Cost-Effectiveness of Risedronate Treatment for Preventing Osteoporotic Fractures in Swiss Postmenopausal Women

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Abstract: *Objective*: Osteoporosis is a major public health concern in Switzerland and is associated with an increased rate of bone factures, health care costs, mortality and loss of quality of life. Risedronate has been shown to effectively prevent fractures in patients with osteoporosis. We examined the cost-effectiveness of risedronate from the Swiss health care perspective for the treatment of osteoporosis in postmenopausal women.

Methods: A probabilistic Markov model was developed to address this issue. Data for the treatment effect was derived from a meta-analysis and quality of life estimates were extracted from a systematic review. Costs were identified by using Swiss sources and expressed in Swiss Francs (CHF) for the year 2007.

Results: Osteoporotic women 70 years of age with a T-score of -2.5 who are treated over 5 consecutive years with risedronate and vitamin D and calcium, experienced on average 0.064 additional QALYs (95% CI: 0.039 QALYs to 0.091 QALYs) compared to patients treated with vitamin D and calcium alone. Costs in the treatment group were CHF 4341 higher (95% CI: CHF 3,427 to CHF 5,123), yielding an incremental cost-effectiveness ratio (ICER) of CHF 67,681 (USD 63,330; € 44,620) per QALY. For women 70 years of age with a T-score of ≤-2.5 SD the ICER is CHF 13,428 per QALY.

Conclusions: Based on a decision analytic model the results of this economic evaluation suggest that risedronate in the Swiss setting is a cost-effective treatment for osteoporosis in 70-year-old females at the threshold of osteoporosis or with established osteoporosis

Keywords: Osteoporosis, risedronate, cost-effectiveness, decision analytic model, probabilistic sensitivity analysis.

INTRODUCTION

Osteoporosis is a chronic disease leading to low bone mass and increased bone fragility with increased risk of bone fractures. It is more than three times more common in postmenopausal women than in men and the risk of osteoporosis related fractures increases with age [1-3]. The most common osteoporotic fractures are vertebral fractures, hip fractures and wrist fractures [1-3]. Hip fractures are related to considerable morbidity and mortality [4-6] and reduced quality of life [7-9]. As hip fractures generally require hospitalisation, surgery, and subsequent rehabilitation, the treatment costs for hip fractures are high, and osteoporosis induced costs to the health care system are substantial. For Switzerland alone total costs due to osteoporosis and related fractures were estimated to be CHF 357 millions for the year 2000 [1] and it was further estimated that total fracture-related first-year inpatient costs will rise by 31.5% to CHF 584 millions by the year 2020 [10]. With rising expenditure on health care and limited budgets, the value for money of interventions becomes increasingly important.

Pharmacological treatment of osteoporosis consists of antiresorptive and anabolic agents that are combined with calcium and vitamin D [11, 12]. Antiresorptive agents reduce bone remodelling and comprise bisphosphonates such as risedronate, raloxifene a selective estrogen-receptor modulator, calcitonin and strontium ranelate. Bisphosphonates are the most commonly used agents in the treatment of postmenopausal osteoporosis today. In the US, risedronate is used in about 22% of patients receiving bisphosphonate [13]. Several large clinical trials [14-17] and meta-analyses of randomised controlled trials [18-20] have shown that risedronate reduces vertebral and non-vertebral fractures in postmenopausal women with established osteoporosis.

To date, two economic evaluations have been published on the cost-effectiveness of bisphosphonates for the treatment of osteoporosis in postmenopausal women from the Swiss third party payers' perspective [21, 22]. Wasserfallen and colleagues found that treating postmenopausal women with risedronate for 5 years and assuming an offset time of 5 years is associated with an incremental cost-effectiveness ratio between €3000 per QALY and risedronate being cost saving, depending on the age of women at treatment initiation (numbers shown for ages 65 to 75 years) and their fracture risk [22]. Evidence from another published cost-utility analysis on screening-based alendronate use indicated that alendronate use is cost-effective in a Swiss setting [21].

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This economic evaluation explores the cost-effectiveness of risedronate treatment (with calcium and vitamin D) compared to calcium and vitamin D intake alone in postmenopausal women with established osteoporosis in Switzerland from a third party payer perspective. This cost-utility analysis is based on a decision analytic model that allows the course of the disease and the corresponding costs to be projected over time.

METHODS

The Model

We constructed a half-cycle corrected Markov model with Microsoft Excel and Microsoft Visual Basic 6.5 (Microsoft Corporation, Redmond, WA, USA). The model structure is based on a previously published reference model (Fig. **1**) [23]. We modelled a cohort of patients either receiving risedronate plus calcium and vitamin D or a basic treatment with calcium and vitamin D (also called the "no therapy" strategy). The cohort was assumed to start in the well health state in cycle zero and face the monthly risk of experiencing a hip, wrist, vertebral or humerus fracture (cycle length = 1 month), consequently moving to one of the fracture-specific health states.

Throughout the model, patients are at an age-specific risk of death [24]. For the base case analysis the age of the cohort at treatment initiation is 70 years. The time horizon of the analysis is the patients' remaining lifetime.
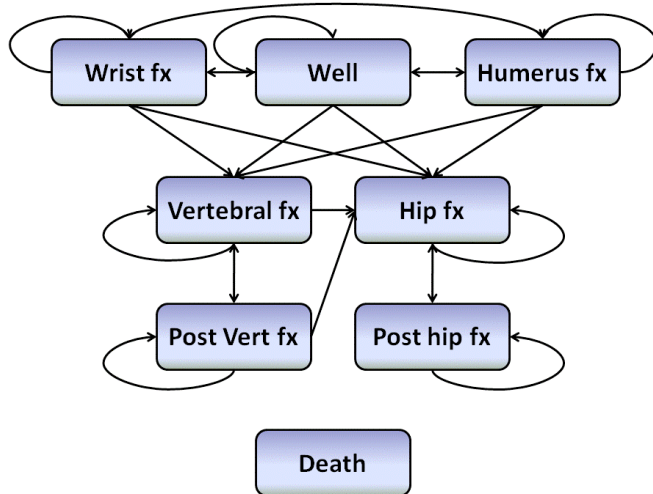
Fig. (1). State transition diagram. Transitions to the death state not shown.

Fracture Risk

Swiss fracture incidences for the four fracture sites were calculated from Swiss data for 10 age groups – each comprising 5 years – for the ages 50 years to 100 years. This was achieved by matching the number of cases with the number of women at risk of experiencing a fracture. The number of cases for 2005 (cases identified by ICD-10 code) per fracture site were obtained from the *Medical Statistics of Hospitals*, published by the Swiss Federal Statistical Office (SFSO) [24]. Swiss age- and gender-specific population statistics data for the year 2005 was obtained from the same source. The quality of the SFSO data is good – on average 98% of all cases are being recorded in the *Medical Statistics*

of Hospitals [24]. Thus, we have accurate and recent estimates of the fracture incidences for Swiss postmenopausal women. Since not all fractures can be attributed to osteoporosis (e.g. it is estimated that only 91% of all hip fractures in 75-84 year old women can be attributed to osteoporosis), we down adjusted the fracture incidences with osteoporosis attribution rates published for Switzerland [1]. All incidences (annual rates) were then transformed into monthly probabilities [25] (Table **1**).

To account for the increased fracture risk in osteoporotic women with a T-score of either -2.5 SD or ≤ -2.5 SD, baseline fracture incidences were adjusted using data published by Kanis *et al.* [26]. It should be noted, that based on the study by Kanis *et al.* osteoporotic women of any age with a T-score of ≤ -2.5 SD have at least a 40% increased fracture risk at any fracture site. In contrast, the relative risk of a fracture at the fracture sites under analysis decreases for women with a T-score of -2.5 SD that are 80 years of age or older [26].

Increased Mortality and Increased Fracture Rates

Women who experienced a hip or vertebral fracture have an increased risk of dying subsequent to the fracture or in the following year. Swiss age-, gender- and fracture-specific data was used in the model to account for the increased mortality after hip and vertebral fractures [6, 27]. Likewise, women with a prior fracture have an increased risk of any subsequent fracture. In the model, fracture site-, age- and gender-specific relative risk data from a meta-analysis was applied to account for the difference in risk between women with or without a prior fracture [28].

Treatment Effects

We derived estimates for the treatment effects of risedronate from a meta-analysis [20] that showed a reduction in the risk of a fracture at all fracture sites. The relative risk (RR) of vertebral fractures was estimated to be 0.63 (95% CI, 0.51 to 0.78) and the RR of hip fractures to be 0.60 (95% CI 0.42 to 0.88). The relative risk of a humerus and wrist fracture was found to be 0.67 (95% CI 0.50 to 0.90) and 0.68 (95% CI 0.43 to 1.08), respectively (Table **2**).

For the base case analysis, a treatment duration of 5 years with full adherence [29], followed by 5 years of offset time was assumed. During the offset time, we assumed that the effectiveness of risedronate will decline linearly from full to no effectiveness.

Quality of Life Data

Health state utility values were incorporated as reported by Kanis *et al.* [37] while age- and gender-specific UK baseline quality of life (QoL) values were obtained from the literature [38] and data provided by Paul Kind (University of York, UK, personal communication). Since no Swiss quality of life data of sufficient quality or utility value were available, this approach was chosen. However, baseline health-related quality of life is likely to be similar in the Swiss and UK populations. The Swiss 2002 health survey [24] contains estimates for baseline QoL values that were obtained from a telephone interview. These values compare very well with the UK data from the national questionnaire survey.

Table 1. **Monthly Fracture Probabilities. Mean Values and Standard Deviations for Different Age Groups, Fracture Sites and T-Scores**

T-score -2.5 SD									
	Hip		Vertebral		Wrist		Humerus		Distribution
Age	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
60-64	0.0001385	0.0000088	0.0000783	0.0000052	0.0003646	0.0000112	0.0001466	0.0000055	beta
65-69	0.0002184	0.0000116	0.0001149	0.0000071	0.0004008	0.0000126	0.0001699	0.0000066	beta
70-74	0.0003470	0.0000135	0.0001429	0.0000076	0.0004236	0.0000127	0.0001796	0.0000066	beta
75-79	0.0007383	0.0000208	0.0002692	0.0000112	0.0004761	0.0000138	0.0002625	0.0000094	beta
80-84	0.0011305	0.0000250	0.0004068	0.0000141	0.0004719	0.0000144	0.0002599	0.0000098	beta
85-89	0.0013466	0.0000314	0.0004774	0.0000187	0.0004661	0.0000177	0.0002566	0.0000120	beta
90-95	0.0015069	0.0000417	0.0004579	0.0000242	0.0003877	0.0000217	0.0002144	0.0000148	beta
95+	0.0015463	0.0000765	0.0003547	0.0000386	0.0002840	0.0000337	0.0001587	0.0000231	beta
T-score <-2.5 SD									
	Hip		Vertebral		Wrist		Humerus		Distribution
Age	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
60-64	0.0002481	0.0000157	0.0001400	0.0000093	0.0006532	0.0000200	0.0002626	0.0000099	beta
65-69	0.0004212	0.0000224	0.0002222	0.0000137	0.0007752	0.0000243	0.0003285	0.0000127	beta
70-74	0.0007209	0.0000281	0.0002968	0.0000159	0.0008832	0.0000265	0.0003744	0.0000138	beta
75-79	0.0016163	0.0000456	0.0005959	0.0000249	0.0010509	0.0000305	0.0005793	0.0000207	beta
80-84	0.0027473	0.0000608	0.0009903	0.0000344	0.0011441	0.0000349	0.0006302	0.0000237	beta
85-89	0.0032645	0.0000760	0.0011603	0.0000453	0.0011361	0.0000430	0.0006255	0.0000292	beta
90-95	0.0040571	0.0001123	0.0012347	0.0000652	0.0010475	0.0000587	0.0005792	0.0000399	beta
95+	0.0041631	0.0002059	0.0009564	0.0001042	0.0007673	0.0000911	0.0004289	0.0000623	beta

SD = standard deviation.

Table 2. **Treatment Efficacy and Costs**

Parameter	Mean	SD	Distribution	Source
Relative Risk for Fracture				
RR hip	0.60	0.046	normal	[20]
RR wrist	0.68	0.092	normal	[20]
RR vertebra	0.63	0.107	normal	[20]
RR humerus	0.67	0.122	normal	[20]
Costs [CHF]				
Hip fracture	19,568	5591	gamma	[30]
Wrist fracture	4,336	830	gamma	[30]
Vertebra fracture	5,456	1753	gamma	[30]
Humerus frature	8,505	2670	gamma	[30]
Hip rehabilitation	5,508	1574	gamma	[31, 32]
Wrist rehabilitation	805	230	gamma	[32, 33]
Vertebral rehabilitation	1,830	523	gamma	[32, 34]
Humerus rehabilitation	1,647	471	gamma	[32, 35]
Risedronate/month	62.75	-	-	[36]
GP visit/year	315	-	-	[21]

SD = standard deviation; RR = relative risk; CHF = Swiss francs; GP = general practitioner.

To estimate age and health-status specific utility values for each health state, the values of the general population were multiplied with the values for women with established osteoporosis. This assumes that the loss in quality of life due to an event is dependent on the pre-event quality of life (e.g. younger people with higher pre-fracture QoL have more to lose) (Table **3**).

Table 3. **Utility Values**

Parameter	Age	Mean	SD	Distribution	Source
Well	60-64	0.81	0.26	beta	[37]
Well	65-74	0.78	0.25	beta	[37]
Well	75+	0.71	0.27	beta	[37]
Hip	60-64	0.65	0.22	beta	[37]
Hip	65-74	0.62	0.22	beta	[37]
Hip	75+	0.56	0.23	beta	[37]
Wrist	60-64	0.81	0.26	beta	[37]
Wrist	65-74	0.78	0.25	beta	[37]
Wrist	75+	0.71	0.27	beta	[37]
Humerus	60-64	0.74	0.24	beta	[37]
Humerus	65-74	0.71	0.23	beta	[37]
Humerus	75+	0.65	0.25	beta	[37]

SD = standard deviation.

Cost Data

Costs for the treatment of the fractures were obtained from the Swiss All Patient Diagnosis Related Groups (APDRG) version 5.1 (Table **2**) [30]. For fractures with more than one diagnosis related group (DRG) available (i.e. cases with and without complications) we combined the costs from all relevant DRGs weighted by the number of cases in 2005. As treatment costs differ between teaching and non-teaching hospitals in Switzerland, we weighted the different costs by the number of total cases treated in teaching and non-teaching hospitals. Fracture patients will require musculo-skeletal rehabilitation after discharge from the hospital [31, 39, 40]. Costs for the rehabilitation add up to the total treatment costs per fracture. Duration and intensity of rehabilitation, and its related costs were estimated based on recommendations of the Cochrane Collaboration and published literature [31, 33-35, 41].

Thus, we estimated the following total treatment costs using cost data for rehabilitation from H+, the association of Swiss hospitals and rehabilitation clinics [32]: hip fracture Swiss Francs (CHF) 19,568, wrist fracture CHF 5,141, vertebral fracture CHF 7,286 and humerus fracture CHF 10,152.

To account for complications in hip fracture surgery (e.g. bacterial infections, loosening of the prosthesis), we conservatively estimated in-hospital treatment costs to increase by 1% [42, 43].

Patients in the health state post-hip and post-vertebral fracture were assumed to have impaired physical functioning and consequently be in need of home care (e.g. help with personal hygiene). Costs for this were obtained from Spitex, a large Swiss home care organisation (Spitex, Basel, personal communication). Monthly home care costs were conservatively estimated at CHF 1,314 (Table **2**).

Patients under risedronate treatment will need at least one annual visit at their general practitioner. Costs for this visit are assumed to amount to CHF 315 (21). Monthly costs for risedronate were obtained from the Swiss Drug Compendium (36) (Table **2**).

Analysis

The estimate of the cost-effectiveness of risedronate therapy compared to no therapy is presented as the incremental cost-effectiveness ratio (ICER; i.e. the ratio of incremental costs over incremental effects) [44] and as the incremental net monetary benefit statistic [45]. We calculated the total health effect and obtained the corresponding resource use for each treatment strategy. The health effect is measured in quality adjusted life years to incorporate any differences in mortality and morbidity into the analysis [46].

All costs in the model are in Swiss Francs (CHF) for the financial year 2007. Costs and health effects are discounted with monthly compounding at an annual discount rate of 3%. We converted CHF to Euros (€) and US dollars (USD) when reporting incremental cost effectiveness rations in the results section [47].

Sensitivity Analysis

Parameter uncertainty is addressed by probabilistic sensitivity analysis (PSA) with 5,000 Monte Carlo simulations [48-50]. Hence, parameters in the model are assigned individual probability distributions by the method of moments fitting [51]. We used normal distributions for the RR parameters, gamma distributions for the cost parameters, and beta distributions for the quality of life and fracture incidence parameters. Uncertainty in all model parameters was based on the same source as for the mean values without any further assumptions.

Through one-way sensitivity analysis, we also explored the effect of different values for parameters that may vary but are not subject to parameter uncertainty and may therefore not naturally be assigned a probability distribution (i.e., starting age, treatment duration, offset time, drug costs and discount rate).

RESULTS

Base Case Analysis

Results for the base case analysis (for women starting treatment at age 70) are shown in Tables **4** and **5**. Females with postmenopausal osteoporosis and a T-score of -2.5 SD aged 70 years and treated with risedronate for 5 consecutive years will experience 8.673 QALYs (95% CI 7.220 QALYs to 9.952 QALYs) compared to 8.609 QALYs (95% CI 7.169 QALYs to 9.871 QALYs) experienced by individuals without risedronate treatment assuming 100% drug adherence. The average total treatment costs under risedronate therapy are CHF 23,714 (95% CI CHF 21,023 to CHF 26,820) compared to CHF 19,373 (95% CI CHF 16,197 to CHF 22,948) for the no treatment strategy. This yields an incremental cost-effectiveness ratio of CHF 67,681 per QALY (USD 63,330; € 44,620).

Women 70 years of age with a T-score of ≤-2.5 SD gain 0.122 QALYs over untreated women (95% CI 0.075 QALYs to 0.171 QALYs) (Tables **4** and **5**). Total costs are CHF 40,736 (95% CI CHF 35,143 to CHF 46,830) for women under risedronate therapy and CHF 39,102 (95% CI CHF 32,543 CHF to 45,980 CHF) for women with no therapy. With incremental costs of CHF 1,634 (95% CI CHF -52 to CHF 3,113) the ICER is CHF 13,428 per QALY (USD 12,561; € 8,852).

Age at Initiation of Therapy

The age of the patients at which the treatment is initiated has a large impact on the estimate of the cost-effectiveness of risedronate. Fig. (**2**) shows the ICER for different ages at which treatment is initiated for osteoporotic women with a T-score of -2.5 SD and ≤-2.5 SD, respectively. For both patient populations, the ICER decreases until a starting age of 80 years. For women with a T-score of <-2.5 SD who start treatment at age 73 or later, treatment with risedronate becomes cost-saving (i.e. more effective and less costly than no treatment).

Treatment Duration and Length of Offset Time

Using a shorter treatment duration of one year (and assuming an offset time of one year), the ICER is CHF

Table 4.   Base Case Results. Costs, Effects and ICER (Mean Values and 95% Confidence Intervals)

Age	Population	Costs Comp. [CHF]	Effects Comp. [QALYs]	Costs Risedronate [CHF]	Effects Risedronate [QALYs]	Incremental Costs [CHF]	Incremental Effects [QALYs]	ICER [CHF/QALY]
70	-2.5 SD	19,373 (16,197 to 22,948)	8.609 (7.169 to 9.871)	23,714 (21,023 to 26,820)	8.673 (7.220 to 9.952)	4,341 (3,427 to 5,123)	0.064 (0.039 to 0.091)	67,681
70	<-2.5 SD	39,102 (32,543 to 45,980)	8.229 (6.867 to 9.360)	40,736 (35,143 to 46,830)	8.351 (6.956 to 9.514)	1,634 (-52 to 3,113)	0.122 (0.075 to 0.171)	13,428

ICER = incremental cost-effectiveness ratio; comp. = comparator; CHF = Swiss francs; QALYs = quality adjusted life years; SD = standard deviation.

Table 5.   Probabilistic Sensitivity Analysis. Incremental Net Benefit and Expected Value of Perfect Information (Mean Values and 95% Confidence Intervals)

Age	Population	INMB [CHF] at CHF 50,000/QALY	INMB [CHF] at CHF 100,000/QALY	P (INMB>0) at CHF 50,000/QALY	P (INMB>0) at CHF 100,000/QALY	EVPI [CHF/Patient] at 50,000/QALY	EVPI [CHF/Patient] at 100,000/QALY
70	-2.5 SD	-1137 (-2810 to 781)	2,066 (-757 to 5,227)	0.110	0.918	57	51
70	<-2.5 SD	4,458 (1,266 to 7,988)	10,551 (5,143 to 16,412)	0.998	1	1	0

INMB = incremental net monetary benefit; CHF = Swiss francs; P = probability; QALY = quality adjusted life year; EVPI = expected value of perfect information; SD = standard deviation.

308,112 per QALY for 70-year-old women with a T-score of -2.5 SD (for women with a T-score ≤-2.5 SD: CHF 139,469 per QALY (USD 130,551; € 91,940). Extending the treatment duration to 10 years lowers the ICER to CHF 36,537 per QALY (USD 34,200; € 24,080) for women with a T-score of -2.5 SD (CHF –3,690 (USD -3,453; € -2432) for women with a T-score of ≤-2.5 SD).
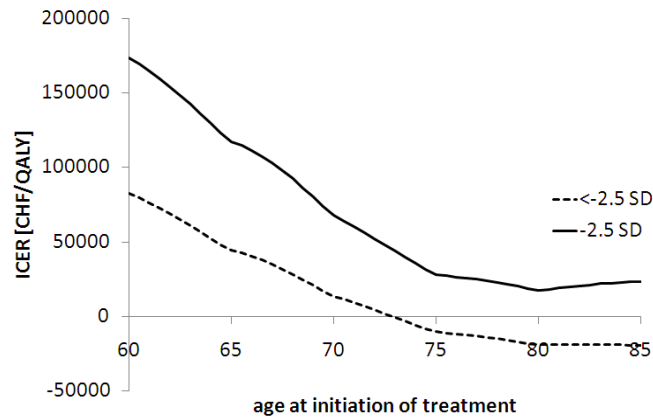
ICER = incremental cost-effectiveness ratio; CHF = Swiss francs; QALY = quality adjusted life year; SD = standard deviation

Fig. (2). Univariate sensitivity analysis on starting age.

Assuming no treatment effect during the offset time increases the ICER to CHF 144,440 per QALY (USD 135062; € 95,194) for 70-year-old women with a T-score of -2.5 SD (women with a T-score ≤-2.5 SD: CHF 54,639 per QALY (USD 51,097; € 36019). Extending the offset time to 10 years lowers the ICER to CHF 39,744 per QALY (USD 37,168; € 26,205) (women with a T-score ≤-2.5 SD: CHF –1,583 per QALY (USD -1,480; € -1,044)).

Drug Costs

After patent expiration and market entry of generic formulations, drug prices and thus costs usually decrease [52]. Assuming that generic risedronate would cost 32% of its brand name formulation (Actonel®), the ICER decreases to CHF 38,339/QALY (USD 35,690; € 25,275) [53].

Time Horizon and Discount Rates

Using a shorter time horizon increases the ICER for both patient populations because not all treatment benefits are captured in the analysis. Applying different discount rates to the analysis yields the expected results.

Probabilistic Sensitivity Analysis and Value of Information Analysis

Probabilistic sensitivity analysis provides an estimate of the probability of risedronate being cost-effective for different willingness to pay values (Table **5**, Figs. **3**, **4**). The applied threshold value is crucial in the decision whether risedronate is cost-effective. For osteoporotic women with a T-score of -2.5 SD, the probability that risedronate is cost-effective is 11% at a threshold value of CHF 50,000 per QALY (USD 46,730; € 32,974), but 92% at the higher threshold value of CHF 100,000 per QALY (USD 93,480; € 65,935). In women with a T-score ≤-2.5 SD who are at greater risk of a fracture, the probability that risedronate is cost-effective is much larger and approaches 100%.

Depending on the threshold value applied, the decision uncertainty varies from large to small values (Fig. **3**). Decision uncertainty can be expressed as the expected value of perfect information (EVPI) (Fig. **4**). For both patient populations, the EVPI reaches a maximum of more than CHF 300 per patient. In practice, the EVPI is negligible for

women with a T-score of ≤-2.5 SD and a willingness to pay of at least CHF 50,000 per QALY. For women with a T-score of -2.5 SD, the total EVPI per patient is CHF 57 assuming the decision maker's willingness to pay is CHF 50,000 per QALY (USD 46,730; € 32,974) and decreases to CHF 51 when a willingness to pay of CHF 100,000 per QALY (USD 93,480; € 65,935) is assumed (Table **5**).
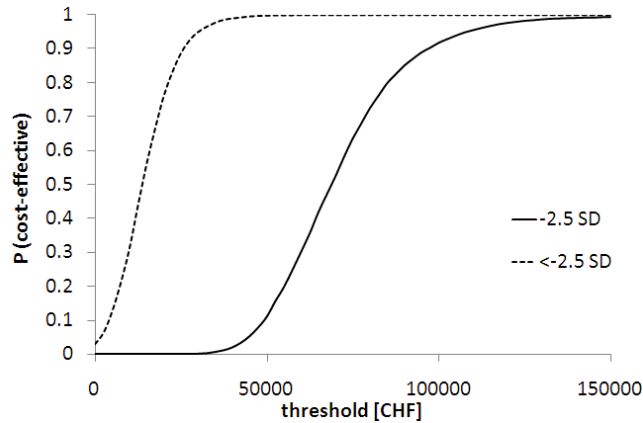
P = probability; CHF = Swiss francs; SD = standard deviation

Fig. (3). Cost-effectiveness acceptability curves (starting age 70 years).
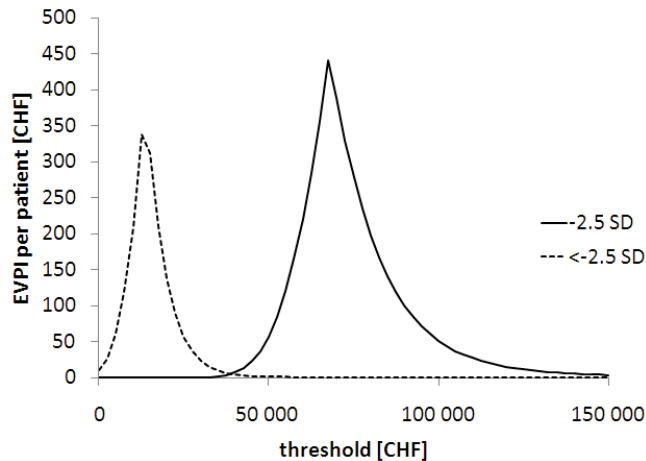
CHF = Swiss francs; SD = standard deviation

Fig. (4). Expected value of perfect information per patient (starting age 70 years).

DISCUSSION

Based on a decision analytic model, we analyzed the cost-effectiveness of risedronate treatment in osteoporotic women in a Swiss setting. For a variety of scenarios, we have shown that the treatment of osteoporosis with risedronate is cost-effective. The cost-effectiveness of risedronate is dramatically influenced by the age of patients at treatment initiation. Older patients are at a higher risk for any of the modelled fractures (hip, wrist, vertebral and humerus fractures), and thus, will have a larger treatment benefit at the same treatment costs. If we assume a constant relative risk reduction from risedronate over age, the treatment prevents more fractures when the treated population is older. Therefore, risedronate is more likely to be cost-effective in older patient populations. This general

finding is supported by various cost-effectiveness analyses [26, 54-56].

Although there is no official data on the decision makers' willingness to pay value per quality adjusted life year for Switzerland, when assuming a threshold level of CHF 100,000 per QALY (USD 93,480; € 65,935), risedronate treatment is cost-effective for postmenopausal osteoporotic women with a T-score of ≤-2.5 SD and an age of 58 years or older (data not shown). For women with a T-score of -2.5 SD risedronate treatment becomes cost-effective for women 68 years or older, assuming the same threshold value.

In a recently published structured review of the literature, Fleurence and colleagues [57] found that in most studies, (from Denmark, USA, UK and Sweden) bisphosphonate therapy is unlikely to be cost-effective in women younger than 50 years of age. Bisphosphonate therapy is most cost-effective in women at 70 years of age or older. For the age group 60 to 69 years, the authors conclude that there is uncertainty concerning the cost-effectiveness of bisphos-phonate therapy. A cost-utility analysis for alendronate carried out for 9 European countries reported incremental cost-effectiveness ratios of cost saving to € 46,326 per QALY depending on the country for 69-year-old women with low bone mineral density and without a previous fracture [58]. For Germany, the estimate was € 33,079 per QALY. These values correspond to estimates of the ICER of about CHF 89,000 per QALY (Italy) and CHF 52,000 per QALY (Germany) in 2007 Swiss francs. Compared to these two countries, our estimate of CHF 80,050 per QALY for 69-year-old women lies in between these values. This is in line with the findings by Ström *et al.* [58] who report a general pattern of smaller cost-effectiveness estimates for countries at higher latitude and larger ICERs for countries located further south. A reason for this may be the varying pattern of fracture incidences across different countries [58].

Our study has several strengths such as the rigorous way in which the model was set up and populated with data. Using a previous published model structure, the results of our analysis are more easily comparable to other studies, although generalisability may still be limited since we applied our analysis to a Swiss setting. To date, there exist only two other cost-utility analyses of a bisphosphonate that have been published for a Swiss setting [21, 22]. Wasserfallen and colleagues estimated the cost-effectiveness of risedronate for osteoporosis treatment and fracture prevention using a previously published decision analytic model [22]. Overall, the decision model of Wasserfallen *et al.* and our model seem to be comparable. Both decision models are Markov models that at least include the three most common types of fractures. In both decision models, the treatment effect is assumed to decline after discontinuation of therapy, increased mortality after a hip fracture is included, and rehabilitation costs are modeled. In addition, the study perspectives, time horizons and discount rates are the same. Thus, it is not surprising that the conclusions derived from the models are very similar. Both models provide comparable effect estimates: 70-year old risedronate treated patients – assuming an offset time of 2 years – yield 8.812 QALYs with Wasserfallen *et al.*'s model and 8.324 QALYs with our model. For the same patient

group, Wasserfallen and colleagues estimated that risedronate treatment prevents 23 hip fractures per 1000 women over their remaining lifetime. This estimate is almost equivalent to the estimate of 19 prevented hip fractures per 1000 women derived from our model. Nevertheless, the actual cost-effectiveness estimates derived from our analysis are higher than Wasserfallen *et al*.'s. We found a larger relative difference in the treatment effect (favoring risedronate) and at the same time a larger relative difference in total treatment costs (favoring no treatment). This deviation in the output of the two models is likely due to some aspects in which the two models differ from each other: the source and magnitude of the osteoporosis attribution rates, the inclusion of a humerus fracture health state in our model, the estimate of hip fracture related mortality, and the source and quality of the clinical data for the treatment efficacy (i.e. one clinical trial *vs* estimates from a meta-analysis in our model).

The greatest strength of our study compared to the study by Wasserfallen and colleagues is the way in which we carried out the sensitivity analysis. We not only performed an univariate sensitivity analysis - as Wasserfallen *et al*. did - in which we assessed the impact of single model inputs on the results, but also took full account of parameter uncertainty with a probabilistic sensitivity analysis [22]. Our results (with the corresponding confidence intervals) truly reflect uncertainty in the model's input parameters as determined by their sampling uncertainty. We were then able to estimate the probability of risedronate being cost-effective for different threshold values (see Table 6 and Fig. **3**).

Schwenkglenks *et al*.'s study analyzed the cost-utility of a mass-screening programme followed by 5 years of alendronate treatment [21]. This approach is different to ours and the ICERs are not comparable, since with Schwenkglenks *et al*.'s screening approach, women with T-scores of -2.5 SD and ≤-2.5 SD would be identified and subsequently treated. Thus, patient populations with different fracture risks cannot be distinguished anymore.

One of the limitations of our analysis is that we assumed full drug compliance throughout the 5 years treatment period. It is known that in actual practice, compliance with bisphosphonate treatment is suboptimal [59-61]. Modelling the impact of less than full compliance in decision analytic models has been discussed previously, but recommendations for handling this issue are inconclusive [62, 63]. While assuming full compliance may underestimate the ICER, this is in line with a variety of cost-effectiveness analyses published to date [23, 26, 64, 65, 58]. In the cost utility analyis of Wasserfallen *et al*. compliance did basically not affect the study findings in the sensitivity analysis [22]. We did not model the potential adverse event of osteonecrosis of the jaw. As this may be seen as a limitation of our study, the current clinical evidence is inconclusive and the incidence of osteonecrosis of the jaw is estimated to be in the range of 1 case in 100 00 patient years to 1 case in 100 000 patient years [66-69].

Apart from the usual probabilistic sensitivity analysis, we calculated the expected value of perfect information (EVPI) for our base line scenarios for two willingness-to-pay values. Expected value of perfect information places a monetary value on the opportunity loss that will arise both in monetary units and health benefits foregone, when the wrong decision is adopted [70]. For osteoporotic women with a T-score of ≤-2.5 SD, the EVPI is very small at a threshold level of CHF 50,000 per QALY and approaches zero for larger threshold values. This means that the decision uncertainty is too small, that further information (that could inform the decision of whether risedronate is cost-effective for 70-year-old women with a T-score of ≤-2.5 SD) will be of any value. In contrast to that, EVPI for 70-year-old women with a T-score of -2.5 SD is relatively large for potentially relevant threshold values between CHF 50,000 per QALY (USD 46,730; € 32,974) and CHF 100,000 per QALY (USD 93,480; € 65,935). Collecting new data could be cost-effective in order to be able to make this decision on the basis of more sound evidence.

CONCLUSION

The results of our study suggest that risedronate treatment for preventing osteoporotic fractures in Swiss postmenopausal women is cost-effective for women with a T-score of ≤-2.5 SD. Risedronate treatment is cost-effective for osteoporotic women with a T-score of -2.5 SD at age 69 years or older. Risedronate may be cost-effective for younger women, depending on the decision maker's willingness to pay value per QALY.

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