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Original Research

Cost effectiveness and cost utility of risedronate for osteoporosis treatment and fracture prevention in women: a Swiss perspective

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Abstract

Objectives: To assess the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) of risedronate compared to no intervention in postmenopausal osteoporotic women in a Swiss perspective.

Methods: A previously validated Markov model was populated with epidemiological and cost data specific to Switzerland and published utility values, and run on a population of 1,000 women of 70 years with established osteoporosis and previous vertebral fracture, treated over 5 years with risedronate 35 mg weekly or no intervention (base case), and five cohorts (according to age at therapy start) with eight risk factor distributions and three lengths of residual effects.

Results: In the base case population, the ICER of averting a hip fracture and the ICUR per quality-adjusted life year gained were both dominant. In the presence of a previous vertebral fracture, the ICUR was below €45,000 (£30,000) in all the scenarios. For all osteoporotic women ≥ 70 years of age with at least one risk factor, the ICUR was below €45,000 or the intervention may even be cost saving. Age at the start of therapy and the fracture risk profile had a significant impact on results.

Conclusion: Assuming a 2-year residual effect, that ICUR of risedronate in women with postmenopausal osteoporosis is below accepted thresholds from the age of 65 and even cost saving above the age of 70 with at least one risk factor.

Keywords: risedronate, cost-utility analysis, hip fracture, osteoporosis, modelling studies, vertebral fracture, Switzerland

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Introduction

Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing patients to an increased risk of fracture[1]. Because of demographic changes and increasing life expectancy, osteoporosis is a growing public health concern. Fractures lead to increased mortality and to decreased quality of life, not only during the acute phase[2], but also on a long-term basis[3]. In 1990, in Europe, the estimated direct costs of osteoporotic fractures were €36 billion. They are expected to rise to €76.8 billion by the year 2050[4]. In Switzerland, fractures related to osteoporosis are the first cause of hospital stays for women and the second cause (after chronic obstructive pulmonary disease) for men[5,6]. Population-level osteoporosis-related direct medical inpatient costs per year will rise from €446 million in the year 2000 to €591 million in the year 2020[7]. These figures correspond to 1.6% and 2.2% of Swiss healthcare expenditures in 2000.

Therefore, interventions to reduce fracture risk in osteoporosis are desirable from a health policy perspective. Oral bisphosphonates are the main treatment for preventing fractures in osteoporosis, with demonstrated efficacy in increasing bone mineral density (BMD) and reducing bone turnover, which reduces the incidence of fractures. In a recent review, risedronate and alendronate were the only bisphosphonate treatments to show non-vertebral anti-fracture efficacy in a robust assessment of the anti-fracture efficacy of osteoporosis therapy using intention-to-treat populations in trials with patients' follow-up of 3 years or more[8]. Risedronate has been shown to reduce the risk of vertebral, non-vertebral and hip fractures by approximately 50%[9–11]. In addition, these studies have shown a safety profile similar to placebo, even in patients with active gastrointestinal diseases.

While the clinical outcomes of treatment for osteoporosis are well established, the economic benefit still needs to be investigated. The use of health economic models is necessary to integrate epidemiological, clinical and economic data, to adjust for country-specific variations, and to extrapolate the results from the limited time frame of clinical trials to a long-term perspective. Applying a Markov model to a UK setting and using an upper cost-utility threshold of £30,000 per quality-adjusted life year (QALY) gained as recommended by the National Institute for Health and Clinical Excellence[12], intervention with risedronate was shown to be cost effective in women aged 60 years and older with a BMD T-score ≤–2.5 and prior vertebral fracture and cost savings were found from the age of 70[13]. Risedronate treatment was cost effective from the age of 65 for women with a prior vertebral fracture and a T-score of –2.5 standard deviation (SD) and also for women with a T-score ≤–2.5 SD but without a prior vertebral fracture. In contrast, in women aged 60–80 years and at the threshold of osteoporosis (T-score = –2.5 SD), but without a prior vertebral fracture, treatment exceeded the threshold for cost effectiveness. When applying the same model to

four European countries, differences in cost effectiveness were mainly explained by different costs (fracture and treatment costs), fracture risks and discount rates[14].

There has been some debate about what is the most appropriate risk threshold at which intervention should be considered. Traditionally, a low BMD (T-score ≤–2.5 SD) was defined as a threshold for a proposed intervention. Several risk factors, including age, previous fracture, family history of hip fracture and the use of oral glucocorticosteroids, provide more information about fracture risk than a low BMD alone. Thus, the intervention threshold should be based on fracture probability rather than on a specific level of BMD[15].

For this reason the authors' wanted to assess the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) of risedronate compared to no intervention for the treatment of osteoporotic women in Switzerland, taking into account different age groups and fracture risk factors. The analysis was based on the results of large double-blind, randomised, controlled studies and applied to the Swiss setting by using a Markov cohort model populated with local mortality, fracture incidence and cost data, and published utility values.

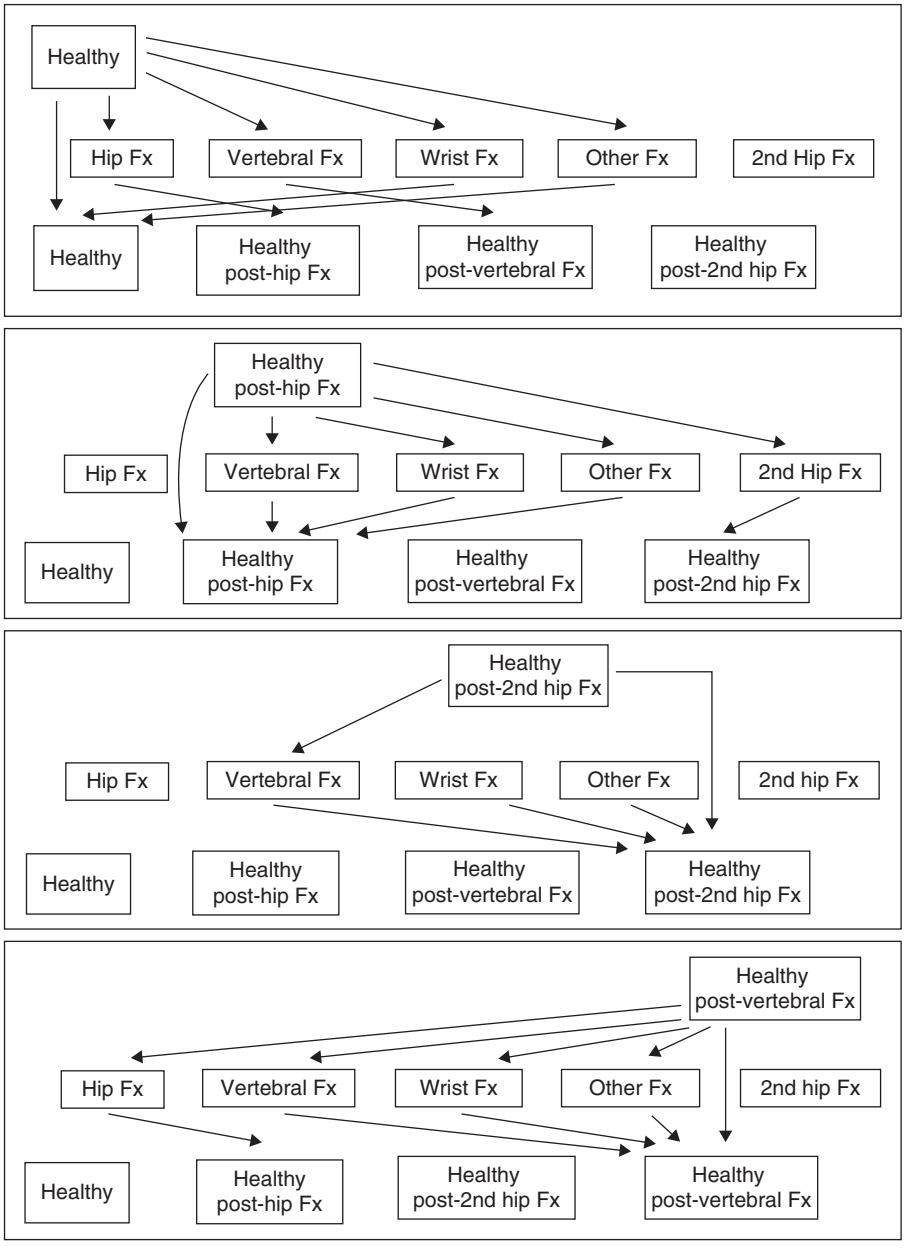
Methods

Model

A Markov model (Clinical and Economic Impact of Osteoporosis CLIO version 2.0), which has undergone an extensive validation process to ensure that it accurately simulates the long-term disease outcomes associated with osteoporosis in women between the ages of 50 and 100 years for a variety of populations was used[16]. This model uses time-dependent transition probabilities of a 1-year cycle length. Long-term states, where patients can remain for more than one cycle, include 'healthy', 'healthy post-vertebral fracture', 'healthy post-hip fracture', 'healthy post-second hip fracture' and 'dead', the latter being an absorbing health state. Transient states, where patients remain for only one cycle, include 'vertebral fracture', 'hip fracture', 'second hip fracture', and 'wrist fracture'. Non-vertebral fractures are optional in the model, but these fracture types were not considered in this study.

As shown in Figure 1, all patients of the cohort begin in the long-term state 'healthy', where each year they have a probability of suffering from a fracture, remaining healthy or dying. Patients who are dying move to the absorbing 'dead' state. Patients sustaining a fracture move to the 'vertebral fracture', 'hip fracture', or 'wrist fracture' state, according to their specific probability. After 1 year in one of these states, patients may suffer from a new fracture or not, or die. Patients not experiencing a new fracture and not dying move back to the 'healthy' state after wrist fracture, or to the 'healthy post-vertebral' state after vertebral fracture, or to the 'healthy post-hip fracture' state after hip fracture. Once in one of the post-fracture healthy states, patients may experience

Figure 1. Allowable state transitions due to fractures based on starting health state.



FX, fracture.
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a new fracture each year, die or remain in the state. Patients who sustain a new fracture (except for a second hip fracture) and do not die will return back to the corresponding healthy post-fracture state. When patients have sustained a second hip fracture, they enter the 'healthy post-second hip fracture' state, where they may remain, experience non-hip fractures, or die.

Model population

In the base case analysis, a cohort of 1,000 women with baseline characteristics of the vertebral fracture trial setting[9,11], namely 70-year old women with a previous vertebral fracture, was taken assuming they all were at BMD T-score ≤–2.5 SD. The intervention was risedronate treatment for 5 years in addition to calcium and vitamin D compared to no intervention (calcium plus vitamin D alone). Since an effect on BMD and possible fractures seems to persist after stopping the intervention, a residual effect of 2 years with a linear decline from 100% to 0% during the offset time was assumed[17–19]. In sensitivity analyses, the starting age of the cohort was changed to 60, 65, 75 and 80 years. In addition to the risk 'previous vertebral fracture', two other fracture risk factors, namely 'maternal history of hip fracture' and 'history of any fracture since the age of 50' were introduced into the model, leading to eight different groups of patients based on the different combinations of these three risk factors (2^3). Finally, the residual effect after stopping therapy was varied between 0, 2 and 5 years in order to test for its impact on the outcomes. These five cohorts with eight risk factor groups and three residual effects led to 120 scenarios, which were compared and their ICERs was expressed as cost per any fracture averted, cost per hip fracture averted and their ICUR as cost per QALY gained.

Relative risk of osteoporosis fracture

In order to reflect the incidence of osteoporosis fractures in specific target populations, one has to consider the prevalence of a risk factor in the general population, and the risk of fracture in the target population is compared to the age-matched cohort with an average prevalence of risk factors. In the absence of a published Swiss database for BMD and other risks, data of the Studies of Osteoporotic Fractures (SOF)[20,21] were used (Appendix 1). Age-specific mean T-scores of the target populations were provided by the third National Health and Nutrition Examinations Survey (NHANES III)[22]. Taking the base case (at 70 years) as an example, the age-specific T-score for the general population, the mean T-score for the target population BMD T-score ≤–2.5 SD and the Z-score were –1.99, –3.07 and 1.08, respectively. The risk of fracture in the target group relative to the age-matched group due to low BMD was then calculated as (relative risk [RR] per SD change in BMD)$^{(Z\text{-score})}$. This means the base case population is $2.53^{1.08} = 2.725$ times more likely to suffer a hip fracture compared to the age-matched group. The RR for the three risk factors other than BMD was adjusted using general population prevalence data and the RR of fracture for the risk factor. The applied formula was: average

RR = p × RR + (1-p) × 1, where RR = 1 denotes the risk if the population did not have the risk factor and p denotes the prevalence of the risk factor at a specific age in the target population. The adjusted RR is then given by: adjusted RR = RR/average RR.

Once the RRs for each risk factor had been adjusted to account for the prevalence of the risk factor in the age-matched population, the combined relative risk were computed by multiplying the adjusted RRs. Combined RRs for hip, vertebral and wrist fractures were calculated for the five age cohorts at the start of therapy (60, 65, 70, 75 and 80 years). These different risks, by type of fracture, are displayed in Table 1.

Inputs to the model

Incidence of osteoporosis fractures in the general population

The incidence rates of hip, vertebral and wrist fractures incorporated into the model were based on hospitalisation rates for fractures in Switzerland. Age-related incidences of hospitalisation due to fractures for women were calculated with absolute numbers of hospitalisations from the Medical Statistics database divided by the corresponding population numbers (both data sources from Swiss Federal Statistical Office (SFSO)[23]. The medical statistics data cover 91.2% of all Swiss hospitals and 81.1% of all admissions. Due to mandatory membership, this database is considered as representative for all hospitals. Therefore, the incidences of hospitalisation were extrapolated to 100%. These data were adjusted with published age-specific osteoporosis attribution rates (ranging between 0.8 and 0.95 for both hip and vertebral fractures, and 0.7 and 0.8 for wrist fractures)[24] in order to estimate the incidence of osteoporosis-related fractures as summarised in Table 2. The incidences of the general population were adjusted with the age-related combined RRs in Table 1 to get the fracture incidence rates in the target populations.

Efficacy of risedronate treatment

Risedronate was shown to reduce hip fracture risk by 43% after 3 years of treatment[13]. The corresponding numbers for vertebral and wrist fractures were 37% and 22%, respectively[13]. An extension study showed that this efficacy was maintained and even increased when treatment was administered for 5 years[25]. The residual effect was simulated for 0, 2 and 5 years in base case and sensitivity analyses, respectively. The residual effect consists in a linear decline from 100% to 0% during the offset time.

Compliance

The premature discontinuation of risedronate therapy was incorporated and the used rate derived from a published study, which showed that it amounted to 50% over 5 years[26]. This value was confirmed by expert opinion and further distributed as follows: 10% of patients would stop treatment in the first 3 months, 15% in the rest of the first year, 10% in the second year, and 5% per year in the last 3 years. The model assumes that patients who discontinue treatment within the first

Table 1. Calculated combined relative risks of osteoporotic fractures using SOF data and age-specific mean T-scores provided from NHANES III; patients BMD <–2.5 SD; age at start of therapy[18,19].

	*1**	*2†*	*3‡*	*60 years*	*65 years*	*70 years*	*75 years*	*80 years*
Hip fracture	No	No	No	4.1764	4.1764	2.7250	2.7250	1.8282
	No	No	Yes	5.2623	4.8663	3.1248	3.0890	2.0432
	No	Yes	No	5.4920	5.2648	3.4289	3.4518	2.3074
	No	Yes	Yes	6.9199	6.1344	3.9320	3.9129	2.5788
	Yes	No	No	7.0456	6.4074	4.0345	3.9141	2.5284
	Yes	No	Yes	8.8775	7.4657	4.6263	4.4369	2.8257
	Yes	Yes	No	9.2650	8.0771	5.0766	4.9581	3.1911
	Yes	Yes	Yes	11.6739	9.4113	5.8214	5.6203	3.5664
Vertebral fracture	No	No	No	2.0504	2.0504	1.6546	1.6546	1.3540
	No	No	Yes	2.8152	2.5208	1.9897	1.9584	1.5718
	No	Yes	No	2.5548	2.4715	1.9915	2.0020	1.6336
	No	Yes	Yes	3.5077	3.0386	2.3949	2.3696	1.8964
	Yes	No	No	8.0621	5.6570	4.0784	3.7288	2.7468
	Yes	No	Yes	11.0692	6.9551	4.9044	4.4135	3.1886
	Yes	Yes	No	10.0453	6.8188	4.9090	4.5118	3.3141
	Yes	Yes	Yes	13.7922	8.3835	5.9033	5.3402	3.8471
Wrist fracture	No	No	No	1.6679	1.6679	1.4315	1.4315	1.2410
	No	No	Yes	2.6953	2.2596	1.8746	1.8298	1.5405
	No	Yes	No	2.1316	2.0533	1.7596	1.7700	1.5294
	No	Yes	Yes	3.4446	2.7818	2.3041	2.2624	1.8985
	Yes	No	No	1.5428	1.5598	1.3446	1.3499	1.1762
	Yes	No	Yes	2.4931	2.1131	1.7608	1.7254	1.4600
	Yes	Yes	No	1.9717	1.9202	1.6528	1.6690	1.4495
	Yes	Yes	Yes	3.1862	2.6015	2.1642	2.1334	1.7993

SOF, Studies of Osteoporotic Fractures; NHANES III, National Health and Nutrition Examination Survey; BMD, bone mineral density.
* Previous vertebral fracture.
† Maternal history of hip fracture.
‡ History of any fracture since the age of 50.

3 months receive no treatment benefit, however, the cost of therapy for 3 months is applied.

Mortality

The annual mortality rates of women for the year 2005 were derived from the statistical directory of the death causes for Switzerland prepared by the SFSO[19]. The age-specific relative mortality risks in the first year following a hip fracture were derived from Trombetti *et al*[27]. These mortality risks were multiplied with the Swiss age-specific mortality rates of women in the general population, yielding an annual mortality rate in the year following a hip fracture. In order to adjust for causally determined hip fracture

Table 2. Fracture incidence based on 10,000 acute hospitalisations.

Age (years)	*Hip Fracture*	*Vertebral fracture*	*Wrist fracture*
50–54	2.5	14.6	4.7
55–59	5.5	15.5	7.7
60–64	8.6	16.7	11.5
65–69	20.0	25.8	15.1
70–74	37.0	36.0	20.7
75–79	75.2	60.1	25.5
80–84	160.2	90.4	30.0
85–89	296.1	124.0	33.4
90–94	391.3	124.1	36.1
95–100	412.7	123.1	14.6

mortality, the proportion of deaths averted by preventing a hip fracture was estimated at 23%[13,28]. This number was used to calculate a revised mortality rate in the year following a hip fracture. The model excludes excess mortality due to vertebral and wrist fractures.

Costs

Age-specific costs related to fracture treatment were assessed taking a healthcare perspective. Only direct costs were considered to measure the economic effect. Unit costs were collected from official prices and tariffs for Switzerland. Costs were given at the 2005 price level, and Swiss francs (CHF) transformed into Euros € at the exchange rate of €1 = CHF1.6. Daily inpatient costs of €863 for acute-care hospitals including special clinics, €388 for rehabilitation facilities, and €142 for nursing homes were extracted from the medical statistics database and the socio-medical institutions database of SFSO, respectively[23]. Drug costs were derived from the list of specialities[29]. Diagnostics and other services were calculated with the Medical Tariff [30]. Both costs and effects were discounted at a rate of 3%.

Fracture costs

Fracture costs included cost of acute care in hospitalisation, rehabilitation, ambulatory treatment and long-term care in nursing homes. Hospitalisation and rehabilitation costs were estimated by multiplication of the mean length of stay (MLoS) per fracture type in each age group with the corresponding cost per day as displayed in Table 3. The MLoS in acute hospitals and special clinics were calculated based on ICD-10 primary codes from the medical statistics database[23]. The MLoS for vertebral and for wrist fractures in rehabilitation clinics were analysed according to primary codes for rehabilitation together with secondary codes per fracture type from the medical statistics database[23]. As described in limitations, this analysis was not applicable for rehabilitation stays of hip fractures. Therefore, MLoS for inpatient rehabilitation was taken from Trombetti *et al*[27]. Rehabilitation costs were

Table 3. MLoS and cost of hospitalisation, rehabilitation, ambulatory care and nursing home of osteoporotic fractures, by fracture type and age group.

	50–64 years		*65–74 years*		*75–84 years*		*85+ years*	
	MLoS (days)	*Cost (€)*	*MLoS (days)*	*Cost (€)*	*MLoS (days)*	*Cost (€)*	*MLoS (days)*	*Cost (€)*
Hospitalisation								
Hip	15.0	12,944	17.8	15,354	20.2	17,441	18.6	16,084
Vertebral	14.5	12,500	15.6	13,484	17.4	15,019	19.9	17,186
Wrist	5.3	4,544	6.0	5,144	8.9	7,665	13.7	11,852
Rehabilitation								
Hip	59.0	17,404	59.0	17,404	59.0	17,404	59.0	16,084
Vertebral	22.8	5,040	24.0	4,344	25.5	3,581	22.9	17,186
Wrist	22.5	706	21.1	828	32.1	1,129	18.7	11,852
Ambulatory care								
Hip	–	4,026	–	4,026	–	4,026	–	4,026
Vertebral	–	2,250	–	2,250	–	2,250	–	2,250
Wrist	–	1,750	–	1,750	–	1,750	–	1,750
Nursing home post hip fracture								
1st year	274	1,223	274	3,320	274	5,067	274	6,989
Subsequent	365	1,629	365	4,422	365	6,750	365	9,310

MLoS, mean length of stay.

weighted with the percentage of patients discharged from acute hospitals to rehabilitation clinics, which were provided by the medical statistics database. The rehabilitation rate for acute hip fractures was derived from the Centre Hospitalier Universitaire Vaudois database, and amounted to 76% for hip fracture, 31–57% for vertebral fracture, and 8–13% for wrist fracture[31]. Based on published data, ambulatory treatment costs for hip, vertebral and wrist fractures were estimated at €4,026, €2,250 and €1,750, respectively[32]. Long-term care costs after hip fracture were calculated for newly admitted women in nursing homes in the year following hip fracture (restricted to 9 months) and for subsequent years. The nursing home admission rate post-hip fracture was reported at 18% mainly observed in women above the age of 85 years[27,33]. Nursing home costs were adjusted for younger women by assuming a linear decline of admission rate that came to 13, 8.5, and 3.1% in the age groups 75–84 years, 65–74 years, and 50–64 years, respectively.

Intervention costs

The cost of the drug was derived from the public price of a weekly tablet of risedronate 35 mg (€475.90 per year)[29]. Monitoring costs included medical visits twice a year (€51.10) and a bone density measurement once a year (€60.60)[30]. Thus, the total cost of intervention yielded €587.60

per patient per year. These intervention costs were taken as being specific to risedronate therapy although routine visits and bone density measurements may also occur in the comparison group.

Discounting

Costs and outcomes (fractures and utilities) were discounted at a rate of 3% per year after the first year.

Utility

The model estimated the QALYs experienced by the cohort. QALYs are produced by multiplying the number of years spent in a health state by the utility weight for that state. Utility values were not available for Switzerland and therefore were taken from Swedish general population[34]. The model determined utility weights by subtracting absolute utility decrements associated with fractures from the population-based, age-specific general utility values that are shown in Appendix 2. Utility decrements due to fracture were computed separately for the first and subsequent years (Appendix 3). The utility values used for pre-fracture states in each age group and the utility decrements due to fracture type varied between 0.180 for hip fracture and 0.025 for wrist fracture[2,36]. Two principal assumptions were made in order to estimate reasonable utility decrements for fracture states where no published data were available. Firstly, the utility decrement due to a fracture is not additive with the long-term effects of previous fractures. Secondly, if the utility decrease due to a fracture is less than the utility decrease due to a previous fracture then the lower value is used. For example, someone with a previous hip fracture has a utility decrease of 0.090. If they experience a wrist fracture, with an associated utility decrease of 0.025, the utility decrease for the patient remains 0.090.

Sensitivity analyses

Univariate sensitivity analyses were accomplished to point out striking input parameters. The parameters fracture incidence of the general population, the utility decrements due to fracture events and the risk reduction achieved with risedronate (considering other published efficacy rates[13,14,35]) were varied by ± 30%. All cost parameters were varied by ± 50% and included the cost of intervention, the inpatient fracture treatment cost and the outpatient fracture treatment cost. The residual effect after 5 years of risedronate administration was set to 0 and five years with a linear offset. Patients who prematurely discontinued risedronate therapy were assumed to benefit 20 or 80%: 5% or 20% during first 3 months; 10% or 35% during next 9 months; 5% or 10% during year 2; and 0% or 5% during year 3, 4 and 5. The probability of a new nursing home admission after hip fracture was set to 10 or 25% at the age above 85 years and by applying a linear decline to 0% at the age of 50 years. The discount rate was varied to 0 or 6%.

The influence of these parameters was investigated for the base case scenario for women at 70 years starting risedronate therapy with a previous vertebral fracture and, in addition, for the lowest risk (60 years

without any history of fracture) and highest risk scenario (80 years with all three types of fracture risks) to encompass the entire risk profile horizon assuming a 2 years residual effect after 5 years treatment.

Results

Base case analysis

For the base case cohort of 1,000 women with one previous vertebral fracture starting a 5-year treatment with risedronate at the age of 70, and assuming a residual effect of 2 years, the drug saved 23 hip, 23 vertebral and 2 wrist fractures. With the intervention, 38 QALYs were gained (8.774 QALYs per patient without intervention, 8.812 QALYs with risedronate treatment). Total cost amounted to €55,626 for no intervention and €54,908 for risedronate therapy producing cost savings of €722 per patient.
The averted fractures with risedronate therapy produced savings €2,816, which overcompensated by one third the intervention cost of €2,094. In scenarios where the total cost of risedronate therapy emerged higher than without intervention, the ICERs were obtained by dividing the incremental costs per patient by the corresponding incremental effectiveness values resulting from the difference of no intervention versus risedronate treatment.

Outcomes due to risk profiles

The ICERs for any fracture averted, by age group, fracture risk factor and residual effect after stopping therapy are displayed in Appendix 4, the corresponding ICERs for an averted hip fracture in Appendix 5, and the ICURs in Table 4. An example was selected to be shown in detail: it is characterised by having a previous vertebral fracture and a maternal history of hip fracture, but no history of any fracture since the age of 50. At the age of 60, these conditions lead to a combined annual RR of 9.27 for a hip fracture, 10.05 for a vertebral fracture and 1.97 for a wrist fracture. An intervention with risedronate for 5 years with no residual effect resulted in an ICER of €26,739 for any fracture averted (Appendix 4), €102,080 per averted hip fracture (Appendix 5) and in an ICUR of €27,386 per QALY gained (Table 4).

Effect of age and various risk factors

The effect of age on the ICERs and the ICURs of risedronate treatment demonstrated clearly that they decreased when age at start of treatment increased. For each of the eight scenarios combining the three risk factors, independent of a risedronate residual effect for 0, 2 or 5 years, there is a progressive decrease of ICER and ICUR from 60 to 80 years (Appendix 4, 5, Table 4). Interestingly, risedronate treatment induced savings in 100 of 120 (83%) scenarios. The age threshold for savings starts with women ≥60 years of age having two risk factors (previous vertebral fracture, no maternal history of hip fracture but history of any fracture since the age of 50 years) and assuming a residual effect of 5 years, respectively. For all women ≥65 years of age and a BMD T-score ≤–2.5 SD (24 scenarios), risedronate treatment was below the accepted threshold of €45,000 except for one scenario, assuming 0 years

Table 4. Age-specific incremental cost-utility ratios (€), by type of risk profile and length of residual effect after stopping therapy.

	Combined risk			*Incremental cost per any fracture averted (€)*				
	*1**	*2†*	*3‡*	*60 years*	*65 years*	*70 years*	*75 years*	*80 years*
No residual effect	No	No	No	118,635	47,676	31,738	Dominant	Dominant
	No	No	Yes	87,837	34,496	20,188	Dominant	Dominant
	No	Yes	No	88,811	30,387	14,660	Dominant	Dominant
	No	Yes	Yes	64,808	19,705	5,354	Dominant	Dominant
	Yes	No	No	40,152	10,339	Dominant	Dominant	Dominant
	Yes	No	Yes	26,027	2,510	Dominant	Dominant	Dominant
	Yes	Yes	No	27,386	287	Dominant	Dominant	Dominant
	Yes	Yes	Yes	Dominant	Dominant	Dominant	Dominant	Dominant
2-year residual effect	No	No	No	75,794	21,337	4,351	Dominant	Dominant
	No	No	Yes	59,978	11,267	Dominant	Dominant	Dominant
	No	Yes	No	53,202	7,834	Dominant	Dominant	Dominant
	No	Yes	Yes	35,473	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	19,389	Dominant	Dominant[$]	Dominant	Dominant
	Yes	No	Yes	8,516	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	9,235	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	22	Dominant	Dominant	Dominant	Dominant
5-year residual effect	No	No	No	46,665	3,000	Dominant	Dominant	Dominant
	No	No	Yes	29,069	Dominant	Dominant	Dominant	Dominant
	No	Yes	No	28,835	Dominant	Dominant	Dominant	Dominant
	No	Yes	Yes	15,199	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	4,603	Dominant	Dominant	Dominant	Dominant
	Yes	No	Yes	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	Dominant	Dominant	Dominant	Dominant	Dominant

* Previous vertebral fracture.
† Maternal history of hip fracture.
‡ History of any fracture since the age of 50.
$ Result of base case scenario.

residual effect (e.g. no risk factor or one of the two other risk factors; Table 4). Given a 2-year residual effect after stopping a 5-year risedronate treatment, 28 of the 40 scenarios would produce cost savings and even 37 scenarios would have an ICUR below €45,000 (Table 4).

When each one of the three risk factors were considered, the presence of a previous vertebral fracture had the most important effect on cost per fracture averted and cost-utility ratio (Appendix 4, 5, Table 4). Indeed, the unique presence of a previous vertebral fracture with no other risk factor is associated with cost savings in all age groups with the exception of the group aged 60 years when assuming a residual effect of 0 or 2 years, but even in these cases the risedronate treatment is to be considered as below accepted cost-effectiveness thresholds (Table 4).

Sensitivity analyses

Since the base case is dominant, and no ICUR can be calculated, the impact of univariate sensitivity analyses on the QALYs and the savings is shown in Table 5. Parameter changes favouring the no intervention strategy resulted in moderate to strong decreases in savings up to an incremental cost almost twice the baseline savings. Given the assumed variance, the inpatient treatment cost of fractures had the strongest influence, generating an ICUR of €16,469, which remained below the accepted cost-utility threshold of €45,000. Other parameters that also had a strong impact were the fracture risk reduction achieved with risedronate, the duration of the residual risedronate effect after the end of therapy, the intervention cost and the probability of new nursing home admission after hip fracture. Parameters with minor influence were the fracture incidence, the discount rate, the compliance and the outpatient fracture treatment cost. However, in all dominant scenarios, the impact on QALYs and savings does not translate into differences in ICUR.

The results of the sensitivity analyses for the scenario at the age of 60 with the lowest risk profile showed the expected increase on ICURs and were all above the accepted threshold of €45,000, while those for the scenario at the age of 80 years with the highest risk profile were all dominant (data not shown).

Discussion

A validated Markov cohort model was used, integrating most recent Swiss epidemiological and economic data. The ICERs of intervention with risedronate were analysed in addition to calcium and vitamin D for 5 years compared with calcium and vitamin D alone for the treatment of osteoporosis in postmenopausal women. Intervention at different ages was taken into account and also different risk factors with respect to fracture. No comparison were made with other treatments, since there are no studies comparing the efficacy of two treatments against fractures.

The main lessons learned from this study are as follows: first, there is a measurable

Table 5. Univariate sensitivity analysis of savings, ICUR* and QALYs gained for base case scenario†.

Parameter varied	*Range of variation*	*Favours risedronate*	*Change from baseline (%)*	*Favours no intervention*	*Change from baseline (%)*
Fracture incidence	Incidence +30%/-30%	-1,292 0.045	-79 -18	-54 0.030	93 21
Fracture risk reduction, effect of risedronate	Hip, vertebral, wrist, each +30%/-30%	-1,579 0.050	-119 -32	129 0.026 ICUR: 4,901	118 32
Residual effect of risedronate	Linear offset, 5 years/0 years	-1,489 0.046	-106 -21	-12 0.030	98 21
Compliance (premature discontinuation of risedronate therapy)	Patients who discontinue: 20%/80% (5%/20% first 3 months, 10%/35% next 9 months, 5%/10% in year 2, 0%/5% in year 3, 4 and 5)	-1,014 0.045	-40 -18	-291 0.025	60 34
Probability of new nursing home admission after hip fracture	25%/10%, linear decline from above 85 years to 0% at 50 years	-1,324 0.038	-83 0	-53 0.038	93 0
Utility decrements	Relative utility reduction, +30%/-30%	-722 0.049	0 -29	-722 0.027	0 29

ICUR, incremental cost-utility ratio; QALY, quality-adjusted life year; BMD, bone mineral density.

* If risedronate therapy is dominant the negative values indicate the savings (in €), if risedronate therapy incurred incremental cost the ICUR is indicated additionally.

† Baseline refers to base case scenario: women 70 years, previous vertebral fracture, 5 years target duration of risedronate, 2 years residual effect, 50% compliance, 18% new nursing home admission post-hip fracture, 3% discounting, leading to –€722 in savings and 0.038 QALYs gained.

Table 5. Univariate sensitivity analysis of savings, ICUR* and QALYs gained for base case scenario† (continued)

Parameter varied	*Range of variation*	*Favours risedronate*	*Change from baseline (%)*	*Favours no intervention*	*Change from baseline (%)*
Intervention cost, cost of risedronate and BMD diagnostic	-50%/+50%	-1,769 0.038	-145 0	325 0.038 ICUR: 8,588	145 0
Inpatient treatment cost of fractures (hospital, rehabilitation, nursing home)	+50%/-50%	-2,067 0.038	-186 0	623 0.038 ICUR: 16,469	186 0
Cost of outpatient fracture treatment	+50%/-50%	-785 0.038	-9 0	-659 0.038	9 0
Discount rate	Cost, fracture and utility discounting, 0%/6%	-1,080 0.046	-50 -21	-462 0.032	36 16

ICUR, incremental cost-utility ratio; QALY, quality-adjusted life year; BMD, bone mineral density.
* If risedronate therapy is dominant the negative values indicate the savings (in €), if risedronate therapy incurred incremental cost the ICUR is indicated additionally.
† Baseline refers to base case scenario: women 70 years, previous vertebral fracture, 5 years target duration of risedronate, 2 years residual effect, 50% compliance, 18% new nursing home admission post-hip fracture, 3% discounting, leading to –€722 in savings and 0.038 QALYs gained.

economic benefit in treating elderly women. In fact, the older the women with osteoporosis (BMD T-score ≤–2.5 SD), the more favourable the cost-utility ratio. There is even a point at which there is a benefit to society from treating these women, since the treatment is cost saving. Second, in common with other studies, this analysis clearly showed that the presence of risk factors is a key consideration in the decision to treat or not to treat. This finding is in agreement with those of Kanis *et al*[15]. Third, costs must be defined for each country individually, based on the risk of fracture associated with the specific population and on specific healthcare costs. Treatment guidelines including health economic aspects are necessary and can be used in combination with fracture risk prediction algorithms to improve patient selection for osteoporotic intervention. Treating a 70-year-old Swiss woman with densitometric evidence of osteoporosis but no history of fractures showed a cost per QALY gained of €4,351 (treatment with risedronate for 5 years with a residual effect of 2 years).

Data on cost effectiveness published in the literature are still scarce. By making use of another Markov cohort model in four European countries, the corresponding costs per QALY gained ranged from €21,148 in Sweden, €41,294 in Belgium, €53,947 in Finland to €80,100 in Spain[14]. The costs per QALY gained in Switzerland are between those observed in Sweden and Belgium. In addition, this model, which was developed by Johnell *et al*[37], was validated by running it on the Swedish populations with the Tosteson model used in this study. Interestingly, the Tosteson model renders a slightly higher cost-effectiveness ratio. One major reason was that the model used in this study does not assume increased mortality neither after vertebral fracture nor beyond the first year after hip and vertebral fracture as does the Johnell model. This comparison underlines the conservative approach of this study model.

Another economic study with an international perspective including Europe, North America, Asia and Australia aimed to define an intervention threshold[38]. For example, for women starting therapy at an age of 70 years, the accepted threshold for cost effectiveness corresponded to hip fracture probabilities ranging from 5.6% in Japan to 14.7% in Spain[38].

Compliance is a problem in the management of all chronic conditions, especially in osteoporosis. Almost 50% of women stop their treatment after 1 year[26,39]. The compliance is slightly greater with a weekly regimen[39]. Non-adherence reduces the effectiveness of treatment and exposes patients to an increased risk of fracture with a consequently increased rate of hospitalisation and use of healthcare services[40]. It is therefore necessary to take compliance into account in health economic studies, although the role of compliance is not mentioned in most cost-effectiveness studies in the treatment of osteoporosis[14]. This study adds new data to this field, because it incorporated compliance rates into the model.

The analysis was restricted to certain well-defined clinical situations. It did not

take into account women with normal bone densitometry or findings corresponding to osteopenia (BMD T-score ≤–2.5 SD) for several reasons. First, the vast majority of double-blind, randomised and controlled studies showing the anti-fracture benefit of osteoporosis treatments included women with densitometric evidence of osteoporosis. Second, it has been shown that the cost-utility ratio in women with osteopenia treated with alendronate, a bisphosphonate with anti-fracture efficacy very close to that of risedronate, is unfavourable[41]. In these women with no history of fractures, the cost per QALY gained ranged from €55,000 to €263,000. Moreover, the very thorough economic analysis conducted in Great Britain by the Health Technology Assessment Programme, covering all treatments of osteoporosis, confirmed an economic benefit (<£30,000 corresponding to €45,000 for a unit of QALY gained; £1 equalled €1.50 on the 25th July 2007) almost exclusively in women with densitometric evidence of osteoporosis and a previous history of fractures[12]. The presence of a typically osteoporotic fracture is usually recognised as an indication that treatment should be started, irrespective of the BMD value[42]. This situation has not been modelled due to lack of available data, as treatment studies have mainly included women with a BMD T-score ≤2.5 SD. These examples clearly show the need to take a decision as a function of a given fracture risk.

This study has a number of limitations. First, not all osteoporosis fractures that may occur at any skeletal site were included and therefore the entire benefit of risedronate in averting fractures were underestimated. However, hip, vertebral and wrist fractures are the most frequent osteoporosis fracture types, representing 82% of all incident osteoporosis fractures in Swiss women[6]. Second, the incidence of inpatient rehabilitation periods is under-assessed as it is based only on the primary diagnosis. It should be remembered that a complication that prolongs the period of inpatient rehabilitation, such as pneumonia or heart failure, often becomes a primary diagnosis in the coding process. The fracture therefore becomes a secondary diagnosis and does not appear in this data. Third, although Swiss data was used wherever possible, the authors had to resort to some Swedish (utility) or American data (e.g. RRs; adjusting mortality causally related to hip fracture; compliance rates) when they were missing Switzerland. Fourth, the efficacy of risedronate was taken into account against fractures only with respect to the hip, vertebrae and wrist, in other words the most common fractures. It has, in fact, been demonstrated that risedronate reduces the risk of all non-vertebral fractures. However, considering each fracture independently would present a much greater risk of inaccuracy. Fifth, as there are no published Swiss incidence data of radiographic fractures, fracture incidence is based on fractures that came to clinical attention. However, the model does not differ between hospitalised and not hospitalised fractures. Instead, it applies the selected efficacy rate irrespective of where the fracture would have been treated. The focus on hospitalised fractures implicates a potential

underestimation of the risedronate effect because the benefit of prevented non-hospitalised fractures by stopping reduction in quality of life and avoiding ambulatory treatment costs were not included in the analysis. Sixth, the model does not adjust for the (increasing) fracture risk caused by a vertebral fracture occurring during the simulation by the model, even some studies report that patients with vertebral fractures are at increased risk of all types of fractures[42–44]. The major reason is that the fracture rates in age-controlled matched pairs of patients with and without vertebral fractures are lacking in Switzerland and these would have been needed to calculate a conditional fracture risk. To implement a calculated conditional fracture risk based on assumptions would not have fulfilled the model criteria for validity or reliability. Seventh, unpublished SOF data was used for RR and prevalence of fracture in the general population. However, since many risk factors are not independent, the combined risk can be overestimated if the RR values for each risk factor are taken from independent sources. Therefore it seems that the SOF data are a more adequate source since the RRs come from the same regression equation so that all interactions between risk factors are considered (compare Tables 1 and 2 in Appendix 1). In general, the limiting factors, which were imposed on this study, give a conservative economic approach.

This study showed that in Switzerland the benefit of treating a patient with densitometric osteoporosis is mainly related to age and the presence of a common fracture. The decision to treat should therefore be taken as a function of the patient's risk profile and not on the basis of the bone densitometry value alone.

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Appendix 1

Relative risk of fracture by fracture type and risk factor due to Studies of Osteoporotic Fractures database[44].

Fracture type	*Per SD decrease in BMD**	*Previous vertebral fracture*	*History of maternal hip fracture*	*Previous clinical fracture since age 50*
Hip	2.530[†]	1.687	1.315	1.260
Vertebral	1.594	3.932	1.246	1.373
Wrist	1.394	0.925	1.278	1.616

SD, standard deviation; BMD, bone mineral density.
* BMD at femoral neck.
[†] BMD of hip published in Refs 20,21.

Relative risk of fracture by fracture type and risk factor due to published sources.

Fracture type	*Per SD decrease in BMD**	*Previous vertebral fracture*	*History of maternal hip fracture*	*Previous clinical fracture since age 50*
Hip	2.6[1]	1.9[4]	1.8[6]	1.5[6]
Vertebral	1.6[2]	4.1[2]	1.0[7]	4.1[9]
Wrist	1.5[3]	1.9[5]	1.0[8]	1.5[10]

BMD, bone mineral density.
* BMD at femoral neck.
Sources:
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Appendix 2

Population-based age-specific patient utility for pre-fracture states[33].

Age	*Age-specific utility*
	General population
50–54	0.9
55–55	0.9
60–64	0.9
65–69	0.79
70–74	0.79
75–79	0.63
80–84	0.63
85–89	0.63
90–94	0.63
95–100	0.63

Appendix 3

Utility decrements due to fracture.

Clinical event and time period	*Patient history during model*		
	Has no previous fracture	*Had previous hip fracture*	*Had previous vertebral fracture*
Hip fracture			
Utility decrease during the year	0.180[42]	0.180*	0.180*
Utility decrease in subsequent years	A 0.090[31]		
		0.090*	0.090*
Vertebral Fracture			
Utility decrease during the year	0.160[2]	0.160*	0.160*
Utility decrease in subsequent years	B 0.080*	0.090†	0.080*
Wrist Fracture			
Utility decrease during the year	0.025*	0.090†	0.080‡

* No data sources available; values shown are assumptions.
† Assumption based on value in cell A.
‡ Assumption based on value in cell B.

Appendix 4

Age-specific incremental cost per any fracture averted (€), by type of risk profile and length of residual effect after stopping therapy.

	Combined risk			*Incremental cost per any fracture averted (€)*				
	*1**	*2†*	*3‡*	*60 years*	*65 years*	*70 years*	*75 years*	*80 years*
No residual effect	No	No	No	141,781	50,012	28,577	Dominant	Dominant
	No	No	Yes	97,843	34,774	17,535	Dominant	Dominant
	No	Yes	No	104,007	31,242	12,888	Dominant	Dominant
	No	Yes	Yes	70,325	19,408	4,532	Dominant	Dominant
	Yes	No	No	41,271	9,640	Dominant	Dominant	Dominant
	Yes	No	Yes	24,364	2,216	Dominant	Dominant	Dominant
	Yes	Yes	No	26,739	257	Dominant	Dominant	Dominant
	Yes	Yes	Yes	13,696	Dominant	Dominant	Dominant	Dominant
2-year residual effect	No	No	No	88,949	21,904	3,806	Dominant	Dominant
	No	No	Yes	58,003	11,112	Dominant	Dominant	Dominant
	No	Yes	No	61,134	7,876	Dominant	Dominant	Dominant
	No	Yes	Yes	37,797	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	19,385	Dominant	Dominant	Dominant	Dominant
	Yes	No	Yes	7,736	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	8,752	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	19	Dominant	Dominant	Dominant	Dominant
5-year residual effect	No	No	No	53,234	2,978	Dominant	Dominant	Dominant
	No	No	Yes	30,937	Dominant	Dominant	Dominant	Dominant
	No	Yes	No	32,162	Dominant	Dominant	Dominant	Dominant
	No	Yes	Yes	15,715	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	4,418	Dominant	Dominant	Dominant	Dominant
	Yes	No	Yes	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	Dominant	Dominant	Dominant	Dominant	Dominant

* Previous vertebral fracture.
† Maternal history of hip fracture.
‡ History of any fracture since the age of 50.

Appendix 5

Age-specific incremental cost per averted hip fracture (€), by type of risk profile and length of residual effect after stopping therapy.

	Combined risk			*Incremental cost per any fracture averted (€)*				
	*1**	*2†*	*3‡*	*60 years*	*65 years*	*70 years*	*75 years*	*80 years*
No residual effect	No	No	No	323,834	92,146	49,784	Dominant	Dominant
	No	No	Yes	248,134	67,613	31,826	Dominant	Dominant
	No	Yes	No	239,262	58,086	22,514	Dominant	Dominant
	No	Yes	Yes	180,852	38,238	8,277	Dominant	Dominant
	Yes	No	No	154,442	23,688	Dominant	Dominant	Dominant
	Yes	No	Yes	103,161	5,833	Dominant	Dominant	Dominant
	Yes	Yes	No	102,080	644	Dominant	Dominant	Dominant
	Yes	Yes	Yes	59,481	Dominant	Dominant	Dominant	Dominant
2-year residual effect	No	No	No	193,849	39,540	6,504	Dominant	Dominant
	No	No	Yes	139,902	21,151	Dominant	Dominant	Dominant
	No	Yes	No	134,291	14,355	Dominant	Dominant	Dominant
	No	Yes	Yes	92,532	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	68,647	Dominant	Dominant	Dominant	Dominant
	Yes	No	Yes	30,974	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	31,674	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	78	Dominant	Dominant	Dominant	Dominant
5-year residual effect	No	No	No	111,510	5,279	Dominant	Dominant	Dominant
	No	No	Yes	71,544	Dominant	Dominant	Dominant	Dominant
	No	Yes	No	67,983	Dominant	Dominant	Dominant	Dominant
	No	Yes	Yes	36,939	Dominant	Dominant	Dominant	Dominant
	Yes	No	No	14,948	Dominant	Dominant	Dominant	Dominant
	Yes	No	Yes	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	No	Dominant	Dominant	Dominant	Dominant	Dominant
	Yes	Yes	Yes	Dominant	Dominant	Dominant	Dominant	Dominant

* Previous vertebral fracture.
† Maternal history of hip fracture.
‡ History of any fracture since the age of 50.