TITLE

Trends in and Relation between Hip Fracture Incidence and Osteoporosis Medication Utilization and Prices in Estonia in 2004-2015

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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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MINI-ABSTRACT

Osteoporosis medicines reduce osteoporotic fractures. There is a very strong negative correlation between the consumption of medicines and the price of an average daily dose indicating that affordability is a key factor that could increase consumption of antiosteoporotic medicines and through that reduce fractures.

ABSTRACT

Purpose Osteoporosis is a major cause of morbidity and mortality in the modern world. Our study aims to describe the trends in incidence of hip fractures in relation to drug utilization patterns and the average price of antiosteoporotic medicines in Estonia.

Methods Data on hip fractures was obtained from the medical claims database of Estonian Health Insurance Fund (EHIF). Consumption and price data was obtained from the Estonian State Agency of Medicines (SAM). Consumption is presented using WHO defined daily doses methodology and the prices reflect the average wholesale price of medicines.

Results From 2004 to 2010 there was a non-significant increasing trend in standardized hip fracture incidence in Estonia, but from 2010 to 2015 the trend turned to a significant decrease of 4.5% per year. The consumption of osteoporosis medication increased significantly from 2004 to 2009 by yearly average of 41.2%. After 2009 the consumption levelled. On contrast the average price of one daily dose of osteoporosis medication decreased significantly from 2004 to 2009 by 16.9% per year and the decrease also levelled after 2009. This gives a very strong negative correlation of -0,93 ($p<0,001$) between the consumption of antiosteoporotic medication and the average price of a daily dose of medication during the study period.

Conclusions The statistically significant decline of standardized incidence of hip fractures from 2010 onward could at least in part be the result of the high increase in consumption of antiosteoporotic medicines which in turn is strongly negatively correlated with the average price of osteoporosis medicines.

KEY WORDS

Estonia; Hip fracture; Incidence; Osteoporosis; Adherence; Drug utilization

1. INTRODUCTION

Osteoporosis is a major cause of morbidity and mortality in the modern world [1]. It is characterized by reduced bone mass and disruption of bone architecture, resulting in increased bone fragility and increased fracture risk [2]. Fractures cause pain, degrade quality of life and are often disabling [3]. Osteoporosis itself is usually asymptomatic until a fracture occurs [4] and osteoporosis has clinical and public health importance only because of these fractures [5].

The efficacy of drug treatment in osteoporosis ultimately depends on the demonstration of a reduction in the risk of fracture [6]. Today there is a wide selection of effective pharmacological treatment options available (bisphosphonates, the parathyroid hormone teriparatide, the selective estrogen receptor modulator raloxifene, denosumab and strontium ranelate) [7].

The secular trends of fractures have been shown to follow different patterns in different parts of the world [8] indicating the need for local research on the subject. Understanding the reasons for the changes in rates of hip fractures may help understand ways to reduce rates of hip fractures worldwide [8]. The possible drivers for changes in fracture rates are osteoporosis medication use, urbanization, birth cohort effects, changes in bone mineral density and BMI and/or lifestyle interventions such as smoking cessation, improvement in nutritional status and fall prevention [9].

The influence of osteoporosis medication use on the trend of fractures has been pointed out as one of the main reasons for the decrease in fracture incidence [10, 11]. But it has been acknowledged that the results need to be also verified in local populations and countries [12].

Although the connection between the increasing utilization of medication and the price of drugs has been suggested for other drug classes [13] specific data concerning the changes in utilization of osteoporosis drugs depending on their price is scarce.

The trends in incidence of hip fractures has been studied before in Estonia [14]. Our study aimed to prolong the time period of the analysis and describe the trends in relation to drug utilization pattern. In addition we studied the changes in average price of daily dose of antiosteoporotic medicines in Estonia. The correlation between osteoporosis medicines consumption and the price of medicines has not been very well established yet and could provide useful information for decision makers to take further action when regulating drug prices.

2. METHODS

2.1. Hip fractures

We used hip fractures as a proxy for osteoporotic fractures as they are considered the most serious consequences of osteoporosis [15] with 1-year mortality around 20-25% around the globe [16]. Data on incidence of hip fractures was obtained from the medical claims database of the Estonian Health Insurance Fund (EHIF). Health care providers submit treatment bills to EHIF and we used those bills to identify the number of hip fracture diagnosis according to ICD-10 (S72.0-S72.2). Only the initial bill with the diagnosis was taken into account for each patient in any given year. The EHIF database covers the insured population of Estonia, which is around 95% of total population and 100% of pensioners [17]. We included both men and women and all age-groups in our study as the consumption data also included total consumption of osteoporosis medicines. Data on population in a given year was obtained from Statics Estonia [18] that publishes the official population of Estonia. As the study period is 11 years long and Estonian population is ageing, incidence of hip fractures is presented as standardized incidence rates using the age distribution of the Estonian population of the year 2009 in 5-year age groups as the base of standardization.

2.2 ATC/DDD methodology

Drug utilization was analyzed using the anatomical therapeutic chemical (ATC) classification and defined daily dose (DDD) methodology that is developed and maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The methodology is used in most of the European countries to serve as the tool for drug utilization research. The national statistics of the medicines' consumption gathered by governmental bodies is usually based on this methodology to keep track of changes in drug utilization [17].

All the active substances used in Estonia that affect bone structure and mineralization are included in the ATC group M05B, which is further divided into groups of plain bisphosphonates, bisphosphonate combinations and other drugs affecting bone structure and mineralization (e.g. strontium ranelate and denosumab). In terms of efficacy against hip fractures these substances are rather similar [19].

The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is described as a unit of measurement and is not always reflecting the recommended dose or the actual prescribed daily dose. For drugs against osteoporosis this is not the case as the doses used do not differ and the defined daily doses

applied by the WHO depict very well the actual doses used. This allows to evaluate the number of patients receiving the treatment in a period of time rather accurately.

The number of DDDs is reported as per 1000 inhabitants per day (DDD/1000 inhabitants/day or DID). We used the 2016 version of the ATC/DDD classification in the study.

Consumption data included in the study is available on the internet published by the Estonian State Agency of Medicines (SAM) [20] and represent wholesale sales data to general or hospital pharmacies. The data covers 100% of sales of antiosteoporotic medicines in Estonia.

The average prices of medicines daily doses were also obtained from SAM and were calculated using wholesale prices with value added tax (VAT) excluded. The currency in Estonia was changed from kroon to euro in the beginning of 2011, but as the exchange rate was always the same (1 euro=15.647 kroons) the prices in kroons were just calculated to euros.

2.3 Data analysis

Statistical analysis were done using MS Excel 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 [21]. We consider statistically significant p-values less than 0.05.

Relation between the consumption of antiosteoporotic medication and the average price of a daily dose of medication is presented by Spearman correlation coefficient as both indicators are non-normally distributed.

3. RESULTS

On average there were around 1500 hip fractures per year in Estonia during the study period. The standardized rate of hip fractures in 5-year age groups in Estonia and the Estonian population in the years 2004-2015 is presented in table 1.

As shown on figure 1 the trend of standardized hip fractures incidence rate in Estonia from 2004 to 2015 can be divided into two different periods. In the first period from 2004 until 2010 there was an increasing trend of hip fractures on average 1.19% per year with the highest fracture rate in 2009 but the trend was not statistically significant. Then the trend changed direction and from 2010 to 2015 there was an average annual decrease in standardized incidence rates of hip fractures of 4.46% ($p<0.05$).

The consumption of medication against osteoporosis during our study may also be divided into two different periods (figure 2). Initially the increase in consumption was very steep with an average of 41.21% ($p<0.05$) per year. This period raised the consumption from 0.8 DDD/1000 inhabitants/day in 2004 to 3.9 DDD/1000 inhabitants/day in 2009, which is almost a 5-fold increase. Since 2009 the consumption levelled with a statistically non-significant trend for increase until the end of the study period.

The change in preferred active substances in Estonia is shown on figure 3. The choice of drugs increased over the years and the preferences of active substances changed during the study period. In 2004 and 2005 only plain bisphosphonates were used. In 2006 the first combined preparation appeared on the Estonian market - the combination of alendronic acid and colecalciferol. From 2006 the only addition to the selection of active substances has been denosumab in 2010. In 2015 the medicine with the highest share of consumption was alendronic acid and colecalciferol combination with 59% out of the total of antiosteoporotic drugs.

The average price of a daily dose of antiosteoporotic medication moved in opposite direction to the consumption (figure 2). From the year 2004 to 2009 the average price decreased on average 16.85% ($p<0.05$) every year. From 2009 to 2015 the decrease in the average price of a daily dose was less expressed with an average annual decrease of 4.74% which was not statistically significant.

There is a very strong negative correlation of -0.94 ($p<0.001$) between the consumption of antiosteoporotic medication and the average price of a daily dose of medication during the study period.

4. DISCUSSION

Due to aging of population and changes in people's lifestyle the overall number of fractures would be expected to increase as a result [22]. This is what we saw for Estonia for the years 2004 to 2009 as our study found a similar trend in the standardized incidence rate of hip fractures as reported before [14] with the rate increasing initially but then starting to decrease. The trend is similar to what has been observed in most of the developed countries with initial increase in trend and a following decrease [8]. The turning point was a bit earlier in the western countries though with the trend turning to decline for instance in Scandinavia in the 1990s [9] while in Estonia the turning point was in the late 2000s. The main reason for the increase in hip fractures has been speculated to be urbanization [9]. The decline on the other hand might be the result of several factors. Increase of osteoporosis medicines use for one but

also the increase of average BMI, improved general health, decline in the number of smokers [23] and falls prevention campaigns [24]. The number of women over 55 with BMI over 25 did not change drastically in Estonia in the 1990s and the 2000s with the average percent being 70.0 in the 1990s and 71.5 in the 2000s [25]. The percent of non-smokers amongst women aged over 55 has decreased in Estonia as in the 1990s on average 81% stated themselves to be non-smokers but 66% stated this in the 2000s [25]. So in the Estonian context the decrease in hip fracture incidence seems to be more related to general health improvement and medicines consumption as we have had no falls prevention campaigns. Jürisson, et al. [14] also discuss that the reduction in fracture rate can be explained in addition to the increase in bisphosphonate use by reductions in falls-related comorbidity because of improved general health and prevention and treatment of chronic diseases. The life expectancy at 65 in Estonian women increased from 17.9 to 20.3 years (2.4 years) during our study period [25].

There was virtually no effective osteoporosis treatment in Estonia in the 1990s and the use of bisphosphonates started in the early 2000s [20]. Initially the consumption was still extremely low, because the medications were very expensive and there was no reimbursement by EHIF. There are several factors that influence drug use but the most important of those are the availability and affordability of medication [26]. What helped to increase the number of patients getting antiosteoporotic medicines in the 2000s was the number of clinical trials carried out in Estonia at that time. Approximately 20 trials were conducted and in addition to the patients who got the intervention also the patients who were in the control group got vitamin D and calcium supplements and information about their condition, which in turn could help decrease the number of fractures.

Reimbursement of 75% (or 90% if the patient was older than 63) of the cost of the drug by EHIF for patients with a fragility fracture and DXA T-score ≤ -2.5SD was introduced in 2007. Before the reimbursement was 50% but no more than 12.8€ per prescription. The 75% reimbursement group did not have such an upper limit which made the drugs considerably cheaper for patients. Also the introduction of generics was during the same period with the first alendronic acid generics introduced in 2007 after which the total consumption more than doubled within just two years. With medications being more affordable to patients the adherence to treatment is also expected to improve [27] and patients are able to take the drugs for longer periods, which is vital with quality of treatment kept in mind. This could also work the other way around of course as doctors and patients become more aware of the importance of medication adherence and implement treatment better than before the consumption of

medicines increases. It has been shown that in addition to medicines' cost also interpretation of one's disease and perception of possible benefits and risks of treatment improves adherence [28].

The consumption of antiosteoporotic drugs has not increased much since 2010. It can be related to the fact that reimbursement system for the drugs against osteoporosis is not changed and there is still only a limited group of patients (fragility fracture + DXA T-score ≤ -2.5SD) who get medications reimbursed at 75% or 90% (patients over 63) rate and others have a 50% co-payment, which makes the drugs still rather expensive for older people who need them the most. Fisher, et al. [12] saw an increase of hip fracture incidence very quickly after drop in the number of bisphosphonate prescriptions. We saw a continuing decline but the Estonian consumption steadied not decreased. It has been argued that the consumption of osteoporosis medication is responsible for only a part of the change in incidence of hip fractures [23] but the turning points in trends of consumption and fractures have been shown to be compatible also in other studies [10, 15] as we see in Estonia - four years after the introduction of higher reimbursement rate for antiosteoporotic medicines the standardized incidence rate of hip fractures started to decrease.

As we see a very strong negative correlation between the average price of a daily dose and the overall consumption one could expect even higher consumption if patients in risk of fracture in addition to patients with an actual fracture would be offered higher reimbursement rate. Price of medication is still rather substantial for this group of patients as for most patients who get higher reimbursement the medicines should be affordable. The consumption of antiosteoporotic drugs is not to be regarded as sufficient in Estonia as the population at risk of osteoporosis is assessed to be around 80 000 people [29] and according to our study, treatment was received daily by approximately 6300 patients in 2015. This is < 10% of patients with osteoporosis risk. The defined daily dose methodology allows assessing the average number of patients taking osteoporosis medication each day though. The number of patients who have had medication is bound to be higher as medicines are not taken continuously throughout a year and some patients stop taking the medicine after a while and others start treatment at some point. The same conclusions are stated also in EU osteoporosis report that use of pharmacological prevention of osteoporosis is significantly less than optimal, suggesting that a change in healthcare policy concerning the disease is warranted [29].

Current data suggest that consumption of drugs against osteoporosis might have an effect on fracture rate and price of medication has an effect on consumption. What will happen with hip

fracture rates in a few years as the increase in consumption has stopped and levelled remains to be seen. The use of antiosteoporotic drugs is one of the factors that have an effect on hip fracture rate and more detailed analysis about gender and fracture type may give us additional information. As the drug sales data are not patient gender or age specific we were not able to follow importance of these factors during this study. Also treatment duration, adherence and other factors showing patient behaviour are not reflected in sales data and an additional study is needed to investigate this in depth using actual prescriptions data.

The main limitations of the study lie with the methods of data collection. As EHIF data captures initial bills for any given year if a patient had several fractures within a year it would not be registered in the data. The number of multiple fractures in a year is supposedly not big though. The drug consumption data is based on sales data from drug wholesalers and depicts sales to pharmacies, so it does not directly show the amount of medicines received by patients and furthermore even if a patient purchased the medicines from a pharmacy it is unknown whether one actually administered them.

5. CONCLUSIONS

The age standardized incidence of hip fractures turned to a statistically significant decline after a trend for increase in the beginning of the study. Though improved general health and prevention and treatment of chronic diseases contribute to this it could be at least in part the result of the high increase in the consumption of antiosteoporotic medications during the first decade of the century.

The increase in consumption of medicines correlates in turn strongly with the decline in the average daily dose price of oral antiosteoporotic medicines. The price cannot drop indefinitely of course which means that further reduction in expenses to patients in Estonia can come from broadening the reimbursement to patients in risk of osteoporotic fractures rather than offering reimbursement only for patients who have had a fracture.

Our study describes the trends in hip fracture incidence, consumption of antiosteoporotic medicines and the price of these medicines. Whether there is a causal relationship between these factors is hard to establish but it is certain that further action to prevent osteoporosis and the resulting fractures is needed and the measures taken should be many fold ranging from preventive actions to optimizing the access to medicines.

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7. TABLES

Table 1. Population in Estonia by age groups and Estonian 2009-standardized incidence rates per 100,000 persons in Estonia in the years 2004–2015

	Population									
Age group	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
0-1	13,560	14,155	14,590	15,275	15,825	15,870	15,855	15,329	14,374	13,801
1-4	51,340	52,125	53,305	54,990	57,260	59,635	61,395	62,683	62,673	61,100
5-9	62,845	61,935	61,495	61,515	62,335	63,615	64,955	66,631	69,019	71,692
10-14	84,970	77,795	72,070	67,355	63,630	61,535	60,655	60,208	60,144	60,830
15-19	102,700	102,170	100,040	96,200	90,580	83,465	76,465	70,908	66,327	62,666
20-24	98,810	98,920	98,640	99,035	99,860	100,435	100,355	98,334	94,437	88,927
25-29	95,935	95,205	94,545	94,045	94,310	95,195	95,605	95,596	96,172	97,120
30-34	97,320	96,425	95,070	93,965	93,280	92,625	91,955	91,331	90,864	91,187
35-39	90,545	90,795	91,935	93,430	94,330	94,250	93,540	92,438	91,390	90,607
40-44	98,630	95,950	92,590	89,450	87,725	87,375	87,945	89,376	90,951	91,763
45-49	98,090	97,800	97,545	97,195	96,090	94,505	92,225	89,282	86,559	85,011
50-54	92,485	92,605	92,895	92,670	92,915	93,260	93,245	93,372	93,351	92,546
55-59	78,625	83,300	86,165	87,290	87,450	87,135	87,515	88,135	88,256	88,652
60-64	73,495	69,090	65,935	65,380	68,265	72,985	77,530	80,492	81,843	82,177
65-69	73,495	74,760	75,415	74,540	70,790	66,345	62,595	59,957	59,659	62,500
70-74	60,825	59,630	59,295	59,960	61,620	63,835	65,220	66,141	65,774	62,703
75-79	47,290	48,655	49,715	50,300	49,960	48,920	48,305	48,410	49,473	51,284
80-84	25,725	27,745	29,475	30,970	32,430	33,745	34,950	36,047	36,852	36,955
85+	15,865	15,715	16,090	17,115	18,435	19,785	21,165	22,769	24,578	26,476
Total	**1,362,550**	**1,354,775**	**1,346,810**	**1,340,680**	**1,337,090**	**1,334,515**	**1,331,475**	**1,327,439**	**1,322,696**	**1,317,997**
	Standardized hip-fracture incidence per 100,000									
Age group	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
0-1	7.4	0.0	0.0	0.0	0.0	0.0	0.0	6.5	0.0	0.0
1-4	3.9	1.9	0.0	1.8	5.2	3.4	3.3	0.0	3.2	1.6
5-9	1.6	3.2	3.3	4.9	0.0	0.0	0.0	3.0	0.0	0.0
10-14	3.5	7.7	2.8	4.5	3.1	11.4	4.9	5.0	1.7	4.9
15-19	5.8	2.9	7.0	5.2	4.4	6.0	3.9	0.0	1.5	4.8
20-24	2.0	2.0	3.0	3.0	2.0	1.0	1.0	9.2	3.2	2.2
25-29	3.1	1.1	0.0	3.2	3.2	5.3	4.2	5.2	2.1	12.4
30-34	9.2	4.1	4.2	6.4	6.4	5.4	7.6	4.4	6.6	2.2
35-39	9.9	18.7	12.0	6.4	10.6	10.6	13.9	15.1	0.0	6.6
40-44	9.1	20.8	16.2	8.9	25.1	10.3	6.8	19.0	9.9	10.9
45-49	23.4	33.7	39.0	17.5	31.2	32.8	26.0	32.5	24.3	25.9
50-54	45.4	43.2	42.0	48.6	44.1	42.9	47.2	38.6	52.5	33.5
55-59	61.0	73.2	68.5	64.2	54.9	72.3	65.1	68.1	75.9	58.7
60-64	102.0	141.8	98.6	123.9	106.9	112.4	126.4	119.3	84.3	101.0
65-69	178.2	173.9	184.3	154.3	132.8	180.9	190.1	178.5	140.8	129.6
70-74	256.5	318.6	278.3	250.2	284.0	278.8	297.5	287.3	231.1	256.8
75-79	507.5	452.2	500.9	453.3	530.4	570.3	490.6	518.5	430.5	454.3

80-84	929.1	947.9	939.8	881.5	1103.9	1066.8	1021.5	951.5	827.6	871.3
85+	1960.3	2055.4	1939.1	1986.6	2017.9	2259.3	2116.7	2130.1	2123.9	1926.3
Total	**109.9**	**116.8**	**112.0**	**106.4**	**116.1**	**123.2**	**118.1**	**117.4**	**103.0**	**102.5**

8. FIGURES

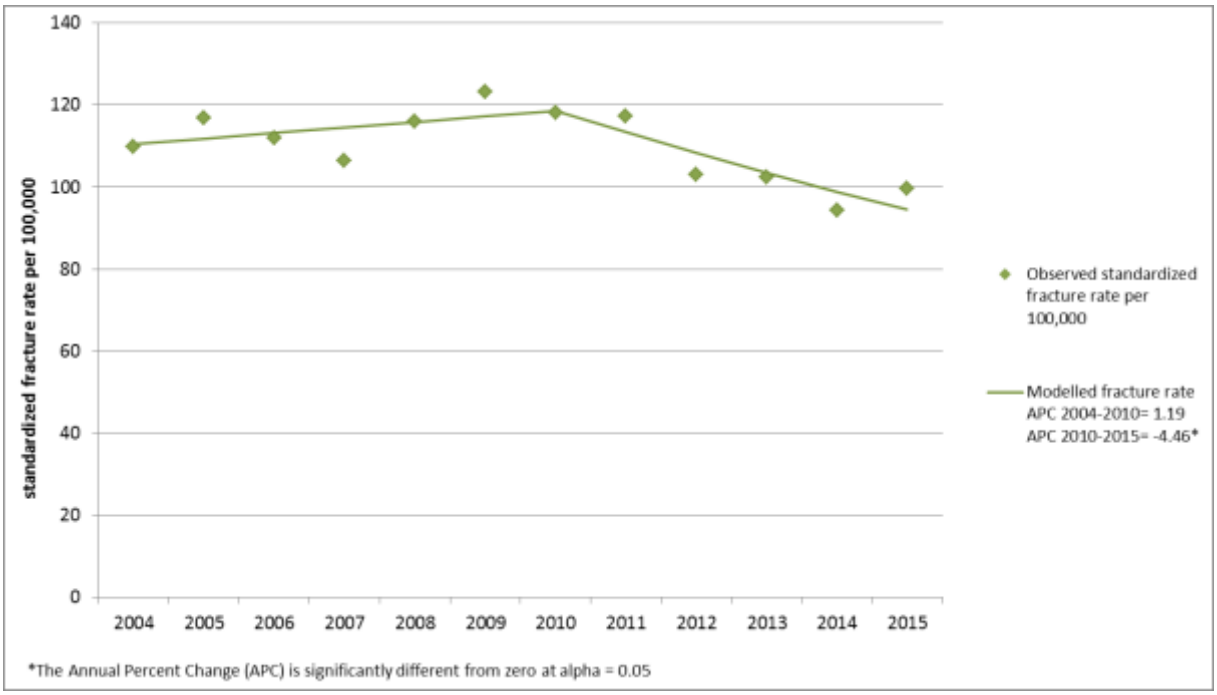

Fig. 1 The standardized incidence rate and the modelled trend of hip fractures (ICD-10 codes S72.0-S72.2) per 100,000 persons in Estonia in 2004-2015.

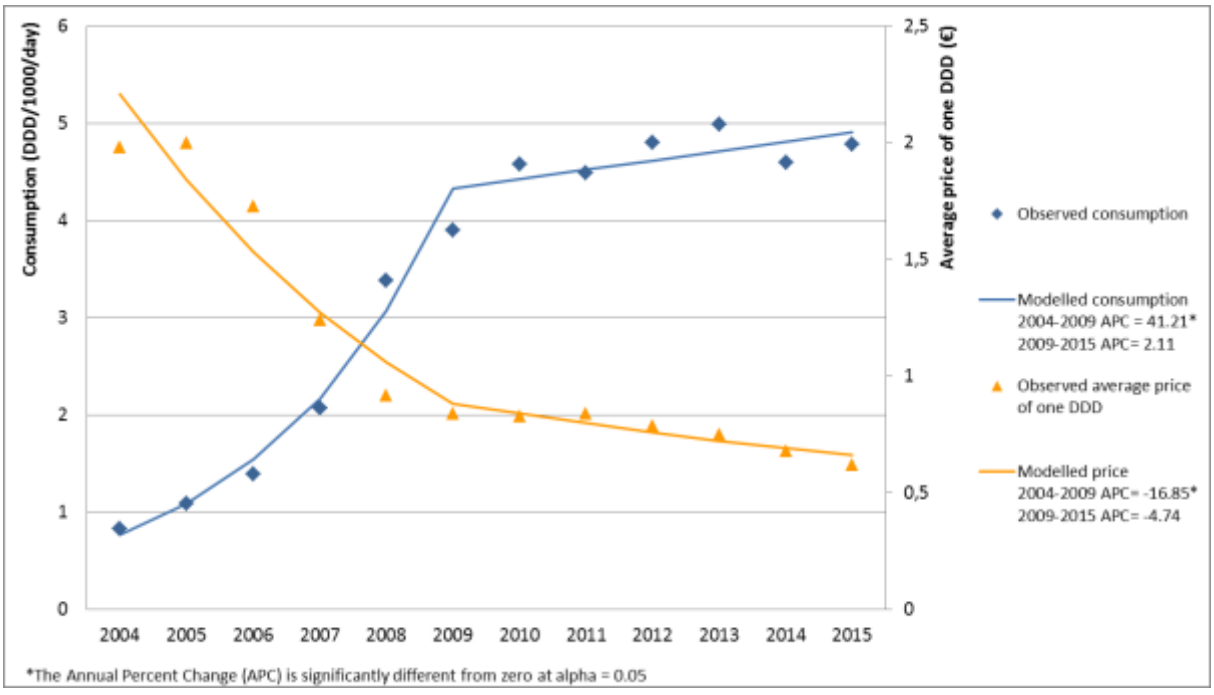

Fig. 2 The actual and modelled trends of consumption of osteoporosis medication represented as the number of defined daily doses per 1000 inhabitants per day (DDD/1000/day) and the average price of osteoporosis medication (ATC group M05B) daily dose in euros in Estonia in 2004-2015.

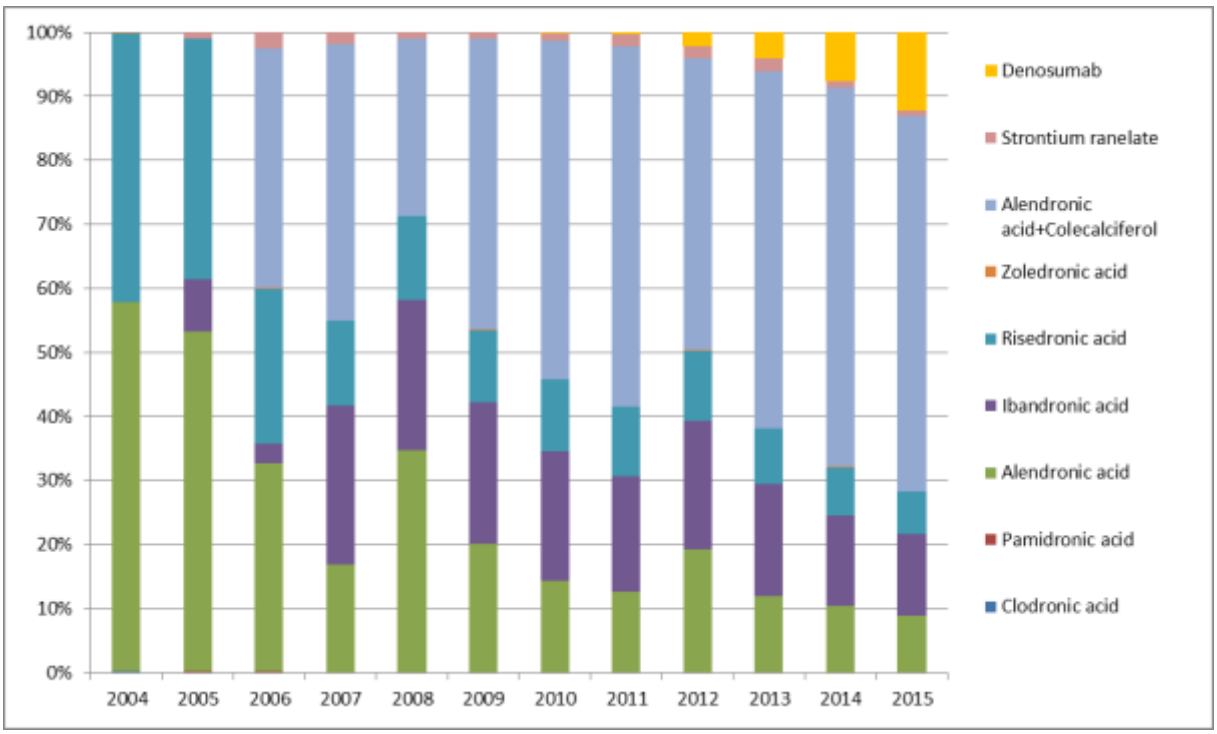

Fig. 3 The consumption of drugs against osteoporosis (ATC group code M05B) in Estonia in 2004 to 2015 expressed as the proportion of different active substances used out of the total.