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# Antifracture Efficacy of Currently Available Therapies for Postmenopausal Osteoporosis

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## Abstract

Osteoporosis is a systemic bone disease characterized by low bone mass and bone mineral density, and deterioration of the underlying structure of bone tissue. These changes lead to an increase in bone fragility and an increased risk for fracture, which are the clinical consequences of osteoporosis. The classical triad for consideration in osteoporosis is morbidity, mortality and cost. Vertebral fracture is an important source of morbidity in terms of pain and spinal deformity. On the other hand, hip fracture is associated with the worst outcomes and is widely regarded as a life-threatening event in the elderly; it is the source of the bulk of the cost of the disease in contemporary healthcare.

The prevention of osteoporosis-associated fracture should include fall prevention, calcium supplementation and lifestyle advice, as well as pharmacological therapy using agents with proven antifracture efficacy. The most commonly used osteoporosis treatments in Europe are the bisphosphonates alendronate, risedronate, ibandronate and zoledronic acid; the selective estrogen receptor modulator (SERM) raloxifene; teriparatide; and strontium

ranelate. Recent additions include the biological therapy denosumab and the SERM bazedoxifene. In this review, we explore the antifracture efficacy of these agents with the aim of simplifying treatment decisions. These treatments can be broadly divided according to their mode of action. The antiresorptive agents include the bisphosphonates, the SERMs and denosumab, while the bone-forming agents include parathyroid hormone and teriparatide. Strontium ranelate appears to combine both antiresorptive and anabolic activities. We collated data on vertebral and hip fracture efficacy from the pivotal 3-year phase III trials, all of which had a randomized, double-blind, placebo-controlled design. The relative reductions in risk in the osteoporosis trials range from 30% to 70% for vertebral fracture and 30% to 51% for hip fracture. This translates into 3-year number needed to treat values of between 9 and 21 for vertebral fracture and from 48 upwards for hip fracture.

International guidelines agree that agents that have been shown to decrease vertebral, nonvertebral and hip fractures should be used preferentially over agents that only demonstrate vertebral antifracture efficacy. This is the case for alendronate, risedronate, zoledronic acid, denosumab and strontium ranelate. Finally, therapeutic decisions should be based on a balance between benefits and risks of treatment, which must be carefully considered in each particular case both by the physician and the patient. Indeed, no single agent is appropriate for all patients and, therefore, treatment decisions should be made on an individual basis, taking into account all measures of treatment effect and risk before making informed judgments about the best individual treatment option.

## 1. Osteoporosis and Osteoporotic Fracture

Osteoporosis is a systemic bone disease characterized by low bone mass and bone mineral density (BMD), and deterioration of the underlying structure of bone tissue. These changes lead to an increase in bone fragility and an increased risk for fracture, which is the clinical consequence of osteoporosis.<sup>[1,2]</sup> Although an age-related decline in BMD is observed in both men and women, a greater loss is observed in postmenopausal women. This is partly because women have a lower peak bone mass and partly because of the hormonal changes that occur at the menopause. Estrogens play an important role in preserving bone mass during adult life in women and bone loss occurs as levels of the hormone decline with the onset of menopause.

The incidence of postmenopausal osteoporosis is growing due to changing demographics and increasing life expectancy. Notably, in Europe, the size of the female population over 50 years of age is expected to increase by 26% between 2000

and 2050.<sup>[3]</sup> Moreover, the greatest increases in population are predicted in exactly the age group in which hip fracture is most common. With greater numbers of women living into old age and with an increasing lifespan, the burden of osteoporosis-related fractures, particularly of the vertebrae and hip, is becoming a major health concern.

The classical triad for consideration in osteoporosis is morbidity, mortality and cost. Although vertebral fractures are not always symptomatic, they can become a source of morbidity in terms of acute or chronic pain as well as spinal deformity.<sup>[4]</sup> Moreover, vertebral fracture can result from relatively mild trauma in osteoporosis, e.g. during routine activities such as bending or lifting light objects; only about a quarter of cases result from falls.<sup>[5]</sup> They are also associated with a significantly increased risk for subsequent fracture.<sup>[6-8]</sup>

All fractures result in some degree of morbidity, but fractures at the hip are associated with the worst outcomes. The risk of hip fracture rises dramatically in women from the age of 70 years onwards,<sup>[9]</sup> with a median age for hip fracture of

approximately 83 years.<sup>[10]</sup> Hip fracture is associated with many secondary complications, including a rapid loss of physical and mental health and functional capacity,<sup>[11,12]</sup> and an increased risk of mortality. Indeed, hip fracture is widely regarded as a life-threatening event in the elderly, even after prefracture health status is taken into account.<sup>[12-17]</sup> In terms of long-term outcomes, only about a third of hip-fracture patients regain their original level of function,<sup>[14]</sup> with nearly one in five requiring residential care.<sup>[18]</sup>

To complete the triad, osteoporosis is a costly disease in terms of public health. The bulk of the cost is attributable to hip fracture because of the loss of autonomy, and the related costs of nursing care and rehabilitation, as well as the need for surgical procedures. Total healthcare costs associated with osteoporosis are difficult to calculate because they include the costs of acute hospital care, loss of working days for family carers, long-term care and medication.<sup>[19]</sup> Estimates from 1998 suggest that osteoporosis patients occupy more than 500 000 hospital-bed nights per year in the European Community and cost over €3500 million annually in hospital healthcare alone.<sup>[20]</sup> The International Osteoporosis Foundation (IOF) estimated that the number of osteoporotic fractures in Europe in 2000 was 3.79 million, of which 890 000 were hip fractures. The total direct costs resulting from these fractures was estimated at €31.7 billion, which was expected to increase to €76.7 billion by 2050 on the basis of expected demographic changes.<sup>[21]</sup> A 2008 IOF report estimates direct medical costs for osteoporotic fractures at more than €36 billion annually.<sup>[22]</sup>

Given the serious health and economic implications of osteoporotic fracture, it appears essential to invest in the prevention of osteoporosis-associated fracture for the maintenance of the health, quality of life and independence of postmenopausal women.<sup>[1,23]</sup> This can be achieved by minimizing or eliminating factors that may contribute to fractures, such as fall prevention, assessment and correction of calcium intake and lifestyle advice, including recommendation for weight-bearing exercise.<sup>[1,23]</sup> This should be accompanied by pharmacological intervention in at-risk women in order to improve bone strength and reduce fracture risk.

In the past decade, the number of medications to treat osteoporosis has markedly increased, considerably complicating clinical decision making. The most commonly used osteoporosis treatments in Europe are currently the selective estrogen receptor modulator (SERM) raloxifene; the bisphosphonates alendronate, risedronate, ibandronate and zoledronic acid; agents derived from parathyroid hormone (PTH); and strontium ranelate.<sup>[1,23]</sup> Recent additions to the therapeutic armamentarium include denosumab and the SERM bazedoxifene. Despite the range of agents available, there are few clinical trial data comparing the antifracture efficacy of active treatments head-to-head, making it difficult for physicians to evaluate the relative advantages of the available therapies and make informed decisions for their patients. In an attempt to address this issue, this paper reviews the respective antifracture efficacy of currently available therapies for postmenopausal osteoporosis.

## 2. Modes of Action of Agents Used in Osteoporosis

Treatments for osteoporosis can be broadly divided according to their mode of action. The majority of the agents act by slowing bone resorption, thereby preventing the relentless bone loss underlying the disease. In Europe, currently available antiresorptive agents for the prevention and treatment of postmenopausal osteoporosis include four bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), two SERMs, raloxifene and bazedoxifene, and a biological therapy, denosumab, a fully human monoclonal antibody against the receptor activator for nuclear factor- $\kappa$ B ligand (RANK-L). By contrast, the anabolic agents such as PTH and teriparatide promote bone formation, effectively reconstructing the bone lost due to disease. Strontium ranelate appears to combine both antiresorptive and anabolic activities.

The bisphosphonates are stable analogues of pyrophosphate, but contain a carbon in the backbone of the molecule (P-C-P in bisphosphonate) instead of an oxygen (P-O-P in pyrophosphate). They have a strong affinity for bone

hydroxyapatite.<sup>[24]</sup> The addition of side chains of different lengths and structures allows many structural variations, producing bisphosphonates with a range of potencies and properties, which affects the clinical doses required. Oral bisphosphonates are poorly absorbed, hence the requirement for them to be taken on an empty stomach, with no food or drink for the next 30 minutes. Once absorbed, they rapidly localize to the skeleton, where they inhibit bone resorption by reducing recruitment and activity of osteoclasts and increasing osteoclast apoptosis. The bisphosphonates principally act by prevention of further bone loss and are associated with moderate increases in BMD.

Denosumab is the most recent antiresorptive agent to be approved for the treatment of osteoporosis. Denosumab is a monoclonal antibody against RANK-L.<sup>[25]</sup> RANK-L stimulates the differentiation, activity and survival of osteoclasts, and is implicated in the pathogenesis of postmenopausal osteoporosis and other skeletal disorders associated with a high rate of bone remodelling.<sup>[26]</sup> By inhibiting the action of RANK-L, denosumab reduces the differentiation, activation and survival of osteoclasts. It has a potent action in slowing the rate of bone remodelling.<sup>[27]</sup>

The SERMs bind to the estrogen receptor and act as estrogen agonists or antagonists, depending on the target tissue. Although the precise mechanism by which they act is not yet fully understood, it is believed that the two different estrogen-receptor isoforms ER $\alpha$  and ER $\beta$  influence the action of the estrogen receptors in different tissues. Thus, whether the ER $\alpha$  or ER $\beta$  subtype is predominant in the target tissue appears to account for how SERMs perform different functions (pure agonist action when interaction with ER $\alpha$  is predominant and pure antagonist action when interaction with ER $\beta$  is predominant).<sup>[28]</sup>

Evidence that PTH or its amino-terminal analogues can act as bone-specific anabolic agents led to the hypothesis that such treatments might be particularly effective in reducing fracture rates in osteoporosis.<sup>[29]</sup> The skeletal effects of PTH depend on the pattern of systemic exposure. While continuous exposure to PTH, as seen in hyperparathyroidism, leads to an increased differentiation of osteoclasts and increased bone resorption,

intermittent administration results in new bone formation by preferentially stimulating osteoblasts.<sup>[30]</sup> Both PTH and teriparatide (a recombinant polypeptide consisting of the initial 34 amino acids of human PTH) activate the PTH/PTH-related protein (PTHrP) receptor, which is widely distributed but particularly expressed in bone and renal tissue. Its activation increases the number of osteoblasts, thus stimulating production of new trabecular and cortical bone formation.<sup>[31]</sup>

Strontium ranelate is composed of two atoms of stable strontium combined with ranelic acid, which acts as carrier.<sup>[32,33]</sup> It is the only agent available for the treatment of postmenopausal osteoporosis that appears to have both anabolic and antiresorptive effects.<sup>[34]</sup> The anabolic effects of strontium ranelate include an increase in preosteoblast replication, osteoblast differentiation, collagen type I synthesis and bone matrix mineralization. In parallel, it also inhibits osteoclast differentiation and activity so that the overall balance of bone turnover is in favour of bone formation, which translates into enhanced bone strength.

### 3. Antifracture Efficacy of Osteoporosis Treatments

In the absence of head-to-head trials, indirect comparisons are increasingly being used for the evaluation of a wide range of healthcare interventions.<sup>[35]</sup> This article reviews the antifracture efficacy of currently available therapies for postmenopausal osteoporosis by collating data from the pivotal 3-year phase III fracture intervention trials that were used for the registration of the different compounds (table I). The two outcomes selected for consideration were vertebral and hip fracture over 3 years, as these are the most common sites for osteoporotic fracture; they also constitute the osteoporotic events associated with the most morbidity. Hip fracture is reported, rather than nonvertebral fracture, since the latter is a composite of fractures at different sites with differing definitions according to the clinical trial. The hip fracture data are therefore easier to compare among trials.

All of the trials in table I had a randomized, double-blind, placebo-controlled design with the



**Table I.** Baseline characteristics of patients in the pivotal, phase III, vertebral and hip fracture trials over 3 years of agents currently available in Europe for the treatment of postmenopausal osteoporosis

Osteoporosis treatment	Study	N of patients (placebo/treatment)	Mean age (years)	Prevalent fractures (%)	Mean femoral neck BMD (T-score or absolute value)	
					placebo	treatment
Vertebral fracture trials						
Alendronate	FIT 1 <sup>[36]</sup>	1005/1022	71	Inclusion	0.56 g/cm <sup>2</sup>	0.57 g/cm <sup>2</sup>
Ibandronate	BONE <sup>[37]</sup>	975/977	69	93–94	–2.0 SD	–2.0 SD
Risedronate	VERT-NA <sup>[38]</sup>	820/821	69	79–85	0.60 g/cm <sup>2</sup>	0.59 g/cm <sup>2</sup>
Risedronate	VERT-MN <sup>[39]</sup>	408/408	71	Inclusion	0.58 g/cm <sup>2</sup>	0.57 g/cm <sup>2</sup>
Zoledronic acid	HORIZON <sup>[40]</sup>	3861/3875	73	62–64	0.53 g/cm <sup>2</sup>	0.53 g/cm <sup>2</sup>
Denosumab	FREEDOM <sup>[26]</sup>	3902/3906	72	23–24	–2.15 SD	–2.17 SD
Raloxifene	MORE <sup>[41]</sup>	770/769	69	36–38	0.57 g/cm <sup>2</sup>	0.57 g/cm <sup>2</sup>
Lasofoxifene	PEARL <sup>[42]</sup>	2744/2748	67	28	–2.2 SD	–2.2 SD
Bazedoxifene	No acronym <sup>[43]</sup>	1885/1886	66.5	56	–1.8 SD	–1.7 SD
Teriparatide	FPT <sup>[29]a</sup>	448/444	69	Inclusion	0.64 g/cm <sup>2</sup>	0.64 g/cm <sup>2</sup>
Strontium ranelate	SOTI <sup>[44]</sup>	719/723	69	Inclusion	0.59 g/cm <sup>2</sup>	0.59 g/cm <sup>2</sup>
Hip fracture trials						
Alendronate	FIT 1 <sup>[36]</sup>	1005/1022	71	Inclusion	0.56 g/cm <sup>2</sup>	0.57 g/cm <sup>2</sup>
Risedronate	HIP <sup>[45]</sup>	3134/6197	79	30–31	–3.7 SD	–3.7 SD
Zoledronic acid	HORIZON <sup>[40]</sup>	2853/2822	73	62–64	0.53 g/cm <sup>2</sup>	0.53 g/cm <sup>2</sup>
Denosumab	FREEDOM <sup>[26]</sup>	3902/3906	72	23–24	–2.15 SD	–2.17 SD
Strontium ranelate	TROPOS <sup>[46]</sup>	995/982	80	57–59	–3.6 SD	–3.6 SD

a Follow-up over 21 months.

**BMD** = bone mineral density; **SD** = standard deviation.

incidence of fracture at 3 years as the primary endpoint. In this manner, we can compare trials with a common comparator and identical treatment outcome. Table I excludes a number of studies for a variety of reasons. Meta-analyses and post-marketing surveillance studies are not included due to differences in baseline characteristics of the populations and the intrinsic limitations of these studies. We have also omitted agents and dosages that are not currently available in Europe for the treatment of postmenopausal osteoporosis (notably etidronate, which is not a first-line therapy).<sup>[1,23]</sup>

For each trial, we review both relative and absolute measures of treatment effect. This includes event rates on treatment and placebo, as well as relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT) to prevent one adverse outcome (fracture). This global approach updates that adopted by the American Society of Health System Pharmacists in 2008,<sup>[47]</sup> bringing the data into a European setting. It is also in line with the prin-

ciples of evidence-based medicine<sup>[48]</sup> and the most recent CONSORT (Consolidated Standards of Reporting Trials) statement, which state that all measures of treatment effect be included in reports of clinical trial results.<sup>[49,50]</sup>

### 3.1 Alendronate

The large alendronate trial FIT (see table II for a list of trial acronyms) recruited postmenopausal women aged 55–81 years with low femoral-neck BMD (defined as  $\leq 0.68$  g/cm<sup>2</sup> representing a T-score of approximately 2.1 standard deviations [SD] below the mean peak bone mass in young adults) and had two distinct arms based on the presence or absence of an existing vertebral fracture.<sup>[36]</sup> FIT 1 enrolled 2027 women who had morphometric vertebral fractures identified on radiographs at baseline. Women were initially randomized to alendronate 5 mg/day or placebo but the alendronate dose was increased to 10 mg/day at 24 months because of evidence from other trials

**Table II.** Clinical trial acronyms

Acronym	Definition
BONE	oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe
FIT	Fracture Intervention Trial
FIT 1	Vertebral Fracture Arm of the Alendronate Fracture Intervention Trial
FPT	Fracture Prevention Trial
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
HIP	Hip Intervention Program
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
MORE	Multiple Outcomes of Raloxifene Evaluation
PEARL	Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene
SOTI	Spinal Osteoporosis Therapeutic Intervention
TROPOS	Treatment Of Peripheral Osteoporosis
VERT-MN	Vertebral Efficacy with Risedronate Therapy Multinational
VERT-NA	Vertebral Efficacy with Risedronate Therapy North America

that 10 mg/day was more effective than 5 mg/day in increasing bone mass and had a similar safety profile. After a mean follow-up of 2.9 years, the relative risk of vertebral fracture with alendronate was 0.53 (95% CI 0.41, 0.68). New vertebral fractures occurred in 78 (8%) women in the alendronate

group and in 145 (15%) women in the placebo group (table III). These results give an RRR of 47%, an ARR of 7% and an NNT of 15, which means that 15 patients would need to be treated with alendronate for 3 years to prevent one vertebral fracture. In the FIT 1 trial, the incidence of hip fracture was a secondary endpoint.<sup>[36]</sup> The relative risk of hip fracture with alendronate was 0.49 (95% CI 0.23, 0.99). At 3 years, the incidence of hip fracture was 1% with alendronate and 2% with placebo (table IV). These results give an RRR of 51%, an ARR of 1% and an NNT of 91, which means that 91 patients would need to be treated with alendronate for 3 years to prevent one hip fracture.

3.2 Risedronate

Two pivotal vertebral antifracture efficacy studies have been conducted with risedronate. VERT-NA and VERT-MN were randomized, double-blind, placebo-controlled, parallel-group trials, and were conducted under similar protocols, although the inclusion criteria differed slightly.<sup>[38,39]</sup> In both studies, women could be enrolled if they were at least 5 years postmenopausal, no older than 85 years of age and had radiographic evidence of at least two prevalent vertebral fractures. In VERT-NA, women could also be enrolled if they had one prevalent vertebral

**Table III.** Outcome measures for vertebral fracture over 3 years with currently available osteoporosis treatments calculated from the results of randomized, double-blind, pivotal phase III trials vs placebo

Treatment	Study	Fracture incidence (%)		RRR (%)	ARR (%)	NNT
		placebo	treatment			
Alendronate	FIT 1 <sup>[36]</sup>	15.0	8.0	47	7.0	15
Risedronate	VERT-NA <sup>[38]</sup>	16.3	11.3	41	5.0	20
Risedronate	VERT-MN <sup>[39]</sup>	29.0	18.1	49	10.9	10
Ibandronate	BONE <sup>[37]</sup>	9.6	4.7	62	4.9	21
Zoledronic acid	HORIZON <sup>[40]</sup>	10.9	3.3	70	7.6	14
Denosumab	FREEDOM <sup>[26]</sup>	7.2	2.3	68	4.8	21
Raloxifene	MORE <sup>[41]</sup>	21.2	14.7	30	6.5	16
Lasofoxifene <sup>a</sup>	PEARL <sup>[42]</sup>	9.5	5.7	40	3.9	26
Bazedoxifene	No acronym <sup>[43]</sup>	4.1	2.3	42	1.8	56
Teriparatide <sup>b</sup>	FPT <sup>[29]</sup>	14.0	5.0	65	9.0	12
Strontium ranelate	SOTI <sup>[44]</sup>	32.8	20.9	41	11.9	9

a Data over 5 years.

b Data over 21 months.

**ARR** = absolute risk reduction; **NNT** = number needed to treat (to prevent one event over 3 years); **RRR** = relative risk reduction.

**Table IV.** Outcome measures for hip fracture over 3 years with currently available osteoporosis treatments calculated from the results of randomized, double-blind, pivotal phase III trials vs placebo

Treatment <sup>a</sup>	Study	Fracture incidence (%)		RRR (%)	ARR (%)	NNT
		placebo	treatment			
Alendronate	FIT 1 <sup>[36]</sup>	2.2	1.1	51	1.1	91
Risedronate	HIP <sup>[45]</sup>	3.9	2.8	30	1.1	91
Zoledronic acid	HORIZON <sup>[40]</sup>	2.5	1.4	41	1.1	91
Denosumab	FREEDOM <sup>[26]</sup>	1.2	0.7	40	0.3	334
Lasofosifene <sup>b</sup>	PEARL <sup>[42]</sup>	1.2	0.9	NS		
Strontium ranelate	TROPOS <sup>[46]</sup>	6.4	4.3	36	2.1	48

a No data for ibandronate, raloxifene, bazedoxifene or teriparatide.

b Data over 5 years.

**ARR**=absolute risk reduction; **NNT**=number needed to treat (to prevent one event over 3 years); **NS**=not statistically significant; **RRR**=relative risk reduction.

fracture and a lumbar spine BMD  $\leq 0.83$  g/cm<sup>2</sup>, representing a T-score of  $-2.0$  SD. In VERT-NA, 2458 women were randomized to risedronate 2.5 mg/day (discontinued after 1 year) or 5 mg/day or placebo for 3 years.<sup>[38]</sup> The relative risk of vertebral fracture with risedronate was 0.59 (95% CI 0.43, 0.82). New vertebral fractures occurred in 61 (11%) women in the risedronate 5 mg group and 93 (16%) women in the placebo group (table III). These results give an RRR of 41%, an ARR of 5% and an NNT of 20. In VERT-MN, 1226 women were randomized to risedronate 2.5 mg/day (discontinued after 2 years) or 5 mg/day or placebo for 3 years.<sup>[39]</sup> The relative risk of vertebral fracture with risedronate was 0.51 (95% CI 0.36, 0.73). New vertebral fractures occurred in 53 (18%) women in the risedronate 5 mg/day group and 89 (29%) women in the placebo group (table III). These results give an RRR of 49%, an ARR of 11% and an NNT of 10 for vertebral fracture over 3 years.

HIP was a study specifically designed to evaluate the effect of risedronate on the incidence of hip fracture.<sup>[45]</sup> Postmenopausal women were enrolled in two groups: (i) 5545 women aged 70–79 years with osteoporosis confirmed on the basis of low BMD (femoral neck BMD T-score more than  $-4$  SD or lower than  $-3$  SD with a non-skeletal risk factor for hip fracture [e.g. propensity to fall]); and (ii) 3886 women aged  $\geq 80$  years on the basis of a low femoral neck BMD T-score or the presence of one or more non-skeletal,

fall-related risk factors for hip fracture. Women were randomized to daily treatment with risedronate 2.5 mg, risedronate 5.0 mg or placebo. The primary endpoint was the incidence of radiographically confirmed hip fracture. The relative risk of hip fracture with risedronate was 0.70 (95% CI 0.6, 0.9). At 3 years the incidence of hip fracture was 3% for women in the risedronate group and 4% for women in the placebo group (table IV). These results give an RRR of 30%, an ARR of 1% and an NNT of 91 for hip fracture over 3 years.

### 3.3 Ibandronate

The BONE trial recruited postmenopausal women aged 55–80 years with one to four prevalent vertebral fractures and a mean lumbar spine BMD T-score of  $-2.0$  to  $-5.0$  SD in at least one vertebra.<sup>[37]</sup> The study randomized 2946 women to oral ibandronate administered either daily (2.5 mg/day) or intermittently (20 mg every other day for 12 doses every 3 months) or placebo for 3 years. The relative risk of vertebral fracture with ibandronate 2.5 mg was 0.38 (95% CI 0.25, 0.58). New vertebral fractures occurred in 5% of women in the daily ibandronate group and 10% of women in the placebo group (table III). These results give an RRR of 62%, an ARR of 5% and an NNT of 21. The efficacy of ibandronate against hip fracture has not been demonstrated in a pivotal phase III study.



### 3.4 Zoledronic Acid

The most potent bisphosphonate, zoledronic acid, which is administered once yearly as an intravenous infusion, has been developed to overcome the limited gastrointestinal absorption and poor patient adherence associated with oral bisphosphonates. The HORIZON trial included 7765 postmenopausal women aged 65–89 years with BMD T-scores of  $-2.5$  SD or lower at the femoral neck, with or without evidence of existing vertebral fracture, or a T-score of  $-1.5$  SD or lower with evidence of  $\geq 2$  mild or  $\geq 1$  moderate vertebral fractures.<sup>[40]</sup> Just under two-thirds of women had baseline fractures. Patients were randomized to receive a 15-minute, 5 mg infusion of zoledronic acid ( $n = 3889$ ) or placebo ( $n = 3876$ ) at baseline, 12 months and 24 months; follow-up continued to 3 years. The primary endpoints were new vertebral fracture in patients not taking concomitant osteoporosis medications and hip fracture in all patients. The relative risk of vertebral fracture with zoledronic acid was 0.30 (95% CI 0.24, 0.38). New vertebral fractures occurred in 3% of women in the zoledronic acid group and in 11% of women in the placebo group (table III). In terms of relative and absolute risk of vertebral fracture over 3 years, these results give an RRR of 70%, an ARR of 8% and an NNT of 14. In the HORIZON trial, the hazard ratio for hip fracture with zoledronic acid was 0.59 (95% CI 0.42, 0.83). At 3 years, the incidence of hip fracture was 1% (52 women) in the zoledronic acid group and 3% (88 women) in the placebo group (table IV). These results give an RRR of 41%, an ARR of 1% and an NNT of 91 for hip fracture over 3 years.

### 3.5 Denosumab

The FREEDOM trial recruited 7868 postmenopausal women aged 60–90 years with a lumbar spine BMD T-score of less than  $-2.5$  to  $-4.0$  SD. Approximately 23% of the FREEDOM population had at least one prevalent vertebral fracture at the time of entry into the study.<sup>[26]</sup> Women were randomized to receive either denosumab 60 mg subcutaneously ( $n = 3902$ ) or placebo ( $n = 3906$ ) every 6 months. The primary endpoint

was new vertebral fractures at 3 years. The relative risk of vertebral fracture with denosumab was 0.32 (95% CI 0.26, 0.41). New vertebral fractures occurred in 2% of women in the denosumab group and in 7% of women in the placebo group (table III). These results give an RRR of 68%, an ARR of 5% and an NNT of 21. Hip fracture was a secondary endpoint in the FREEDOM trial.<sup>[26]</sup> After 3 years, the postmenopausal osteoporotic women receiving denosumab had a slightly reduced risk of hip fracture with a cumulative incidence of 0.7% in the denosumab group versus 1% in the placebo group, giving an ARR of 0.3% and an NNT of 334. In relative terms, the hazard ratio was 0.60 (95% CI 0.37, 0.97;  $p = 0.04$ ), indicating a relative decrease in risk of 40%.

### 3.6 Raloxifene

Raloxifene was the first SERM approved for the prevention and treatment of osteoporosis in postmenopausal women. The MORE study recruited 7705 women aged 31–80 years, at least 2 years postmenopausal with osteoporosis defined as low BMD or radiographically apparent vertebral fractures.<sup>[41]</sup> Prior to randomization, patients were stratified to one of two study groups at the time of radiographic screening: 5064 were assigned to study group 1 if they had no vertebral fractures but a femoral neck or lumbar spine BMD T-score of  $>2.5$  SD; and 2641 were assigned to study group 2 if they had vertebral fractures. Within each substudy, women were randomly assigned to treatment with raloxifene 60 or 120 mg/day or placebo for 3 years. Only the results for the 60 mg/day dose are presented here, because this is the currently marketed dose in Europe. The relative risk of vertebral fracture with raloxifene was 0.70 (95% CI 0.6, 0.9). New vertebral fractures occurred in 113 (15%) women in the raloxifene group and in 163 (21%) women in the placebo group (table III). These results give an RRR of 30%, an ARR of 7% and an NNT of 16 for vertebral fracture over 3 years. The clinical efficacy of raloxifene against hip fractures over 3 years has not been investigated in a pivotal phase III study.

### 3.7 Lasofoxifene

Evidence for lasofoxifene in the treatment of postmenopausal osteoporosis comes from the PEARL study.<sup>[42]</sup> PEARL recruited 8556 women between the ages of 59 and 80 years with a BMD T-score of  $-2.5$  SD or less at the lumbar spine; a prevalent vertebral fracture was not an entry requirement and only 28% had at least one prevalent baseline radiographically defined vertebral fracture. Women were randomized to lasofoxifene at a dose of either 0.25 or 0.5 mg/day or placebo. Only the results for the 0.5 mg/day dose are presented here because this will be the marketed dose in Europe. The trial was planned to continue for 5 years; vertebral fracture was the primary endpoint for the first 3 years of the trial. The hazard ratio for vertebral fracture with lasofoxifene 0.5 mg/day was 0.58 (95% CI 0.47, 0.70), indicating an RRR of 42%. Lasofoxifene 0.5 mg/day was associated with a reduction in the absolute incidence of radiographic vertebral fractures at 3 years of 9.5 (13.5 vs 23 fractures per 1000 patient-years; 95% CI 5.2, 13.7). The PEARL trial data allow calculation of relative and absolute risk over 5 years (but not 3 years) [table III]. Therefore, the RRR for vertebral fracture over 5 years with lasofoxifene is 40%, with an ARR of 4% and an NNT of 26. In the same study, lasofoxifene failed to demonstrate a significant effect against hip fractures (hazard ratio 0.77 [95% CI 0.46, 1.27; not significant]).

### 3.8 Bazedoxifene

The bazedoxifene vertebral fracture risk study is the first osteoporosis treatment trial that has used an active comparator (raloxifene) in addition to placebo. The trial included 7492 women aged 55–85 years at least 2 years postmenopausal with osteoporosis.<sup>[43]</sup> Women without prevalent vertebral fracture were required to have femoral neck or lumbar spine BMD T-scores between  $-2.5$  and  $-4.0$  SD, whereas women with prevalent vertebral fracture were required to have a femoral neck and lumbar spine T-score no lower than  $-4.0$  SD. An average of 56% of women had a prevalent vertebral fracture at baseline. Partici-

pants were randomized to bazedoxifene 20 or 40 mg/day, raloxifene 60 mg/day or placebo. Only the results for the bazedoxifene 20 mg/day dose are presented here because this will be the marketed dose in Europe. The primary endpoint was the incidence of new radiographically confirmed vertebral fractures among women in the bazedoxifene and placebo groups after 3 years of treatment. Compared with placebo, the relative risk of vertebral fracture with bazedoxifene 20 mg was 0.58 (95% CI 0.38, 0.89). New vertebral fractures occurred in 2% of women in the bazedoxifene 20 mg group and 4% of women in the placebo group (table III). These results give an RRR of 42%, an ARR of 2% and an NNT of 56 for vertebral fracture over 3 years. The clinical efficacy of bazedoxifene against hip fractures over 3 years has not been investigated in a pivotal phase III study.

### 3.9 Teriparatide

The efficacy of teriparatide for reducing the incidence of new vertebral fracture was examined in the FPT.<sup>[29]</sup> Women were eligible for inclusion if they were at least 5 years postmenopausal with at least one moderate or two mild vertebral fractures on radiographs of the thoracic and lumbar spine. For women who had fewer than two moderate vertebral fractures, an additional inclusion criterion was a BMD T-score of the lumbar spine or proximal femur at least  $-1$  SD. Women were randomized to daily injections of teriparatide 20  $\mu$ g ( $n = 541$ ), teriparatide 40  $\mu$ g ( $n = 552$ ) or placebo ( $n = 544$ ). The study was terminated early because a long-term teriparatide carcinogenicity study in rats revealed the occurrence of skeletal proliferative lesions, including osteosarcoma.<sup>[51]</sup> These findings were later determined to be unlikely to have significant predictive ability in humans and a dose of teriparatide 20  $\mu$ g was subsequently approved by various regulatory agencies for the treatment of osteoporosis. In the FPT the relative risk of vertebral fracture with teriparatide 20  $\mu$ g was 0.35 (95% CI 0.22, 0.55). New vertebral fractures occurred in 5% of women in the teriparatide 20  $\mu$ g group and 14% of women in the placebo group (table III). These results give an RRR of 65%, an

ARR of 9% and an NNT of 12, which means that 12 patients would need to be treated for 21 months (the median treatment duration) to prevent one vertebral fracture of any severity. Efficacy against hip fractures has not been demonstrated in a pivotal phase III study with teriparatide.

### 3.10 Strontium Ranelate

The vertebral antifracture efficacy of strontium ranelate was examined in the SOTI trial in postmenopausal women with established osteoporosis.<sup>[44]</sup> The study recruited 1649 women aged  $\geq 50$  years with osteoporosis (lumbar spine BMD of  $\leq 0.84$  g/cm<sup>2</sup>) and at least one radiographically confirmed vertebral fracture. The women were randomized to strontium ranelate 2 g/day or placebo for 3 years. The relative risk of vertebral fracture with strontium ranelate was 0.59 (95% CI 0.48, 0.73). New vertebral fractures occurred in 21% of women in the strontium ranelate group and in 33% of women in the placebo group (table III). These results give an RRR of 41%, an ARR of 12% and an NNT of 9.

The TROPOS trial was designed to assess the effectiveness of strontium ranelate in preventing nonvertebral fractures in postmenopausal women with osteoporosis. Women were eligible for the study if they had femoral neck BMD corresponding to a T-score of less than  $-2.5$  SD and were aged over 74 years, or between 70 and 74 years but with one additional fracture risk factor.<sup>[46]</sup> The 5091 women were randomized to strontium ranelate 2 g/day or placebo for 3 years. In the high-risk fracture subgroup (women  $>74$  years of age and with a femoral neck BMD T-score of  $-2.4$  SD or less), the relative risk for hip fracture was 0.64 (95% CI 0.41, 0.997). At 3 years, the incidence of hip fracture was 4% in the strontium ranelate group and 6% in the placebo group, leading to an RRR of hip fractures of 36%, an ARR of 2% and an NNT of 48 (table IV).

## 4. Discussion

Selecting the most appropriate agent for an individual patient requires the assessment of the relative value of a particular intervention versus

all other relevant interventions of choice. With recent additions to the therapeutic armamentarium, physicians now have at their disposal a wide range of osteoporosis treatments. On the other hand, randomized controlled trials are often designed for registration purposes and only include a placebo comparison or one active comparator. Head-to-head comparisons of all available agents are unlikely to become available because of the prohibitive costs and sample size that such a study would require. As a result, information on the efficacy of osteoporotic treatments relative to one another remains limited.

In this article, data from the pivotal phase III randomized controlled trials used as part of the European regulatory process have been surveyed to analyse vertebral and hip antifracture efficacy of currently available osteoporosis treatments. International guidelines generally agree that agents that have been shown to decrease vertebral, non-vertebral and hip fractures should be used preferentially over agents that demonstrate vertebral antifracture efficacy alone.<sup>[1,47,52]</sup> This is the case for the bisphosphonates alendronate, risedronate and zoledronic acid, as well as denosumab and strontium ranelate. These agents are therefore reasonable options to consider as first-line therapy, particularly for patients who have a high risk for hip fracture.

The relative reductions in risk in the osteoporosis trials range from 30% to 70% for vertebral fracture (table I) and 30% to 51% for hip fracture (table III). This translates into 3-year NNT values of between 9 and 21 for vertebral fracture (table I) and from 48 upward for hip fracture (table III). Six of the agents have NNT values for vertebral fracture above the average of 16, while four have NNT values for hip fracture of  $<100$ . The strategy of assessing ARR in terms of NNT has been endorsed by a number of international and national guidelines in osteoporosis.<sup>[1,23,47]</sup> While it is not without limitations, this underlines the importance of treating osteoporosis both to prevent fracture and to reduce the associated healthcare burden. It also gives some indication of the value of careful selection of treatment.

One limitation of comparing randomized controlled trials is linked to the dangers of comparing

populations at differing levels of risk at baseline. For example, the studies reviewed here were similar with regard to mean age, baseline BMD, and calcium and vitamin D supplementation, but did differ in terms of rate of prevalent fracture at baseline. Prevalent vertebral fracture was an inclusion criteria in the clinical studies with alendronate, risedronate, teriparatide and strontium ranelate;<sup>[29,36,39,44]</sup> in the other trials, the percentage of patients with prevalent vertebral fracture at baseline ranged from 23% to 94%.<sup>[26,37,40-42]</sup> This may have contributed to the variations in event rates in the placebo groups of the various trials ranging from 7.2% to 32.8% for vertebral fracture and from 1.2% to 6.4% for hip fracture (tables I and III). On the other hand, agents with demonstrated efficacy in higher risk populations may be prescribed more confidently since they show clear reductions specifically in patients with a high risk of fractures, who are the main target of osteoporosis treatment in real clinical practice. This is also in line with suggested probabilities as inclusion criteria in phase III trials from the Committee for Medicinal Products for Human Use.<sup>[53]</sup> These range from 15% to 20% for vertebral fracture and 5% to 7.5% for hip fracture.<sup>[54]</sup> Five of the agents reviewed here have been proven to have antifracture efficacy in a population within the risk range for vertebral fracture, and one in the risk range for hip fracture. In this context, the FRAX<sup>®</sup> algorithm may prove to be a useful tool in the future to predict the risk of fracture in patients at diagnosis and to guide treatment decisions.<sup>[55]</sup>

Although this article has only considered antifracture efficacy, therapeutic decisions are based on a balance between benefits and risks of treatment, which must be carefully considered in each particular case both by the physician and the patient. While the osteoporosis treatments are generally considered safe, they have been associated with some rare adverse reactions.<sup>[56,57]</sup> Even mild adverse reactions can constitute considerable barriers to adherence and persistence, and should therefore be carefully assessed with modification of mode of drug administration, dosing regimen and cost if necessary.<sup>[1,23]</sup> On the other hand, rare adverse reactions to osteoporosis treatments

should never be considered as a reason not to treat a woman at risk of fracture.

Any comparison of antifracture efficacy should go hand in hand with a comparison of the effect on bone strength and structure. All of the existing treatment options alter one or more determinants of bone strength in terms of tissue properties, microarchitecture (e.g. trabecular number, thickness and connectivity, and cortical porosity) and dynamic change (e.g. mineral apposition rate or activation frequency). Interpretation of comparative data for these properties is complex. For example, raloxifene has the most pronounced effects on tissue quality,<sup>[58,59]</sup> while teriparatide reduces tissue hardness in trabecular bone but has the greatest effect on bone volume.<sup>[58,60]</sup> Bisphosphonates increase stiffness but not hardness, and do not alter bone volume significantly.<sup>[58,59]</sup> Finally, bone biopsies performed in patients treated with denosumab show a strong downregulation of the bone remodelling induced by this agent, without any effect on bone architecture.<sup>[27]</sup>

As regards microarchitecture, teriparatide and strontium ranelate have been compared in a head-to-head trial, and appear to have similar effects on microarchitecture.<sup>[61]</sup> A recent head-to-head comparison of alendronate and strontium ranelate in women with postmenopausal osteoporosis indicated that the latter improved cortical and trabecular parameters as well as bone volume, while the bisphosphonate had no such significant effect.<sup>[62]</sup> Understanding of treatments may well improve if bone turnover and microarchitecture were to be included in trial endpoints. On the other hand, while these results go some way to assist in comparing treatments, the ultimate goal of osteoporosis treatment remains to prevent fractures.

These considerations of the impact on bone structure indicate other potential routes for comparison of agents via their mode of action. For the time being, we are limited to assessment in terms of an antiresorptive mode of action versus a bone-forming action. In the future, we may expect surrogate markers of bone remodelling to play a greater role in the assessment of patients at diagnosis and the monitoring of treatment efficacy.<sup>[63]</sup>



## 5. Conclusions

Randomized controlled trials provide solid evidence that the bisphosphonates, the SERMs, denosumab, teriparatide and strontium ranelate prevent vertebral fractures compared with placebo. There is also sound evidence for the prevention of hip fracture with alendronate, risedronate, zoledronic acid, denosumab and strontium ranelate. No single agent is appropriate for all patients and therefore treatment decisions should be made on an individual basis, taking into account all measures of treatment effect and the patient's baseline risk before making informed judgments about the best individual treatment option.

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## References

- Kanis J, Burlet N, Cooper C, et al. European Guidance for the diagnosis and treatment of osteoporosis in postmenopausal women. *Osteoporos Int* 2008 Apr; 19 (4): 399-428
- Reginster J-Y, Rizzoli R. Innovation in skeletal medicine. In: Reginster J-Y, Rizzoli R, editors. *Innovation in skeletal medicine*. Issy-les-Moulineaux: Elsevier, 2007: 7-9
- Kanis JA, on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary healthcare level. Technical report. Sheffield: WHO Centre for Metabolic Bone Diseases, 2007: 38
- Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fracture with back pain and function: a prospective study. *Ann Intern Med* 1998 May; 128 (10): 793-800
- Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006 Jun; 367 (9527): 2010-8
- Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001 Jan; 285 (3): 320-3
- Center JR, Bliuc D, Nguyen TV, et al. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007 Jan; 297 (4): 387-94
- Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 2004 Aug; 35 (2): 375-82
- Cooper C, Campion G, Melton 3rd LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992 Nov; 2 (6): 285-9
- Rizzoli R, Bruyere O, Cannata-Andia JB, et al. Management of osteoporosis in the elderly. *Curr Med Res Opin* 2009 Oct; 25 (10): 2373-87
- Boonen S, Singer AJ. Osteoporosis management: impact of fracture type on cost and quality of life in patients at risk for fracture. *Curr Med Res Opin* 2008 Jun; 24 (6): 1781-8
- Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. *CMAJ* 2009 Sep; 181 (5): 265-71
- Cauley J, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. *Osteoporos Int* 2000; 11 (7): 556-61
- Leibson CL, Tosteson AN, Gabriel SE, et al. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. *J Am Geriatr Soc* 2002 Oct; 50 (10): 1644-50
- Richmond J, Aharonoff GB, Zuckerman JD, et al. Mortality risk after hip fracture. *J Orthop Trauma* 2003 Jan; 17 (1): 53-6
- Empana JP, Dargent-Molina P, Beart G. Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. *J Am Geriatr Soc* 2004 May; 52 (5): 685-90
- Abrahamsen B, van Staa T, Ariely R, et al. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009 Oct; 20 (10): 1633-50
- Salkeld G, Cameron ID, Cumming RG, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ* 2000 Feb; 320 (7231): 341-6
- Rabenda V, Manette C, Lemmens R, et al. The direct and indirect costs of the chronic management of osteoporosis: a prospective follow-up of 3440 active subjects. *Osteoporos Int* 2006; 17 (9): 1346-52
- International Osteoporosis Foundation. Osteoporosis in the European Community: a call to action. An audit of policy developments since 1998 [online]. Available from URL: <http://www.iofbonehealth.org/download/osteofound/filemanager/publications/pdf/eu-report-2001.pdf> [Accessed 2010 Sep 1]
- Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone* 2006 Feb; 38 (2 Suppl. 1): S4-9
- International Osteoporosis Foundation. Osteoporosis in the European Union in 2008: ten years of progress and ongoing challenges [online]. Available from URL: <http://www.sante.public.lu/publications/maladies-traitements/osteoporose/osteoporosis-eu-2008/osteoporosis-eu-2008.pdf> [Accessed 2010 Sep 1]
- Body JJ, Bergmann P, Boonen S, et al. Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. *Osteoporos Int* 2010 Oct; 21 (10): 1657-80
- Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008 Sep; 83 (9): 1032-45
- Delmas PD. Clinical potential of RANKL inhibition for the management of postmenopausal osteoporosis and other metabolic bone diseases. *J Clin Densitom* 2008 Apr-Jun; 11 (2): 325-38



26. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009 Aug; 361 (8): 756-65
27. Reid I, Miller P, Brown J, et al., on behalf of the Denosumab Phase 3 Bone Histology Study Group. Effects of denosumab on bone histomorphometry: the freedom and stand studies. *J Bone Miner Res* 2010 Oct; 25 (10): 2256-65
28. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators: mechanisms of action and application to clinical practice. *N Engl J Med* 2003 Feb; 348 (7): 618-29
29. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001 May; 344 (19): 1434-41
30. Whitfield JF, Morley P, Willick GE. Parathyroid hormone, its fragments and their analogs for the treatment of osteoporosis. *Treat Endocrinol* 2002; 1 (3): 175-90
31. Reeve J. Recombinant human parathyroid hormone. *BMJ* 2002 May; 324 (7347): 435-6
32. Marie PJ. Strontium ranelate: a dual mode of action rebalancing bone turnover in favour of bone formation. *Curr Opin Rheumatol* 2006 Jun; 18 Suppl. 1: S11-5
33. Reginster JY, Deroisy R, Neuprez A, et al. Strontium ranelate: new data on fracture prevention and mechanisms of action. *Curr Osteoporos Rep* 2009 Sep; 7 (3): 96-102
34. Deeks ED, Dhillon S. Strontium ranelate: a review of its use in the treatment of postmenopausal osteoporosis. *Drugs* 2010 Apr; 70 (6): 733-59
35. Song F, Loke YK, Walsh T, et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009 Apr; 338: b1147
36. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures: Fracture Intervention Trial Research Group. *Lancet* 1996 Dec; 348 (9041): 1535-41
37. Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004 Aug; 19 (8): 1241-9
38. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999 Oct; 282 (14): 1344-52
39. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000; 11 (1): 83-91
40. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007 May; 356 (18): 1809-22
41. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999 Aug; 282 (7): 637-45
42. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med* 2010 Feb; 362 (8): 686-96
43. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008 Dec; 23 (12): 1923-34
44. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004 Jan; 350 (5): 459-68
45. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women: Hip Intervention Program Study Group. *N Engl J Med* 2001 Feb; 344 (5): 333-40
46. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: TROPOS study. *J Clin Endocrinol Metab* 2005 May; 90 (5): 2816-22
47. MacLaughlin EJ, Rael CL. ASHP therapeutic position statement on the prevention and treatment of osteoporosis in adults. *Am J Health Syst Pharm* 2008 Sep; 65 (3): 343-57
48. Sackett DL, Straus SE, Richardson WS, et al., editors. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone, 2001
49. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010 Mar; 340: c869
50. Schulz KF, Altman DG, Moher D. CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010 Mar; 340: c332
51. Gallagher JC, Genant HK, Crans GG, et al. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. *J Clin Endocrinol Metab* 2005 Mar; 90 (3): 1583-7
52. Agence française de sécurité sanitaire des produits de santé. Traitement médicamenteux de l'ostéoporose post-ménopausique, 2006 [online]. Available from URL: [http://www.afssaps.fr/Infos-de-securite/Recommandations-de-bonne-pratique/Traitement-medicamenteux-de-l-osteoporose-post-menopausique-recommandations-de-bonne-pratique/\(language\)/fre-FR](http://www.afssaps.fr/Infos-de-securite/Recommandations-de-bonne-pratique/Traitement-medicamenteux-de-l-osteoporose-post-menopausique-recommandations-de-bonne-pratique/(language)/fre-FR) [Accessed 2010 Sep 1]
53. Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis. Ref CPMP/EWP/552/95Rev.2. London: CHMP, 2006
54. Kanis JA, McCloskey EV, Johansson H, et al. Development and use of FRAX in osteoporosis. *Osteoporos Int* 2010 Jun; 21 Suppl. 2: S407-13
55. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008 Apr; 19 (4): 385-97
56. Abrahamsen B. Adverse effects of bisphosphonates. *Calcif Tissue Int* 2010 Jun; 86 (6): 421-35
57. Musette P, Brandi ML, Cacoub P, et al. Treatment of osteoporosis: recognizing and managing cutaneous adverse reactions and drug-induced hypersensitivity. *Osteoporos Int* 2010 May; 21 (5): 723-32
58. Brennan TC, Rizzoli R, Ammann P. Selective modification of bone quality by PTH, pamidronate or raloxifene. *J Bone Miner Res* 2009 May; 24 (5): 800-8

59. Allen MR. Surface-specific bone formation effects of osteoporosis pharmacological treatments. *Clin Rev Bone Miner Metab* 2008; 6 (1-2): 62-9
60. Benhamou CL. Effects of osteoporosis medications on bone quality. *Joint Bone Spine* 2007 Jan; 74 (1): 39-47
61. Meunier PJ, Boivin G, Marie PJ. About the comparison of two anabolic agents, teriparatide and strontium ranelate, in treated osteoporotic women [letter]. *J Bone Miner Res* 2009 Dec; 24 (12): 2066
62. Rizzoli R, Laroche M, Krieg MA, et al. Strontium ranelate and alendronate have differing effects on distal tibia bone microstructure in women with osteoporosis. *Rheumatol Int* 2010 Aug; 30 (10): 1341-8
63. Roux S. New treatment targets in osteoporosis. *Joint Bone Spine* 2010 May; 77 (3): 222-8

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