Osteoporos Int (2006) 17: 996–1007
DOI 10.1007/s00198-006-0094-1

ORIGINAL ARTICLE

The cost-effectiveness of risedronate in the treatment of osteoporosis: an international perspective

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Received: 24 August 2005 / Accepted: 15 February 2006 / Published online: 29 March 2006

Abstract *Introduction:* Risedronate, a bisphosphonate for treatment and prevention of osteoporosis, has been shown in several clinical trials to reduce the risk of fractures in postmenopausal women with osteoporosis. The cost-effectiveness of risedronate treatment has previously been evaluated within different country settings using different model and analysis approaches. The objective of this study was to assess the cost-effectiveness of risedronate in postmenopausal women in four European countries—Sweden, Finland, Spain, and Belgium—by making use of the same modelling framework and analysis setup. *Methods:* A previously developed Markov cohort model for the evaluation of osteoporosis treatments was used to estimate the cost-effectiveness of risedronate treatment. For each country, the model was populated with local mortality, fracture incidence, and cost data. Hip fractures, clinical vertebral fractures, and wrist fractures were included in the model. *Results:* The incremental cost per quality-adjusted life years (QALY) gained from a 5-year intervention with risedronate compared to "no intervention" in 70-year-old women at the threshold of osteoporosis [T-score = −2.5 based on National Health and Nutrition Examination Survey (NHANES) III data] and previous vertebral fracture was estimated to be €860, €19,532, €11,782, and €32,515 in Sweden, Finland, Belgium, and Spain, respectively. Among 70-year-old women at the threshold of osteoporosis without previous fracture the estimated cost per QALY gained ranged from €21,148 (Sweden) to €80,100 (Spain). The differences in cost-effectiveness between countries are mainly explained by different costs (fracture and treatment costs), fracture risks, and discount rates. Based on cost per QALY gained threshold values found in the literature, the study results indicated risedronate to be cost effective in the treatment of elderly women with established osteoporosis in all the

Financial support was obtained via an unrestricted grant from The Alliance for Better Bone Health.

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included countries. *Conclusions:* At a hypothetical threshold value of €40,000 per QALY gained, the results in this study indicate that risedronate is a cost-effective treatment in elderly women at the threshold of osteoporosis (i.e., a T-score of −2.5) with prevalent vertebral fractures in Sweden, Finland, Belgium, and Spain.

Keywords Belgium · Cost-effectiveness · Finland · Fracture · Osteoporosis · Postmenopausal women · Risedronate · Spain · Sweden

Introduction

Osteoporosis is a major cause of morbidity and mortality in the elderly [1]. Because of demographic changes and increasing life expectancy, it is a growing public health concern. The European Commission (EC) has forecast a 135% increase in hip fracture incidence and a 57% increase in the prevalence of vertebral fractures in the European Union (EU) over a 50-year period [2]. The increasing number of fractures also makes osteoporosis a growing economic concern and a burden on the health care systems in Europe. In 1990, the number of osteoporotic fractures estimated in Europe was 2.7 million, with an estimated direct cost of €36 billion, of which €24.3 billion were accounted for by hip fracture. From demographic changes alone, the costs are expected to rise to €76.8 billion by the year 2050 [3]. In order to justify resource allocation and patient selection for new technologies for treatment of osteoporosis and prevention of fractures, it is becoming increasingly important to determine the cost-effectiveness of all therapies.

Bisphosphonates are well established for the treatment of postmenopausal women at high risk of fracture [4]. The bisphosphonate risedronate has been shown to reduce the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women by approximately one half [5–7]. In addition, these studies have shown that risedronate exhibits a safety profile similar to placebo, even in patients with active gastrointestinal diseases [5–7]. Besides the clinical profile of a therapy, it is also important to consider consequences of treatment in terms of costs and health effects both in the short- and long-term perspective. To capture all relevant consequences of a therapy, it is necessary to extrapolate results from the limited time frame of the clinical trial, for several reasons [8]. One is that the effect of treatment may persist for longer than that measured in the clinical trial; and another is that costs, quality of life, and epidemiological patterns vary between countries, which will give different estimates on the cost-effectiveness of treatment.

The cost-effectiveness of risedronate has been evaluated separately for several countries [9–13] using health economic models integrating epidemiological, clinical and economic data. Unfortunately, comparison between studies is problematic since the model constructs differ, as do base cases. Assumptions also differ about the effects of risedronate on fracture risk. As of yet, there are no studies that have evaluated the cost-effectiveness of osteoporosis treatments for several countries using the same model and analytic approach. The objective of this study was to assess the cost-effectiveness of risedronate in postmenopausal women in four European countries—Sweden, Finland, Spain, and Belgium—by making use of the same modelling and analysis framework. For each country, the model was populated with local mortality, fracture incidence, and cost data.

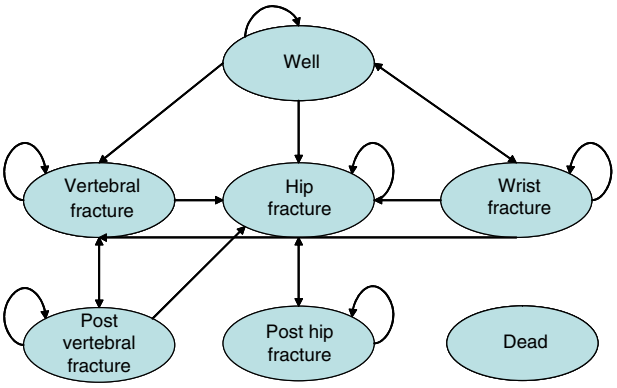
Materials and methods

The study was performed taking a health care perspective. To measure the economic effect, only direct costs were considered; indirect costs and costs in added years of life were not included. To measure health effects, we used both life years gained (i.e., considering only mortality) and quality-adjusted life years gained (QALYs; i.e., also taking into account quality of life). We report our main findings in terms of an incremental cost-effective ratio (ICER). In this regard, we calculated both the incremental cost per life year gained (cost-effectiveness analysis) and the incremental cost per QALY gained (cost-utility analysis, also incorporating quality of life). The ICERs were estimated using a state transition Markov cohort model based on clinical trial data and country-specific fracture incidence rates, mortality rates, and costs.

Model

The simulation model used in this study was based on Markov cohort methodology [14]. The Markov cohort model has previously been validated and used to evaluate cost-effectiveness of treatments for osteoporosis [9, 15–17] and hormone replacement therapies [18]. The model has also been used to predict fracture risks and mortality, making it well validated and calibrated [19–21] The cycle length was set to 1 year, and all patients were followed through the model until they reached 100 years of age or died.

All patients begin in the "healthy" state, where each year they have a probability of having a fracture, remaining healthy, or dying (Fig. 1). If a patient dies, she moves to the absorbing "dead" health state. If a patient sustains a fracture, she moves to the "hip fracture," "vertebral fracture," or "wrist fracture," health state. After 1 year in one of these states, the patient can move back to the "healthy" state, move to one of the postfracture health states for hip and vertebral fractures (because costs and effects after hip and vertebral fractures last for more than 1 year, a patient moves to a "postvertebral fracture"/"posthip fracture" health state after 1 year), have a new fracture, or die. We imposed conservative structural assumptions to the model regarding patient movement to health states by not allowing for additional vertebral or wrist fractures after hip fracture occurrence. Conversely, it is possible to have hip fractures after vertebral and forearm fractures. This



Note that the arrows to the dead state are omitted in order to simplify the figure.

Fig. 1 Schematic diagram of the transition states used in the model

assumption, made to simplify the model, slightly underestimates the number of vertebral and forearm fractures.

For validation purposes, cost-effectiveness was also estimated using another published and validated osteoporosis model described in Tosteson et al. [22].

Model population

Base-case analysis populations were taken from baseline characteristics of women in the risedronate vertebral fracture trial setting [5, 6], namely, women aged 70 years with one or more prior vertebral fractures (radiographically defined). An assumption was made that all women were at the bone mineral density (BMD) threshold for osteoporosis (T-score = −2.5 SD). Cost-effectiveness of treatment was assessed in women with and without prior vertebral fractures. In sensitivity analyses, the starting age was altered, ranging from 60 to 80 years, and the T-score level ranged from −1 to −3.5.

Fracture incidence

The model incorporated risk of forearm, clinical vertebral, and hip fracture. Hip fracture incidence rates were based on studies conducted within the individual countries. Swedish hip fracture incidence rates were derived from a study by Kanis et al. [23] and Finnish incidence rates from Kannus et al. [24]. For Belgium, incidence rates were calculated by combining data on hip fracture hospitalizations from the Ministry for Social Affairs [25] and population data from the National Institute of Statistics [26]. Spanish incidence rates were derived from the Mediterranean Osteoporosis Study (MEDOS) [27]. Data from Seville were used, except in the age group 50–54 where, due to missing data, the incidence from Madrid was used instead.

The incidence of hip fractures increases exponentially with age. Therefore, where incidence data were not available for the highest ages, logistic regression was fitted to the observational data to estimate the missing fracture incidence rates. If risks were only available for broader age intervals, linear interpolation was used to differentiate the fracture risks within the interval. Appropriate local data were not available on clinical vertebral and wrist fracture incidence rates for Finland, Belgium, and Spain. In Johnell et al. [28] a strong correlation between discharges for hip and vertebral fractures was found across Europe. Based on these observations we made the assumption that there is a similarity in the proportionality of risks between fracture types in Europe. Making this assumption allowed for calculation of the missing fracture incidence rates by assuming that the ratio of clinical vertebral fracture to hip fracture and wrist fracture to hip fracture incidence rates in a Swedish-based study [23] are similar to that of the other countries. For wrist and vertebral fractures, linear extrapolation was used to estimate incidence rates for ages with missing data. The population fracture risks are summarized in Table 1.

Table 1 Population fracture risks (per 1,000)

	Sweden			Finland			Belgium			Spain		
	Hip	Vertebral	Wrist	Hip	Vertebral	Wrist	Hip	Vertebral	Wrist	Hip	Vertebral	Wrist
Age												
50	0.63	1.62	4.01	0.55	1.42	3.51	0.37	0.95	2.35	0.10	0.25	0.61
55	0.57	1.59	4.40	0.55	1.54	4.25	0.55	1.51	4.19	0.26	0.72	2.00
60	1.38	2.45	5.23	1.17	2.07	4.42	0.87	1.55	3.30	0.42	0.74	1.58
65	2.64	3.85	6.42	2.19	3.19	5.33	1.61	2.34	3.91	0.84	1.22	2.04
70	4.56	6.42	8.19	3.22	4.54	5.78	3.20	4.52	5.76	2.84	4.00	5.10
75	10.06	9.78	9.81	8.58	8.34	8.37	6.01	5.84	5.86	6.10	5.93	5.95
80	18.17	11.42	11.38	13.94	8.76	8.72	13.51	8.49	8.46	18.00	11.31	11.27
85	30.82	14.50	13.15	25.37	11.93	10.83	22.37	10.52	9.55	28.60	13.45	12.21
90	46.24	19.28	14.94	36.79	15.34	11.89	30.51	12.72	9.86	33.73	14.06	10.90
95	61.66	24.06	16.73	48.22	18.81	13.09	36.74	14.34	9.97	38.27	14.93	10.39
100	77.08	28.84	18.52	59.65	22.32	14.33	41.62	15.57	10.00	42.82	16.02	10.29
Source:	[76]	[76]	[76]	[24]	[a]	[b]	[25, 26]	[a]	[b]	[27]	[a]	[b]

[a]Calculated as: (hip fracture risk in Sweden/vertebral fracture risk in Sweden)*hip fracture risk in country (Finland/Belgium/Spain)
[b]Calculated as: (hip fracture risk in Sweden/wrist fracture risk in Sweden)*hip fracture risk in country (Finland/Belgium/Spain)

Relative risk (RR) of fracture

The population fracture incidence rates had to be adjusted to more accurately reflect the risk in the target patient groups. A method to calculate relative fracture risks for different patient groups relative to the population fracture risks based on BMD and prevalent fractures is described in Kanis et al. [21]. This approach has also been used in the cost-effectiveness study of risedronate in the UK by Kanis et al. [9]. RR of fractures were estimated based on the relationship between low BMD and the risk of fracture derived from a meta-analysis by Marshall et al. [29]. RR of fracture for each standard deviation of BMD below the age-adjusted mean used were 2.6, 1.8, and 1.4 for hip fracture, vertebral fracture, and wrist fracture, respectively. BMD levels for the population were based on suggested reference values for estimating T-score levels from the National Health and Nutrition Examination Survey (NHANES) III [30]. This gives the assumption of similar BMD levels in the included countries. Additionally, relative risk calculations took into account the relationship between prior vertebral fracture and subsequent fractures found in another meta-analysis by Klotzbuecher et al. [31] and the prevalence of vertebral fractures in the general population. The increased risks of fracture due to prevalent vertebral fracture (RR of hip fracture: 2.3; RR of vertebral fracture: 4.4; RR of wrist fracture: 1.4) are adjusted for age but not for BMD and were therefore down-adjusted by 10% [32].

Fracture risk reduction with risedronate

RR reduction for patients treated with risedronate 5 mg daily was derived from a meta-analysis of three large, double-blind, placebo-controlled, phase III studies [5–7]. Two of the studies examined the effects on vertebral fracture as the primary endpoint, and the third examined the effects on hip fracture risk. The meta-analysis examined the proportion of patients sustaining a fracture independently of the follow-up period using a fixed effects model (a conservative analysis). Only women in whom BMD was adequately characterized were included in the analysis. For hip fracture, the combined analysis for the relative risk reduction (RRR) was 43% (RR=0.57, 95% CI=0.41–0.79). For vertebral fractures, RRR was 37% (RR=0.63, 95% CI=0.53–0.76). For forearm fractures, the estimate for nonvertebral fracture was used, and the RRR was 22% (RR=0.78, 95% CI=0.68–0.91). These RRRs of risedronate treatment were also used in the cost-effectiveness of risedronate in the UK study by Kanis et al. [9] and are close to those estimated by Cranney et al. [33].

A key assumption concerning the long-term effectiveness of all bone-active agents is the duration of the effect on fracture risk after treatment has stopped, namely, the "offset time." In the case of bisphosphonates, an effect on BMD and possible fractures appears to persist when treatment is stopped [34–36]. One possible explanatory factor among others could be that patients who were taking bisphosphonates, upon therapy discontinuation, temporarily maintain higher BMD levels compared with untreated patients. This will result in a residual effect on fracture risk. However, it is not known if or how long it takes for BMD to reach the same levels as for untreated patients. It is unlikely that the offset time is 0 (i.e., after treatment termination, the fracture risk will immediately be the same as for untreated patients); and it is also unlikely that offset time persists indefinitely. In this study, the base-case treatment duration was assumed to be 5 years, followed by an offset time of 5 years, during which time the effect is linearly reduced to 0. A scenario assuming no offset time was examined in sensitivity analyses. In addition, a treatment time of 3 and 10 years followed by a 5-year offset time was tested.

Costs

All unit costs were to the greatest possible extent collected locally; costs and references are listed in Table 2. Costs were inflated using national consumer price indexes for all items and are given at the 2003/2004 year price level. Swedish costs were converted to Euro (€) at the average exchange rate for 2003 (€1=SEK 9.1250) [37]. Discount rates for costs and effects were based on current recommendations and guidelines for health economic evaluation in each respective country. Both costs and effects were discounted at a rate of 3% in Sweden [37, 38], 6% in Spain [39], 5% in Finland [40] and Belgium [41], and 3% and no discount rate for all countries in sensitivity analyses.

Fracture costs

Fracture costs were divided into acute costs, occurring in the first year following fracture, and longer-term costs, which persist for the remainder of the patient's life. Where cost data were not available in the first year after fracture (wrist fracture in Finland and Spain and vertebral and wrist fracture for Belgium), costs were calculated as a fraction of the cost of hip fracture at age 70 according to the hip morbidity equivalents established by Kanis et al. [42]. Hip fracture costs in the second and following years after fracture are based on the assumption that 10% of all patients remain at a nursing home for the rest of their lives [15]. The conservative assumption was made that there were no costs associated with vertebral or wrist fractures during the second and following years after a fracture.

Cost of intervention (administration of risedronate)

The cost of intervention was comprised of costs for drugs (5 mg risedronate daily) and costs for monitoring bisphosphonate therapy. Monitoring costs include the annual costs of a physician visit and a BMD measurement every other year. In the model, it was assumed that all patients received medication during the intervention period. Thus, the annual

Table 2 Costs (€)

Cost component	Sweden [reference]	Finland [reference]	Belgium [reference]	Spain [reference]
Hip first year	50–64 years: 9,397 65–74 years: 10,230 75–84 years: 18,067 85–100 years: 25,253 (77)	7,439 (78)	16,624 (79)	6,759 (12)
Hip following[a]	6,060 (80)	4,563 (81)	2,013 (79)	1,554 (12)
Vertebral first year	3,562 (58)	1,430[b]	3,677[c]	2,107 (12)
Wrist first year	2,263 (58)	454 (42, 78)[c]	1,015 (42, 79)[c]	413 (12, 42)[c]
Physician visit	128[d]	80 (81)	20 (82)	51 (83)
Risedronate[e]	443 (84)[e]	551 (85)[f]	421 (86)[e]	547 (87)[f]
BMD measurement	149 (88)	90 (89)	38[g]	96(89)

[a]10% of the cost of nursing home care per year
[b]Based on an expert panel of three clinicians
[c]Costs are calculated as a fraction of hip fracture cost, according to the number of hip fracture morbidity equivalents at age 70
[d]Based on the average cost of a physician visit at 6 different county councils
[e]Cost per year, based on a pack of 84 tablets
[f]Cost per year, based on a pack of 28 tablets
[g]Personal communication, Patrick Haentjens

cost of intervention was added to the incremental cost of all health states (except the health state "dead").

Mortality

Age-specific normal mortality rates for women in the various countries were obtained from national sources [43–46]. In the first year after a hip fracture, women have been found to have an excess mortality varying from 1.5 to >13, depending on age. The excess risk is of similar magnitude in the first year after vertebral fracture and decreases in subsequent years after both fracture types. These age-differentiated excess mortality data after hip and vertebral fractures, derived from a Swedish-based population study, were applied to all countries in the model [47, 48].

Since fractured patients have a high degree of comorbidity, the excess mortality cannot be entirely attributable to the fracture event. Kanis et al. [49] estimated that only 23% of the mortality after hip fracture may be causally linked to the hip fracture event, and Parker and Anand [50] estimated that 33% of the deaths 1 year after hip fracture were totally unrelated to the hip fracture, 42% possibly related, and 25% directly related. Along with these findings, it was assumed that 30% of the excess mortality (compared with normal mortality) after a hip fracture could be associated with the hip fracture event. This assumption was also used in the model for excess mortality after vertebral fractures. In line with current evidence, wrist fractures were not assumed to be associated with any extra mortality [51, 52].

The patient sample in the study from which mortality rates of vertebral fracture were derived was fairly small. Therefore, in a sensitivity scenario, an age-standardized mortality ratio of 1.66 in the first year following vertebral fracture and no excess mortality in the following years was used [53].

Quality of life

Country-specific quality of life weights for the general population at different ages were only available for Sweden, Finland, and the UK [54–56]. The age-differentiated quality of life weights for the Swedish population utilities were estimated in a time trade-off study by Lundberg et al. [54]. For the UK population, age-differentiated time trade-off EQ-5D values were used [55]. In Finland, quality of life weights at different ages were derived by applying the UK time trade-off tariff to the EQ-5D health state descriptive data from a representative population sample in 1992 [56, 57]. For Belgium and Spain, UK quality of life values for the population were applied [55].

Empirical estimates of the reduction in quality of life the year after osteoporotic fractures were derived from a prospective Swedish study [58, 59], which estimated the impact on quality of life in the year after a fracture event. The multiplier used for hip fracture in the first year was 0.792 and for the forearm 0.977, close to values derived by Brazier et al. [60]. For vertebral fractures, we calculated a multiplier of 0.626. This utility loss of 0.374 is larger than suggested by the National Osteoporosis Foundation (NOF) (0.05) based on expert opinion, and by Brazier et al. (0.10) [60, 61], but more in line with recent empirical findings [62–65]. A sensitivity analysis was performed using a more conservative multiplier of 0.9 for the first year after a vertebral fracture and no loss in quality of life in subsequent years. There are no direct empiric measurements of disutility after the first year following a vertebral fracture. Based on available data [60, 66–68] it was conservatively assumed that the loss of utility in the second and subsequent years is 0.05, giving a multiplier of 0.929 [59]. Quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [69]. Wrist fractures were not assumed to be associated with any utility loss after the first year following fracture.

Table 3 Results from the base-case analyses of intervention with risedronate at the age of 70 years among women with or without prior spine fracture in four European countries

	Sweden		Finland		Belgium		Spain	
	Prior spine fracture		Prior spine fracture		Prior spine fracture		Prior spine fracture	
	Yes	No	Yes	No	Yes	No	Yes	No
Cost effectiveness analysis[a]								
Incremental cost (€)	89	1,142	1,504	2,050	919	1,404	2,146	2,403
Incremental effectiveness (life years gained)	0.076	0.038	0.053	0.025	0.051	0.021	0.039	0.017
ICER[c] (€) (incremental cost/life years gained)	1,176	30,063	28,377	82,000	18,020	66,857	55,026	141,353
Cost utility analysis[b]								
Incremental cost (€)	89	1,142	1,504	2,050	919	1,404	2,146	2,403
Incremental utility (QALYs)	0.104	0.054	0.077	0.038	0.078	0.034	0.066	0.03
ICER[c] (€) (incremental cost/QALYs gained)	860	21,148	19,532	53,947	11,782	41,294	32,515	80,100

ICER incremental cost-effective ratio, *QALY* quality-adjusted life years
[a]Health outcome expressed in natural units (life years gained)
[b]Health outcome incorporates quality of life (QALYs gained)
[c]Incremental cost effectiveness ratio

Results

Base-case analyses

Results from the base-case cost-effectiveness analyses of intervention with risedronate at the age of 70 years are shown in Table 3, followed by results from sensitivity scenarios in Table 4. For Sweden, Finland, Belgium, and Spain the cost per QALY gained was estimated to €860; €19,532; €11,782, and €32,515, respectively, among 70-year-old women with previous vertebral fracture and a T-score of −2.5 SD. The cost per life-year gained of risedronate ranged from €1,176 for Sweden to €55,026 in Spain.

Intervention with risedronate in women with a T-score of −2.5 SD but without prior vertebral fracture had higher cost-effectiveness ratios compared with those with a prior vertebral fracture, ranging from €21,148 (Sweden) to €80,100 (Spain) per QALY gained and from €30,063 (Sweden) to €141,353 (Spain) for the cost per life-year gained.

Stochastic analysis

In Fig. 2, the results from a stochastic analysis, using the distribution of efficacy for treatment, based on 70-year-old women with previous vertebral fracture and a T-score of −2.5 SD, are presented in the form of acceptability curves. Assuming a willingness to pay of €40,000 for a gained unit of QALY, risedronate was found to be cost-effective in 100% of all simulations for Sweden and Belgium. Intervention was cost-effective in 98.4% and 86.8% of the simulations for Finland and Spain, respectively. These estimations have to be interpreted with caution because the analysis only captures variation in the effect of treatment. Other variables, such as costs and health utilities, were not attributed distributions.

Table 4 Cost utility [€/quality-adjusted life years (QALY) gained], base-case and sensitivity scenarios around the base-case assumptions in women aged 70 years treated with risedronate

	Sweden		Finland		Belgium		Spain	
	Prior spine fracture		Prior spine fracture		Prior spine fracture		Prior spine fracture	
	Yes	No	Yes	No	Yes	No	Yes	No
Base case	860	21,148	19,532	53,947	11,782	41,294	32,515	80,100
No offset time	19,747	56,621	38,845	95,033	23,989	69,960	51,258	128,411
3 years duration treatment	d-ed[c]	14,719	13,527	41,788	7,864	31,864	25,375	66,849
10 years duration of treatment	1841	26,160	26,651	68,081	13,880	46,819	35,343	83,970
No discount rate	d-ed[c]	10,743	8,882	29,937	6,281	24,511	19,215	47,226
3% overall discount rate	860	21,148	14,942	48,685	9,412	34,074	25,346	62,995
Utility loss vertebral fracture, 0.9/1.00[a]	1,133	26,941	26,878	70,693	16,088	53,067	45,332	106,779
Mortality risk after vertebral fracture[b]	d-ed[c]	25,091	23,477	64,055	14,759	50,496	40,013	96,794

[a]Multiplier of 0.9 in first year and 1.00 thereafter
[b]Relative risk of mortality = 1.66 in the first year after vertebral fracture, and no excess risk in following years after vertebral fracture
[c]d-ed: dominant strategy (i.e., risedronate associated with higher effects and lower costs compared to no treatment)

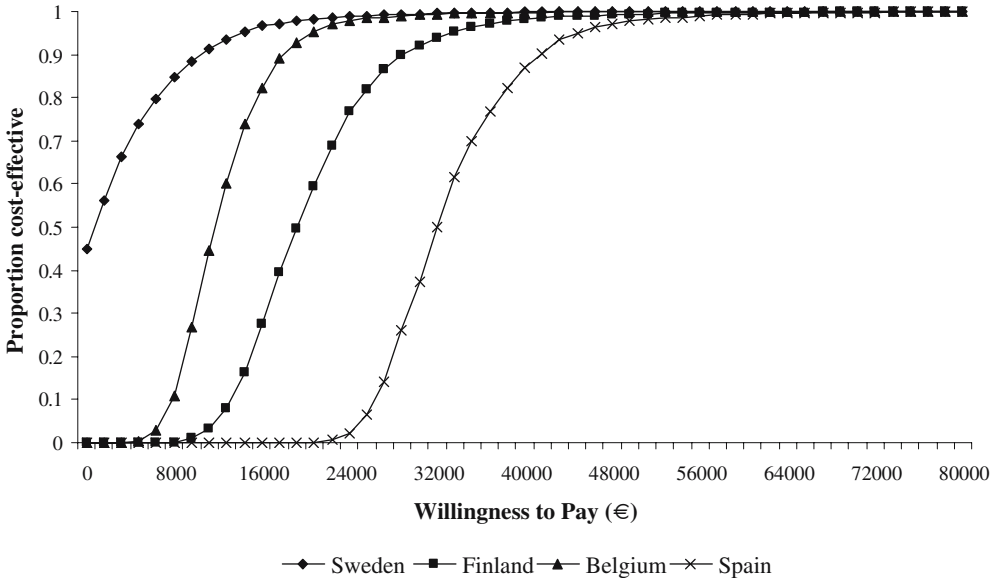


Fig. 2 Cost-effectiveness acceptability curves for risedronate in women 70 years old and with prior vertebral fracture (a stochastic analysis with 2,000 simulations)

Sensitivity analysis

Effect of age

Analysis of the effect of age on the cost-effectiveness of risedronate treatment is shown in Fig. 3 (for patients with prior fracture) and Fig. 4 (for patients without prior fracture). Cost-effectiveness ratios decreased with older starting age. At a hypothetical threshold value of €40,000 per QALY gained, risedronate was cost-effective at all ages 60–80 years for Swedish, Finnish, and Belgian patients with previous vertebral fractures. The cost per QALY gained fell below €40,000 at a starting age of 67 years and older for Spanish patients. In women without prior vertebral fracture (Fig. 4), the ICER goes below €40,000/QALY only for Sweden at all starting ages and Belgium from starting ages of 72 years and older.

The higher fracture incidence rates for women at older ages lead to greater potential benefits of treatment since more fractures are likely to be averted compared with women at younger ages. However, the change in the ICERs does diminish with increasing age (i.e., the slope flattens out) because the relevant benefits of reduced fracture morbidity in older patients versus the general population at higher ages decreases. These effects can be observed for all included countries by a decreasing incremental QALY for starting ages over 70 years. However, it was only for Finland where this effect led to a slight increase in the cost-effectiveness ratio from a starting age of 70.

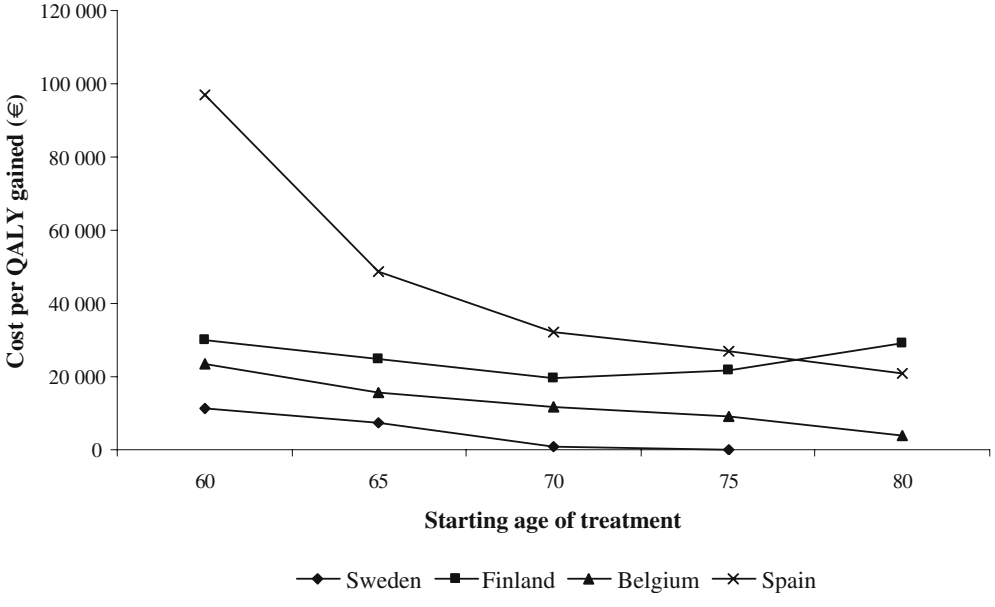


Fig. 3 Cost-effectiveness [€/quality-adjusted life years (QALY) gained] of risedronate by age in women with prior vertebral fracture

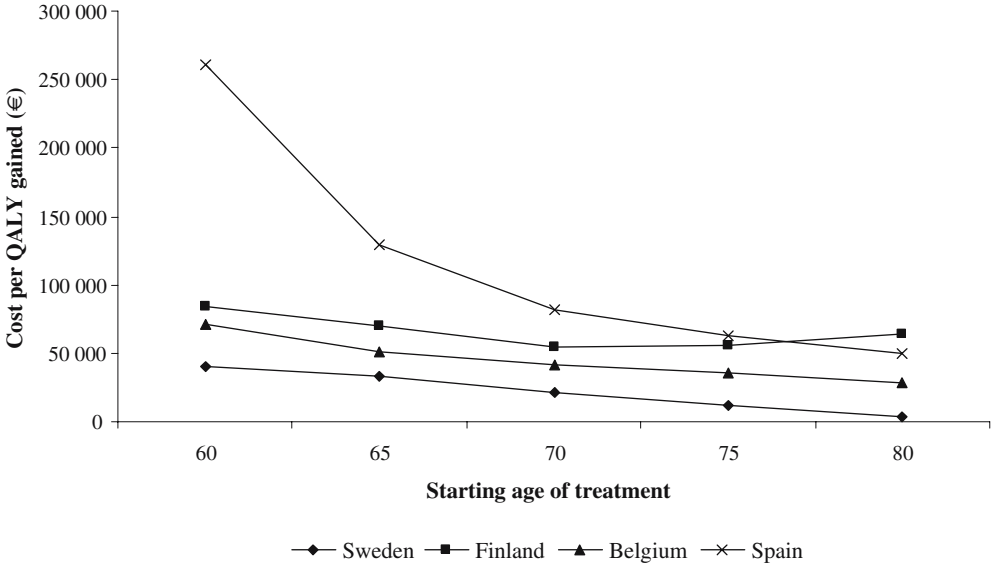


Fig. 4 Cost-effectiveness [€/quality-adjusted life years (QALY) gained] of risedronate by age in women without prior vertebral fracture

T-scores

The cost-effectiveness ratio dropped considerably with decreasing T-score values, which can be seen in Figs. 5 and 6. The reason for this is that the risk of fracture increases with decreasing BMD, and so does the potential benefit of the treatment.

Offset time and treatment duration

In the base case a 5-year offset time (or residual effect of treatment on fracture risk after the intervention period) was assumed. The assumption of offset time of the effect of treatment after the intervention period, as expected, led to less favorable or higher cost-effectiveness ratios (Table 4). Using a 3-year treatment duration while maintaining the 5-year offset time improved the cost-effectiveness of treatment. Extending the intervention period to 10 years lead to a slight increase in the cost-effectiveness ratios compared with the base case. That is, longer duration with risedronate therapy [15 years (10 years of treatment, 5 years of offset]) instead of 10 years (5 years of treatment, 5 years of offset)] prevents more fractures but does not completely offset the increased cost of intervention (Table 4).

Discounting

Using no discount rate, the incremental cost-effectiveness ratios fell markedly. In all countries, the cost per QALY gained was below €30,000 for women with a prior vertebral fracture and a T-score of −2.5. For women with a T-score of 1 2.5 but without previous vertebral fracture, the cost per QALY gained was below €50,000 in all countries (Table 4). Using a 3% discount rate for both costs and effects improved the cost-effectiveness for Belgium,

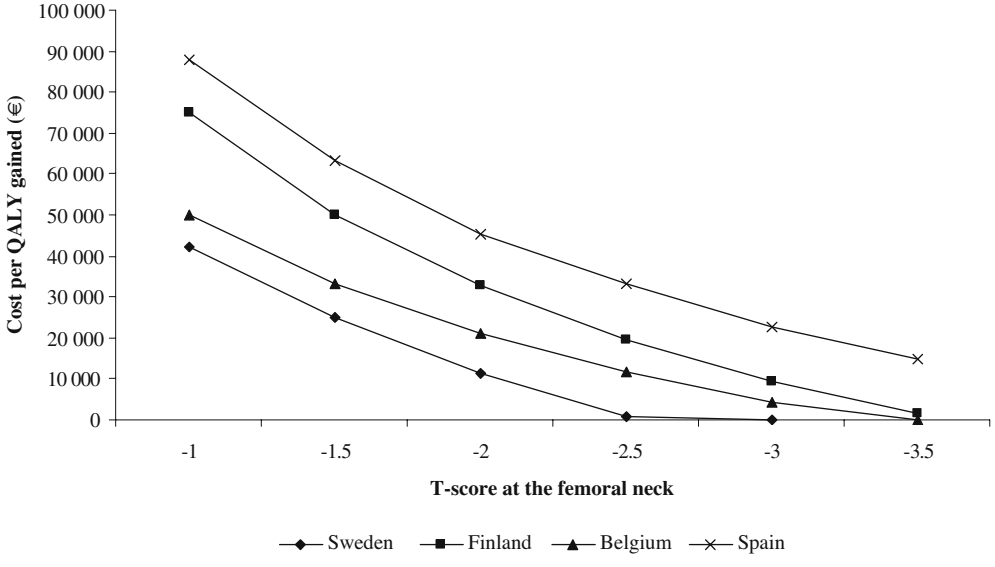


Fig. 5 Cost-effectiveness [€/quality-adjusted life years (QALY) gained of risedronate at different T-scores in women with prior vertebral fracture

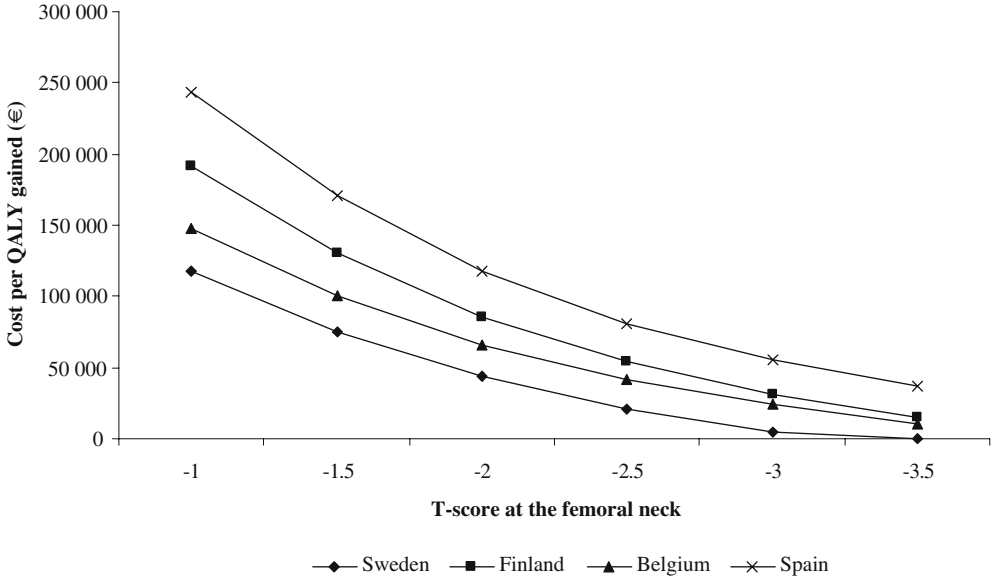


Fig. 6 Cost-effectiveness [€/quality-adjusted life years (QALY) gained] of risedronate at different T-scores in women without prior vertebral fracture

Finland, and Spain compared with the base cases in which higher discount rates were used.

Utilities for vertebral fracture

Compared with base-case simulations, cost-effectiveness ratios worsened somewhat when the utility loss associated with vertebral fractures was decreased.

Mortality associated with vertebral fracture

An excess mortality of 1.66 in the first year and none in subsequent years after vertebral fractures had a negative, but a rather small, effect on cost-effectiveness results compared with base-case estimations.

Model validation

Simulations were run in the Tosteson et al. [15] model, which was populated to the greatest extent possible with the same Swedish data used in the simulations above. For 70-year-old women at the threshold of osteoporosis with a previous vertebral fracture, the average number of hip fractures the first 10 years were 20.2% and 14.6% for untreated and treated patients, respectively. The corresponding values in the study model were 20.2% and 14.1%, i.e., the two models predict the number of fracture events very similarly. The cost per QALY gained was estimated to be €4,174 in the Tosteson model, which is comparable with the €860 per QALY gained estimated in the study model. One reason the Tosteson model renders a slightly higher cost-effectiveness ratio is that it does not take into account increased mortality after vertebral fracture and increased mortality beyond the first year after hip and vertebral fracture, which is included in the study model. Another reason is a slight difference in the calculation of utility loss after fracture. In the Tosteson model, quality of life is decreased in absolute numbers while in the study model, it is decreased proportionately.

Discussion

The current health economic model uses the most recent clinical trial, cost, and epidemiologic data to conduct cost-effectiveness analyses of risedronate compared with no treatment in multiple groups of women with a variety of risk factors for fracture. We have not undertaken any comparison with other treatments available for osteoporosis since no comparative studies of efficacy are available, and the large untreated population of osteoporotic women in these countries makes "no treatment" an important and relevant comparator group. The principal finding of the present study is the diversity in cost-effectiveness between countries. Overall, compared with no treatment, risedronate had the lowest incremental cost-effectiveness ratios for Sweden compared with the other countries. The largest difference in base-case analyses was between women with previous fracture in Sweden and Spain, with a relative difference of €31,655 and an absolute difference of 38 in the cost per QALY gained. The differences in cost-effectiveness between countries are mainly explained by different costs (fracture and treatment costs), fracture risks, and discount rates. For example, in the sensitivity analysis, it was shown that the cost per QALY gained difference between Sweden and Spain was reduced to €24,486 when the same discount rates were used. When the Swedish fracture costs were applied to Spain, the difference decreased further to €9,242, and when the Swedish fracture incidences were used for both countries, the difference was €84.

The threshold we used for cost-effectiveness was €40,000/QALY gained, though willingness to pay will

vary from country to country. There are currently no available official guidelines as to when an intervention can be considered cost effective in any of the investigated countries. Suggested threshold values for the incremental cost per QALY gained found in the literature have been €66,000 (SEK600,000) in Sweden [70], €6,000–€30,000 in Spain [71], and €43,000 (£30,000) in the UK [72]. Kanis and Jönsson [73] have suggested a general threshold value per QALY gained for the evaluation of interventions in osteoporosis of €30,000 (€50,000, including costs in added life years). The World Health Organization (WHO) Commission on Macroeconomics and Health suggested that interventions with a cost-effectiveness ratio lower than three times the gross domestic product (GDP) per capita for each averted disability-adjusted life year (DALY) should be considered cost effective [74]. The DALY and the QALY are measured on the same scale (0 to 1) but are based on different methodologies and, therefore, are not directly comparable. Moreover, it is not specified in the WHO report what costs are to be considered when relating to this threshold value. Therefore, whether risedronate can be judged cost effective or not given our results is a decision that must be made by the relevant decision makers in each country.

In both base-case and in sensitivity analyses, the estimated ICERs for the Swedish patient populations were below €40,000/QALY gained for all scenarios except in women with no prior vertebral fracture when assuming no offset time and at T-scores values of −2 or higher. In Finland and Belgium, the cost per QALY gained of risedronate for women with a T-score of −2.5 and previous vertebral fractures were below €40,000 in all of the estimated scenarios. For women without previous fracture, the cost-effectiveness was less evident. Spain, on the other hand, showed markedly higher ICERs, ranging, in the base case, from €32,515 for women with prior vertebral fracture to €80,100 in women without prior fracture.

Why a difference here? There are other studies that have investigated the cost-effectiveness of risedronate in elderly women [10, 11, 13, 75]. These studies have all in some way found risedronate to be a cost-effective treatment. However, they are quite difficult to compare since they differ in assumptions about patient characteristics, effect of treatment, and modelling assumptions. One recent study using the same construct used in this study indicated that risedronate was cost effective in a UK setting [9]. The cost per QALY gained of treatment with risedronate in UK women aged 70 years with previous vertebral fracture and a T-score of −2.5 was estimated to about €15,000.

It is assumed that the endpoint estimate of efficacy derived from the intervention studies applies to the 5-year treatment interval used for health economic modelling. A conservative value was used for offset time since previous studies have shown that assumptions concerning offset time have a critical effect on cost-effectiveness analysis. In the present analysis, variations in offset time had marked effects on cost-effectiveness.

Unfortunately, data availability differed between countries. Only for the Swedish analysis was there a full set of country-specific data available for all input parameters. For the other countries, there was, to some extent, a lack of country-specific data. There was especially a lack of information about costs, quality of life (health utilities), and risks of vertebral fractures. These missing data had to be extrapolated from other settings, thus bringing more uncertainty to the results. Our assumptions concerning vertebral fracture risk may be overly conservative, however. The risk of hip fracture varies markedly between countries [27], even within Europe, and we assumed a similar heterogeneity in risk of vertebral fractures. However, the heterogeneity in risk of morphometric vertebral fractures is much less than for hip fractures. If this were also true for clinical vertebral fractures, then this would decrease the difference between countries in terms of cost-utility results.

The estimated cost-effectiveness ratios in base-case simulations can be considered conservative since base-case analyses were conducted on patient groups at the threshold of osteoporosis (i.e., a T-score −2.5). As seen in the sensitivity analysis on T-scores, patients with a lower T-score (and thus a lower BMD) would have a higher relative risk of fracture and correspondingly lower cost-effectiveness ratios.

Conclusions

At a hypothetical threshold value of €40,000 per QALY gained, results in this study indicate risedronate to be a cost-effective treatment in elderly women at the threshold of osteoporosis (i.e., a T-score of −2.5) with prevalent vertebral fractures in Sweden, Finland, Belgium, and Spain. Also, the cost-effectiveness of risedronate in women at the threshold of osteoporosis without prevalent vertebral fractures appears to be strongest in Swedish patients.

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