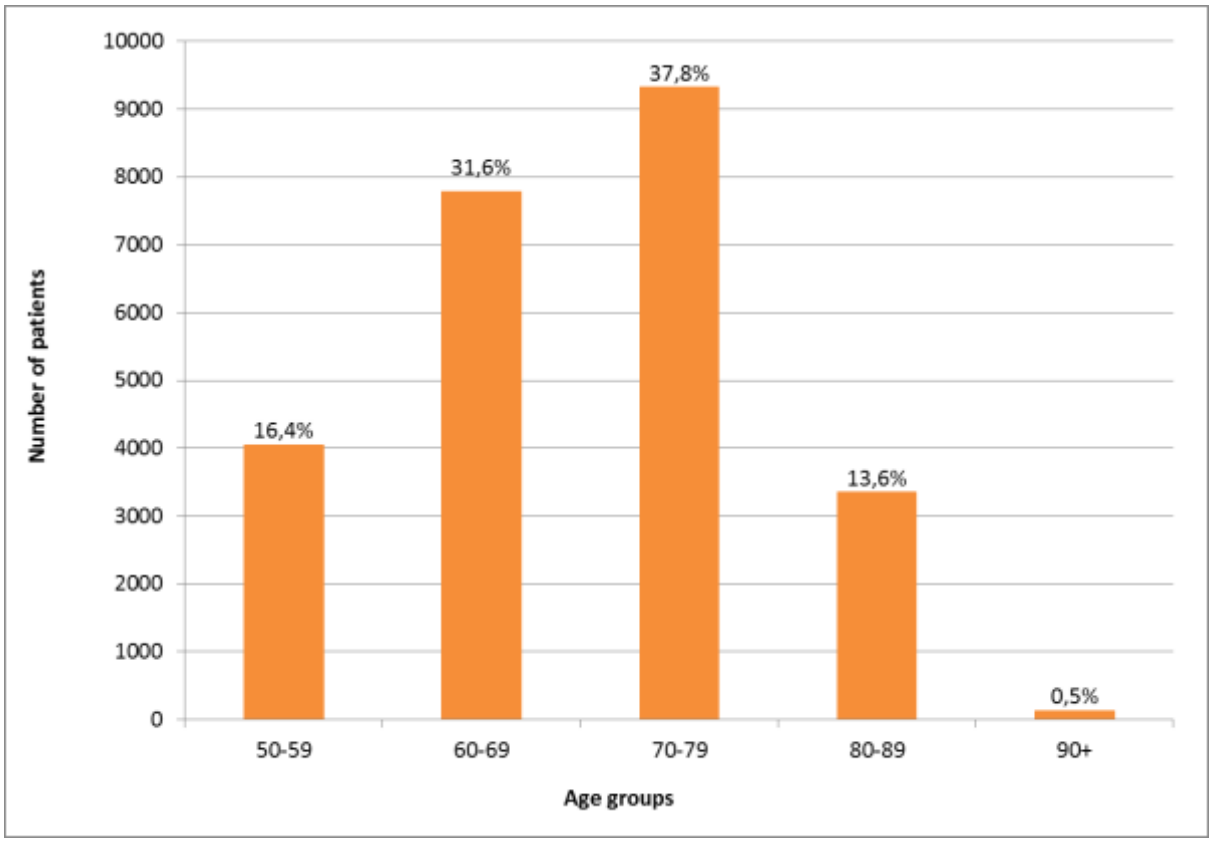

Fig. 1 Age distribution of patients starting treatment with osteoporosis medication (ATC group M05B) in Estonia in 2001-2015.

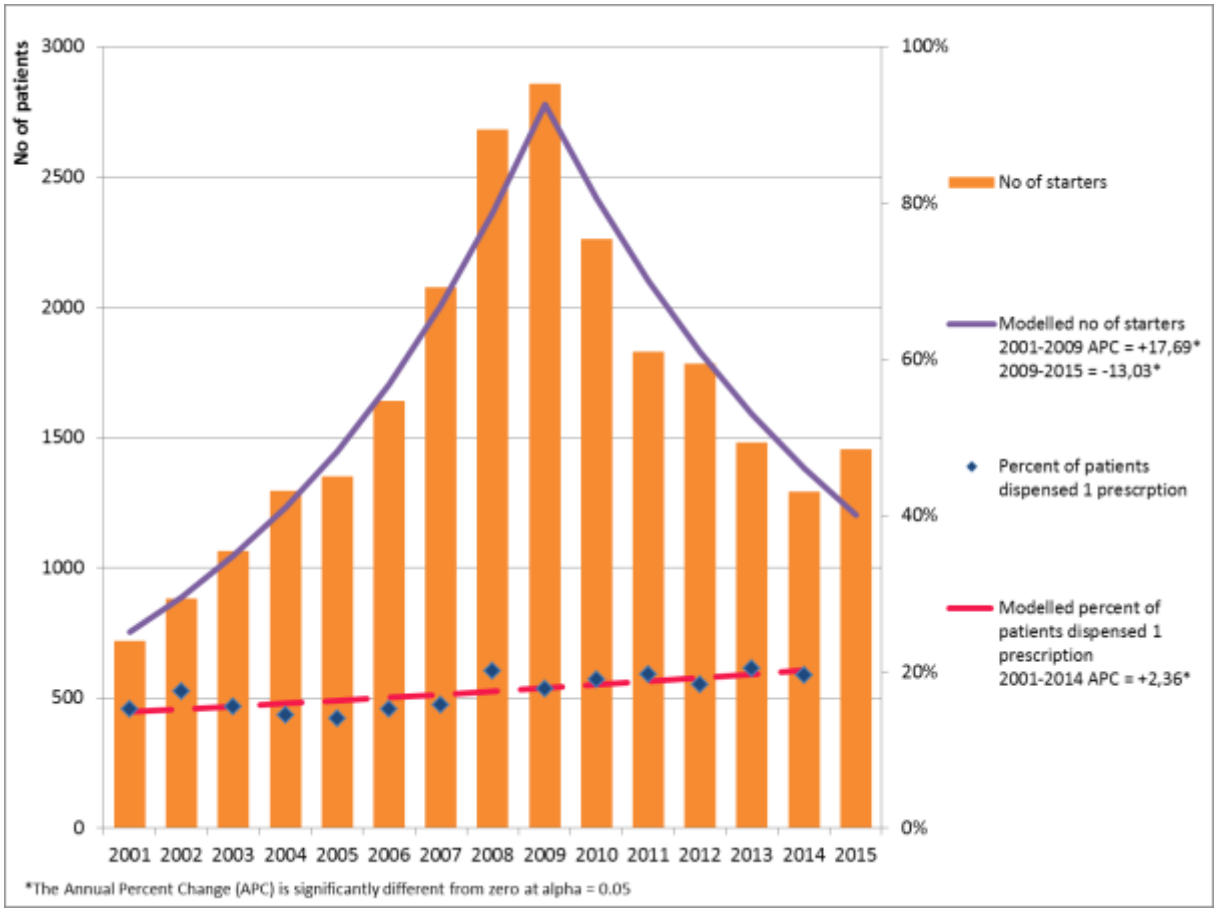

Fig. 2 The yearly number of patients who started treatment with osteoporosis medication and the modelled trends of all starting patients and those patients who were dispensed only one prescription.

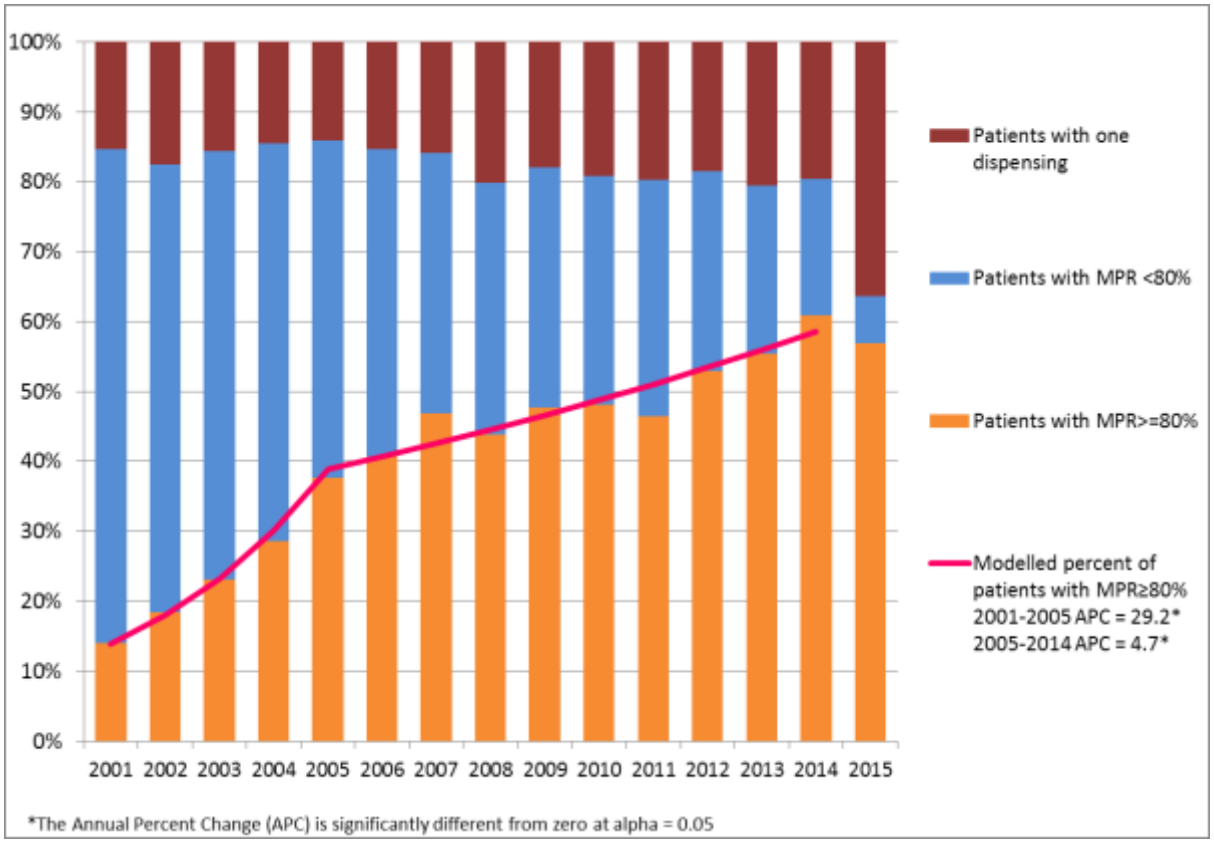

Fig. 3 The implementation of osteoporosis treatment in Estonia according to the year the treatment was initiated. Data presented as percent of patients who had medication possession ratio (MPR) ≥80%, under 80%, who were dispensed only one prescription and the modelled annual change in the percentage of patients with MPR≥80%.

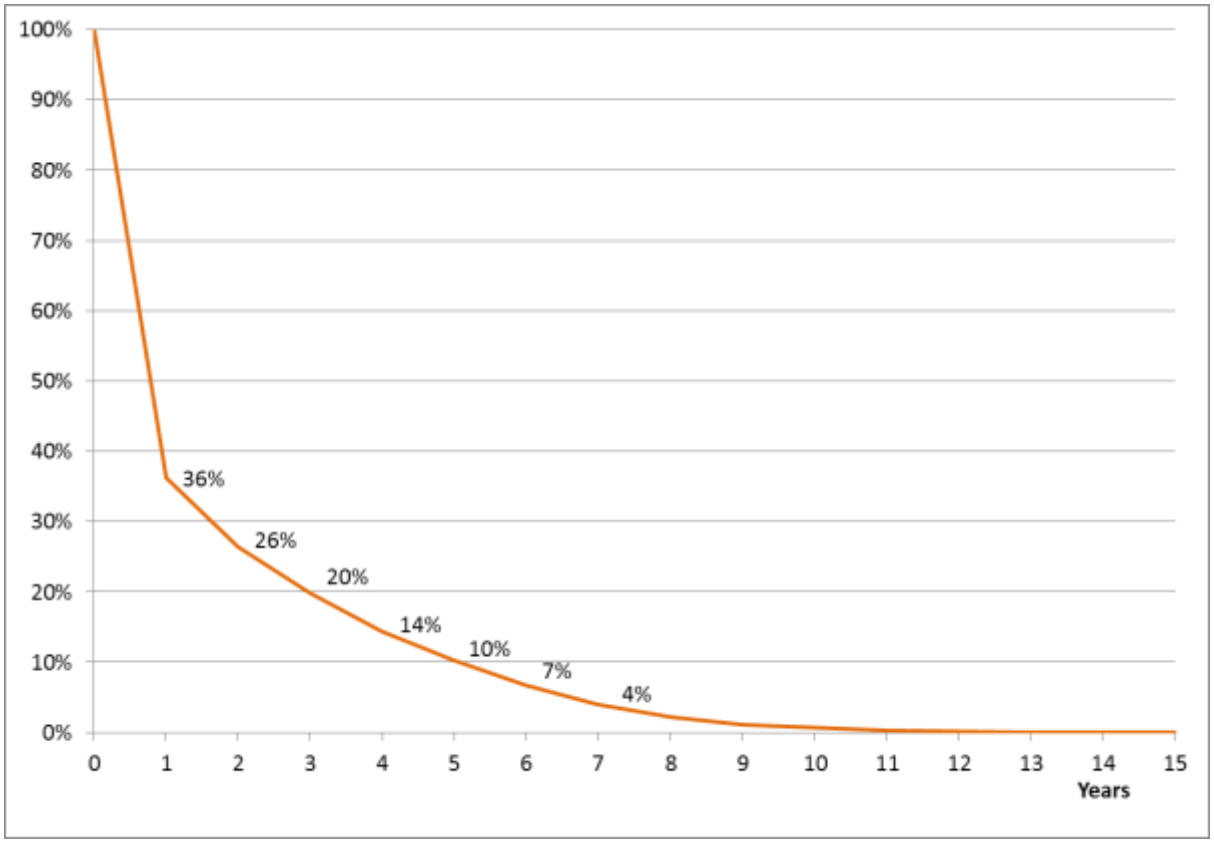

Fig. 4 The percent of patients persisting with treatment with MPR≥80% after a given number of years