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ORIGINAL ARTICLE

Cost-effectiveness of pharmacological fracture prevention for osteoporosis as prescribed in clinical practice in France, Germany, Italy, Spain, and the United Kingdom

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Abstract

Summary This study estimated the cost-effectiveness of pharmacological fracture prevention as prescribed in the five largest European countries (EU5) using the IOF reference cost-effectiveness model. Pharmacological fracture prevention as prescribed in clinical practice was cost-saving (provided more QALYs at lower costs) compared to no treatment in each of the EU5.

Purpose To estimate the real-world cost-effectiveness of pharmacological fracture prevention as prescribed in the five largest European countries by population size: France, Germany, Italy, Spain, and the United Kingdom (UK) (collectively EU5).

Materials and methods We analyzed sales data on osteoporosis drugs in each of the EU5 to derive a hypothetical intervention that corresponds to the mix of osteoporosis medication prescribed in clinical practice. The costs for this treatment mix were obtained directly from the sales data, and the efficacy of the treatment mix was estimated by weighing the treatment-specific fracture risk reductions from a published meta-analysis. Subsequently, we estimated the cost-effectiveness using costs per quality adjusted life year (QALY) of the intervention compared to no treatment in each of the EU5 using the International Osteoporosis Foundation (IOF) reference cost-effectiveness model. The model population comprised postmenopausal women, mean age 72 years with established osteoporosis (T-score ≤ -2.5) among whom 23.6% had a prevalent vertebral fracture. The model was populated with country-specific data from the literature.

Results Pharmacological fracture prevention as prescribed in clinical practice was cost-saving (provided more QALYs at lower costs) compared to no treatment in each country. The findings were robust in scenario analyses.

Conclusions Pharmacological fracture prevention as prescribed in clinical practice is cost-saving in each of the EU5. Because of the under-diagnosis and under-treatment of post-menopausal osteoporosis, from a health economic perspective, further cost-savings may be reached by expanding treatment to those at increased risk of fracture currently not receiving any treatment.

Keywords Costs and costs analysis · Cost-benefit analysis · Cost-effectiveness · Osteoporosis · Osteoporotic fracture · Preventive medicine · Practice patterns

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Introduction

Osteoporosis is characterized by decreased bone mass and microarchitectural deterioration of the bone, leading to increased risk of fragility fracture—fractures resulting from minimal trauma such as a fall from standing height or less. The consequences of fragility fracture range from painful, but frequently transient, effects after wrist fracture to severe pain, disability, and even death after hip and vertebral fracture.

The prevalence of osteoporosis—and therefore the risk of fragility fracture—increases with age. Hence, the burden of osteoporosis is expected to increase with aging populations, and the number of individuals worldwide at high risk of fragility fracture has been estimated to increase two-fold from 158

million in 2010 to 319 million in 2040 [1]. From a European perspective, osteoporosis is a major public health problem, with an estimated 3.5 million fragility fractures sustained in 2010, resulting in costs of approximately EUR 35 billion and 1.2 million quality adjusted life years (QALYs) lost [2].

Pharmacological therapy is a cornerstone of osteoporosis management, but it has been argued that uptake of pharmacological therapy is suboptimal [3, 4]. For example, only a minority of patients receive pharmacologic therapy after having sustained a hip fracture [3]—even though there is a clear agreement that the majority of hip fractures are osteoporosis related and that patients with osteoporosis-related hip fracture should receive pharmacologic therapy to prevent secondary fractures [5]. From a public health perspective, the aging populations in Europe combined with patent expiry of effective treatment should arguably result in an increase in treatment uptake. However, treatment uptake appears to have reached a plateau or is decreasing [2, 6, 7]. The reasons for this trend are not clear but concerns over safety and cost-effectiveness of pharmacological therapy may be important [8].

There is a substantial number of studies on the cost-effectiveness of pharmacological fracture prevention in osteoporosis, and such studies are summarized in two recent systematic reviews [9, 10]. Nevertheless, differences in modeled interventions, settings, and perspectives render a general conclusion of the cost-effectiveness of pharmacological intervention as prescribed in general practice difficult. Therefore, there is a need to estimate the cost-effectiveness of pharmacological fracture prevention of current treatment practice. To the extent pharmacological therapy is cost-effective, there may be scope to treat more patients and hence reduce the perceived treatment gap. Therefore, we conducted a study with the objective to estimate the real-world cost-effectiveness of pharmacological fracture prevention as prescribed in the five largest Europe countries by population size: France, Germany, Italy, Spain, and the United Kingdom (UK) using an updated version of the International Osteoporosis Foundation (IOF) reference cost-effectiveness model [11].

Methods

The updated IOF reference model, implemented in Microsoft Excel®, previously used to estimate the cost-effectiveness of denosumab treatment was adjusted to fit the purposes of the current study [12–14]. The model is a Markov cohort model with health states for being well, hip fracture, post-hip fracture, vertebral fracture, post-vertebral fracture, wrist fracture, 'other' fracture, and death. The model cycle length is 6 months, and patients are followed from model entry until death or age 100 years, with transition probabilities reflecting fracture and mortality risks derived using the methods described below. Patients enter the model in the 'being well' health state, and during each cycle have a probability of sustaining a fracture, remaining healthy or dying. Patients who sustain a fracture remain in the respective fracture state for 1 year. Thereafter, they can move back to the 'being well' state, sustain a new fracture or, if transitioning from a hip or vertebral fracture go to the respective post fracture states. Death is possible from every state and in every cycle. Patients in the vertebral fracture states can only sustain another vertebral fracture or a hip fracture, while patients in the hip fracture states can only sustain another hip fracture. Therefore, the model underestimates the number of fractures in the cohort. We addressed this limitation by estimating the number and consequences of these missed 'downstream' fractures (see below).

The model estimated costs and QALYs for a cohort of osteoporotic women, aged 72 at model entry and with a T-score of − 2.5 or below, in line with the definition of osteoporosis. Twenty-four percent of the women were assumed to have a previous vertebral fracture, according to the prevalence observed in the FREEDOM trial [15], a trial that recruited patients with T-scores between − 2.5 and − 4.0.

Fracture incidence

Fracture incidence for the model population was based on age-stratified general population fracture incidence for each country, and adjusted to the modeled population through risk ratios associated with bone mineral density (BMD) decreases [16] and increased prevalence of previous fracture [17, 18] in relation to the general age- and sex-matched population. The relative risks of hip fractures given a previous vertebral fracture were taken from a meta-analysis performed by Kanis and colleagues [17], where age-dependent data were provided. Age-independent values from a meta-analysis by Klotzbuecher and colleagues [18] were used for the increased risk of sustaining a vertebral-, wrist, or 'other' fracture with a prior vertebral fracture. Since the relative risks reported by Klotzbuecher and colleagues were not adjusted for BMD, they were adjusted down by 10%. The risk associated with a T-score at or below − 2.5 was estimated by dividing the distribution below a given T-score into 0.1 SD wide increments and producing a weighted average of these relative risks according to the distribution of patients and risks in the different increments. This method was applied because the relative risk of fracture increases exponentially with decreasing BMD. Descriptions and examples of the algorithms and examples of the applied algorithms can be found in the literature [19, 20].

Hip fracture incidence data were identified for all countries and smoothed over ages [21–25]. Where fracture incidences for other sites were missing, it was assumed that the ratios between hip fracture incidence and the fracture of interest were the same as that observed in Sweden [26, 27]. The incidences used are shown in Table 1.

Table 1 Fracture incidence

Fracture incidence per 10,000 person years (in women)	Age	Hip fracture[a]	Vertebral fracture (clinical)[b]	Wrist fracture[c]	Other fractures[b]
France	50	2	5	11	12
	60	6	11	22	23
	70	20	28	36	56
	80	66	42	42	113
	90	222	92	72	389
Germany	50	2	1	18	14
	60	10	18	44	38
	70	35	37	69	98
	80	104	93	90	176
	90	272	141	86	477
Italy	50	3	8	19	20
	60	9	17	36	36
	70	37	52	67	105
	80	151	95	94	256
	90	305	127	98	534
Spain	50	4	10	21	26
	60	2	21	31	49
	70	25	48	45	89
	80	102	89	63	239
	90	260	145	85	591
UK	50	4	10	21	24
	60	7	12	43	28
	70	35	50	65	100
	80	115	72	73	195
	90	342	142	95	469

[a] Source of data: France: Briot et al. 2015 [24], Germany: Bleibler et al. 2014 [25], Italy: Pisticelli et al. 2011 [22], Spain: Darbá et al. 2015 [23], UK: Singer et al. 1998 [21]

[b] Source of data: Germany: Bleibler et al. 2014 [25], Spain: Darbá et al. 2015 [23]; inputs for other countries are estimated from hip fracture incidence and ratios between hip and vertebral fractures in Sweden [27, 28]

[c] Source of data: Germany: Bleibler et al. 2014 [25], Spain: Darbá et al. 2015 [23], UK: Singer et al. 1998 [21]; inputs for other countries are estimated from hip fracture incidence and ratios between hip and wrist fractures in Sweden [27, 28]

Treatment

Patients entering the model were assumed to receive treatment for osteoporosis according to 2016 sales data for each country obtained from IMS. Treatment efficacy in terms of relative risks of fractures for the individual treatments was weighted according to their market shares in the respective country (Table 2). Generics were assumed to consist of alendronate, risedronate, and SERMs, according to their branded distributions. This assumption was tested in sensitivity analysis where all generics were assumed to be represented by alendronate. The individual treatment efficacies were taken from a recent and robust meta-analysis by Freemantle and colleagues (2013) [29] and results from the random-effects meta-analysis were used. In cases where efficacy estimates were not reported for certain drugs or fracture types in Freemantle et al. [29], efficacy estimates were extracted from the 2008 NICE systematic review [30]. Treatment was assumed for 5 years, and the composition of treatment was assumed constant over this time. Reflecting sustained effect of pharmacological fracture prevention after treatment discontinuation for bisphosphonates [31, 32] (accounting for the majority of pharmacological therapy in the model (Table 2)) and in line with previous models [9, 10], we assumed a linear decline of the treatment effect over 5 years post-treatment discontinuation.

We assumed that all patients were persistent with treatment for 5 years and we tested this assumption in sensitivity analysis.

We compared the cost-effectiveness of modeled intervention to 'No treatment'. This approach is similar to estimate the cost-effectiveness of a given treatment to placebo in a traditional cost-effectiveness analysis framework.

Table 2 Unit costs and drug market shares

		France	Germany	Italy	Spain	UK
Fracture costs	Hip fracture	€ 11,901	€9671–€11,875	€ 16,528	€10,306–€18,969	£8787
	Vertebral fracture	€ 6165	€4126–€6369	€4266–€14,615	€4021–€13,776	£4453
	Wrist fracture	€ 2112	€2694–€3227	€ 2495	€ 1995	£1393
	Other fractures	€4280–€5528	€3723–€6086	€4115–€10,181	€3481–€8887	£1393
Other costs	Visit to the GP	€ 23	€ 30	€ 21	€ 37	£36
	Daily cost of nursing home	€ 101	€ 104	€ 98	€ 88	£66
	Cost of BMD measurement	€ 42	€ 38	€ 91	€ 114	£69
	Yearly cost of drug	€ 186	€ 209	€ 188	€ 201	£42
Drug market shares	Alendronate	29%	3%	90%	15%	1%
	Generics	41%	66%	0%	31%	92%
	Ibandronate	0%	2%	0%	5%	1%
	Denosumab	10%	21%	8%	33%	5%
	Strontium ranelate	0%	1%	0%	0%	1%
	Risedronate	6%	3%	0%	8%	1%
	SERMs	3%	1%	1%	8%	0%
	Zoledronate	11%	3%	1%	0%	0%

UK United Kingdom, *GP* general practitioner, *BMD* bone mineral density, *SERMs* selective estrogen receptor modulators

Costs

Direct costs of fractures were included for each country (Table 2) [23, 25, 33–37]. Where available in the underlying sources, age-stratified costs of fracture per age were used. Except for the UK, where detailed information was available, the costs of 'other' fractures were weighted according to the incidence of the fracture types, where fractures of the femur and pelvis were assumed similar in cost to hip fractures, fractures of the humerus, tibia, and fibula assumed similar in cost to vertebral fractures and fractures of the rib, clavicle, scapula, and sternum were assumed similar in cost to wrist fractures. Given that the incidences of the fractures at the sites comprising 'other' fracture vary by age, costs of 'other' fracture also vary by age. Reflecting data availability for the UK, costs of non-hip-non-vertebral fracture were applied to both wrist and 'other' fracture. As a consequence of hip fracture, a proportion of patients were assumed to transfer to long-term nursing home care. Patients transferring to a nursing home were assumed to remain there for the rest of their lives.

Similar to treatment efficacy, costs of treatment were based on actual IMS sales data from 2016. The yearly cost of treatment was calculated from the mean cost per day of anti-resorptive treatments for each country and therefore reflects the actual costs of the blend of branded and generic medications in each country. In addition, patients on treatment were assumed to have one visit to the general practitioner per year and one bone mineral density scan every second year. Although the different countries have different recommendations for discounting in cost-effectiveness modeling, costs and effects were discounted at a rate of 3.5% per annum in all country analyses for comparability reasons.

The analyses also included indirect costs in terms of informal care, using previously published data on the number of hours of informal care received by the patient after a fracture [38]. Informal care was valued with the willingness-to-pay for a 1-h reduction of informal care per week reported for Spain and the UK [39]. Value of informal care for other countries was imputed from the Spanish estimate using purchasing power indices [40].

Utility

For comparability reasons, all patients in the well state were assumed to have the health-related quality of life (HRQoL) reported by age for the UK general population. Decreases in HRQoL as a consequence of fracture were included as utility multipliers. Utility multipliers for the first year with hip, vertebral, and wrist fractures were included as reported by Svedbom et al. [41]. These multipliers were estimated from the International Costs and Resource use in Osteoporosis Study (ICUROS), which collected EQ-5D data at different time points after fractures, as well as a recall of HRQoL prior to fracture. 'Other fracture' was conservatively assumed to impact HRQoL to the same extent as a wrist fracture. The first-year utility multipliers used were 0.55 for hip fractures, 0.68 for vertebral fractures, and 0.83 for wrist and other fractures. Hip and vertebral fractures impacted HRQoL also in subsequent years; it was assumed that a patient in the post-hip fracture and post-vertebral fracture states had 84% and 85%, respectively, of the utility estimated for an age- and sex-matched patient in the 'being well' state.

Mortality

Age- and sex-specific mortality was included for each country. In addition, increased mortality associated with hip and vertebral fractures was included. The first- and subsequent years standardized mortality rates (SMRs) for hip and vertebral fractures were used as reported in Jönsson et al. [12]. Some studies suggest that the excess mortality observed after fracture is not solely due to the fracture event [42–45]. Given this evidence, the model assumed that 30% of the excess mortality after hip, vertebral, and 'other' fracture was associated with the fracture event. It was assumed that the duration of the increased mortality after fracture lasted for 8 years based on two studies by Kanis et al. [42, 43].

Additional downstream fractures

Given the structural limitations of the Markov model framework, the number of vertebral, wrist, and 'other' fractures in the model cohort are underestimated. We estimated the numbers and consequences of these disregarded fractures outside the Markov process using the following approach: the numbers of additional fractures by type in each cycle were estimated by multiplying the number of subjects in each higher hierarchy state with the incidence rate of the lower hierarchy fracture type in the model population. The acute (1 year) costs of these additional fractures were estimated by multiplying the numbers of additional fractures in each cycle with the relevant 1-year fracture costs (Table 2). The acute disutilities of the additional fractures were accounted for in three steps: first, the health state utility value (HSUV) for a lower hierarchy fracture was derived by multiplying the HSUV of the higher hierarchy fracture with the utility multiplier of the lower hierarchy fracture. Thereafter, a disutility (i.e., an absolute health utility decrement) of the down-stream fracture was estimated by taking the differences between the two HSUVs. Finally, we reduced the QALYs accrued in each cycle with the estimated disutilities.

In the acute hip fracture and the post hip fracture states, the long-term consequences of vertebral fractures are disregarded. Therefore, the number of patients in those states affected by the long-term consequences of a prior vertebral fracture was estimated. This was done by calculating the share of subjects suffering the consequences of a hip fracture who have suffered a vertebral fracture within the relevant time period (ever for health utility and 8 years for mortality). First, the incremental share of subjects with vertebral fracture is divided by the share of subjects without a prior history of vertebral fracture at the beginning of the considered period. Subsequently, considering this share for weighting, the relative risk for increased mortality post-fracture was applied. The SMR applied for the post vertebral fracture states was also applied to in this population.

Sensitivity analysis

We ran four scenario analyses. The first scenario analysis altered the mix of generic treatments. Instead of assuming that the blend of generic treatments was the same as the blend of branded treatments, we assumed that all generic prescriptions were for alendronate. In this analysis, treatment costs did not change reflecting that the actual mean costs per patient and day were obtained from actual sales data. However, the efficacy of the treatment mix was altered. The second scenario analysis altered the treated population. Instead of modeling treatment of patients with a T-score of − 2.5 or below, we modeled treatment of patients with a prior vertebral fracture. In this scenario analysis, the T-score was set to − 1.8, equating the mean T-score in 72-year-old women derived from Looker et al. [46]. The third scenario analysis excluded the down-stream fracture functionality from the model, and therefore, this scenario analysis takes the same approach as most previous models. The fourth scenario modeled real-world persistence using data from a large retrospective UK study [47]. In this scenario, the proportion of patients persistent at 6 months, 12 months, 36 months, and 60 months were set at 44.2%, 32.2%, 16.0%, and 9.3%, respectively. The proportion of patients persistent at intermediate time-points were estimated using linear interpolation.

Results

Base case analysis

The results of the base case analysis show that pharmacological intervention decreases costs in the largest countries of the EU (France, Germany, Italy, Spain, and the UK) compared to no treatment. The costs of treatment, including costs of drugs, GP visits, and dual-energy X-ray absorptiometry (DXA) scans, were offset by lower costs resulting from fractures compared to no treatment (Fig. 1). The fracture costs constituted the largest proportion of total cost, followed by costs for nursing home as a consequence of hip fractures. Due to the high uptake of generic osteoporosis drugs, and thereby low cost of drugs, the cost of a yearly GP visit and a DXA scan every second year exceeded the cost of drugs in the UK. Base case total and incremental costs comparing no treatment to treatment are shown in Table 3.

The estimated numbers of QALYs were higher with treatment compared to no treatment, reflecting gains in both survival and HRQoL across all countries. Due to the cost-savings associated with treatment in combination with survival gains and improved HRQoL, pharmacological intervention dominates the alternative of no treatment, i.e., produces additional QALYs at reduced costs. Cost-savings ranged from €229 to €2486 per patient for Germany and Italy, respectively, whereas QALY gains ranged from 0.08 to 0.15 per patient for France and Italy, respectively.

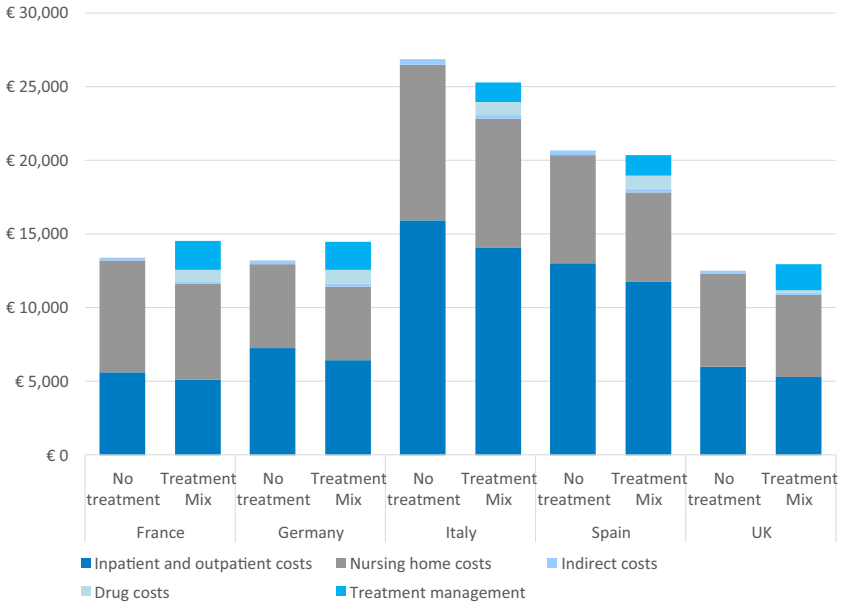

Fig. 1 Cost results stratified by country treatment and cost category

Sensitivity analyses

Results of the four scenario analyses run by country are presented in Table 4. In the first two scenario analyses (intervention threshold set to prior vertebral fracture and generic bisphosphonates composed of alendronate only), incremental costs generally decreased further and incremental QALYs increased further. In the third scenario analysis—in which down-stream fractures were disregarded—treatment remained cost-saving, albeit the QALY and costs benefits associated with treatment were reduced. In the fourth scenario analysis (modeling real-world persistence), incremental costs and incremental QALYs gained decreased and treatment remained cost-saving in all countries.

Table 3 Cost-effectiveness results

		Fracture-related costs (€)	Treatment costs (€)	Total costs (€)	Life years (undiscounted)	Life years (discounted)	QALYs (discounted)	Incremental cost per QALY gained
France	No treatment	€ 13,384	€ 0	€ 13,384	16.86	12.44	9.07	
	Osteoporosis treatment	€ 11,959	€ 1037	€ 12,996	16.88	12.46	9.15	
	Increment	−€ 1425	€ 1037	−€ 388	0.03	0.02	0.08	Cost-saving
Germany	No treatment	€ 13,211	€ 0	€ 13,211	14.89	11.30	8.12	
	Osteoporosis treatment	€ 11,831	€ 1151	€ 12,982	14.93	11.34	8.23	
	Increment	−€ 1380	€ 1151	−€ 229	0.05	0.03	0.11	Cost-saving
Italy	No treatment	€ 26,839	€ 0	€ 26,839	16.10	12.00	8.45	
	Osteoporosis treatment	€ 23,208	€ 1145	€ 24,353	16.16	12.04	8.60	
	Increment	−€ 3631	€ 1145	−€ 2486	0.06	0.04	0.15	Cost-saving
Spain	No treatment	€ 20,638	€ 0	€ 20,638	16.51	12.25	8.74	
	Osteoporosis treatment	€ 18,456	€ 1333	€ 19,790	16.55	12.28	8.86	
	Increment	−€ 2182	€ 1333	−€ 849	0.04	0.03	0.11	Cost-saving
UK	No treatment	£11,230	£0	£11,230	14.86	11.23	8.04	
	Osteoporosis treatment	£10,131	£500	£10,631	14.91	11.27	8.15	
	Increment	−£1099	£500	−£599	0.05	0.03	0.10	Cost-saving

Table 4 Incremental costs and effects in sensitivity analyses

	Fracture-related costs	Treatment costs	Total costs	Life years (discounted)	QALYs (discounted)	Incremental cost per QALY gained
Sensitivity analysis 1—all generics assumed to be alendronate						
France	−€ 1490	€ 1037	−€ 453	0.02	0.08	Cost-saving
Germany	−€ 1539	€ 1151	−€ 388	0.03	0.12	Cost-saving
Italy	−€ 3652	€ 1145	−€ 2507	0.04	0.15	Cost-saving
Spain	−€ 2361	€ 1333	−€ 1028	0.03	0.12	Cost-saving
UK	−€ 1304	€ 500	−€ 804	0.04	0.12	Cost-saving
Sensitivity analysis 2—prior fracture used as intervention threshold						
France	−€ 1440	€ 1037	−€ 403	0.02	0.09	Cost-saving
Germany	−€ 1464	€ 1151	−€ 313	0.04	0.13	Cost-saving
Italy	−€ 3920	€ 1145	−€ 2775	0.05	0.18	Cost-saving
Spain	−€ 2486	€ 1333	−€ 1153	0.04	0.14	Cost-saving
UK	−£1134	€ 500	−£ 634	0.04	0.13	Cost-saving
Sensitivity analysis 3—exclude down-stream fractures						
France	−€ 1353	€ 1037	−€ 316	0.02	0.07	Cost-saving
Germany	−€ 1234	€ 1151	−€ 83	0.03	0.09	Cost-saving
Italy	−€ 3178	€ 1145	−€ 2033	0.03	0.12	Cost-saving
Spain	−€ 1877	€ 1333	−€ 543	0.03	0.10	Cost-saving
UK	−£ 1049	€ 500	−£ 549	0.03	0.09	Cost-saving
Sensitivity analysis 4—real-world persistence						
France	−€ 287	€ 221	−€ 67	0.01	0.02	Cost-saving
Germany	−€ 274	€ 246	−€ 28	0.01	0.02	Cost-saving
Italy	−€ 740	€ 244	−€ 497	0.01	0.03	Cost-saving
Spain	−€ 442	€ 284	−€ 158	0.01	0.02	Cost-saving
UK	−£238	£107	−£131	0.01	0.02	Cost-saving

Discussion

This study found that current prescription of pharmacological therapy is cost-saving in each of the five largest European countries (France, Germany, Italy, Spain, and the UK). Hence, pharmacological fracture prevention is not merely cost-effective in those countries, but effectively generates a net increase in available resources for the health care sector. While such results are positive, they highlight the potential for economic inefficiencies in the current treatment practice. All else being equal, further cost-savings may be reached by expanding treatment to those at increased risk of fracture and not receiving any treatment.

It is important to note that these findings pertain to the current prescription of pharmacological therapy and that these practices may not be the most cost-effective practice. For example, substitution of relatively expensive branded bisphosphonates by generic alendronate which may be less costly and at least equally effective could further improve cost-effectiveness. On the other hand, government policies that dictate sequence of therapy (i.e., which drugs are used first line, second line, etc.) also influence practice patterns, with the effect of shifting potentially more effective agents towards use in higher-risk populations.

In this context, it may be notable that we assume that individual pharmacological fracture prevention treatments are distributed equally, whereas in reality, it is possible that more effective agents are prescribed to a population at relatively high risk of fracture. Such channeling would render our results conservative given that more effective agents avoid more fracture in higher-risk patients than in lower-risk patients and thereby such channeling would result in a net decrease in costs and a net increase in QALYs compared to the current scenario.

The findings were robust in scenario analysis. Firstly, when the hypothetical treatment threshold was set to a prior vertebral fracture instead of a T-score of − 2.5, cost-savings increased further for four countries (France, Germany, Italy, and Spain) and remained stable in the UK. Secondly, when generic prescriptions were assumed to consist of alendronate only, cost-savings also increased further, reflecting that alendronate is the most effective bisphosphonate in the meta-analysis used to inform the model [29]. Finally, when down-stream fractures were disregarded, the QALY and costs benefits with treatment were reduced, albeit treatment remained cost-saving in all five countries.

Most other studies estimate cost-effectiveness *at* an intervention threshold, e.g., at a T-score of − 2.5 [9, 10]. While this approach is reasonable for establishing that treatment is cost-effective in all treated patients, it is not ideally suited for estimating the cost-effectiveness of current treatment practice that includes patients at or below a given intervention threshold. Most patients who are eligible for treatment are below the threshold and have higher fracture probability, and thus (other things being equal) have better cost-effectiveness compared to patients whose fracture probability is equal to the threshold. This may lead to greater fracture relative risk reductions than the summary estimate of efficacy for the treatment mix, and thus improved cost-effectiveness.

The fact that we evaluated cost-effectiveness at or below a threshold (T-score ≤ − 2.5) and that the modeled intervention reflects current treatment practice rather than one specific treatment renders the findings from the study difficult to compare to other studies. However, a systematic review of cost-effectiveness evaluations of osteoporosis found that branded pharmacological intervention was generally cost-effective at usual willingness to pay thresholds in women aged over 65–69 with low BMD [9] when compared to 'no treatment' and in many cases cost-saving in patients over 80 years. Overall, the finding in this study is in line with previous literature. However, the fact that pharmacological fracture prevention may be cost-saving rather than cost-effective may not previously have been appreciated.

The estimated range of country-specific per patient cost-savings and QALYs gained ranged from €229 to €2486 and 0.08 to 0.15 QALYs, respectively. In terms of factors driving this variability, it is not possible to quantify to what extent the observed differences are due to different estimation methods or true local differences. Both components are almost certainly affecting the results, but the fact that intervention was cost-saving in all countries indicates that the overall finding from the study is robust.

This study has several limitations. Firstly, the data underlying the model were extracted from sources that relied on different methodologies and were of variable quality. For example, the data on relative risk of fracture with prevalent vertebral fracture do not account for BMD and were therefore down-adjusted by 10%. Furthermore, some data needed to be imputed, particularly in the case of fracture related costs. Secondly, we made assumptions on the distribution of treatment in the population that may not be realistic. In real-life, some patients with lower fracture risk are also likely to be treated. Likewise, a number of patients at high risk of fracture, e.g., those who experience a fracture, do not receive pharmacological treatment. In this context, it may also be noted that we only use age, T-score, and previous fracture as risk factors for fracture whereas other factors such as smoking and glucocorticoid use also may affect the fracture risk and may also be included in guidelines in the relevant countries. Finally, we assumed that treatment effect was constant across fracture risks for all treatments.

This study also has some strengths. We used a model framework that is well accepted and described [11–14] and improved it by implementing a 'down-stream' fracture module. The down-stream fracture module allowed us to circumvent the hierarchical limitations imposed by the Markov model framework. Therefore, in contrast to these previous publications, the cost-effectiveness estimates presented here account for consequences of wrist, 'other', and vertebral fracture affecting patients with hip fracture, and the consequence of wrist and 'other' fractures in patients who suffer the consequences of a vertebral fracture. In this context, it may be noted that we—in the absence of data on the matter—assume that the consequences of fracture are the same regardless of prior fracture status. Furthermore, we estimated cost-effectiveness in the potentially treated population rather than at a threshold, arguably providing more accurate estimates of the cost-effectiveness of treatment in clinical practice. Finally, the fact that we had real-world data on the volume of osteoporosis medications also means that we can estimate an average treatment effect and costs that reflects clinical practice.

Future research in this area is needed. One study that would complement our knowledge of the real-word cost-effectiveness of pharmacologic therapy would be to use a more granular approach to estimate fracture risk, such as the fracture risk assessment tool FRAX. A larger undertaking would be to screen Electronic Medical Records (EMRs) to identify patients who initiate pharmacological therapy and estimate the cost-effectiveness of the intervention in those patients. Such a study could be conducted retrospectively and thus validate a model-based approach. In addition, better model input data would reduce the uncertainty of cost-effectiveness modeling. In this context, better data on costs may be especially valuable.

Conclusion

In conclusion, recognizing the uncertainties inherent in cost-effectiveness modeling, this study shows that current treatment with pharmacologic intervention in France, Germany, Italy, Spain, and the UK is cost-saving in each country. These findings support the notion that addressing the existing treatment gap will result in cost-savings when treatment is expanded to individuals at increased risk of fracture currently not receiving any treatment.

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Compliance with ethical standards

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Conflict of interest None.

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