Osteoporos Int (2011) 22:2347–2355
DOI 10.1007/s00198-010-1474-0

ORIGINAL ARTICLE

A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX®

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Received: 19 July 2010 / Accepted: 12 October 2010 / Published online: 2 February 2011

Abstract
Summary The aim of the present study was to determine the efficacy of strontium ranelate as a function of baseline fracture risk. Treatment with strontium ranelate was associated with a significant 31% decrease in all clinical osteoporotic fractures (vertebral fractures included). Hazard ratios for the effect of strontium ranelate on the fracture outcome did not change significantly with increasing fracture probability.
Introduction Two previous studies have suggested that the efficacy of intervention may be greater in the segment of the population at highest fracture risk as assessed by the FRAX® algorithms. The aim of the present study was to determine whether the anti-fracture efficacy of strontium ranelate was dependent of the level of fracture risk.
Methods The primary data of the two phase III studies (SOTI and TROPOS) of the effects of strontium ranelate in postmenopausal osteoporosis were combined. Country-specific probabilities were computed using the FRAX® tool (version 2.0). The primary outcome variable comprised all clinical osteoporotic fractures (including clinical vertebral fractures). Interactions between fracture probability and efficacy were explored by Poisson regression.
Results The 10-year probability of major osteoporotic fractures (with BMD) ranged from 2.5% to 90.8%. FRAX®-based hip fracture probabilities ranged from 0.1% to 90.3%. The incidence of clinical osteoporotic fractures (vertebral fractures excluded) and morphometric vertebral fractures increased with increasing baseline fracture probabilities. Treatment with strontium ranelate was associated with a 31% (95% CI=20–39%) decrease in osteoporotic clinical fractures and a 40% decrease in vertebral fractures assessed by semiquantitative morphometry (95% CI=31–48%) Hazard ratios for the effect of strontium ranelate on the fracture outcomes did not change significantly with increasing fracture probability.
Conclusion Strontium ranelate significantly decreased the risk of osteoporotic clinical fractures, non vertebral fractures and morphometric vertebral fractures in women. Overall, the efficacy of strontium ranelate was not dependent of the level of fracture risk assessed by FRAX

Keywords FRAX · Meta-analysis · Randomised controlled trials · Strontium ranelate

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Introduction

Strontium ranelate is an orally active agent developed for the management of postmenopausal osteoporosis. Its mechanism of action is not completely known. It has been proposed that strontium ranelate both inhibits bone resorption and stimulates bone formation through the activation of the calcium-sensing receptor and the OPG/RANKL system [1–3] suggesting that the agent may uncouple the bone remodelling process [4–7] and improve thereby the architecture and strength of bone [8–10]. However, the modest effect of strontium ranelate on biochemical markers of bone turnover [11–13] and bone histology [14] suggests that the improved strength of bone is also due to an improvement in the material or structural properties of bone [9, 15].

Irrespective of the mode of action, several studies have reported anti-fracture efficacy of strontium ranelate, at spinal and non-vertebral sites, in women with postmenopausal osteoporosis with or without prior vertebral fractures [11,

12, 16, 17]. Two placebo-controlled phase III studies of the effects of strontium ranelate in postmenopausal osteoporosis have been reported (the Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) studies). The SOTI study [11] showed that strontium ranelate decreased the risk of vertebral fracture with no significant effect on non-vertebral fracture. The TROPOS study [12] also showed a decreased risk of vertebral fracture and a significant effect on non-vertebral fracture after 3 and 5 years of treatment. In the same study, a reduction in hip fracture rates was reported in a post hoc subgroup analysis in patients considered to be at high risk. This subgroup was selected on the basis of age and low BMD, both of which are important clinical risk factors for fracture. This in turn suggests that strontium ranelate may have greater efficacy in women at greater fracture risk. This view is consistent with previous reports in two phase III studies that examined the effects of the bisphosphonate, clodronate in elderly women [18] and the SERM, bazedoxifene on clinical fractures [19]. In both studies, the relative risk reduction for fracture was greater the higher the baseline fracture probability.

Against this background, the aim of the present study was to seek interactions between strontium ranelate-induced effects on fracture risk in the combined populations of the SOTI and TROPOS studies and baseline fracture probability determined by FRAX® as now requested for new phase III studies by the European regulatory body [20]. The hypothesis to be tested was that strontium ranelate reduced the risk of fracture in women irrespective of pre-treatment fracture probability.

Methods

The phase III studies

Details of both phase III studies have been previously described [11, 12]. In brief, both were multicentre randomised double-blind, placebo-controlled trials conducted in 11 European countries and Australia that examined the effects of 2 g of oral strontium ranelate daily or placebo for 3 years. Calcium and vitamin D supplements were given to both groups.

The SOTI study recruited 1,649 postmenopausal women with low bone mineral density and at least one vertebral fracture [11]. Women were eligible for study if they were at least 50 years old, had been postmenopausal for at least 5 years, had had at least one vertebral fracture after minimal trauma confirmed by spinal radiography, and a lumbar spine bone mineral density (BMD) of 0.84 g/cm^2 or less (measured with Hologic instruments). The primary endpoint was the effect at 3 years of strontium ranelate on the risk of vertebral fracture assessed by semiquantitative vertebral morphometry. The relative risk of morphometric vertebral fractures decreased (RR=0.59; 95% CI=0.48 to 0.73) as did the risk of a clinical vertebral fracture (RR=0.62; 95% CI=0.47 to 0.83). Non-vertebral fractures occurred in 234 women over the study (RR=0.90; 95% CI=0.69 to 1.17).

The TROPOS study also recruited postmenopausal women (n=5,091). They were eligible for study if they had a femoral neck BMD<0.60 g/cm² (corresponding to a T score of −2.1 SD using the Third National Health And Nutrition Examination Survey (NHANES III) data and were >74 years of age, or aged between 70 and 74 years but with one additional fracture risk factor for fracture [12]. The primary endpoint was the incidence of non-vertebral fractures. Treatment with strontium ranelate was associated with a 16% risk reduction in all non-vertebral fractures over a 3-year follow-up period compared to the effect of placebo (RR=0.84; 95% CI=0.70 to 0.995). The risk of a major non-vertebral osteoporotic fracture was decreased by 19% (RR=0.81; 95% CI=0.66 to 0.98). The risk of hip fracture in the ITT population was reduced by 15% but this was not of statistical significance. In a high-risk fracture subgroup (women aged≥74 years and with femoral neck BMD T score<−2.4 SD according to NHANES III), treatment was associated with a 36% reduction in risk of hip fracture, an effect that was statistically significant. Yearly, vertebral x-rays showed a risk reduction of new vertebral fracture by 39% over 3 years in the strontium ranelate group—an effect that persisted at 5 years.

Probability estimates

The 10-year probability of a major osteoporotic fracture (clinical spine, forearm, humerus, or hip fracture) and the probability of hip fracture were computed using FRAX® (http://www.shef.ac.uk/FRAX; version 2.0) [21–23]. The primary analysis used baseline 10-year probability of major fracture (clinical spine, forearm humerus or hip fracture); the 10-year probability of hip fracture was used in a sensitivity analysis.

For each probability, calculations were made using information on the clinical risk factors alone and with the addition of femoral neck BMD. For the primary analysis, we used the more complete model that included femoral neck BMD for the calculation of fracture probability of a major osteoporotic fracture, but we additionally examined probabilities computed without the use of BMD.

Country specific FRAX® models (version 2.0) were used where possible (France, Germany, Italy, Spain, Switzerland and the UK). In the absence of a FRAX® model for a particular country, a surrogate country was chosen, based

on the likelihood that it was representative of the index country (Australia, Belgium, Denmark, Greece, Hungary and Poland).

Characterisation of risk factors

Risk factors available for the calculation of fracture probabilities were determined from a data base supplied by Servier. A total of 366 women were excluded from analysis of SOTI and TROPOS because they had not taken medication or had no follow-up data on the relevant fracture outcome, and for consistency we used this 'Full Analysis Set'.

Of the 6374 women, 3176 were given placebo and 3,198 given strontium ranelate. Age was available for all patients (mean=74.8 years, range=50–100 years). Thirty-two patients were older than 90 years. Since the FRAX® algorithms consider probabilities up to the age of 90 years, women over this age were considered to be aged 90 years for the purposes of computing probabilities. Height and weight for the estimation of BMI was not available in 106 women (1.7%). Estimates of femoral neck BMD were available in all but 17 women (0.3%) using Hologic equipment and BMD results were converted to a *T* score using the US normative database from the third National Health and Nutrition Examination Survey III [24]. Women who did not have a BMD test, but had a BMI value recorded, were included in the analysis of probabilities calculated without BMD. Women who did not have a BMI value recorded but had a BMD test result were not included in the analysis of probabilities calculated with BMD. Summary statistics of the continuous variables are shown in Table 1.

For the dichotomous risk factors (see Table 1), a history of a previous fracture of any kind was documented in 4,000 patients. There was no missing information. Where patients were noted to have a morphometric vertebral deformity at baseline, this was counted as a prior fracture. Prior vertebral fractures were determined using a semiquantitative grading scale [25, 26].

For a parental history of hip fracture, incomplete information was available from the dataset since the question asked for was a parental history of osteoporotic fracture. In all, 6,360 women had information on a parental history of osteoporotic fracture. A positive history was noted in 1,497 women (24%). In these 1,497 women, the assumed distribution of a parental history of hip fracture was determined by simulation. The simulations were based on examining the conditional probability of the association of a risk factor with age, BMI and the 0/1 variables by logistic regression. The associations were taken from the relationship between all clinical risk factors including BMI and femoral neck BMD in the cohorts with relevant information used to develop the FRAX® model [21]. Further details of the approach are given elsewhere [27]. In sensitivity analysis, simulated data were excluded and a 'yes' response was assigned to all patients with a parental history of osteoporotic fracture.

There were 549 patients (9%) documented as current smokers. There was no missing information.

For the current or past use of oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids), a response was completed in all but 562 patients. In these patients, ancillary records on concomitant medication were examined. The data base was subsequently amended giving a no response in 6,280 and a yes response in 94 women.

There were 66 patients (1%) documented as having rheumatoid arthritis. There was no missing information.

There were 1,717 women categorised with a secondary cause of osteoporosis, 4,657 with no secondary cause and missing information in seven women. The case records were examined in these seven women who were all previously given bisphosphonates. These women were categorised as not having secondary osteoporosis.

For an alcohol intake three or more units daily, a yes response was noted in 61 patients (1%).

Table 1 Characteristics of patients at entry to the TROPOS/SOTI trials and prevalence (%) of dichotomous risk factors

	n	Mean/prevalence	SD	Range
Age (years)	6,374	74.78	6.33	50–100
BMI (kg/m^2)	6,268	25.64	4.06	14.4–50.6
Femoral neck *T* score (SD)	6,357	−3.05	0.66	−6.2–+0.7
Previous fracture	6,374	63		
Parental history of hip fracture	6,373	6		
Current smoking	6,374	9		
Glucocorticoids	6,374	1		
Rheumatoid arthritis	6,374	1		
Other secondary osteoporosis	6,374	27		
Alcohol, 3+units per day	6,374	1		

Outcome variables

For the purposes of the present study, the primary outcomes of interest were:

Osteoporotic clinical fractures [28] (includes clinical vertebral fractures and fractures of wrist, pelvic–sacrum, ribs–sternum, clavicle, humerus, proximal femur; excludes fractures of the hands, feet, skull and facial bones) and vertebral fractures assessed by semiquantitative morphometry

We additionally examined the effect of strontium ranelate on:

Hip fracture
Any non vertebral fracture
Osteoporotic non vertebral fracture (as defined in the study protocols, i.e., excluding clinical vertebral fracture)
Clinical vertebral fractures.
All clinical fractures (i.e., includes clinical vertebral fractures)

Vertebral radiographs were obtained annually. A new vertebral fracture was defined by a change in the score of a vertebra from grade 0 at base line to a subsequent grade of 1 or more. A vertebral fracture was considered to be a clinical fracture if there was associated acute back pain, a decrease in body height of at least 1 cm, or both.

Non-vertebral fractures were confirmed by a radiologic evaluation or from a hospital report. Osteoporotic fracture were categorised as those occurring at sites susceptible to osteoporosis as previously described [28].

When only one fracture per category per patient (the first one) was counted, there were 739 fractures of which 658 were osteoporotic including 169 hip fractures. When clinical vertebral fracture were included among the fractures there were 1,119 first fractures of any kind of which 1,041 were designated as osteoporotic fracture.

When radiographs taken after the end of follow-up were excluded, new vertebral fractures were documented in 834 women. There were 742 clinical vertebral fractures in 500 patients.

Analytic approach

This was an intention to treat analysis. The analysis of the effect of treatment was undertaken combining the data from the two studies.

A Poisson model was used to study the relationship between age, the time since baseline, treatment, calculated 10-year probability on the one hand, and on the other hand, the risk of fracture [29]. Person years were used (in contrast to a linear logistic model). The hazard function was assumed to be $\exp(\beta_0 + \beta_1 \cdot \text{current time from baseline} + \beta_2 \cdot \text{current age} + \beta_3 \cdot 10 \text{ year probability} + \beta_4 \cdot \text{treatment} + \beta_5 \cdot 10-\text{year probability} \cdot \text{treatment})$. The beta coefficients reflect the importance of the variables as in a logistic model, and $\beta_x=0$ denotes that the corresponding variable does not contribute to fracture risk. Hazard ratios (HR) for treatment effect and 95% confidence intervals (95% CI) were computed as a continuous variable. For presentation, hazard ratios were shown at the 10th, 25th, 50th, 75th, and 90th percentile of fracture probability.

Results

Distribution of fracture probability

The 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture) and a hip fracture was calculated with and without BMD for the country chosen. Mean probabilities are shown in Table 2.

As would be expected, the inclusion of simulated data decreased marginally the computed probabilities since,

Table 2 A 10-year probability of fracture according to FRAX® (FRAX® version 2.0) estimated at baseline in the SOTI and TROPOS study combined

Probability model	*n*	Mean	SD	Range
Excluding simulated data[a]				
Osteoporotic fracture without BMD	6,254	22.22	11.46	2.3–85.2
Hip fracture without BMD	6,254	11.71	9.89	0.1–81.7
Osteoporotic fracture with BMD	6,238	27.19	14.00	2.5–90.8
Hip fracture with BMD	6,238	15.79	13.40	0.1–90.3
Including simulated data				
Osteoporotic fracture without BMD	6268	20.20	10.22	1.4–85.2
Hip fracture without BMD	6268	9.86	7.91	0.1–81.7
Osteoporotic fracture with BMD	6252	24.34	11.95	2.5–90.8
Hip fracture calculated with BMD	6252	13.01	10.36	0.1–90.3

[a] A yes response for parental history of hip fracture was used for all subjects with a parental history of any osteoporotic fracture

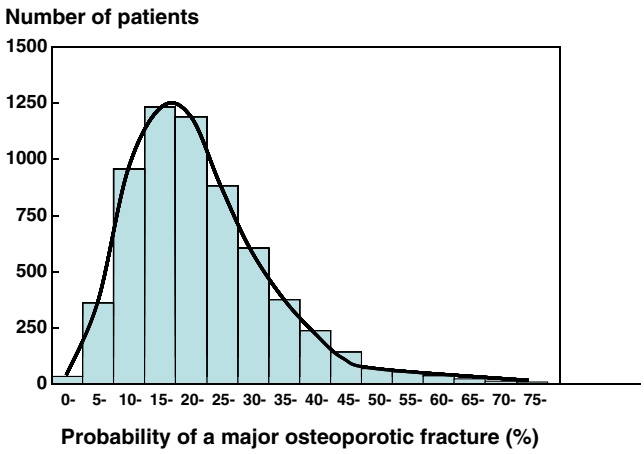

Fig. 1 The distribution of probabilities of a major osteoporotic fracture in the TROPOS/SOTI study population with the inclusion of BMD

when excluded, a yes response was entered into the FRAX® model for a parental history of hip fracture on a larger number of women. Probabilities were marginally higher when BMD was included in the calculation of probability, indicating that mean BMD was lower than that expected for the general population.

The distribution of 10-year probabilities according to probability intervals is shown in Figs. 1 and 2 for a major fracture and for hip fracture. For both variables, the distributions were skewed to the left.

Relation between probabilities and fracture incidence

When placebo-treated patients were divided into quartiles of fracture probability (major fracture) where BMD was included in the calculation of FRAX®, the incidence of morphometric vertebral fracture rose with each quartile of probability from 4.7/100 patient years to 9.4/100 patient years in the fourth quartile of probability. The incidence of non-vertebral osteoporotic fracture in placebo-treated patients was lower than for vertebral fracture, but also rose with each quartile of probability from 3.0/100 patient years in the first quartile to 5.7/100 patient years in the fourth quartile of probability in placebo-treated patients (Table 3). Similarly, there was a progressive rise in clinical osteoporotic fracture (with clinical vertebral fracture).

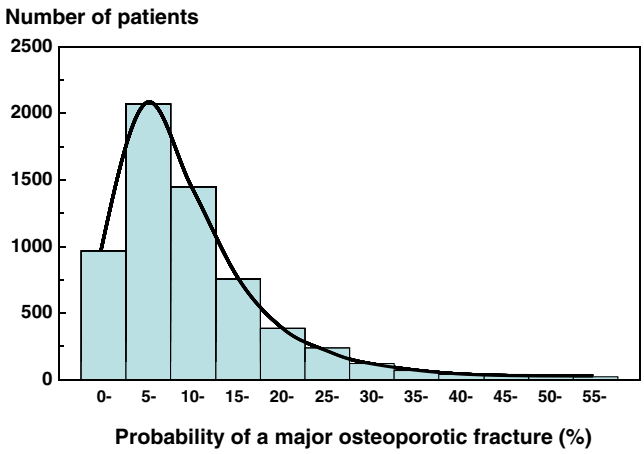

Fig. 2 The distribution of probabilities of hip fracture in the TROPOS/SOTI study population with the inclusion of BMD

Overall effects of treatment

Patients were followed for up to 4.6 years. Strontium ranelate decreased the risk of all osteoporotic clinical fractures by 31%—an effect that was statistically significant (Table 4). The inclusion of all clinical fractures, irrespective of their association with osteoporosis, had little influence on the effect size, and the effect of treatment remained significant. When clinical vertebral fractures were excluded, strontium ranelate was associated with a 13% decrease in all clinical non-vertebral fractures, an effect that was of borderline statistical significance (see Table 4). When only osteoporotic clinical non-vertebral fractures were considered, the effect size was larger (16%) and was statistically significant. There was no significant effect on hip fracture.

Clinical vertebral fractures decreased by 50% and there was a significant decrease in incident morphometric vertebral fractures by 40%.

Interaction between treatment and fracture probability

Table 5 shows the effects of strontium ranelate on clinical osteoporotic fractures according to the 10-year probability

Table 3 The relationship of incident fracture (fractures/100 patient years) in placebo-treated patients by quartiles of fracture probability

	Quartile			
Fracture outcome	I	II	III	IV
Clinical fractures				
All clinical osteoporotic fractures	5.80	6.05	8.75	10.30
All clinical fractures	6.25	6.67	9.33	10.75
Non-vertebral OP fractures	2.97	3.43	5.36	5.72
All non-vertebral fractures	3.38	4.01	5.88	6.24
Hip fracture	0.33	0.62	1.32	1.82
Vertebral fractures				
Morphometric	4.68	5.60	6.56	9.41
Clinical vertebral fracture	3.06	2.87	3.71	4.80

For all fracture outcomes, higher fracture risks were observed with higher baseline probability ($p<0.001$)

Table 4 Overall effects of strontium ranelate compared to placebo according to the fracture outcome selected

Fracture outcome	HR	95% CI	*p*
Clinical fractures			
All	0.71	0.63–0.80	<0.001
Osteoporotic	0.69	0.61–0.78	<0.001
Non-vertebral fractures			
All	0.87	0.75–1.00	=0.053
Osteoporotic	0.84	0.72–0.98	=0.028
Hip	0.95	0.70–1.28	>0.30
Vertebral fractures			
Clinical	0.50	0.41–0.60	<0.001
Morphometric	0.60	0.52–0.69	<0.001

of a major osteoporotic fracture. Note that the outcome includes clinical vertebral fracture. Strontium ranelate was associated with a significant reduction in clinical osteoporotic fractures across the full range of baseline probabilities. Hazard ratios tended to increase with increasing fracture probability, but the interaction between treatment effect and fracture probability was not significant with or without the inclusion of BMD in the FRAX® model.

Similar conclusions were derived when considering all clinical fractures, non-vertebral clinical fractures, non-vertebral osteoporotic fracture or when using the FRAX model for hip fracture probability (data not shown) in that there was no significant interaction between fracture probability and hazard ratio.

In the case of hip fracture, hazard ratios tended to decrease with increasing fracture probability when BMD was included (Table 6). By contrast, hazard ratios were constant with increasing fracture probability when BMD was excluded from the FRAX® model (data not shown). In neither instance was the effect significant or the interaction between treatment effect and fracture probability significant.

In the case of morphometric vertebral fracture, significant efficacy was observed over the entire distribution of fracture probabilities. As noted for clinical fracture outcomes, hazard ratios tended to increase with increasing fracture probability (Fig. 3). The effect was not marked and the interaction between treatment effect on vertebral fracture and fracture probability was not significant with or without the inclusion of BMD in the FRAX® model (p=0.1 and 0.2, respectively). In the case of clinical vertebral fracture, the hazard ratio remained constant over the entire range of probabilities with no significant interaction (p>0.30) when BMD was included in or excluded from the FRAX model (see Table 6).

Hip fracture probabilities

Hip fracture probabilities estimated by FRAX® were on average threefold lower than those for a major fracture (see Table 2) and as in the case of a major osteoporotic fracture, also showed a skewed distribution (see Fig. 2)

The use of hip fracture probability as a risk variable showed that whereas the efficacy of strontium ranelate on all fracture outcomes appeared to decrease with increasing probability, there was, however, no significant interaction between treatment efficacy and fracture probability. The effect was similar when BMD was excluded when calculating the probability. These results mirrored those seen with the use of a major osteoporotic fracture as the risk variable.

Discussion

The present study, although it could not avoid post hoc status, aimed to avoid subgroup analysis and additionally combined data from the two phase III studies. It is relevant that there were no differences between the two studies in the effect on BMD, markers of bone turnover [30] or on the risk of new vertebral fractures, findings that support the pooling of the two studies.

The present study showed a marked effect of strontium ranelate on all clinical osteoporotic fractures with a relative risk reduction (RRR) of 31%. It should be noted that the outcome variable of clinical fractures by definition included

Table 5 Hazard ratio between treatments (strontium ranelate versus placebo) for all clinical osteoporotic fractures at different values of 10-year probability (%) of a major osteoporotic fracture calculated with and without BMD

	Probability calculated without BMD			Probability calculated with BMD		
Percentile	10-year probability (%)	HR	95% CI	10-year probability (%)	HR	95% CI
10th	9.0	0.64	0.59–0.77	11.5	0.62	0.51–0.74
25th	12.6	0.66	0.56–0.77	16.0	0.64	0.54–0.75
50th	18.3	0.68	0.60–0.77	22.2	0.66	0.58–0.76
75th	26.0	0.71	0.62–0.81	30.2	0.70	0.61–0.79
90th	33.5	0.74	0.62–0.89	39.8	0.74	0.63–0.88

Table 6 Hazard ratio between treatments (strontium ranelate versus placebo) for hip fracture and for clinical vertebral fracture at different percentiles of 10-year probability (%) of a major osteoporotic fracture calculated with BMD

	Hip fracture			Clinical vertebral fracture		
Percentile	10-year probability (%)	HR	95% CI	10-year probability (%)	HR	95% CI
10th	11.5	1.03	0.63–1.69	11.5	0.49	0.39–0.63
25th	16.0	1.01	0.66–1.54	16.0	0.49	0.40–0.60
50th	22.2	0.98	0.70–1.38	22.2	0.48	0.39–0.59
75th	30.2	0.95	0.70–1.28	30.2	0.48	0.36–0.63
90th	39.8	0.90	0.62–1.31	39.8	0.49	0.39–0.63

clinical vertebral fractures. When these were dropped from the outcome (i.e., non-vertebral fracture), treatment was associated with a significant reduction in fracture risk though hazard ratios were somewhat lower (RRR=16%). The exclusion of clinical vertebral fractures may be of relevance for regulatory purposes, but their exclusion is not clinically intuitive in that they contribute to morbidity, some mortality and to costs in much the same way as do other clinical fractures [28, 31]. The effects of strontium ranelate on morphometric vertebral fractures were consistent with previous estimates and showed a 40% decrease in risk.

The primary aims of this analysis were to explore the effects of strontium ranelate on clinical fractures and on morphometric vertebral fractures in relation to baseline fracture probability estimates using FRAX®. With regard to all clinical osteoporotic fractures, a specific aim was to seek possible treatment interactions. The present analysis showed no evidence of a significant interaction of fracture probability with efficacy. The finding was similar with the addition or absence of BMD in the FRAX® model, the inclusion or exclusion of simulated data or the fracture probability used (hip fracture or major osteoporotic fracture). These data suggest, therefore, that the effectiveness of strontium ranelate for clinical fracture and morphometric fracture is comparable over the whole range of FRAX® probabilities. The findings are consistent with previous analyses of strontium ranelate that showed no significant interaction between treatment and baseline BMD and no difference in efficacy in women with or without other clinical risk factors for fracture or high and low bone turnover [32]. We chose to use the probability of a major osteoporotic fracture as the index of fracture risk rather than the 10-year probability of hip fracture, since the former more closely related to the outcome variable. In the event, a sensitivity analysis using hip fracture probability gave more or less identical results.

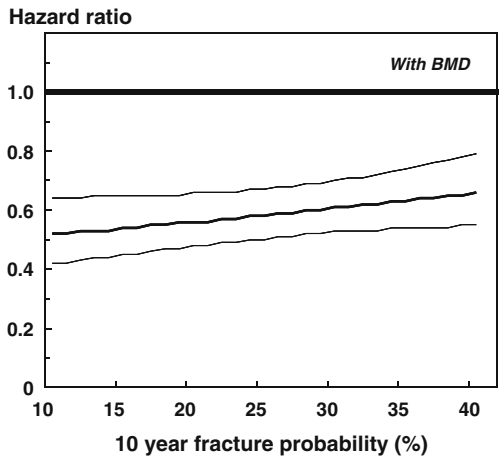

Fig. 3 Probability of major fracture (computed with BMD included) and the effects of strontium ranelate on morphometric vertebral fractures (HR+95% confidence intervals). The interaction term between efficacy and fracture probability was not significant (p=0.1)

The findings from the present study are similar to those recently described for raloxifene [33] but are in contrast with retrospective assessments of two other phase III studies. The first was a 3-year prospective, randomised, placebo-controlled trial of oral clodronate [34]. Women aged 75 years or more living in the general community, identified from general practice registers, were given 800-mg oral clodronate or matching placebo daily over 3 years [18]. Baseline risk factors, including age, BMI, prior fracture, glucocorticoid use, rheumatoid arthritis, smoking and maternal history of hip fracture, were used to compute the 10-year probability of a major osteoporotic fracture. Femoral neck BMD was also measured at entry. The purpose of this analysis, as was the case for the present study, was to seek interactions between fracture probability and treatment efficacy examined by Poisson regression. A more marked trend for a greater fracture reduction at higher fracture probabilities was observed, with or without the use of BMD. The interaction was statistically significant when BMD was excluded from the probability calculation [34]. Efficacy was evident at fracture probabilities that exceeded 20%. These data are very similar to the results of a second analysis that showed a significant effect of bazedoxifene on clinical fractures with fracture probabilities that exceeded 17% [19].

A possible explanation for the absence of relationship between the anti-fracture efficacy of strontium ranelate and the probability of fractures might be that risk factors competed in their interaction with efficacy. For example, if advancing age were associated with greater efficacy whereas low BMD were associated with decreased efficacy, these effects would mask any overall interaction between effectiveness and fracture probability. However, analysis of the efficacy of strontium ranelate by the components of FRAX® suggests that such competing interactions do not explain the absence of interaction between treatment and baseline fracture risk (data not shown). The patients included in the trials of strontium ranelate had high pre hoc fracture risks. It is possible, therefore that any attenuation of efficacy with low fracture probabilities might be seen in patients at much lower risk than those recruited to SOTI or TROPOS. The mean 10-year probability of a major fracture computed with BMD in the FRAX model was 24% in the present study and 21% in the study of raloxifene [33] but only 10.9% in patients studied with bazedoxifene [19]. This observation is consistent with the hypothesis. However, in women participating in the clodronate study the mean 10-year probability was 18%—a value much closer to that of the present study. It will be important to assess further phase III studies in order to shed light on the disparate findings.

A further finding of the present study is that FRAX® results were a significant predictor of fracture outcomes. This may not seem surprising given that FRAX® has been extensively validated [35], but the validation has been largely, though not exclusively [18, 19] confined to population-based cohorts rather than to high-risk populations.

The absolute risk of fracture depends upon age and life expectancy as well as the current relative risk. The IOF and the WHO recommend that risk of fracture should be expressed as a short-term absolute risk, i.e., probability over a 10-year interval as fulfilled by FRAX®. Against this background, the CHMP revised its guidelines on the evaluation of medicinal products in the treatment of primary osteoporosis [20] which came into effect at the end of May 2007. A major departure from previous guidance is that there is no longer any distinction between prevention and treatment, but an emphasis on the study of patients at high risk from fracture. The preferred metric for expressing risk is the 10-year probability of fracture, in line with the recommendations of the WHO. Suggested probabilities as inclusion criteria are given as 15–20% for spine fracture, 5–7.5% for hip fracture and 10–15% for major non-vertebral fractures. These are intended to approximate the fracture risks in previous phase III studies. In the present study, the average probabilities far exceeded these recommendations. For example, the average 10-year probability of hip fracture with BMD included, was 13.0% (see Table 3), probabilities that exceeded the 5–7.5% figure of the CHMP. It is notable that the distribution of probabilities is skewed, but approximately 85% of the population had FRAX® hip fracture probabilities that exceeded 5%. Thus the findings of the present analysis indicate that the patients recruited to the SOTI/TROPOS studies are of comparable or higher risk than that proposed by the CHMP. Moreover, the efficacy of strontium ranelate on fracture risk is demonstrated over the entire range of FRAX® probabilities.

We conclude that treatment with strontium ranelate was associated with a significant 31% decrease in all clinical osteoporotic fractures (vertebral fractures included) and a 12significant 40% decrease in morphometric vertebral fractures compared to treatment with placebo. Hazard ratios for the effect of strontium ranelate on the fracture outcome did not change significantly with increasing baseline fracture probability and the efficacy of strontium ranelate on fracture risk is thus demonstrated over the entire range of FRAX® probabilities.

Acknowledgements This work was an independent study funded by a grant from Servier. We thank Dr Patricia Chatelain for her help with the preparation and transfer of the data.

Conflicts of interest None.

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