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ORIGINAL ARTICLE

An economic evaluation of strontium ranelate in the treatment of osteoporosis in a Swedish setting

Based on the results of the SOTI and TROPOS trials

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Abstract
Introduction Strontium ranelate is a new therapy for the treatment and prevention of osteoporosis that has been shown in two phase III clinical trials (the Spinal Osteoporosis Therapeutic Intervention [SOTI] and the Treatment Of Peripheral OSteoporosis Study [TROPOS] trials) to reduce the risk of osteoporotic fractures at the vertebral, non-vertebral and hip level in postmenopausal women. The aim of this study was to estimate the potential cost-effectiveness of strontium ranelate in the treatment of osteoporosis in postmenopausal Swedish patients.
Methods A Markov cohort model was adapted to fit patients corresponding to the patients in the SOTI and TROPOS clinical trials. The model was populated with Swedish cost and epidemiological data. In the base case, the cost-effectiveness was estimated for 69-year old women with low bone mineral density (BMD) and prevalent vertebral fractures (SOTI) and for 77-year old women with low BMD (TROPOS). The cost-effectiveness analysis had a societal perspective.
Results In the base case analysis, the cost per quality-adjusted life years (QALY) gained of strontium ranelate patients compared to no treatment patients was estimated at SEK 472,586 and SEK 259,643, including costs in added life years, based on the SOTI and the TROPOS trials, respectively. Excluding cost in added life years, the cost per QALY gained was estimated at SEK 336,420 (SOTI) and SEK 165,680 (TROPOS). In subgroup analyses, in patients 74 years and older with a T-score lower than −2.4 and patients older than 80 years of age, strontium ranelate was found to be cost saving compared to no treatment.
Conclusions The results in the base case analyses and the sensitivity analyses of this study indicate that, compared to no treatment, strontium ranelate is cost-effective in the treatment of postmenopausal women with low BMD.

Keywords Cost-effectiveness · Osteoporosis · Postmenopausal · Strontium ranelate

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Introduction

Strontium ranelate is a new osteoporotic treatment, consisting of two atoms of stable strontium and ranelic acid, which has been shown to reduce the risk of osteoporotic fractures in two large phase III clinical trials (the Spinal Osteoporosis Therapeutic Intervention study [SOTI] and the TReatment Of Peripheral OSteoporosis Study [TROPOS]) [1, 2].

Besides the improved clinical aspects of a new treatment technology, it is also important to evaluate whether the treatment is good value for money compared to other relevant treatment strategies within the same disease area.

The most common way to assess the economic value of a novel treatment strategy is to perform incremental cost-effectiveness analysis, where different treatment alternatives are compared in terms of costs (i.e. intervention costs and disease costs) and consequences (e.g. life-years or quality-adjusted life years [QALY]). In a cost-effectiveness analysis, all relevant costs and effects should be captured, no matter when in time they occur. It has, therefore, often become necessary to use simulation models that can extrapolate the clinical results beyond the limited time frame of the clinical trial. Another reason that motivates the use of simulation models is that cost-effectiveness assessments have to be based on country-specific data in terms of costs, disease risks, mortality and quality of life, in order to provide a good and relevant decision basis for decision makers in each country. A third reason why modelling is necessary is that it is often not possible to estimate the cost-effectiveness based on information solely from the clinical trial, making it necessary to synergise data from different sources in a model environment.

The objective of this study was, based on the clinical results on fracture risk in the SOTI and TROPOS trials, to estimate the cost-effectiveness, in a societal perspective, of strontium ranelate in the treatment of osteoporosis in Swedish women using a further development of a previously used Markov cohort simulation model.

Methods and materials

Target patient groups

The analysis mainly focussed on two patient groups; first, 69-year-old postmenopausal women who have low bone mineral density (BMD) (mean femoral neck T-score of −2.8 and mean lumbar T-score of −3.6) and a high proportion of prevalent vertebral fracture (87%), based on the results from the SOTI study; then, postmenopausal women corresponding to patients in the TROPOS study, i.e. 77-year-old women with low BMD (mean femoral neck T-score of −3.1) and, to some extent, prevalent vertebral fracture (33%). The cost-effectiveness was estimated for Swedish patients similar to the patients in the SOTI and TROPOS trials with respect to the effect of treatment, fracture risk and age. The cost-effectiveness was also estimated based on some subgroup analyses based on the two clinical trials.

The cost-effectiveness model

The cost-effectiveness was assessed using a Markov cohort model previously developed and utilised to estimate the cost-effectiveness of osteoporotic therapies in Sweden [3–5], Denmark [6] and the UK [7]. The model structure is shown in the state transition diagram in Fig. 1. A new feature of the model version used in this model was the introduction of a new health state that represents other osteoporotic fracture types than just the "classical" hip, vertebral and wrist fracture types. Fracture types to be included in this new health state depend on the scenario that is analysed and the availability of data. The cycle length is one year and all patients are followed through the model from the age of treatment initiation until they are 100 years old or deceased. There is always a probability of remaining in the same state or passing away. All of the patients begin in the *well* health state. The patient cohort starting in the *well* state is adjusted according to their baseline characteristics. That is, if the patients have a prevalent fracture before intervention, their quality of life and mortality will be adjusted accordingly. Each year, a patient has a probability of having a fracture, remaining healthy or dying. If a patient dies, she will move to the *dead* health state and remain there for the rest of the simulation (arrows to the *dead* health state are excluded in the figure for simplification). From the *post-hip* state, it is only possible to stay in the post-hip state, have another hip fracture or to die. Consequently, patients who have had a hip fracture cannot experience any future wrist, vertebral or other osteoporotic fractures and patients in the vertebral and post-vertebral states cannot have a wrist fracture. The probability of having a vertebral or a wrist fracture after a hip fracture is low and the consequences on mortality and the quality of life after having experienced multiple, different fractures has been poorly investigated. Nevertheless, the approach is conservative, since it will underestimate slightly the number of vertebral and wrist fractures.

To be able to run the model, it has to be populated with data. The model data can be divided into three categories; clinical data, epidemiological data and health economic data. Clinical data are the effects that the treatments have on the relevant patient groups. Epidemiological data are

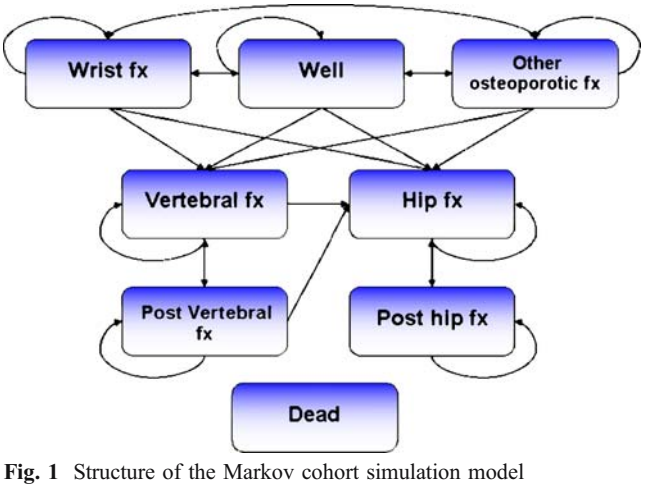

Fig. 1 Structure of the Markov cohort simulation model

information (e.g. fracture risks and mortality rates) about the disease that is treated and health economic data are the costs and health effects that are associated with disease events (e.g. fractures) included in the model.

Clinical data

The Spinal Osteoporosis Therapeutic Intervention (SOTI) study was a 5-year long multinational (11 European countries and Australia included) randomised double-blind, placebo-controlled study, with a main statistical analysis over 3 years, including 1,649 postmenopausal women aged 50 years or more (mean age=69 years) with at least one radiographically confirmed vertebral fracture and a lumbar spine BMD lower than 0.840 g/cm^2 [1]. However, central reading of the baseline radiographs after randomisation showed that 87% of patients had confirmed vertebral fractures. The primary endpoint was the number of patients experiencing new vertebral fractures over 3 years. A secondary endpoint was the number of patients with new non-vertebral osteoporotic fractures. The main finding in terms of fracture risk in the SOTI study was that, compared to placebo strontium, ranelate reduced the incidence of new radiographical vertebral fractures by 41% (RR=0.59; 95% CI=0.48–0.73) and new clinical vertebral fractures by 38% (RR=0.62; 95% CI=0.47–0.83) over 3 years. Pooling the vertebral and non-vertebral fractures demonstrated a significant fracture risk reduction of 32% (RR=0.68; 95% CI= 0.57–0.81) [1].

The base case analysis based on the SOTI study assumed only an effect on clinical vertebral fracture risk for patients treated with strontium ranelate. Due to the lack of power, the results are not significant for other types of osteoporotic fractures. In a sensitivity analysis, a risk reduction with strontium ranelate on hip, wrist and other osteoporotic fractures was tested.

The Treatment Of Peripheral OSteoporosis Study (TRO POS) was a 5-year multinational (11 European countries and Australia included) randomised double-blind, placebo-controlled study, with a main statistical analysis over 3 years, including 5,091 osteoporotic women above 70 years of age (mean age=77 years) with a femoral neck BMD below 0.600 g/cm^2. At baseline, 33% of the patients had at least one vertebral fracture. The primary endpoint was the time to occurrence of the first non-vertebral fracture. A secondary endpoint was the occurrence of vertebral fractures. Over 3 years, it was found that, compared to placebo, strontium ranelate reduced the incidence of major osteoporotic fractures by 19% (RR=0.81; 95% CI=0.66–0.98), the risk of non-vertebral fractures by 16% (RR=0.84; 95% CI=0.70–0.91) and the risk of radiographical vertebral fractures by 39% (RR=0.61; 95% CI=0.51–0.73) [2]. Major osteoporotic fractures included fractures at the wrist, pelvic-sacrum, ribs-sternum, collarbone, humerus and proximal femur.

In the TROPOS base case analysis, strontium ranelate was assumed to reduce the risk of hip and wrist fracture using the estimated fracture risk reduction for major non-vertebral fractures, i.e. by 19%, and the risk of clinical vertebral fracture using risk reduction estimated for radiographical vertebral fractures, i.e. by 39%. In a sensitivity analysis, the cost-effectiveness was assessed including other osteoporotic fracture types.

The cost-effectiveness was also estimated based on a subgroup of patients in the TROPOS study that were 74 years or older with a femoral neck T-score of −2.4 according to the NHANES III data [8], which showed a significant fracture risk reduction at the hip (RR=0.64; 95% CI=0.412–0.997). The mean age in this patient group was 80 years and 50% had prevalent vertebral fractures at baseline. The cost-effectiveness was also assessed based on a patient subgroup from a pooled analysis of the SOTI and TROPOS studies including patients over 80 years of age (mean age=83 years) with 50% prevalence of vertebral fractures at baseline, where the vertebral fracture risk was significantly reduced by 32% (RR=0.68; 95% CI=0.497–0.923) and any osteoporotic fracture by 31% (RR=0.69; 95% CI=0.519–0.920) [9].

The incidence rates of emergent adverse events were comparable between groups in both clinical trials. The most common adverse events (pooled data SOTI and TROPOS) were diarrhoea (6.5% and 4.6% in the strontium ranelate group and in the placebo group, respectively) and nausea (6.6% and 4.3% in the strontium ranelate group and in the placebo group, respectively) [10]. However, after the first three months after treatment initiation, there was no longer any difference between the groups [1, 2]. The costs and quality of life impact of these adverse events will be minor, in a yearly perspective, and were not included in the cost-effectiveness analyses.

As the cost-effectiveness analysis was based on the results from the clinical trials, it was assumed that the patients were given treatment for 3 years. The persistence of the fracture risk reduction after discontinuation of strontium ranelate treatment is not known. It is likely that the fracture risk reducing effect of strontium ranelate treatment does not immediately disappear after treatment discontinuation and it also as likely that the effect does not persist forever. A study including patients previously treated in the phase II trials STRATOS and PREVOS [11–13] showed that the BMD (both lumbar and femoral) decreased after treatment withdrawal, but after 1 year, there was still a beneficial effect on the BMD compared to the BMD at baseline. This suggests that there may be a sustained effect of treatment on fracture risk after treatment is stopped. Given this, and in line with other studies evaluating the cost-effectiveness of osteoporosis therapies [3, 7, 14–17] which assume a residual effect of treatment after treatment is stopped, we assumed a residual treatment

effect on fracture risk for 3 years after the withdrawal of strontium ranelate treatment. During this "offset time," the fracture risk reduction declined linearly to zero. In a sensitivity analysis, the cost-effectiveness was also estimated assuming no effect of treatment after the intervention period, as well as an offset time of 5 years.

Epidemiological data

The risk of fractures at the hip, clinical vertebrae and the wrist in a general Swedish female population were derived from a population based study from Malmö [18]. Linear extrapolation was used to estimate the risk above the age of 89 years. The incidence of other osteoporotic fractures were derived from a paper by Kanis et al. [19]. These risks were mainly based on Swedish data, but some data were imputed from fracture risk data from the US (Olmsted County; Rochester) [20].

Fracture risks have to be adjusted to accurately reflect the increased fracture risk in the target patient groups compared to that of the general population. The relative risk of fracture for the target patient groups compared to the population fracture risk was calculated from the BMD and the prevalence of vertebral fractures in the patient groups. The method used to calculate the relative risk of fractures have previously been described by Kanis et al. [21] and de Laet et al. [22]. The formula for the estimation of the relative risk of fracture based on the BMD ($RRfx_{\mathrm{BMD}}$) can be expressed as:

$$RRfx_{\mathrm{BMD}} = exp\left(-ln\left(RRfx_{sd}\right)(-Z\text{ - }score) - \frac{\left(ln\left(RRfx_{sd}\right)\right)^2}{2}\right) \quad (1)$$

where $RRfx_{\mathrm{sd}}$ is the increase in age-adjusted relative risk of fracture associated with a one standard deviation decrease in BMD (2.6, 1.8 and 1.4 for hip fracture, vertebral fracture and wrist fracture, respectively [23]) and the *Z*-score is the number of standard deviations that a BMD value is below the age matched mean BMD. The *Z*-scores were calculated using the reference BMD population values at the femoral neck from NHANES III [8]. These relative risks of fractures for the target patient groups have also got to account for the relationship between prevalent vertebral fractures, subsequent fractures and the prevalence of vertebral fractures in the general population. The calculation is defined as:

$$RRfx = RRfx_{\mathrm{BMD}} \times \left(\frac{RRprev_{vfx}}{RRprev_{vfx} \times Vfx\_prevalence + (1 - Vfx\_prevalence)}\right) \quad (2)$$

where $RRprev_{vfx}$ are the increased risks of fracture due to prevalent vertebral fracture and $Vfx\_prevalence$ is the prevalence of vertebral fractures in the population at a given age. The relative risk of fractures due to prevalent vertebral fracture used (2.3 for hip fracture, 4.4 for vertebral fracture and 1.4 for wrist fracture) are adjusted for age but not for BMD and were, therefore, down-adjusted by 10% [24, 25].

Using this method, the relative risk of fractures was calculated for the different target patient groups in the various cost-effectiveness estimations. Because these relative risk calculations are associated with a fair amount of uncertainty, the relative risks of fractures were varied over wide intervals in a sensitivity analysis (from 1 to 6).

Mortality rates for the general female population in Sweden are based on the years 1998–2001 [26]. Hip and clinical vertebral fractures lead to an increased mortality compared to the normal population [27–31]. Swedish age-differentiated hip and clinical vertebral mortality rates in the first and following years after a fracture event were derived from a study by Oden et al. [32] and Johnell et al. [33], respectively.

Osteoporotic patients have been found to have a higher degree of frailty compared to the general population, implicating that the excess mortality after fractures among osteoporotics are not entirely attributed to the fracture event [34, 35]. It has been estimated that 33% of the deaths one year after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25% directly related [36]. In another study on Swedish hip fracture patients, only 17%–32% of all deaths were found to be causally related to the fracture depending on age [37]. Along with these findings, we assumed that only 30% of the excess mortality (compared to normal mortality) after a hip and a vertebral fracture were associated with the fracture event itself. In a sensitivity analysis, it was assumed that all excess mortality was associated to the fracture event and nothing could be attributed to co-morbidity. There are no indications that wrist fractures are associated with any excess mortality [27, 28]. Also, because of the lack of information, it was conservatively assumed that other osteoporotic fracture types were not associated with an increased mortality.

Health economic data

All costs are in year 2004 values and are given in the Swedish Krona (SEK). When needed, foreign currencies were converted into SEK using the average exchange rate (e.g. 8.089 SEK/$) for the year 2004. Costs were inflated using the Consumer Price Index from Statistics Sweden [26]. As recommended in guidelines for economic evaluations issued by the Swedish Pharmaceutical Benefits Board, a yearly discount rate of 3% was used to adjust future costs

and effects to a net present value [38] using compounded discount rate calculations (expressed as $\exp^{-r*t}$, where r is the discount rate and t is the time). In sensitivity analysis, the discount rates of 5% and 0% were used. Also, a scenario using a 3% rate for costs and a 0% rate for effects was tested.

Fracture costs can be divided into acute costs, which occur the first year following the fracture, and long-term costs, which can persist several years after fracture or even for the remainder of the lifetime of the patient. Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral and wrist fracture were derived from studies conducted by Zethraeus et al. [39, 40]. Hip fracture costs for the second and following years were based on the age-differentiated proportion of patients that come from own living before fracture and that reside in nursing homes 1 year after fracture (data on file). These patients were assumed to remain in nursing homes for the rest of their lives [15] at a daily cost of SEK 1,605 [41].

There are currently no data on the fracture-related cost of clinical vertebral fractures after the first year in Sweden. In a Dutch-based study by de Laet et al. [42], the incremental cost of a morphometrically diagnosed vertebral fracture was estimated at $549/year for 3 years, which is approximately SEK 4,441. In a sensitivity analysis, this estimate was used as the cost for the second and following years after a clinical vertebral fracture. Wrist fracture was assumed to incur costs only in the first year after fracture.

Data on costs related to other osteoporotic fractures are very scarce, bordering non-existing. To estimate these costs, a method described in more detail by Kanis et al. [19] was used. The cost was calculated as a fraction of the cost of a hip fracture. The fraction used was 0.25 and was estimated as the relative morbidity of other osteoporotic fractures to hip fractures.

Costs in added life years are the difference between consumption and production for the patient. It has been recommended that these costs be included when conducting a cost-effectiveness analysis [43]. Estimates on the costs in added life years are available for Sweden [44] and were included in the base case simulations. The cost-effectiveness was also estimated excluding costs in added life years.

The intervention costs are considered as follows. The drug price of strontium ranelate is SEK 12.02/day and it is sold in 84-sachet packages [45], giving a yearly drug cost of SEK 4,389. In line with previous standard assumptions about the monitoring of osteoporotic treatments, it was assumed that, besides the drug cost, an intervention with strontium ranelate was associated with one yearly physician visit and a BMD measurement every second year [7–11]. However, given the old age of the patients, it is likely that, in real clinical practice, other health issues are also handled at the yearly physician visit. Therefore, ascribing the entire visit cost to the monitoring of the osteoporosis therapy might give an overestimation of the intervention costs. Also, in clinical practice, it is likely that not all patients would have measurements of BMD because the availability of equipment is still rather limited. In a sensitivity analysis, we, therefore, assumed that intervention was only associated with costs related to a physician visit and a BMD measurement at the initial prescription. Together with the costs of a physician visit (SEK 975) and the cost of a BMD measurement (SEK 1,103) [46], the yearly intervention cost sums to SEK 5,920. Both the treatment and control groups in the clinical trials received calcium and vitamin D supplements, which made it possible to exclude the costs of these agents. All cost data used in the simulations are summarised in Table 1.

Quality of life estimates that are most appropriate for health economic evaluation are measured on a scale ranging from 0 (deceased) to 1 (perfect health). The reduction in the quality of life the year after osteoporotic fractures were

Table 1 Fracture cost and cost in added life year data (SEK 2004 prices) used in the model

Fracture costs	Direct costs mean estimate (age interval) [reference]	Indirect costs mean estimate (age interval) [reference]
Hip fracture		
First year cost	86,087 (50–64); 93,722 (65–74); 165,513 (75–84); 231,344 (85–) [39]	–
Yearly long-term cost	39,350 (50–64); 38,490 (65–74); 60,131 (75–84); 132,942 (85–) [41]*	–
Clinical vertebral fracture		
First year cost	32,633 (all ages) [40]	33,512 (<65) [40]
Yearly long-term cost	4,441 (all ages) [42]**	–
Wrist fracture		
First year costs	20,736 (all ages) [40]***	3,533 (<65) [40]
Other fractures		
First year costs	21,522 (all ages)****	–
Cost in added life years (production-consumption)	70,065 (50–64); −163,469 (65–74); −191,855 (75–84); −302,751 (85–) [44]	

*Based on data on the proportion that is admitted to long-term special living accommodations (data on file)
**Only used in sensitivity analysis
***Only used for the first 3 years after fracture
****Estimated as 0.25 fraction, based on the relative morbidity of other osteoporotic fractures to a hip fracture, of the cost of a hip fracture

derived from a study based on patients recruited at the orthopaedic department at the Malmö University Hospital in the south of Sweden [40]. From this study, the yearly proportional loss in the quality of life after a hip fracture, vertebral fracture and wrist fracture was estimated at 0.203, 0.374 and 0.023, respectively [40]. By relating these estimates to Swedish population utility values (50–59 years: 0.82; 60–69 years: 0.78; 70–79 years: 0.78 and 80 years and above: 0.74) [47], age-differentiated fracture-specific quality of life weights were obtained [48, 49]. The quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [15]. Based on the findings that radiographically defined vertebral fractures reduce the quality of life by approximately 9% when the fracture may have occurred at a previously unknown time [50], it was conservatively assumed that the quality of life loss related to clinical vertebral fractures in the second and following years was 0.05. There are no studies suggesting that wrist fracture is associated with a quality of life reduction in the long term and it was assumed that wrist fracture had an impact on the quality of life only during the first year after fracture.

The proportionate quality of life loss in the first year after other osteoporotic fractures was calculated to 0.902 by using the same method as for costs, i.e. as the proportion of the morbidity of other osteoporotic fractures relative to the hip fracture morbidity. Other osteoporotic fractures were assumed to have no reduction in the quality of life beyond the first year after a fracture event.

Other available empirical estimates on the quality of life related to hip fractures lie close to the estimates used in this study [51, 52]. However, the empirical estimate of the quality of life loss after a vertebral fracture used in this study differs from other estimates. The recommended quality of life loss for all years after a clinical vertebral fracture in Brazier et al. [51] was about 9% [50]. This estimate was used in sensitivity analyses. Because the estimate is based on patients who experienced vertebral fracture at an unknown time, the quality of life loss was used for all years after fracture in one scenario and in another, more conservative scenario, during the first year only.

Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) was defined as:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0}$$

where ΔC is the difference in the total cost between a strontium ranelate intervention (C_1) and no intervention with strontium ranelate (C_0), and ΔE is the difference in effectiveness (i.e. QALYs or life years) between treatment (E_1) and no treatment (E_0) with strontium ranelate.

Stochastic analysis

The uncertainty surrounding the cost-effectiveness estimates were evaluated by sampling values from distributions related to the model parameters (i.e. second-order Monte-Carlo simulation). In this analysis, only the treatment effect was ascribed distributions. The relative fracture risks of strontium ranelate were assumed to be normally distributed in its logarithmic shape with the mean equal to the natural logarithm of the relative risk ratio. The standard deviation could be obtained, since the 95% confidence interval of a normally distributed parameter is calculated as: mean-standard deviation*1.96.

Results

Base case simulations

Cost analysis

The discounted expected lifetime cost of fractures for Swedish women similar to patients in the SOTI study (i.e. 69-year-old osteoporotic women with a high proportion of prevalent vertebral fractures) was calculated at SEK 10,900 (Table 2). A 3-year treatment with strontium ranelate would provide SEK 1,025 in potential savings of fracture-related costs and the cost of the intervention would be SEK 16,633. Because of the high age, the patients have a higher consumption than production. This together with an estimated gain in life of strontium ranelate treatment compared to no treatment gave an extra cost of this gained life time of SEK 6,317 for patients given strontium ranelate

Table 2 Base case cost-effectiveness analysis for patients with SOTI characteristics

	Strontium ranelate treatment	Untreated	Incremental values
Costs (SEK)			
Fracture cost	10,900	11,925	−1,025
Intervention cost	16,633	0	16,633
Consumption-production	2,474,630	2,468,313	6,317
All cost items	2,502,163	2,480,238	21,925
Effects			
Life years	12.49	12.45	0.032
Quality-adjusted life years	9.39	9.34	0.046
Cost-effectiveness (SEK)			
Cost per life year gained	200,377	199,137	678,259
Cost per QALY gained	266,549	265,526	472,586

compared to no treatment. Combining these cost components resulted in an incremental cost of SEK 21,925. Treating Swedish women similar in characteristics to TROPOS patients (i.e. 77-year-old osteoporotic women) would yield SEK 10,088 in saved costs of avoided fractures, SEK 16,144 in intervention costs and SEK 3,434 in the cost of added life years, resulting in an incremental cost of SEK 9,490 (Table 3). The cost offset ratio (saved cost of avoided fractures divided by the intervention costs) is higher for the TROPOS patient group (0.69) than for the SOTI patient group (0.07). This is because strontium ranelate was only assumed to have an effect in the base case simulations on vertebral fractures in the SOTI trial and most of the potential gain of avoiding a vertebral fracture lies in the quality of life savings and not in the cost savings.

Cost-effectiveness analysis

The results from the cost-effectiveness analysis, with base case assumptions, of a 3-year intervention with strontium ranelate are presented in Tables 2 and 3. The cost per QALY gained among women with SOTI characteristics was estimated at SEK 472,586 and among women with TROPOS characteristics at SEK 259,643. The difference in cost-effectiveness between the groups is mainly due to the fact that, in TROPOS, there was a risk-reducing effect on fractures on the hip, vertebral and the wrist, while for SOTI, there was only a treatment effect on the risk of vertebral fractures. Because the target patients are elderly and consume more than they produce, the incremental cost per QALY gained decreased (SOTI: SEK 336,420; TRO POS: SEK 165,680) when excluding the cost in added life years.

Table 3 Base case cost-effectiveness analysis for patients with TROPOS characteristics

	Strontium ranelate treatment	Untreated	Incremental values
Costs (SEK)			
Fracture cost	151,065	161,154	−10,088
Intervention cost	16,144	0	16,144
Consumption-production	2,001,281	1,997,846	3,434
All cost items	2,168,490	2,159,000	9,490
Effects			
Life years	8.73	8.71	0.019
Quality-adjusted life years	6.38	6.34	0.037
Cost-effectiveness (SEK)			
Cost per life year gained	248,378	247,826	503,507
Cost per QALY gained	340,009	340,472	259,643

Stochastic analysis

The results from stochastic analyses with 2,000 samples based on the SOTI and TROPOS base cases where the treatment effects (in terms of the relative risk of experiencing a fracture) were assigned distributions are depicted as acceptability curves in Fig. 2. At an assumed willingness to pay of SEK 600,000, there was an 87% chance that treatment with strontium ranelate was cost-effective for SOTI patients, i.e. the cost-effectiveness ratio fell below the threshold value 1,735 times out of the 2,000 samples. In none of the cases did strontium ranelate dominate the no treatment alternative, i.e. lower costs and higher quality gains. For women with TROPOS characteristics, the cost-effectiveness ratio fell below SEK 600,000 in 91% of the simulations. The stochastic analysis has to be interpreted with caution because the fracture risk reducing effect of strontium ranelate treatment was the only parameter where uncertainty was considered and no account was taken of possible co-variations between the treatment effect parameters.

Subgroup analysis

For patients 74 years or older and with a T-score of −2.4 (NHANES) or less and among patients older than 80 years of age based on the pooled analysis of the SOTI and TROPOS studies, strontium ranelate was found to be a cost-saving treatment alternative (see Table 4), both when cost in added life years were included and excluded.

Sensitivity analyses affecting fracture risks

Assuming a fracture risk reducing effect of strontium ranelate on all osteoporotic fractures improved the cost-effectiveness quite substantially for SOTI (a cost per QALY gained of SEK 285,013), while for TROPOS, the improvement was small (a cost per QALY gained of SEK 241,533) (Table 5). This indicates that fracture types other than the "classical" osteoporotic fractures (hip, vertebral and wrist) have a rather marginal impact on the cost-effectiveness.

Extending the treatment duration and offset-time to 5 years did not markedly change the cost-effectiveness (Table 5). This is because the benefits of two extra years of risk reduction are offset by the added cost of intervention, compared to the base case. When maintaining the 3-year intervention period but extending the offset time to 5 years, the cost-effectiveness slightly improved compared to the base case estimates. When assuming no additional effects of the treatment beyond the 3-year intervention period, the incremental cost-effectiveness worsened quite markedly. This is expected since the time strontium ranelate has a fracture risk reducing effect is halved, whereas the intervention costs are the same.

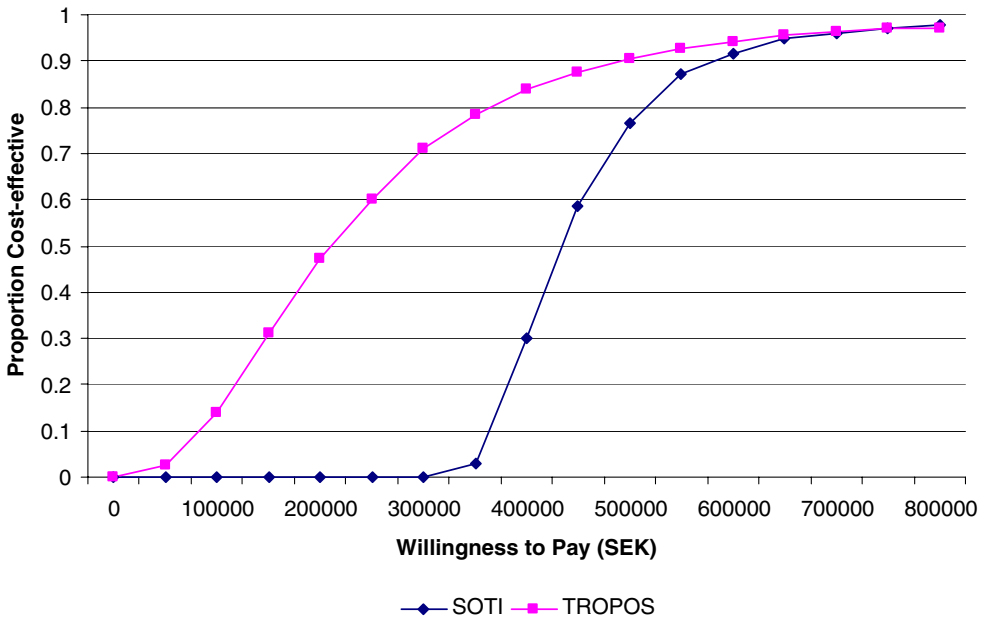

Fig. 2 Acceptability curves

The cost-effectiveness behaves in opposite directions with increasing starting age of strontium ranelate treatment for SOTI patients and TROPOS patients, as shown in Fig. 3. For the TROPOS study, cost-effectiveness improved with age, as might be expected. For the SOTI study, the cost-effectiveness was stable with age up to the age of 72 years. The reason for this is that the non-osteoporosis-related mortality and morbidity increase with age, leading to a lower gain of avoiding a fracture with increasing age. Because the age-related linear increase in vertebral fracture risk does not offset the lower gain of avoiding fracture at higher ages, the cost per QALY gained of treatment among patients with SOTI characteristics (only a risk-reducing effect on vertebral fractures) increases with increasing starting age of treatment. For patients with TROPOS characteristics (fracture risk reducing effect on hip, vertebral and wrist fractures assumed), the cost per QALY gained decreases because the exponential age-related hip fracture risk increases more than offsetting the lower gain of avoiding fractures at higher ages.

Figure 4 and 5 show that the cost per QALY gained decreases the higher the relative risk of each fracture type holding the relative risk of other fracture types constant. In the SOTI-based patient group the relative risks of wrist and hip fractures are not analysed because treatment in this scenario is only assumed to have an effect on the risk of vertebral fractures. For the TROPOS-based patient group the relative risk of hip fracture had a larger impact on the cost-effectiveness than the relative risk of wrist and vertebral fractures.

The lower the baseline T-score value of the target patients, the higher the fracture risk and, thus, the lower the cost per QALY gained, which can be seen in Fig. 6.

Sensitivity analyses affecting mortality

Assuming that the excess mortality after fracture was all due to the fracture event has two implications for the cost-effectiveness. Firstly, when the mortality is increased, the potential gain in terms of a life of avoiding a fracture increases. However, an improved life gain leads to a longer expected life time, which increases the incremental cost if the production is lower than the consumption in the targeted patient groups. These two opposing working effects gave a slightly decreased cost per QALY gained compared to the base case for the SOTI patient group and an increased cost per QALY gained for the TROPOS patient group when all excess mortality was assumed to be related to the fracture event (Table 5).

Sensitivity analyses affecting costs and quality of life

Compared to using a 3% discount rate, no discounting gave lower incremental cost-effectiveness ratios, whilst using a

Table 4 Subscenario cost-effectiveness analyses

	Incremental cost	Incremental QALYs	Incremental life years	Cost per QALY gained	Cost per life year gained
TROPOS≥74 years and T-score<−2.4 (NHANES)	−7 043	0.033	0.016	Cost saving	Cost saving
Pooled analysis >80 years	−4 715	0.035	0.012	Cost saving	Cost saving

Table 5 Sensitivity cost-effectiveness analysis (SEK)

Scenario	SOTI	TROPOS
Base case	472,586	259,643
Effect of treatment on all fractures[a]	285,013	241,533
5-year treatment and 5-year offset time	493,290	292,621
3-year treatment and 5-year offset time	419,825	199,643
No offset time	690,305	482,625
No comorbidity	403,936	345,841
5% overall discount rate	529,002	305,985
Discount rate: costs 3%, effects 0%	341,712	209,937
No discount rate	392,550	187,829
Vertebral fracture costs in the second and following years	449,923	244,581
Management costs, first year only	412,967	187,422
Annual utility loss of vertebral fracture multiplier: 0.909/1.00[b]	824,881	389,172
Annual utility loss of vertebral fracture, multiplier: 0.909 all years	509,057	289,741

[a] RR of strontium ranelate of 0.68 and 0.84 were used for the SOTI and TROPOS based scenarios, respectively.
[b] No reduction in quality in the second and following years after a vertebral fracture.

rate of 5% for both effects and costs they slightly increased (Table 5). The reason for this is that the effect of treatment has long-term consequences (in terms of the quality of life and expected life time) and that most costs (the intervention cost) occur during the treatment period. The same reason applies when discounting the costs but not the effects.

Assuming that vertebral fractures were associated with costs beyond the first year after the fracture event slightly improved the cost-effectiveness, compared to the base case, for both the SOTI- and the TROPOS-based scenarios.

Assuming that the management costs of intervention are lower (a physician visit and a BMD measurement only at the initial prescription) somewhat improved the cost-effectiveness compared to the base cases (Table 5).

Assuming a quality of life reduction after a vertebral fracture in the first year after fracture only, the cost per QALY gained rose to SEK 824,881 for SOTI and SEK 389,172 for TROPOS (Table 5). The cost-effectiveness was more sensitive to changes in the utility loss of vertebral fracture for SOTI than TROPOS because, in SOTI, there was only a treatment effect on vertebral fractures. Using a constant reduction in the quality of life (0.909) for all years after a vertebral fracture slightly worsened to the cost-effectiveness compared to the base cases.

Discussion

There are currently no available estimates giving guidance when an intervention can be considered cost-effective in Sweden. The decision about the cost-effectiveness of a treatment strategy is ultimately taken by the relevant decision maker. However, an estimate of the value of a QALY can be inferred from the value of a statistical life estimated by the Swedish National Road Administration [53]; the value of a QALY is estimated at about SEK 655,000 [54]. This threshold estimate takes into account the cost in added life years. The estimated cost per QALY gained in the base case simulations (SEK 472,586 for SOTI patients and SEK 259,643 for TROPOS patients) is below this value of a QALY, indicating strontium ranelate to be a cost-effective treatment compared to no treatment among postmenopausal Swedish osteoporotic women with similar characteristics as the patients in the SOTI and the TROPOS trials. In sensitivity analysis, varying the value of potentially uncertain parameters, the cost per QALY gained remained fairly stable below SEK 600,000.

In the TROPOS-based patient group, the cost per QALY gained was below SEK 655,000 in all sensitivity scenarios. For patients with SOTI characteristics, the cost per QALY gained was above this value at relative risks of vertebral fracture compared to population fracture risk lower than 1.5 and when assuming that vertebral fractures was associated with a conservative utility loss only in the first year after

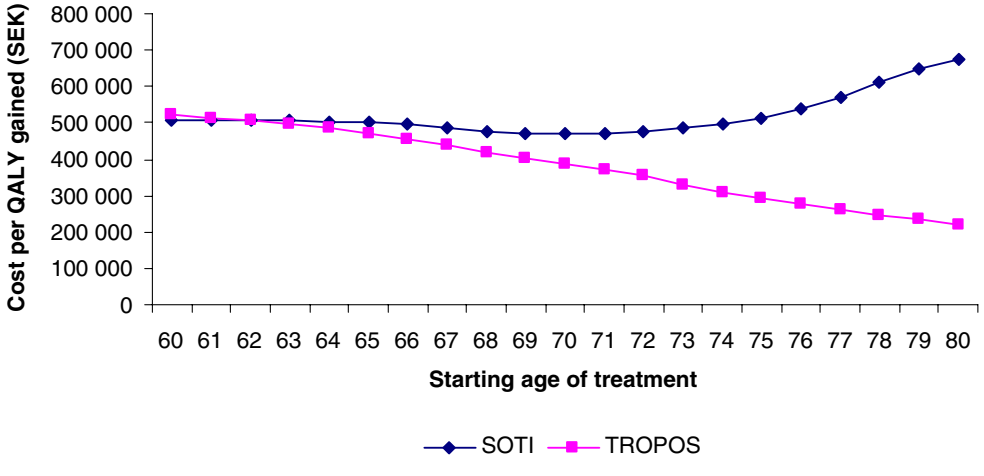

Fig. 3 Cost per quality adjusted life year (QALY) gained (SEK) at different starting ages of treatment

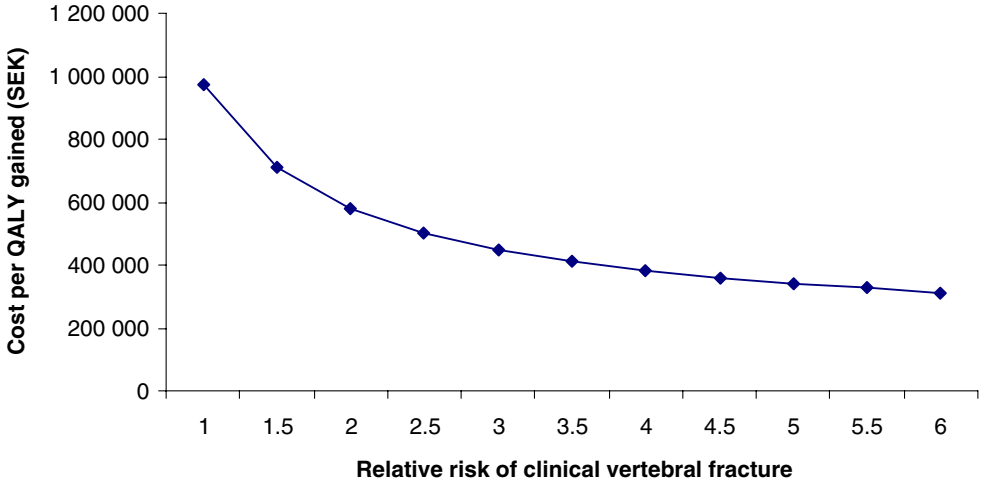

Fig. 4 Cost per QALY gained (SEK) at different relative risks of fracture among women with SOTI characteristics

fracture event. The main reason that the SOTI-based analysis had higher cost-effectiveness ratios was that only an effect on vertebral fracture risk was assumed. When assuming an effect on other osteoporotic fractures, the cost-effectiveness improved markedly. The SOTI study was not empowered to detect any treatment effect on peripheral fractures, though a non-significant risk-reducing trend was found for these fracture types.

Besides strontium ranelate, there are other osteoporotic treatments that have been shown to be cost-effective in the treatment of osteoporosis in Sweden, such as bisphosphonates and raloxifene [3, 4, 55]. The cost per QALY gained of alendronate compared to no treatment for 71-year-old Swedish women with low bone mass and previous vertebral fracture similar in characteristics to patients in the Fracture Intervention Trial have been estimated at SEK 82,000 [3]. The cost per QALY gained of risedronate compared to no treatment for 74-year-old Swedish women was estimated at SEK 298,000 and at SEK 18,000 for patients with osteoporosis and established osteoporosis, respectively [4]. The cost per QALY gained of raloxifene compared to no treatment for Swedish 70-year-old women with low bone mass and no previous vertebral fracture was estimated at SEK 510,000 [55]. All of these studies are based on extrapolations of clinical trials that compared treatment with no treatment. There are several reasons for the difference in estimated cost-effectiveness between these studies. One important factor is differences in the assumed treatment effect. In the alendronate study, treatment reduced the risk of hip, vertebral and wrist fractures. In the risedronate study, only an effect on hip fracture risk was used and in the raloxifene study, there was a risk-reducing effect on vertebral fracture and breast cancer events. Another important reason for the difference in cost-effectiveness is that the target patient groups differed in terms of absolute fracture risk.

A relevant analysis would have been to compare these drugs in a cost-effectiveness analysis. However, the relative efficacy between these therapeutics is not known because no head-to-head clinical trial estimating differences in

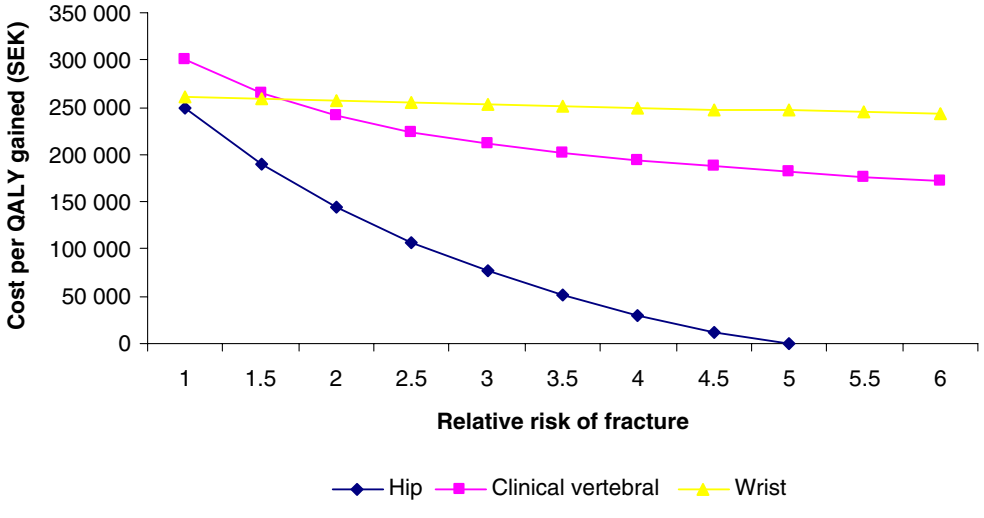

Fig. 5 Cost per QALY gained (SEK) at different relative risks of fracture among women with TROPOS characteristics

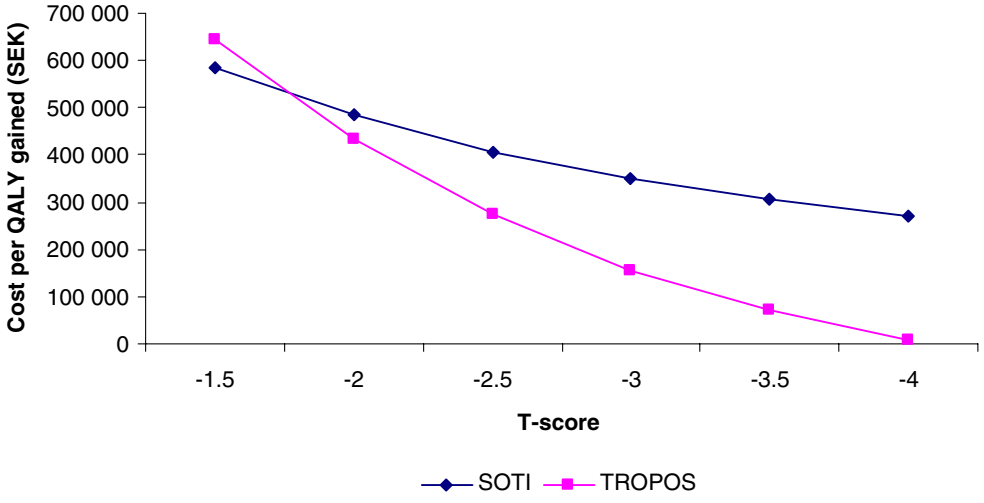

Fig. 6 Cost per QALY gained at different T-score levels

fracture risks have been conducted. Comparing the results between different trials is difficult since they differ in terms of, e.g. study populations, design and methods. Reimbursement agencies may be more interested in understanding the clinical and economic profile versus a gold standard comparator. It is, however, important that scientific economic evaluations are based on evidence. Analyses based on more or less uncertain assumptions about the clinical efficacy of strontium compared with other active treatments may, perhaps, give some information for policy decision-making purposes, but more reliable data are needed before an evidence-based comparison of strontium with other active treatments can be performed.

Apart from the treatment effect, the majority of data were derived from Swedish sources. This can be considered a strength when it comes to interpretation of the cost-effectiveness results in a Swedish environment. However, drawing conclusions about the validity of the results in this study for other countries is problematic, since event risks, mortality and costs differ between countries, which will have an impact on the cost-effectiveness. However, it is likely that countries with similar epidemiological patterns of osteoporosis, e.g. the Scandinavian region, will also show a similar cost-effectiveness.

An issue to consider is how the effect of the treatment has been modelled. In the base case analysis, it was assumed that the treatment was followed by a 3-year linear decline in effect. Although there are currently no estimates available for the effect of strontium ranelate on fracture risk after treatment stops, it has been shown in phase II studies that residual benefits on the BMD were still evident 1 year after stopping treatment [56].

The estimated fracture risk reduction effect of strontium ranelate treatment is based on intention-to-treat (ITT) calculations. That is, the estimated treatment effect also includes patients not complying fully with the treatment. A link between compliance and effect on fracture risk is difficult to derive based on the trial data. Therefore, a 100% compliance rate was assumed in the cost component of the analysis, i.e. all patients were ascribed intervention costs for the whole treatment duration. Assuming full compliance in the model likely leads to overestimated intervention costs in relation to the assumed effectiveness, which, to some extent, include non-compliers. In real clinical practice, the compliance is rarely full, which leads to lower effectiveness and fewer fractures avoided. How this would impact the cost-effectiveness is not entirely clear, since treatment drop-outs also result in lower intervention costs.

The estimated relative risks of fracture that were calculated to reflect the increased fracture risk in the target patient groups compared to the general population fracture are adjusted for the prevalence of prior vertebral fracture, since it is a strong risk indicator for subsequent fractures [25, 57]. However, the impact on fracture risk due to the prevalence of non-vertebral fractures was not accounted for. This, probably, to some extent, underestimates the fracture risk, since the prevalence of non-vertebral fractures at baseline is about 32% in the SOTI and 38% in the TROPOS trials. The reason for not including this risk factor is that reliable estimates on the relative risk of fracture due to prevalent non-vertebral fracture adjusted for prevalent vertebral fracture are scarce.

With respect to the fracture risks used in the model, it should be noted that they are total risks, i.e. not the risk of having a first fracture, but the total number of fractures during the year divided by the number of patients. This means that this risk has to be applied to the entire cohort (except for the dead, of course) in order to produce the correct number of fractures. The model is constructed in a way that only permits one fracture per year/cycle. This slightly underestimates the total number of fractures, since, in real life, it happens that patients have more than one

fracture during a year. However, this does not have any significant impact on the cost-effectiveness estimates, since fracture-related costs and utility losses the year after the fracture event used in the model can be considered to incorporate potential costs and utility losses from other fractures within that year also.

Conclusions

Taking the described limitations and uncertainties into consideration, this study shows that strontium ranelate compared to no treatment is indicated to be cost-effective in the treatment of Swedish women with low bone mineral density (BMD) and who are similar in patient characteristics to that of the Spinal Osteoporosis Therapeutic Intervention (SOTI) and the Treatment Of Peripheral OSteoporosis Study (TROPOS) studies.

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