

Strontium Ranelate Reduces the Risk of Vertebral Fractures in Patients With Osteopenia

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ABSTRACT: Many fractures occur in women with moderate fracture risk caused by osteopenia. Strontium ranelate was studied in 1431 postmenopausal women with osteopenia. Vertebral fracture risk reduction of 41–59% was shown depending on the site and fracture status at baseline. This is the first report of antivertebral fracture efficacy in women with vertebral osteopenia.

Introduction: Women with osteoporosis are at high risk for fracture. However, more than one half of all fractures in the community originate from the larger population at more moderate risk of fracture caused by osteopenia. Despite this, evidence for antifracture efficacy in these persons is limited. The aim of this study was to determine whether strontium ranelate, a new drug that reduces fracture risk in women with osteoporosis, is also effective in women with osteopenia.

Materials and Methods: Data from the Spinal Osteoporosis Therapeutic Intervention study (SOTI; $n = 1649$) and the TRreatment Of Peripheral Osteoporosis (TROPOS; $n = 5091$) were pooled to evaluate the antivertebral fracture efficacy of strontium ranelate in women with lumbar spine (LS) osteopenia with any BMD value at the femoral neck (FN; $N = 1166$) and in 265 women with osteopenia at both sites (intention-to-treat analysis). The women were randomized to strontium ranelate 2 g/d orally or placebo for 3 yr.

Results: No group differences were present in baseline characteristics that may influence fracture outcome independent of therapy. In women with LS osteopenia, treatment reduced the risk of vertebral fracture by 41% (RR = 0.59; 95% CI, 0.43–0.82), by 59% (RR = 0.41; 95% CI, 0.17–0.99) in the 447 patients with no prevalent fractures, and by 38% (RR = 0.62; 95% CI, 0.44–0.88) in the 719 patients with prevalent fractures. In women with osteopenia at both sites, treatment reduced the risk of fracture by 52% (RR = 0.48; 95% CI, 0.24–0.96).

Conclusions: Strontium ranelate safely reduces the risk of vertebral fractures in women with osteopenia with or without a prevalent fracture.

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Key words: osteopenia, vertebral fracture risk reduction, strontium ranelate

INTRODUCTION

THE RISK OF fragility fracture increases as BMD decreases.⁽¹⁾ The 1-yr risk for fracture is higher in the 9.4 million women with osteoporosis than in the 16.8 million women with osteopenia, it is 2.7 times higher for women with osteoporosis and 1.7 times higher for women with os-

teopenia than women with normal BMD. Thus, women with osteoporosis contribute only 18% of all fractures and 26% of the hip fractures in the community,^(2,3) whereas the source of most fractures in the community arises from the larger numbers of women at the more moderate fracture risk caused by osteopenia (T-score between -1 and -2.5 SD).^(4,5)

Despite this, antifracture efficacy of treatments has been studied mainly in women with osteoporosis, in part, because demonstration of antifracture efficacy requires smaller sample sizes in high-risk groups.^(6,7) We examined the antifracture efficacy of strontium ranelate in the subset of women with osteopenia from the 6740 participants of the

Drs Seeman, Spector, and Reginster serve as consultants, advisory board members, clinical trial investigators during the course of the SOTI and TROPOS studies, and speakers for Servier. Drs Devogelaer, Lorenc, Brixen, Balogh, and Stucki served as clinical trials investigators during the course of the SOTI and TROPOS studies.

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two pivotal international, randomized, double-blind, placebo-controlled phase III trials, SOTI and TROPOS.^(8,9) These studies showed that strontium ranelate reduced the risk of vertebral and nonvertebral fractures in women with osteoporosis with or without a prevalent fracture within 12 mo of starting treatment and produced a sustained fracture risk reduction during 3 yr of treatment (41% RR reduction in women with prevalent vertebral fractures from the SOTI trial⁽⁸⁾ and 45% RR reduction in women without prevalent vertebral fractures from the TROPOS trial⁽⁹⁾).

MATERIALS AND METHODS

SOTI assessed the antivertebral fracture efficacy of strontium ranelate in 1649 white postmenopausal women ≥ 50 yr of age and with osteoporosis at the lumbar spine (BMD ≤ 0.840 g/cm²; Hologic) and with at least one prevalent vertebral fracture. TROPOS assessed antinonvertebral fracture efficacy in 5091 white postmenopausal women with osteoporosis at femoral neck (BMD ≤ 0.600 g/cm²; Hologic), corresponding to a T-score < -2.5 according to the centralized normative data and ≥ 74 yr of age, or between 70 and 74 yr of age with one additional fracture risk factor. Data from SOTI and TROPOS were pooled to evaluate the antifracture efficacy of strontium ranelate in women with osteopenia. Because vertebral fracture risk reduction was the endpoint of choice, we considered women with lumbar spine (LS) osteopenia with any BMD value at the femoral neck (FN; $n = 1166$) and women with osteopenia at both sites excluding patients with normal BMD or osteoporosis at FN ($n = 265$) (Fig. 1).

All studies were conducted in accordance with the Declaration of Helsinki and were approved by the local review boards and by Human Research Ethics Committees. Each participant gave written informed consent before enrollment. Before inclusion, patients participated in a run-in study to normalize their calcium and vitamin D status. All women received daily supplements of up to 1000 mg of elemental calcium according to their Ca food intakes (500 or 1000 mg to reach a total daily intake > 1000 mg) and vitamin D according to their serum 25 hydroxyvitamin D levels (800 IU for patients having serum concentrations < 45 nM and 400 IU for all the others). The patients were randomly assigned to 2 g daily of strontium ranelate (two sachets daily of drug powder mixed with water) or placebo for 3 yr.

Lateral thoracic and lumbar radiographs were performed at baseline and annually and in case of suspicion of clinical fracture caused by acute back pain and/or decrease in stature of at least 1 cm. All radiographs were assessed blindly by a central facility (Pr Christian Roux, Paris, France); central readers were aware of the time sequence of each radiograph. The semiquantitative visual assessment of vertebrae T₄–L₄ was performed by the same reader: grade 0 (normal), or grades 1, 2, or 3, a decrease in vertebral height of ~20–25%, ~25–40%, and more than ~40%, respectively.^(9,10) L₅ was graded as 0 (no fracture) or 1 (fracture). A new vertebral fracture was defined as a change from grade 0 at baseline to a higher grade. Vertebral radiographs were mandatory in SOTI (primary study criterion) but not

TABLE 1. ITT POPULATION VERTEBRAL DATA SET ($N = 5082$)
FEMORAL NECK BMD LUMBAR BMD

	Normal	Osteopenia	Osteoporosis
Normal	3	11	12
Osteopenia	133	265	502
Osteoporosis	365	890	2880
Total	501	1166	3394

TROPOS (secondary criterion). In TROPOS, vertebral radiographs were obtained for 3640 patients (71%). In the other cases, they were not performed because of technical (scoliosis) or logistical reasons.

BMD was measured by DXA at baseline and every 6 mo at the lumbar spine (L₂–L₄) and proximal femur. DXA measurement were to be performed on Hologic densitometers (Hologic, Bedford, MA, USA). The same apparatus with the same mode of acquisition were to be used for a specific patient over the entire study period.

All the scans were analyzed centrally. Lumbar, femoral neck, and total hip T-scores were calculated according to the peak bone mass BMD of a reference population described by DO Slosman⁽¹¹⁾ (Geneva, Switzerland). Longitudinal correction factors were used to correct deviations in the measurements of a DXA device throughout time and to check the stability of the device. Furthermore, to reduce between groups variability and to establish uniformity in scan acquisition and analysis between centers, a cross-calibration was performed on each device and analyzed centrally. Therefore, the BMD raw data issued from the center were corrected by calibration and correction factors. Because inclusion was based on the investigator's decision and the center raw data, this explains that some patients were originally considered as osteoporotic at the center and reassessed as osteopenic after correction of the raw data. Because these patients were already included in the study, despite the fact they were osteopenic, they were taken into account in the intention-to-treat (ITT) analysis and described in this paper (Table 1).

The pooled data analyses were performed by ITT in the vertebral full analysis set to assess the vertebral efficacy, defined as all randomized patients receiving at least one dose of strontium ranelate or placebo and in whom a baseline and at least one postbaseline vertebral radiograph was available. The incidence of patients experiencing a new vertebral fracture (product limit estimate of the probability of vertebral fracture) was estimated at each annual radiograph time-point using Kaplan-Meier method. A study-adjusted Cox model was used to compare groups and to estimate the overall treatment effect—RR of strontium ranelate versus placebo and its 95% CI. *p* values were given according to the likelihood ratio test. The type 1 error rate was 5%.

RESULTS

No differences were present in baseline characteristics in treated and control groups that may have influenced fracture outcome (Tables 2 and 3). In the overall group of 1166 women with LS osteopenia (FN BMD at any level), treat-

TABLE 2. ITT POOLED POPULATION

	<i>Patients with lumbar osteopenia (-1 < LS BMD T-score < -2.5) FN BMD T-score at any value (N = 1166)</i>		<i>Patients with osteopenia at both sites -1 ≤ LS and FM BMD T-score < -2.5 No T-score < -2.5 (N = 265)</i>	
	<i>Strontium ranelate (N = 602)</i>	<i>Placebo (N = 564)</i>	<i>Strontium ranelate (N = 136)</i>	<i>Placebo (N = 129)</i>
Age (yr)	74.7 ± 5.7	75.0 ± 5.6	71.6 ± 6.5	71.9 ± 6.1
Time since menopause (yr)	26.2 ± 7.5	26.9 ± 7.6	23.5 ± 8.6	24.4 ± 7.2
Percent patients with at least one prevalent vertebral fracture	39.7	38.5	53.7	48.1
Percent patients with at least one prevalent nonvertebral fracture	36.7	38.6	22.1	28.7
Lumbar spine BMD				
BMD (g/cm ²)	0.887 ± 0.04	0.886 ± 0.04	0.890 ± 0.04	0.891 ± 0.04
T-score	-1.89 ± 0.42	-1.90 ± 0.41	-1.86 ± 0.43	-1.85 ± 0.42
T-score < -2.5 [N (%)]	0	0	0	0
-2.5 ≤ T-score ≤ -1 [N (%)]	602 (100)	564 (100)	136 (100)	129 (100)
T-score > -1 [N (%)]	0	0	0	0
Femoral neck BMD				
BMD (g/cm ²)	0.589 ± 0.07	0.588 ± 0.07	0.670 ± 0.04	0.666 ± 0.04
T-score	-2.80 ± 0.59	-2.81 ± 0.62	-2.07 ± 0.37	-2.11 ± 0.36
T-score < -2.5 [N (%)]	462 (76.7)	430 (76.2)	0	0
-2.5 ≤ T-score ≤ -1 [N (%)]	135 (22.5)	128 (22.7)	136 (100)	129 (100)
T-score > -1 [N (%)]	5 (0.8)	6 (1.1)	0	0

*Values are mean ± SD except as otherwise specified.

TABLE 3. ITT POOLED POPULATION

	<i>Number of patients</i>		<i>Patients with at least one prevalent fracture* [n (%)]</i>	<i>RR and 95% CI</i>	<i>RR reduction (%)</i>	<i>NNT</i>
	<i>Strontium ranelate</i>	<i>Placebo</i>				
Patients with lumbar osteopenia (-1 ≤ lumbar BMD T-score < -2.5) and femoral neck BMD T-score at any value						
With prevalent fracture(s)	N = 376	N = 343	719 (100%)	RR = 0.62; 95% CI [0.44; 0.88] (p = 0.008)	38%	13
Without prevalent fracture	N = 226	N = 221	0	RR = 0.41; 95% CI [0.17; 0.99] (p = 0.039)	59%	25
Patients with skeletal osteopenia LS and FN T-score ≤ -1 and > -2.5/both T-scores > -2.5	N = 136	N = 129	135 (51%)	RR = 0.48; 95% CI [0.24; 0.96], (p = 0.034)	52%	11
Patients with skeletal osteopenia Lumbar or femoral neck T-score ≤ -1 and > -2.5/both T-scores > -2.5	N = 206	N = 203	233 (57%)	RR = 0.38; 95% CI [0.206; 0.701] (p = 0.001)	62%	10

ment reduced the risk of vertebral fracture by 41% (RR = 0.59; 95% CI, 0.43–0.82; p = 0.002; number of women sustaining fractures: n = 60 in the strontium ranelate group, n = 90 in the placebo), by 59% (RR = 0.41; 95% CI, 0.17–0.99; p = 0.039) in the subset of 447 patients with no prevalent fractures (Fig. 2), and by 38% (RR = 0.62; 95% CI, 0.44–0.88; p = 0.008) in the 719 patients with prevalent

fractures (Fig. 2). In the 265 women with osteopenia at both sites, treatment reduced the risk of vertebral fracture by 52% (RR = 0.48; 95% CI, 0.24–0.96; p = 0.034; Fig. 3).

From the previously reported SOTI study,⁽⁸⁾ vertebral fracture risk was highest in women with osteoporosis and a prevalent fracture (32.8% or 382 of 1260). Women with LS osteopenia and a prevalent fracture had a higher fracture

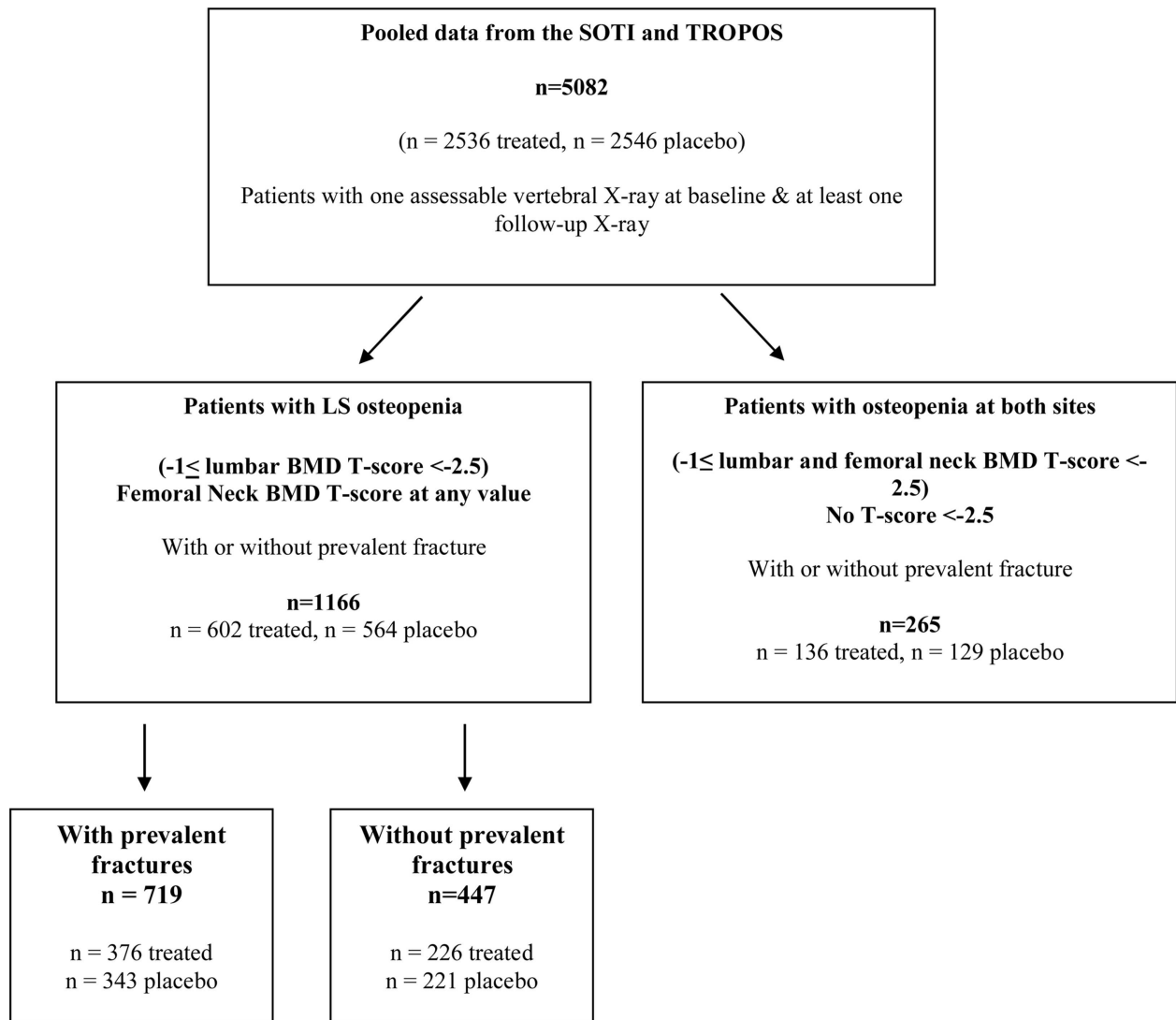


FIG. 1. Study population.

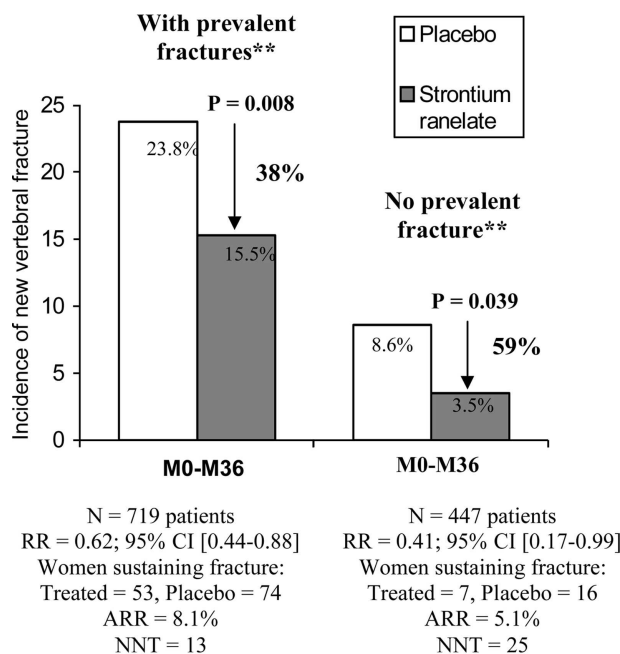
risk (23.8%; Fig. 2) than women with osteoporosis and no prevalent fracture (14.0%).⁽⁹⁾ Treatment reduced the risk of fracture in all groups by 38–59% (Fig. 4). The lowest number needed to treat (NNT) occurred in women with osteoporosis and a baseline fracture due to the high absolute risk. The NNT for women with osteopenia was 13–25 per averted fracture.

DISCUSSION

We report that strontium ranelate reduced the risk for new vertebral fractures by 41% in women with spinal osteopenia (and FN BMD at any value) and by 52% in those with osteopenia in both sites. Fracture risk was reduced in those without and in those with a prevalent fracture.

This is the first study to report antivertebral fracture efficacy in women with vertebral osteopenia. Kanis et al.⁽¹²⁾ reported that raloxifene reduced the risk of vertebral fractures by 49% in women with FN osteopenia. However, in

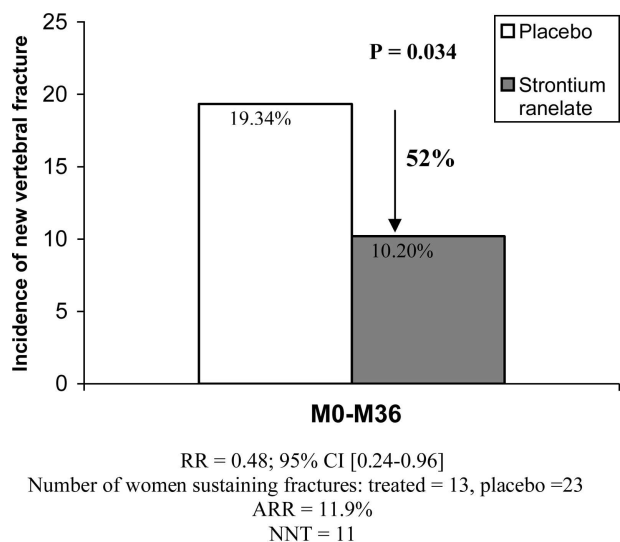
that study, fracture risk reduction was not observed in women with vertebral osteopenia. Quandt et al.⁽¹³⁾ report that alendronate reduced the risk of clinical vertebral fractures by 60% and radiographic vertebral fractures by 43% in women with osteopenia. However, this was reported in the pooled subgroup of patients with FN osteopenia with a prevalent fracture (from FIT 1) plus those patients with FN osteopenia without a prevalent fracture (from FIT 2). There was no significant risk reduction in the group of patients with FN osteopenia without prevalent fractures alone; the 95% CIs overlapped unity for clinical (0.16–1.17) and radiographic (0.38–1.1) fractures. Nor was there evidence of fracture risk reduction in women with vertebral osteopenia. In the study by Heaney et al.,⁽¹⁴⁾ the veracity of the inference that risedronate reduced the risk of vertebral fracture in women with osteopenia is difficult to evaluate because the data source was derived by posthoc pooling of four studies; three were phase 2 BMD studies and the fourth was derived from patients studied in the HIP trial.



* : -1 < lumbar BMD T-score < -2.5

** prevalent vertebral or non vertebral fractures

FIG. 2. Reduction of vertebral fracture risk with strontium ranelate in women with osteopenia* at the LS over 3 yr.



* : -1 ≤ lumbar and femoral neck BMD T-score < -2.5, No T-score < -2.5

FIG. 3. Reduction of vertebral fracture risk with strontium ranelate in women with osteopenia* at the LS and FN over 3 yr.

Furthermore, the evaluation of osteopenia was only based on femoral neck BMD.

The work of Siris et al. and several other investigators has shown that more than one half of all fractures in the community arise in women with osteopenia.⁽⁴⁻⁶⁾ These are likely to be fragility fractures, but by BMD criteria alone,

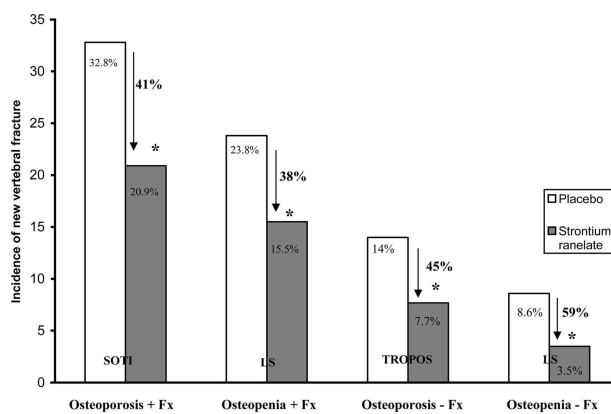


FIG. 4. Efficacy of strontium ranelate in reducing vertebral fracture risk in women with osteoporosis (with or without a prevalent fracture), osteopenia alone, or osteopenia plus a prevalent fracture. +Fx, with prevalent fracture; -Fx, without prevalent fracture. SOTI⁽⁸⁾; TROPOS⁽⁹⁾.

these fractures would not be referred to as “osteoporotic.” The underlying pathogenesis and structural basis for the fragility remains to be determined. However, Sornay-Rendu et al.⁽¹⁵⁾ reported that patients with osteopenia who come to sustain fractures have structural abnormalities such as reduced connectivity, whereas Garnero and Delmas⁽¹⁶⁾ reported that women with osteopenia and high remodeling have increased risk for fracture. Thus, it is likely that, in the setting of a higher peak bone mass, age-related and menopause-related bone loss produce osteopenia and sufficient structural decay to produce bone fragility. The risk of vertebral fracture in women with osteopenia plus a prevalent fracture was higher than the risk in women with osteoporosis alone in the SOTI study.⁽⁷⁾

Thus, there is an imperative to identify and treat women with osteopenia with a prevalent fracture, high remodeling, and/or loss of connectivity. Methods to identify these individuals are available, and this study provides evidence that strontium ranelate is effective in reducing the risk of fracture in all groups by 38–59%. Women with LS osteopenia and no prevalent fracture, whatever the femoral T-score, had the lowest absolute risk. This was reduced by 59%. The NNT for women with osteopenia was 13–25 per averted fracture.

This study had several limitations. Because of the low number of patients, it was not possible to assess the antinonvertebral fracture efficacy of strontium ranelate in osteopenia. Studies designed specifically to examine the effects of therapies in patients with osteopenia of the appendicular skeleton will be needed to address this important source of fractures in the community. In addition, because bone densitometry assessed total projected area of L₁–L₄ rather than the central part of the vertebral bodies, it is possible that endplate sclerosis or osteophytes caused by osteoarthritis may have artifactually increased BMD in some subjects.

Within the constraints of these limitations, we infer that strontium ranelate reduces the risk of vertebral fractures in women with LS osteopenia alone, in patients with osteope-

nia plus a prevalent fracture, and in patients with osteoporosis with or without a prevalent fracture.

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