

# Positive impact of compliance to strontium ranelate on the risk of nonvertebral osteoporotic fractures

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## Abstract

**Summary** Adherence is now one of the major issues in the management of osteoporosis. This paper relates the relationship existing between adherence to strontium ranelate and the risk of subsequent nonvertebral fracture among postmenopausal women with osteoporosis.

**Introduction** The aim of this study is to investigate compliance to strontium ranelate (SR) therapy and the impact of compliance on the risk of nonvertebral fractures among women with osteoporosis.

**Methods** This study was a post-hoc analysis of pooled data from two international, phase III, randomized, placebo-controlled, double-blind studies (the Spinal Osteoporosis Therapeutic Intervention and Treatment Of Peripheral Osteoporosis). A nested case-control study was performed in the strontium ranelate-treated population. Compliance was quantified using the medication possession ratio (MPR).

**Results** Two hundred eighty-five nonvertebral fracture cases (hip fx  $n=70$ ; major nonvertebral fx  $n=213$ ) were identified and matched to 1,425 controls. The mean MPR was 86.8% for controls and 82.6% for cases ( $p<0.001$ ). Women who were compliant to SR had a 38% reduction in all nonvertebral fractures compared with those who were not (OR=0.62; 95%CI[0.47–0.81;  $p<0.001$ ). Considering hip fractures only, the risk was reduced by 50% for compliant patients compared to noncompliant patients (OR=0.50; 95%CI[0.28–0.88];  $p<0.05$ ).

**Conclusion** Our analyses emphasize the importance of good compliance to treatment in order to reduce the risk

of osteoporotic fractures. In particular, there was a greater reduction in the risk of nonvertebral and hip fractures with increase compliance.

**Keywords** Compliance · Hip fracture · Nonvertebral fracture · Strontium ranelate

## Introduction

Osteoporosis is an increasingly important health problem, which leads to a substantial increase in the risk of fractures and concomitant morbidity [1]. This increased propensity to fracture result from an increase in bone fragility due to low bone mass and deterioration of bone quality that occur during aging and after menopause. Osteoporotic fractures are one of the most common causes of disability [2]. Besides the negative impact on the quality of life of patients, such fractures account for a significant and increasing fraction of overall health care expenditures [3, 4]. With the worldwide trend towards aging populations, the incidence of fractures is expected to increase in the future, and treatment is essential for the early prevention of fractures to reduce their considerable burden on patients and health services.

Strontium ranelate is an orally active agent with an original mechanism of action. Experimental studies showed that strontium ranelate, unlike existing therapies, may dissociate bone formation and bone resorption by allowing continued production of bone while decreasing bone resorption [5–7]. Two large phase III trials, the Spinal Osteoporosis Therapeutic Intervention (SOTI) [8] and Treatment of Peripheral Osteoporosis (TROPOS) [9] studies have shown its efficacy at preventing vertebral and nonvertebral fractures, respectively. In a subset of high-risk patients, strontium ranelate was also shown to prevent hip fractures [9].

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However, the success of any chosen therapy depends upon both its effectiveness and also the patient's willingness to adhere to the therapeutic regimen. As is the case with many chronic diseases, the problem of adherence to therapy has emerged as a major challenge to the successful treatment of osteoporosis. Although long-term adherence to treatment is needed for optimal therapeutic benefit for patients with osteoporosis, recent studies have indicated that adherence to antiosteoporotic drug therapy is suboptimal, with more than half of new patients receiving treatment stopping therapy within the first year [10–13]. Poor adherence to treatment regimens is a complex problem, particularly with chronic illness, and is significantly undermining the benefits of medical care. Low adherence can have detrimental effects on medical research trials, reducing the value and the usefulness of studies. According to recent published data, poor compliance with dosing recommendations and premature discontinuation of treatment have been shown to lead to inadequate reduction of biochemical markers of bone turnover [14], insufficient increases in BMD [12, 15, 16], and increased fracture risk [10, 11, 13, 16–19]. Moreover, poor adherence to treatment also has a major impact on healthcare systems and resources. Therefore, it seems important, besides the assessment of the efficacy and the efficiency of antiosteoporosis treatment, to also take adherence to treatment and its impact on the outcomes into account.

The aim of this study was to investigate compliance to strontium ranelate after 3 years of treatment among postmenopausal women. We also assessed the impact of poor compliance on the risk of nonvertebral fracture.

## Material and methods

This study is a post-hoc analysis of pooled data from the SOTI [8] and TROPOS trials [9]. These randomized, double-blind, placebo-controlled clinical trials have been presented in detail previously. Briefly, SOTI investigated the antivertebral fracture efficacy in 1,649 white postmenopausal women with osteoporosis and at least one prevalent vertebral fracture, whereas TROPOS assessed the antinonvertebral efficacy among 5,091 white postmenopausal women with osteoporosis with femoral neck BMD  $\leq 0.600$  g/cm<sup>2</sup> and  $\geq 74$  years of age (or 70 years with one additional risk factor of osteoporotic fracture). Before inclusion either in the SOTI or in the TROPOS study, patients were subjected to a run-in study to initiate normalization of their calcium and vitamin D status. [8, 9]. The duration of this run-in study was 2 weeks to 6 months, depending on the severity of calcium and 25-OH vitamin D deficiency. In both SOTI and TROPOS studies, patients were randomly assigned to receive 2 g/day of strontium ranelate or placebo for 5 years. Subjects were instructed to take the study drug

once daily at bedtime or twice daily. Around 90% of the patients chose the once-daily regimen. Calcium and vitamin D was also prescribed throughout the study.

Results were analyzed on an intention-to-treat (ITT) basis. The ITT was defined as randomized patients having taken at least one sachet of treatment and with at least one postbaseline assessment of nonvertebral fracture occurrence.

Nonvertebral fractures were defined as fractures occurring at a nonvertebral site, with fractures of the coccyx, skull, jaw, face, ankle, and phalanx (fingers and toes) not considered as related to osteoporosis and not taken into account in the analysis. Major nonvertebral fractures were defined as fractures located at the hip, wrist, pelvis and sacrum, ribs/sternum, clavicle, or humerus, corresponding to the most relevant sites for osteoporosis-related fractures, in terms of disability and pain duration. Nonvertebral, major osteoporosis-related and hip fractures were individually analyzed.

In order to investigate the impact of compliance on the risk of nonvertebral fracture, a case-control study was performed both in the strontium ranelate and in the placebo-treated population. For each patient who incurred a nonvertebral fracture during the 3-year follow-up, five matched patients were randomly selected among treated patients who did not incur nonvertebral fracture during the 3-year follow-up in order to constitute the control group. The two matched criteria were age group (<60, 60–69, 70–79, >79) and the duration of follow-up in order that patients (cases or controls) were followed and exposed to strontium ranelate treatment or to placebo during the same duration. In other words, the sachets count was stopped at the time of the first nonvertebral fracture (censure date) for the cases and at a same length of follow-up for the controls.

Compliance to strontium ranelate or to placebo was quantified using the medication possession ratio (MPR) by dividing the cumulative number of sachets taken between the first prescription and the censure date, by the theoretical number of sachets (i.e., the number of sachets that would be taken between the first prescription and the censure date). Patients who had a MPR  $\geq 80\%$  were considered as “compliant.” Other thresholds were used in order to define compliance.

However, we did not have accurate data about the true consumption of sachets at the censure date. As for both studies (TROPOS and SOTI), data were collected every 6 months. Consequently, we computed the MPR for the months leading up to the censure date (i.e., time of incurrance of the first fracture for the cases or same duration for follow-up for the controls) and we adjusted the MPR value by a regression coefficient assessed in the control group. In order to compute this coefficient, the mean duration of follow-up (days) and the mean MPR for

each visit (0, 6, 12, 18, 36 months) were assessed and reported on a graph where a fitting line was plotted. The MPR decrease per day was 4.2 m.

On this basis, the MPR at the censor date was computed as the following example:

Number of days between the inclusion and the last visit before the censor date (a)	Number of days between the inclusion and the censor date (b)	(b-a) *0.0042	MPR at the last visit before the censor date	Adjusted MPR at the censor date
200	250	50*0.0042 =0.21	95	95-0.21 =94.79

For patients who incurred a nonvertebral fracture during the first 6 months of the follow-up, it was not possible to count the number of sachets taken between the inclusion and the date preceding the occurrence of the fracture. These patients as well as the matched controls were excluded from the analysis (For the strontium ranelate-treated population: cases  $n=45$ ; controls  $n=225$ . For the placebo population: cases  $n=57$ ; controls  $n=285$ ).

#### Statistical analysis

The comparisons of the proportion of compliant patients between the cases and controls groups as well as the comparison of the nonvertebral fracture rate between compliant and noncompliant patients were performed with the use of the chi-square test. The comparison of the mean MPR at the censor date between the cases and controls groups, as well as between both strontium ranelate formulation use (once daily or twice daily) was made using the unpaired student's  $t$  test.

We performed analyses regarding the potential differences between the "highly compliant population" (i.e., patients with a  $\text{MPR} \geq 80\%$ ) and the "noncompliant population" (i.e., patients with a  $\text{MPR} \leq 80\%$ ) in the overall strontium ranelate-treated population included in the case-control study for the following variables: age, bone mineral density at baseline, bone mineral density changes between the inclusion and the visit preceding the censor date, treatment regimen (once or twice daily), behavioral differences at baseline (walking, frequency of walking, smoking, need help for daily tasks and/or for personal care). The compliant group was compared to the noncompliant group by chi-square test for qualitative variables and by unpaired student's  $t$  test for quantitative variables.

Two logistic regression models were used in order to estimate the relationship between compliance to strontium ranelate and fracture risk. In the first one, the MPR was included as a continuous variable while in the second, we used

a dichotomous variable for compliance ( $\text{MPR} \geq 80\%$ : yes/no). In both models, the following independent variables were considered: the age, body mass index at baseline, the presence of previous vertebral/nonvertebral fracture (yes/no), and the BMD value at baseline.

An additional analysis in which noncompliance was redefined using different thresholds was also performed. In this analysis, we assessed the reduction in risk of nonvertebral fracture for compliant patients ( $\text{MPR} \geq 80\%$ ) compared to noncompliant patients ( $\text{MPR} \geq 20\%$ ,  $\leq 30\%$ ,  $\leq 40\%$ ,  $\leq 50\%$ ,  $\leq 60\%$ ,  $\leq 70\%$ ), using logistic regression models. Once again, these analyses were adjusted for the following variables: age, BMI at baseline, the presence of previous vertebral/nonvertebral fracture, and the BMD value at baseline.

All results were considered to be statistically significant if the corresponding  $p$  value was below 0.05.

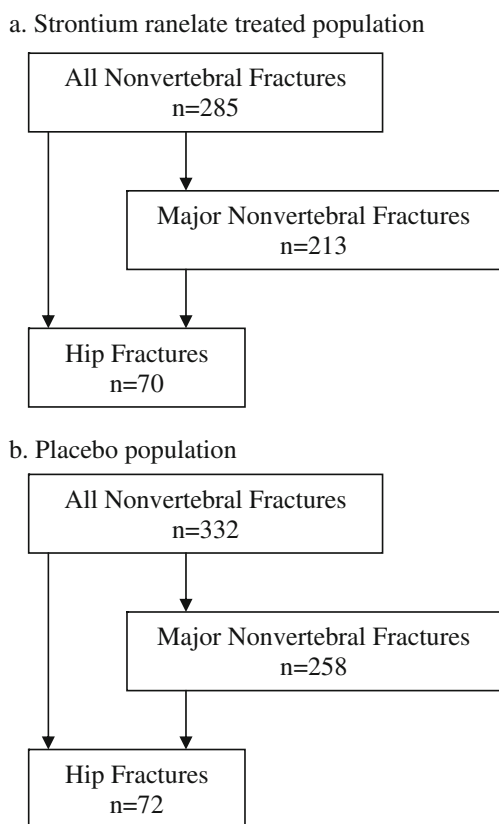
## Results

After 3 years of strontium ranelate treatment, 285 nonvertebral fractures cases (hip fx  $n=70$ ; major nonvertebral fx  $n=213$ ) were identified and matched to 1,425 controls (Fig. 1). In the placebo population, 332 nonvertebral fractures cases (hip fx  $n=72$ ; major nonvertebral fx  $n=258$ ) were matched to 1,660 controls. Table 1 summarizes the baseline characteristics of the population included in the case-control study, both in the strontium ranelate-treated population and in the placebo population. The mean duration of follow-up (i.e., the number of days between the inclusion and the censor date) was 744.5 days and 750.5 days (as well for cases as controls since they were censored at the same time), in the strontium ranelate-treated population and in the placebo population, respectively.

In the strontium ranelate-treated population, the mean MPR was 86.8% for controls and 82.6% for cases ( $p < 0.001$ ). In the placebo population, no statistically significant difference for the mean MPR was observed between the cases and the controls (86.7% vs 87%,  $p \geq 0.05$ ). Overall, 74.8% and 76.9% of patients had a  $\text{MPR} \geq 80\%$  in the strontium ranelate-treated population and in the placebo population, respectively. The mean MPR was 87.32% and 89.23% for the once daily strontium ranelate formulation and for the twice daily strontium ranelate formulation, respectively ( $p \geq 0.05$ ).

Figure 2 shows the distribution of patients according to different levels of compliance for cases and controls in the strontium ranelate treated population and in the placebo population.

In the strontium ranelate-treated population, the proportion of compliant patients was significantly higher among patients exempt from nonvertebral fracture compared to patients



**Fig. 1** Study population. **a** Strontium ranelate-treated population. **b** Placebo population

sustaining a nonvertebral fracture during the 3-year follow-up (76.4% vs 66.7%;  $p < 0.001$ ). In the placebo population, there was no statistically significant difference (76.8% vs 76.9%,  $p \geq 0.05$ ).

Table 2 summarizes characteristics of the highly compliant patients (i.e.,  $\text{MPR} \geq 80\%$ ) and the noncompliant patients in the overall strontium ranelate-treated population included in the case-control study (i.e.,  $n = 1710$  patients [ $n = 285$  cases;  $n = 1,425$  controls]). Compliant patients had a significantly larger BMD increase at the lumbar spine, femoral neck, and total proximal femur than noncompliant patients ( $\leq 0.001$ ). The proportion of patients reporting to walk everyday at baseline was higher among compliant patients compared with those who were not. The proportion of patients declaring to need help for daily tasks and/or personal care was higher among noncompliant patients compared to compliant patients. These results were consistent when the analyses were limited to the cases group ( $n = 285$  cases) or to the controls group ( $n = 1,425$  controls) in the strontium ranelate-treated population (data not shown).

#### Impact of compliance to strontium ranelate on the risk of nonvertebral fracture

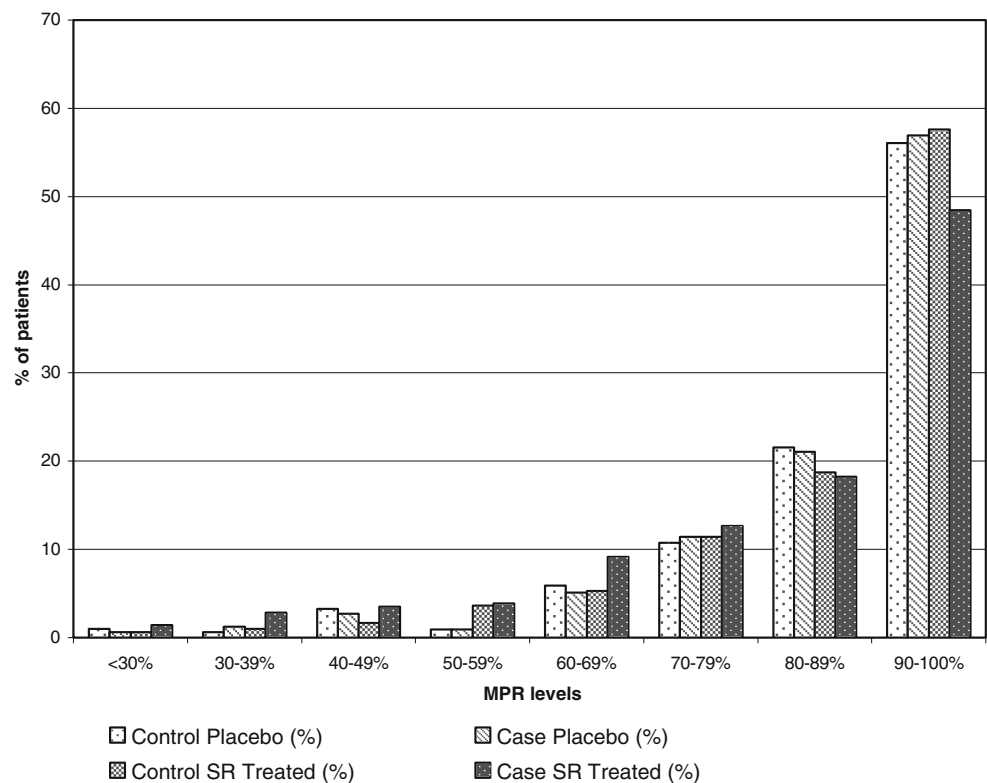
Poor compliance was significantly associated with a greater likelihood of nonvertebral fracture. The logistic regression model estimated that for each increase in the MPR by 1%, the adjusted risk of nonvertebral fracture decreased by 1.5% ( $\text{OR} = 0.985$ ;  $95\% \text{CI} [0.978 - 0.994]$ ;  $p < 0.001$ ; Table 3). The total hip BMD at baseline and the presence of previous osteoporotic fracture (vertebral and/or nonvertebral) were statistically associated with the likelihood of incurring a nonvertebral fracture ( $p < 0.05$ ). Women who were compliant to strontium ranelate had a 38% reduction in all nonvertebral fractures compared with those who were not ( $\text{OR} = 0.62$ ;  $95\% \text{CI} [0.47 - 0.81]$ ;  $p < 0.001$ ; Fig. 3). Compliance to strontium

**Table 1** Baseline characteristics of strontium ranelate-treated population and the placebo population included in the case-control study

	Cases	Controls
<b>Strontium ranelate-treated population</b>		
Age (years)	75.15±7.27	74.74±6.80
Body mass index (kg/m <sup>2</sup> )	25.08±3.89	26.00±4.16
Number of previous vertebral/nonvertebral fractures	2.27±2.75	1.47±2.16
BMD (g/cm <sup>2</sup> )		
Lumbar spine	0.76±0.15	0.79±0.15
Total hip	0.63±0.10	0.68±0.10
Femoral neck	0.54±0.07	0.57±0.07
<b>Placebo population</b>		
Age (years)	75.35±6.73	74.95±6.64
Body mass index (kg/m <sup>2</sup> )	25.57±4.02	25.66±4.02
Number of previous vertebral/nonvertebral fractures	2.23±2.88	1.74±2.36
BMD (g/cm <sup>2</sup> )		
Lumbar spine	0.76±0.14	0.78±0.15
Total hip	0.64±0.10	0.67±0.10
Femoral neck	0.55±0.08	0.57±0.08

Values are the mean ± SD  
BMD bone mineral density

**Fig. 2** Distribution of patients according to different levels of compliance, for cases and controls, in the strontium ranelate-treated population and in the placebo population



ranelate was associated with a 33% reduction in risk of major nonvertebral fractures (OR=0.67; 95%CI[0.49–0.93];  $p<0.05$ ). When the analysis was limited to hip fractures, the risk was reduced by 50% for compliant patients compared to noncompliant patients (OR=0.50; 95%CI[0.28–0.88];  $p<0.05$ ; Fig. 3).

Table 4 reports the reduction in risk of nonvertebral fracture for compliant patients (MPR $\geq$ 80%) compared to noncompliant patients, redefined using different thresholds. There was a trend for a greater reduction risk of fracture for compliant patients compared to decreasing noncompliance levels.

## Discussion

This post-hoc analysis of data from the SOTI and TROPOS studies show that good compliance to strontium ranelate significantly reduced the risk of osteoporosis-related nonvertebral and hip fractures, regardless of other known and important risk factors such as age and history of fractures, over a 3-year study period, in postmenopausal women. Compared with patients who were compliant with therapy, those who did not achieve an MPR of 80% had significantly more nonvertebral fractures. Women who achieved compliance with therapy had a 38% reduction in nonvertebral fractures overall compared with those who were not compliant. This finding is important, given the

significant pain and disability associated with nonvertebral fractures in osteoporotic patients. Moreover, as previously reported [8, 9], high rates of compliance to strontium ranelate were achieved over the 3-year study.

The difference in fracture risk between highly compliant and poorly compliant patients in the present study appeared to be similar than the estimated effect sizes for the principal osteoporosis drugs in recent meta-analyses of randomized, placebo-controlled clinical trials. The relative risk reduction in patients receiving active treatment compared with controls ranged from 37% to 53% [20–23]. Our results are also quite similar to the relative risk reductions for fracture observed in randomized, placebo-controlled bisphosphonates clinical trials where reported rates of compliance were high. [24–29].

Results of previous studies using administrative claims data were not directly comparable to ours because of methodological differences in terms of the population selected, the parameterization of compliance, the duration of follow-up, the analytical techniques used, and differences in populations, practices and health care systems. Moreover, concerns have been expressed about the generalization of results from RCTs, which may underestimate the true rate of nonadherence to OP drugs in the general population.

Despite methodological differences, the magnitude of fracture reduction observed in our study is similar to that demonstrated for several other currently used therapeutic interventions. A 2-year study conducted using healthcare

**Table 2** Characteristics of the compliant and noncompliant patients in the overall strontium ranelate-treated population included in the case-control study ( $n=1,710$ )

	Compliant patients ( $n=1278$ )	Noncompliant patients ( $n=432$ )	<i>p</i> value
Age (years) [mean $\pm$ SD]	74.51 $\pm$ 6.69	75.69 $\pm$ 7.36	<0.05
BMD at baseline (g/cm <sup>2</sup> ) [mean $\pm$ SD]			
Lumbar spine	0.79 $\pm$ 0.15	0.79 $\pm$ 0.15	>0.05
Total hip	0.67 $\pm$ 0.10	0.66 $\pm$ 0.10	<0.01
Femoral neck	0.57 $\pm$ 0.07	0.56 $\pm$ 0.08	<0.01
BMD% changes (g/cm <sup>2</sup> ) [mean $\pm$ SD]			
Lumbar spine	10.55 $\pm$ 9.57	6.18 $\pm$ 9.00	<0.001
Total hip	5.74 $\pm$ 6.66	2.97 $\pm$ 7.43	<0.001
Femoral neck	4.54 $\pm$ 6.25	2.70 $\pm$ 6.68	<0.001
Smoking [%] (yes)	8.92	7.41	>0.05
Treatment regimen			
Once daily [%]	89.33	91.08	>0.05
Walking [%] (yes)	93.9	92.8	>0.05
Without help	10.3	11.7	>0.05
Frequency of walking			
Everyday	70.3	67.1	>0.05
3 to 5 $\times$ per week	16.7	16.2	>0.05
1 to 2 $\times$ per week	13	16.7	>0.05
Need help for daily tasks [%]	22.7	31.7	<0.01
Need help for personal care [%]	3.7	4.8	>0.05
Reasons of noncompliance [%]			
Stop treatment	NA	8.3	
Adverse events	NA	3.7	
Nonmedical reason	NA	4.2	
Major protocol deviation	NA	0.4	

NA not applicable

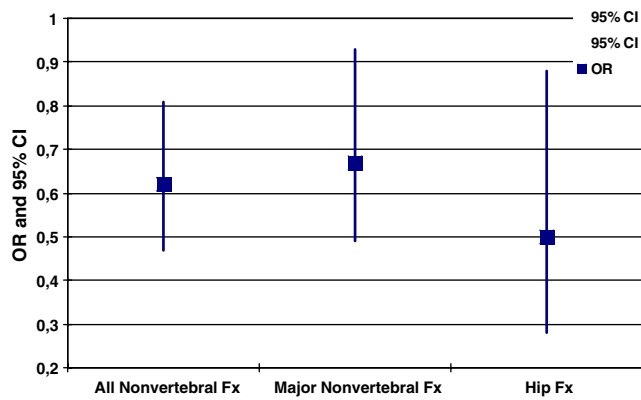
database information on 11,249 women with osteoporosis found that those who took  $\geq 80\%$  of their prescribed medication doses had a 16% lower risk of fracture compared with noncompliant patients [10]. Similar findings were reported from these investigators using database claims from a larger cohort (>38,000) of women with osteoporosis. Low refill compliance, noted in three quarters of participants, was associated with a 17% increase in fracture rates during the follow-up period of 1.7 years [17]. McCombs, using a large medical claims database, demonstrated that persistence

(no interruption in drug purchases for >14 days during a 1-year period) significantly reduced the rate of hip fractures (OR=0.382;  $p<0.01$ ) and vertebral fractures (OR=0.601;  $p<0.05$ ) [11].

Most importantly, Siris et al. estimated the probability of fracture along a gradient of adherence [18]. This retrospective study used two large pharmaceutical databases. The overall fracture rate was 29% lower for women without a refill gap than for those who were not persistent with therapy. Compliant patients had a 21% reduction in fractures overall

**Table 3** Logistic regression analysis: impact of compliance to strontium ranelate (SR) and other factors on the risk of nonvertebral fracture

Factors	Odds ratio	95%CI	<i>p</i> value
Compliance to SR	0.985	0.978–0.994	<0.001
Age (years)	0.997	0.975–1.019	0.76
BMI at baseline	0.969	0.944–1.016	0.27
Presence of previous vertebral/nonvertebral fractures (yes/no)	1.692	1.249–2.292	<0.001
Lumbar spine BMD at baseline	0.603	0.216–1.684	0.33
Femoral neck BMD at baseline	0.127	0.004–3.378	0.22
Total hip BMD at baseline	0.070	0.006–0.836	<0.05



**Fig. 3** Impact of good compliance (MPR $\geq$ 80%) on the risk of nonvertebral, major nonvertebral, and hip fractures, respectively

compared with those who were not compliant. At an MPR from 0% to 50%, the probability of fracture during a period of 24 months remained consistent at about 11% and declined progressively once a threshold value of 50% was achieved. Another recent study found that for each 1% reduction in MPR, the risk of hip fracture increased by 0.4% [13]. Our results are also in line with the results of a nested case-control study reporting an overall fracture risk reduction of 30% [19].

Moreover, all of these studies systematically reported very low rate of compliance in real-life setting, ranging from 26% to 60%. The results of our study show a much higher rate of compliance. We found that 75% of patients were compliant with strontium ranelate therapy over a 3-year of follow-up. Implementing a monitoring protocol in the community where adherence is very low would have a positive impact on compliance with treatment. In fact, in a recent UK study, both nurse monitoring alone and nurse plus bone turnover measurement monitoring improved adherence by 57% [30]. This demonstrates that discussion with a healthcare professional to reinforce the need for long-term therapy may be of equal value for patient

**Table 4** Assessment of risk of nonvertebral fracture for compliant patients compared to noncompliant patients, defined using different levels of MPR

MPR rates	Odds ratio <sup>a</sup>	95%CI	<i>p</i> value
<20% vs $\geq$ 80%	0.26	0.04–1.54	>0.05
<30% vs $\geq$ 80%	0.39	0.12–1.29	>0.05
<40% vs $\geq$ 80%	0.33	0.16–0.69	<0.01
<50% vs $\geq$ 80%	0.37	0.22–0.63	<0.001
<60% vs $\geq$ 80%	0.52	0.34–0.80	<0.01
<70% vs $\geq$ 80%	0.52	0.37–0.72	<0.001
<80% vs $\geq$ 80%	0.62	0.47–0.82	<0.001

<sup>a</sup> Adjusted for age, BMI at baseline, bone mineral density at baseline, and the number of prevalent osteoporotic fractures

compliance as information about response to biochemical markers. A combination strategy integrating more frequent physician contact and monitoring as part of a chronic-disease-management program may be useful to promote adherence.

In order to define “good” compliance, we chose to use a threshold for adequate compliance of 80%, which is consistent with the 75–80% compliance thresholds used in the majority of previous studies evaluating compliance with osteoporosis medication [10, 13, 16–18]. When compliance was redefined using different thresholds, there was a trend for a greater risk of fracture with decreasing compliance levels (data not shown). In studies evaluating the impact of compliance on the risk of fracture, dichotomizing compliance by using a threshold could compromise results because cutoff points are arbitrary and could lead to loss of information. Moreover, patients considered as noncompliant (i.e., MPR $\leq$ 80%) are, by definition, a very heterogeneous group as for their levels of compliance. The effects of modest compliance on fracture rates would be different than those of lowest compliance. In our study, we showed that there was a trend for a greater reduction risk of fracture for compliant patients compared to decreasing noncompliance levels.

This study had a number of limitations that should be noted. Firstly, as mentioned above, compared with clinical practice, compliance to treatment in a clinical trial setting may be enhanced and results in abnormally elevated compliance treatment rates. However, a prospective observational study showed that 12 months after the inclusion, 80% of patients are continuing the therapy with strontium ranelate [31]. Compliance measured on a 5 level scale was “very good” or “good” in 85.8% of patients at 12 months. This study demonstrated the good compliance, persistence, and safety of strontium ranelate in real-life current medical practice. More studies are needed to confirm these findings. Furthermore, a general limitation of adherence studies based on prescription data and administrative claims database is that information on potential clinical confounders such as BMD, calcium and vitamin D deficiency, and history of fractures is not available, unlike to clinical trials. BMD is an important determinant of fracture risk, and BMD testing has been shown to be positively associated with persistence and compliance [32, 33]. In the SOTI and TROPOS studies, as BMD results were not blinded, the knowledge of these results may have had an impact on the compliance. Some studies have suggested that implementing monitoring or giving feedback to patients, such as bone turnover marker or BMD information, as a tool to improve long-term adherence, may result in an improved outcome for patients with postmenopausal osteoporosis [14, 30].

All patients included in our study received calcium and vitamin D during the 3-year follow-up. While several randomized placebo-controlled trials reported positive effects

of calcium and vitamin D supplementation on the risk of hip and all nonvertebral fractures [34–38], some trials in community-dwelling people did not find a significant reduction in fracture risk during calcium and vitamin D supplementation [39–41]. Similarly, studies evaluating vitamin D alone have yielded conflicting results [41–43]. Besides the fact that the exact influence of these supplements on BMD changes and fracture risk is still debated, it should be acknowledged that the intake of these supplements could modify the association between compliance and reduction in fracture risk reported in the present study. It is likely that patients who were compliant to the strontium ranelate treatment were also compliant to both calcium and vitamin D and that compliance to these supplements may play a part in reduction in fracture risk.

Moreover, the relationship observed in our study, as in previous studies, between compliance and fracture risk reduction may also, in part, be explained by the fact that highly adherent patients may engage in more health-oriented behaviors, contributing to a reduction in fracture risk. For example, such women may be more inclined to follow lifestyle recommendations for avoiding fracture, including exercise, correction of eyesight, and organization of the home environment to minimize the risk of falls. An effect such as this was seen in an analysis of the association between adherence to drug therapy and mortality, where good adherence to placebo was associated with positive health outcomes [44]. The authors concluded that adherence to drug therapy may be a surrogate marker for overall healthy behavior. In our study, we observed that a higher proportion of compliant patients reported to walk everyday and to be independent for daily tasks and personal care. Moreover, they had better outcomes concerning BMD changes.

The results should be also interpreted with the knowledge that MPR is an estimate of medication adherence, which do not capture the pattern of medication use. Although MPR only approximates medication-taking behavior, it is currently one of the most widely used measures to approximate drug-taking behavior of patients [45]. The MPR constitutes an improvement over patients' self-reported measures and is not susceptible to common reporting biases. Moreover, pill count is only an indirect measure of medication usage and does not necessarily imply that the drug was taken in the frequency or manner expected. Therefore, compliance levels could have been overestimated. Adequate measurement of compliance is an important challenge. The patient's self-report as well as pill count are usually used, due to their costs and facility. The use of sophisticated techniques such as biologic assays is restricted to research. All these methods have shown their limitations [46–48].

In conclusion, this study confirms the relationship between compliance with osteoporosis treatment and fracture risk. In particular, the results of this study show

that high compliance to strontium ranelate further increases the risk reduction of osteoporosis-related nonvertebral and hip fractures. This finding emphasizes the “good” compliance with strontium ranelate and its importance in obtaining maximal treatment benefit.

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