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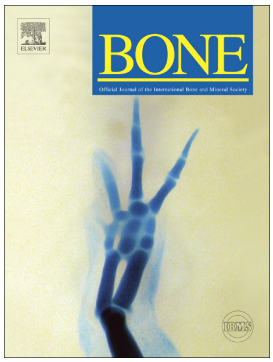

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Hip fracture rates and time trends in use of anti-osteoporosis medications in Denmark for the period 2005 to 2015: Missed opportunities in fracture prevention.

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COMPETING INTERESTS

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ABSTRACT

Background: Declining use of bisphosphonates (BP) in the United States and Europe may lead to a widening of the treatment gap for osteoporosis and an increase in fracture rates. However, a shift to non-bisphosphonates and to hospital administered i.v. BPs could lead to overestimation of the treatment gap if analyses are based exclusively on BP prescriptions. **When a healthcare system successfully narrows the treatment gap by making appropriate use of anti-osteoporosis drugs, we would expect to see declining rates of osteoporotic fractures with much of the decrease being statistically attributable to medication uptake.** We analysed a best-case scenario where all use of BPs, denosumab, raloxifene and PTH analogues - including the oncology area - was contrasted with the trend in hip fracture rates. **This scenario also considered users of raloxifene and teriparatide as covered by osteoporosis drugs though the primary RCT for raloxifene showed no risk reduction in nonvertebral fractures and the RCT for teriparatide risk reductions for non-vertebral fractures but not hip fracture specifically. Sensitivity analyses were also done.**

Methods: We used aggregate statistics on hip fracture events and total use of the above medications estimating the number of persons potentially covered. The reduction in hip fracture rates attributable to treatment was estimated using the absolute risk reduction (ARR) found in real-world users of oral alendronate in Denmark with the ARR in the FIT primary prevention arm as an alternative scenario.

Results: A plateau in use of osteoporosis medications occurred in 2014. Between 2005 and 2015, hip fracture rates declined by 30%. However, only up to 20% of the observed reduction in hip fracture rates was statistically attributable to treatment even in a best-case scenario. **Sensitivity analyses where raloxifene and teriparatide were excluded did not impact on this finding.**

Discussion: Anti-osteoporosis treatment in Denmark reached a plateau in 2014 even in a best-case scenario where all dispensations were assumed to be for osteoporosis. Future studies may be able to distinguish between the oncology area and the osteoporosis indication as well as provide a delineation of age and gender demographics among users of hospital administered osteoporosis medications. About 80% of the decline in hip fracture rates appears to be due to factors other than osteoporosis medication. **The plateau in use of osteoporosis treatment at a level that is too low to make a meaningful impact on societal fracture burden is problematic given the predicted increased age-specific hip fracture rates**.

Keywords: Osteoporosis – Epidemiology – Hip fractures – Treatment – Fracture rates – Public Health

BACKGROUND

When a healthcare system successfully narrows the treatment gap by making adequate amounts of anti-osteoporosis drugs available, we would expect to see declining rates of osteoporotic fractures with a substantial part of the decrease being statistically attributable to medication uptake. However, the last few years have seen a dramatic decrease in the use of osteoporosis medications in the United States[1], [2] and Europe[3], [4] with stagnating use being reported in Japan[5]. For bisphosphonates specifically, sales in the US began declining in 2008/2009 coinciding with FDA warnings about atrial fibrillation and continued after increasing public concerns about atypical femur fractures[1], [2] with use of bisphosphonates declining by about 50%. In the United Kingdom, use has been declining slowly since 2009[3]. This is only partly compensated for by prescription of new osteoporosis drugs such a parathyroid hormone analogues and denosumab[4], leading to international concerns about a widening treatment gap for osteoporosis[6]. Despite this, decreasing hip fracture rates in women and to a small extent in men has been reported in several Western countries. **However, there has been some lack of clarity as to the cause of this. Decreased or even stable fracture rates may indicate that medical treatment was in fact succeeding in keeping total fracture incidence under control. despite increasing longevity with a fast-growing population of the old and the oldest old, but fracture incidence will generally lag behind the trends in use of anti-osteoporosis therapy given the potentially long residence of - especially newer - bisphosphonates.** Because national registers have existed in Denmark for decades[7], [8], this country provides detailed data on the use of drugs licensed for osteoporosis coupled with good quality data on hip fracture surgery and hence hip fracture rates. Also, **Denmark is near the EU average in terms of treatment uptake with 5% of the 50+ population receiving treatment in 2010 both in Denmark and in the EU** [9].

In 2010, we used this data source to demonstrate a 20% decrease in hip fracture rates from 1997 to 2006, though **with only 3.7% of prevented hip fractures in women and a lower proportion in men being statistically attributable to use of osteoporosis medications** [10]. At the time, osteoporosis treatment was entirely dominated by oral medications with little overlap with the oncology area. The present study covers the years 2005 to 2015, a period in time where declines in the use of oral bisphosphonate prescriptions could be expected due to increasing use of hospital administered parenteral anti-resorptives such as denosumab and zoledronic acid. Failure to capture hospital administered osteoporosis drugs could cause an overestimation of the true treatment gap. Therefore, we analysed a best-case scenario where all use of BPs, denosumab, raloxifene and PTH analogues - including the oncology area where fractures will also be prevented but where a higher dose intensity is required - was contrasted with the trend in hip fracture rates over the same period. **In our primary scenario we considered users of raloxifene and teriparatide as covered by osteoporosis drugs though the primary RCT for raloxifene had showed no risk reduction in**

nonvertebral fractures and the RCT for teriparatide risk reductions for non-vertebral fractures but not hip fracture specifically. Hence, we added sensitivity analyses where analyses were repeated without these two medications, both of which had relatively low uptake.

METHODS AND STUDY POPULATION

Statistics were obtained from the Danish National Board of Health and the National Medicines Agency (public access through www.medstat.dk, accessed March 2018) on total sales, hospital and prescription sectors combined, of drugs licensed for treatment of osteoporosis and on surgically treated hip fracture events for the nation covering the period from 2005 to 2015. The medication usage information was retrieved by WHO ATC (https://www.whocc.no/atc_ddd_index) codes (table 1) as the total number of defined daily doses sold. Subsequently, DDD were converted to mg total sales and back-converted to number of persons covered taking into account any differences between the approved dose in osteoporosis and the defined DDD for the medication in question. We deliberately employed a best-case scenario considering all use as being for osteoporosis. In practice, denosumab and parenterally administered bisphosphonates are also widely used for prevention and treatment of skeletal malignancy and hypercalcaemia in the oncology setting, with a small proportion of use being for metabolic bone diseases such as Pagets disease of bone and fibrous dysplasia. The limitations will be discussed below.

Surgical repair for proximal femur fractures (KNFJ) was used as outcome and retrieved from http://esundhed.dk/sundhedsregistre/LPR/Sider/LPR06A.aspx (in Danish) covering the period 2005-2016 (accessed march 2018). This counts number of surgical procedures, i.e. two procedures during one year in the same patient due to say a re-fracture will count as two fractures. Surgical repair (re-surgery) following complications to the primary surgical procedure is coded by different codes and therefore do not interfere with the counting of the number of fractures.

The number of fractures prevented was estimated using two different scenarios, where one used real world Danish treatment data and the other used RCT data from the primary alendronate trial. **Hip fracture rates in Denmark among users of oral alendronate – by far the most widely used anti-osteoporosis therapy – are known in detail from a past study [11] so we first calculated absolute risk reductions (ARR) using these rates.** As we have previously shown that significant differences exist between the subjects of the FIT study and those treated in a real world scenario[12], we based the ARR on the treated event rate and the OR associated with persistent alendronate use over past exposure. **The relative risk reduction for hip fractures used was lower than in the original FIT study of alendronate, in accordance with the greater overall comorbidity in our patients. However, as hip fracture rates** were considerably higher, the ARR in this scenario is 5.7 hip fractures per 1,000 patient years as compared with 3.0 in the primary prevention arm of the alendronate FIT trial[13]. We also, however, considered an alternative primary prevention scenario (taken from alendronate FIT, no prior vertebral fracture)[13] with an absolute risk reduction of 3.0 hip fractures per 1000 person years. In both scenarios, we calculated fractures avoided first based on the extent of drug use in the same calendar year and second, based on the average drug uptake in the

preceding five years**. Because guidelines do not recommend raloxifene as an intervention to prevent hip fractures – there was no difference in hip fracture rates between raloxifene and placebo in the primary RCT[14] we also carried out a sensitivity analysis where raloxifene was not included in the calculation. Exclusion of both raloxifene and teriparatide combined was also evaluated.**

ETHICS

The data were retrieved from publicly available, aggregate data from the Danish health and prescription registries. Specific permissions are not required for access.

RESULTS

Time trends in exposure to osteoporosis drugs at population level 2005-2015

A steady increase in total use of drugs licensed for treatment of osteoporosis occurred from 2005 to 2014, followed by a plateau (fig 1). The population level total exposure to these classes of drugs more than doubled from 44,200 persons covered in 2005 to 121,000 in 2015, corresponding to an increase from 23.5 per 1,000 persons aged 50+ to 56.6 per 1,000. As these numbers include medications dispensed within hospitals it was not possible to break down use on age and gender so these numbers reflect total use divided by the Danish population aged fifty or over. The proportion of intravenous or subcutaneous use increased from 20% in 2005 to 35% in 2015, with denosumab and intravenous bisphosphonates accounting for 17% and 18%, respectively of osteoporosis drug use in 2015 (fig 2). **In parallel with this, SERM use declined dramatically so that while raloxifene accounted for 6.9% of use in 2005, this was only 0.5% in 2015.** Less than 1% of doses were for teriparatide while 63% were oral bisphosphonates. The proportion of parenteral osteoporosis drugs is inflated in this best-case scenario since **these drugs are also used in prevention and treatment of skeletal metastases, treatment of hypercalcaemia and in a small number of patients with rare metabolic bone diseases.**

Hip fracture rates in Denmark 2005-2015

From 2005 to 2015, Danish hip fracture rates (fig 1) declined by 30% from 5.5 to 4.0 per 1,000 for the population aged 50+. The total number of hip fractures decreased by 18% from 10,331 (2005) to 8,497 (2015) and the 50+ population increased from 1.9 million to 2.1 million.

Hip fractures avoided attributable to osteoporosis treatment

Table 2 shows a tabulation of hip fractures avoided under two sets of assumptions. In scenario A (fig 3, solid line), which uses real-world incidence rates from alendronate users of both genders combined, 20% of the decline in hip fracture rates from 2005 to 2015 could be statistically explained by osteoporosis drugs used in the past five years, or 21.2% if only considering the uptake in the year 2015 itself. Despite the greater relative risk reduction in the **FIT scenario (Scenario B)** , hip fracture events in this study were so rare that only 10.6% of the reduction in hip fracture rates (fig 3, dotted line) would have been attributable to osteoporosis treatment. Both scenarios considered men and women together. However, the effect size data in the alternative scenario was derived from women alone and a similar absolute risk reduction in men was assumed for the purpose of this calculation. **As raloxifene use was very low in the 2010 to 2015 period, excluding raloxifene from the calculation**

only marginally reduced the extent of rate decline explained from 20.0% to 18.7%, with a further small reduction to 18.5% if teriparatide was also removed from the analysis.

DISCUSSION

This study shows that the total use of medications licensed for treatment of osteoporosis in Denmark reached a plateau in 2014, even assuming a best-case scenario where all pharmacy and hospital dispensations of osteoporosis drugs is assumed to be for the osteoporosis indication alone. **We also included osteoporosis medications that, while licensed for osteoporosis, lacked proven hip fracture efficacy in the primary RCTs. However, excluding raloxifene and teriparatide from the analysis did not materially alter the findings as described above.** Stagnating or declining use of osteoporosis drugs has been reported in most of Western Europe and even more so in the United States[1], [2] [3], [4]. For bisphosphonates specifically, sales in the US began declining in 2008, coinciding with FDA warnings about atrial fibrillation. Further decreases followed subsequent concerns about atypical femur fractures[1], [2] with use of bisphosphonates declining by about 50%. In the United Kingdom, use has been declining slowly since 2009 [3].

In the present study, eighty percent or more of the observed decline in hip fracture rates for the period 2005 to 2015 appears to be attributable to factors other than osteoporosis medication. Indeed, the calculated treatment uptake is an optimistic estimate as we included also all use within oncology, where the annual total doses per patient are higher and therefore the number of persons covered is a best-case estimate. We chose to focus on surgically repaired primary hip fracture events to be able to capture more than one fracture in a year in the same person without the need for wash out periods in the analytical approach since any repeat surgery for the same fracture will be coded under a distinct procedure code. This allows the analysis to be carried out on aggregate data as discussed below but results in subtly different hip fracture rates from those calculated using Cox methods with wash out periods.

The observation that age specific hip fracture rates have declined in Denmark for reasons other than a period effect (e.g. introduction of intervention in high risk groups) is supported by epidemiology studies using APC models. Hence, in Denmark and Sweden [15] major cohort effects were identified regarding hip fractures. Specifically, fracture risk was particularly low in women born in the 1930s and this translates to a transient decrease in hip fracture rates with an expected increase in age specific rates over the coming years as a more fracture prone generation reaches old age. It is unclear what drives the lower risk in women born in the 1930s but HRT was in widespread use in the 1980s when this birth cohort reached menopause.

Importantly, our analysis shows that the plateau in employment of drugs shown to reduce the risk of low energy fractures **– including those shown to reduce hip fracture risk** - is a real phenomenon and not simply a shift of osteoporosis treatment from oral bisphosphonates, which we can track through prescriptions, to hospital administered parenteral formulations that escape capture in the national prescription database and could give the appearance of a gap in treatment. While the large

decrease in utilisation that happened in the United States [1], [2] has not yet been mirrored in Denmark, the treatment gap for osteoporosis in Denmark still faces a triple jeopardy. **This consists of the predicted [15] higher** age-specific incidence rates for hip fractures, **the growing size of the population aged 65+ and the plateau which has now been confirmed in the employment of medications licensed for the prevention of osteoporotic fractures. Crucially, the findings of this study should not be interpreted as indicating that appropriate prescribing of anti-osteoporosis medications does not prevent hip fractures in this country. What the study shows is that we are failing to take full advantage of the potential for further reducing hip fracture events, because use of anti-osteoporosis medications has plateaued at a level that is too low to make a meaningful impact on societal fracture burden.**

It is not possible to say with any certainty if the plateau in use reached in 2014 marks a delayed response to the safety concerns in terms of osteonecrosis of the jaw, atrial fibrillation and atypical femur fractures at least coincided with the strong decline in bisphosphonate use in the United States States[1]. If driven solely by the same safety concerns, a delay of five years seems long given the rapid dissemination of media reports to physicians and consumers globally. Instead, we may be observing the combined uptake reducing effects of shorter treatment courses and the negative effects of patient concerns on treatment rates, but offset in part by the wider availability of parenteral osteoporosis drugs that may have overcome other treatment barriers.

A limitation to the current study is that it is arguably a best case scenario in the calculation of persons covered because i.v. bisphosphonates and denosumab are given at shorter intervals in the oncology setting. Therefore total sales overestimate the number of persons on treatment when calculated using the lower cumulative annual dose that is used for osteoporosis. Preliminary data suggest about 40% of patients receiving zoledronic acid in Danish hospitals do so on an oncology indication, based on their dosing frequency and hospital diagnosis[16]. **It would certainly be interesting to be able to distinguish between the osteoporosis indication and the oncology setting as set out in the directions for future research below. However, the populations are not distinct as a substantial number of hip fractures occur in patients with a recent or current history of malignant disease. In Danish hip fracture patients, 1.1% of men and 0.8% of women have metastatic cancers with 9% of men and 6% of women having been registered with a malignancy diagnosis in the past three years[17].**

It is a strength of the study that we were able to use the true observed hip fracture rates from alendronate users in the country rather than having to rely on the lower event rates in the primary trials; however, the relative risk reduction derived from observational cohort studies is subject to unmeasured confounding and is not as robust as the relative risk reduction calculated from a randomised study. We chose not to combine the relative risk reduction from the FIT study with the

Danish on-treatment event rates but used the smaller relative risk reduction inferred from the observational cohort data in scenario A. Had we used the larger effect from the trial in scenario A, we would have arrived at twice the number of hip fractures prevented but the greater comorbidity of the real-world **user population likely makes a 70+ % risk reduction too optimistic for contemplation. Due to the low extent of raloxifene use in the last five years of the study, removing raloxifene from the analyses had only a very marginal effect on the results and did not change the overall conclusion that osteoporosis drugs are underused in this population with most of the decline in hip fracture rates being attributable to a short-term decline in population risk level as discussed above.**

Conversely, osteoporosis drugs are effective even at slightly suboptimal adherence with **a Medication Possession Ratio (MPR, a measure of adherence and gaps in treatment) down** to 80%[18] and for long acting osteoporosis drugs like zoledronic acid, the treatment offset can fortunately be several years[19], [20]. Future studies may be able to obtain more detailed patient level data on hospital administered osteoporosis drugs and make a clearer distinction between the oncology area and the osteoporosis indication as well as a clearer delineation of age and gender demographics among users. For the purpose of analysis we also had to assume that the demographics and fracture rates of oral alendronate users in Denmark was representative of the whole spectrum of prescription and hospital administered osteoporosis drugs though we would expect somewhat higher comorbidity and base risks in patients who required parenteral osteoporosis treatment. This too may modestly conservatively bias the number of fractures avoided through treatment, assuming an unchanged RRR but higher event rates in this group of patients.

Taken together, this study confirms that Danish hip fracture rates continued to decline from 2005 to 2015 parallel to the decrease in most other European countries[21] against a backdrop of stagnating use of drugs licensed for osteoporosis. Prior epidemiological studies have suggested that this is mainly caused by a protective cohort effect specific to women born in the 1930s[22] which will be followed by a return to higher age specific fracture rates, with the hip fracture burden further magnified by the increase in the number of the oldest old in Northern Europe and in the number of persons at high risk of fracture[23].

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TABLE 1

Class and ATC code	Product	Person years covered in 2015[1]
SERMs		
G03XC01	raloxifene	589
PTH analogues		
H05AA	PTH analogues	1132
Bisphosphonates		
M05BA01	etidronate	0
M05BA02	clodronate	0
M05BA03	pamidronate	8
M05BA04	alendronate	75597
M05BA06	ibandronate	655
M05BA07	risedronate	515
M05BA08	zoledronic acid	21600
Strontium		
M05BX03	strontium ranelate	290
Biologicals		
M05BX04	denosumab	20660

ATC codes used for retrieval and theoretical number of persons covered based on total drug sales (hospitals and pharmacies) in the country. Source: www.medstat.dk. Please refer to methods section for details.

[1] Assuming osteoporosis dose

TABLE 2

	Hip fracture risk reduction		*Hip fractures avoided 2015 (per 1,000-person years age 50+)*		*Percent of observed rate decrease 2005 to 2015 explained*	
	Relative risk reduction (RRR)	*Absolute risk reduction (ARR)*	*By same year uptake*	*By average uptake last 5y*	*By same year uptake*	*By average uptake last 5y*
Scenario A, **Danish real-world data** (*Abrahamsen, BMJ 2016*) [11]	**0.26**	**5.7**	**0.32**	**0.28**	**21.2 %**	**20.0 %**
Scenario B**, FIT study** primary prevention (*RCT, Black JCEM 2010*) [13].	**0.56**	**3.0**	**0.17**	**0.15**	**11.2 %**	**10.6 %**

Estimated reductions in hip fracture rates in 2015 attributable to use of drugs licensed for treatment of osteoporosis under realistic absolute risk reduction (ARR) assumptions and their relative contribution to the reduction in hip fracture rates in the country over the preceding decade.

LEGENDS

Fig 1

Trend in hip fracture rates (line, main y-axis) and treatment uptake for drugs licensed for osteoporosis in Denmark (bars, secondary y-axis) per 1,000 population aged 50+.

Fig 2

Change in distribution of use of osteoporosis drugs in Denmark from 2005 to 2015 assuming medications are used in the doses approved for osteoporosis treatment. The total number of persons covered increased 2.7-fold over the decade and parenteral osteoporosis drugs increased from 20% to 35%.

Fig 3

Time trend for hip fractures (rates per 1,000 pop age 50+) prevented attributable to overall uptake of drugs licensed for osteoporosis in Denmark 2005 to 2015. Scenario A (solid line) is based on observed on-treatment hip fracture rates for Danish patients treated with alendronate and relative risk reductions derived from observational data. Scenario B (dotted line) is an alternative calculation using the low hip fracture rates in the FIT primary prevention study and the larger relative risk reduction seen here. Please refer to table two for a more detailed breakdown of the calculation for the year 2015.

HIGHLIGHTS

- The use of anti-osteoporotic medications in Denmark reached a plateau in 2014, even when including hospital administered denosumab and zoledronic acid on all indications.
- Between 2005 and 2015, hip fracture rates declined by 30% or 3,200 hip fractures.
- Osteoporosis treatment to prevent hip fractures is underused with only up to 20% of the observed reduction in hip fracture rates statistically attributable to treatment even in this best-case scenario.
- Use of anti-osteoporosis medications has plateaued at a level that is too low to make a meaningful impact on societal fracture burden.
- Restricting the analysis to medications with primary RCT evidence for prevention of hip fractures did not alter the conclusions.

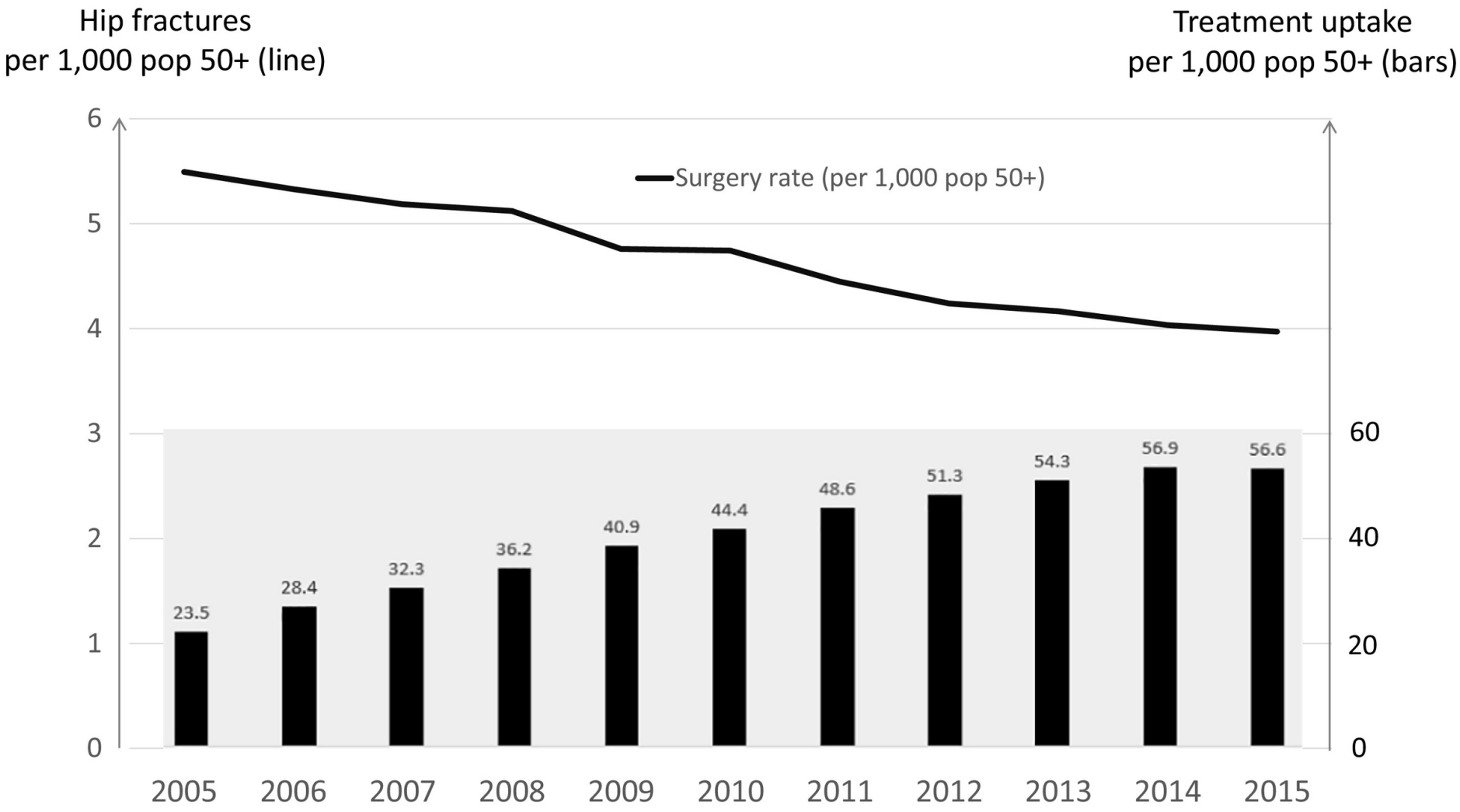
Hip fractures
per 1,000 pop 50+ (line)
Treatment uptake
per 1,000 pop 50+ (bars)
Surgery rate (per 1,000 pop 50+)
6
5
4
3
2
1
0
60
40
20
0
23.5
28.4
32.3
36.2
40.9
44.4
48.6
51.3
54.3
56.9
56.6
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

Figure 1

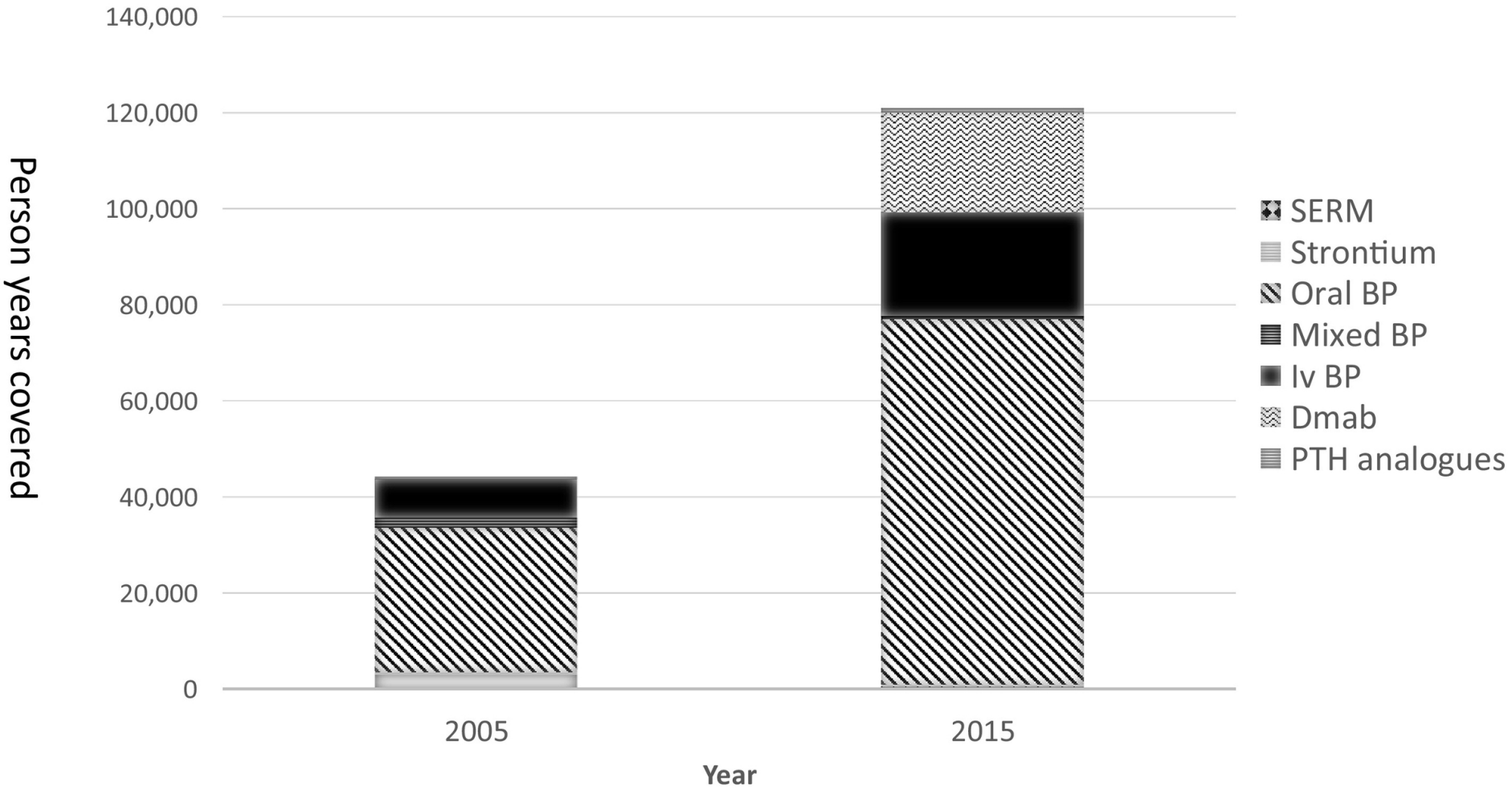
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
Person years covered
2005
2015
Year
SERM
Strontium
Oral BP
Mixed BP
Iv BP
Dmab
PTH analogues

Figure 2

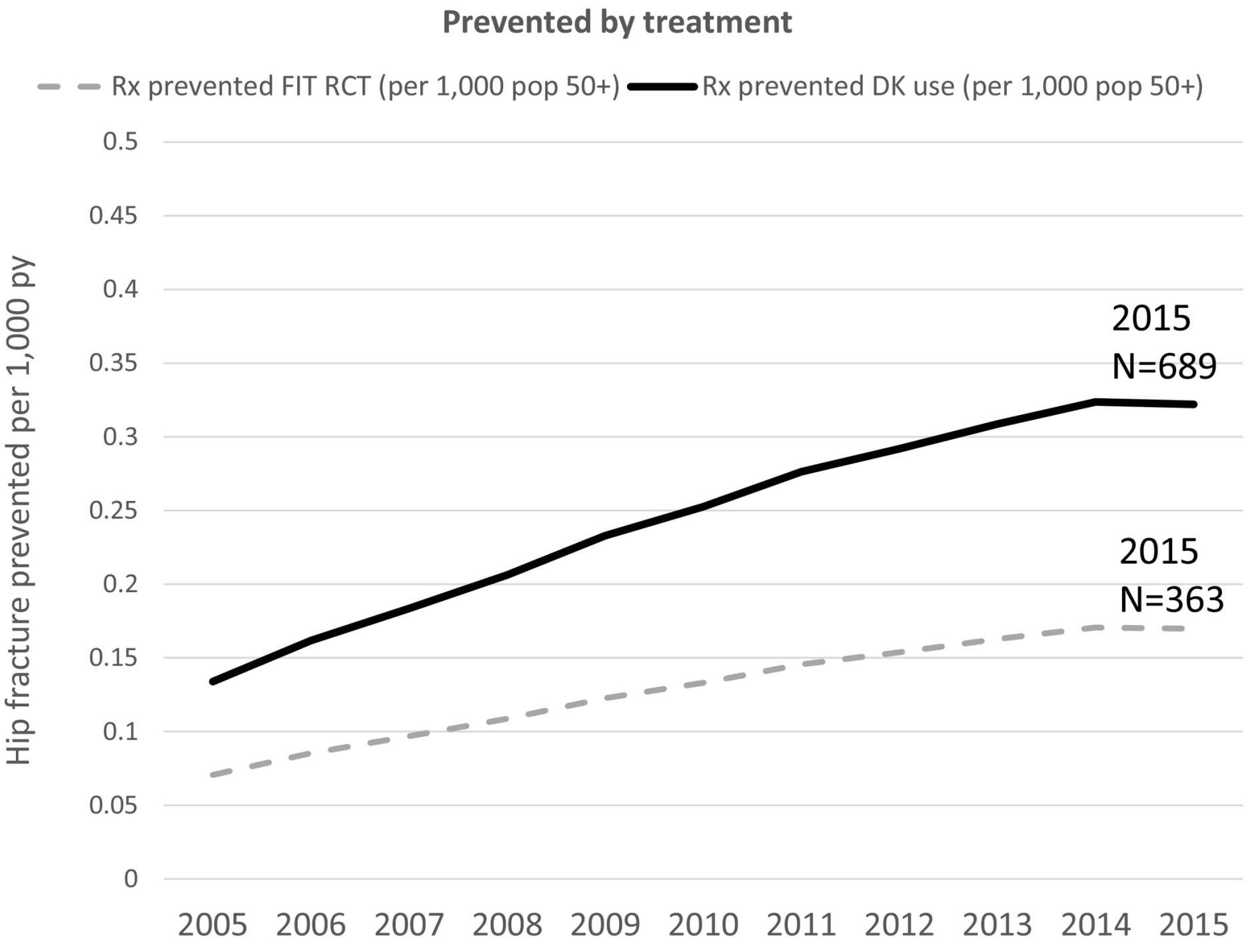
Prevented by treatment
Rx prevented FIT RCT (per 1,000 pop 50+)
Rx prevented DK use (per 1,000 pop 50+)
Hip fracture prevented per 1,000 py
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2015
N=689
2015
N=363

Figure 3