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Article

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Word count: 3321 words (text only); 31 references; 2 tables, 1 box, 1 figure

Target journal: *Rheumatol Int* (IF, 1.327)

Disclosures: J. D. Ringe has received congress grants and honoraria from Sanofi Aventis; MSD, Novartis, P&G, Roche and Servier; J. G. Doherty has received educational, travel, and congress grants from MSD, Alliance for Better Bone Health, Lilly, and Servier

Abstract (248 words)

Postmenopausal osteoporosis is a chronic condition due to decreased bone mass, leading to reduced bone strength and increased fracture risk. Currently available pharmacological treatments include antiresorptive agents (bisphosphonates and raloxifene) and bone-forming agents (strontium ranelate and two different parathyroid peptides). Comparison via reduction in relative risk of fracture may produce artificially high reductions in fracture risk for some agents. Responder analysis based on absolute risk reduction (ARR, the arithmetic difference between events rates with and without treatment over a fixed time) and a related parameter, number needed to treat (NNT, the number of patients needed to treat over a fixed time to prevent one event) may provide more reliable parameters. We reviewed placebo-controlled, randomized, double-blind, pivotal phase 3 trials employed as part of the regulatory process, in order to calculate ARRs and NNTs for vertebral and hip fracture over 3 years for antiosteoporotic agents currently available in Europe. The NNT values to prevent one vertebral fracture over 3 years range from 9 for the strontium ranelate to 21 for ibandronate. NNT values for hip fracture over 3 years range from 48 for strontium ranelate to 91 for three of the bisphosphonates. Our analysis indicates that the bone-forming agent strontium ranelate may have the lowest NNT for the prevention of both vertebral and hip fracture. Responder analysis may enable translation of clinical trial results into guidance for routine clinical practice by indicating the amount of effort needed to prevent the same event in comparable populations with different treatment options.

Introduction

Osteoporosis is a chronic condition characterized by a reduction in bone mass, usually as a consequence of aging, leading to a reduction in bone strength and an increase in the risk of fracture. Because women are particularly susceptible to bone loss after the menopause, by far the most common form is postmenopausal osteoporosis. Current estimates place the lifetime risk of wrist, vertebral, or hip fracture at 45% in Caucasian women aged over 50 [1], though risk estimates such as this are set to escalate in coming years as the population ages. Indeed, postmenopausal osteoporosis already has a phenomenal impact on health care budgets, which are currently expected to double for osteoporosis by the year 2050 [2]. This dramatic increase in cost takes into consideration that older patients are more likely to suffer hip fracture, which is the most disabling and costly osteoporotic fracture [3].

It is important to take these issues into account when making health care decisions, particularly the selection of effective treatment for chronic disease. Postmenopausal osteoporosis is managed partly by lifestyle modification to prevent falls, and dietary supplementation with calcium and vitamin D. However, these strategies have been shown to be of limited effectiveness in reducing actual fracture risk [4-6], and should be accompanied by a pharmacological treatment. Antiosteoporotic agents with known antifracture efficacy are currently divided into two categories: agents that reduce bone resorption (e.g., bisphosphonates and raloxifene); and agents that increase bone formation (e.g., teriparatide and strontium ranelate) [7]. All of these agents have proven efficacy against vertebral fracture, and some of them against hip fracture.

Despite this picture of a chronic condition, with a whole range of effective treatments to choose from, osteoporosis is currently at the center of debate surrounding the presentation of results of clinical trials guiding the selection of treatment strategies. Antiosteoporotic treatments are generally compared using reduction in relative risk (RRR) of fracture, which generally describe the percentage reduction in event rates versus placebo. In a recent article focusing on osteopenia in the *British Medical Journal*, Alonso-Coello et al [8] argued that such comparisons lead to artificially high reductions in fracture risk for some of antiosteoporotic treatments, and that assessments based on absolute risk would be more realistic. In this review, we attempt

to clarify the arguments behind absolute and relative risk for antiosteoporotic treatments currently available in Europe.

Absolute versus relative risk

The most common parameter used in reporting clinical trials in osteoporosis is the RRR, which is defined as the percentage difference in event rates, in this case fracture, between two groups (see **Box 1**) [9,10]. In other words, RRR represents the probability of fracture in the treatment group in proportion to the probability of fracture in the placebo group. The problem with the RRR is that it fails to discriminate between large absolute treatment effects and very small effects in terms of absolute numbers. In contrast, absolute risk reduction (ARR) is defined as the arithmetic difference between events rates over a fixed period of time (see **Box 1**) [9,10]. In the case of an antiosteoporotic agent, this might be the numerical difference between the rate of vertebral fractures over 3 years with treatment and with placebo.

In an example cited by Alonso-Coello et al [8] an RRR of 75% with raloxifene over 3 years in osteoporotic or osteopenic women can mask an ARR of 0.9% [11]. Clearly, this example is taken out of context, but it demonstrates the dangers of making treatment decisions on the basis of relative risk.

A related—and perhaps more accessible—parameter is the number needed to treat (NNT). This is the number of patients needed to treat over a fixed period of time to prevent one event occurring. NNT, which is a point estimate, is easy to calculate since it is the reciprocal of the ARR (NNT=1/ARR) [10,12]. In the above example, the ARR of 0.9% leads to an NNT of 111, implying that we would need to treat 111 osteoporotic or osteopenic women for 3 years with raloxifene to prevent one vertebral fracture from occurring.

The smaller the NNT, the more effective the treatment. How low can we reasonably expect NNT values to go for antiosteoporotic treatment? NNT values of 2 or 3 (i.e., approaching 1) indicates that a treatment is very effective, and have been found, for example, for antibiotic therapy against *Helicobacter pylori* infection [13]. On the other hand, higher values, up to 20 to 40 are considered to indicate clinical effectiveness in the prevention of mortality in cardiac patients [13]. From this, we see

that NNT is driven by absolute risk at baseline, i.e. in the case of osteoporosis the baseline absolute fracture risk [14].

The advantage of the NNT over RRR is that it expresses both the risk without treatment and the risk reduction with treatment in a single figure. In addition, it informs physicians how much effort they must make to prevent one event with respect to no treatment at all, and allows for better comparison with other treatments. This may well be especially important in the absence of head-to-head trials. European regulatory authorities currently recognize NNT as a relevant and easy to use method of extracting benefit-risk data from individual clinical trials [15]. Indeed, responder analysis (ie, ARR and NNT) may enable the translation of clinical trial results into guidance for routine clinical practice, by giving a better indication of treatment effect than RRR [8,16]. Provided the primary outcome and the treatment duration are the same, NNTs and ARRs can be compared for different treatment options in osteoporosis to give a better measure of the impact of treatment than RRRs.

ARR and NTT for antiosteoporotic treatments

Even though the antiosteoporotic class is relatively small, it can be immensely complicated to navigate around the plethora of studies with differing treatment durations in populations at differing baseline risk of fracture. Comparison of antifracture efficacy is fraught with pitfalls, and comparison of NNTs is of no exception. One admirable attempt at this, in a position statement from the American Society of Health-System Pharmacists [17] cited no fewer than 28 different NNT values for just 7 pharmacological therapies in osteoporosis, and many more for dietary supplements and treatments in development.

In order to simplify this situation and increase the accessibility of reliable data, in this article we review the data for antiosteoporotic agents from placebo-controlled, randomized, double-blind, pivotal phase 3 trials for registration by the European regulatory agencies, carried out in postmenopausal osteoporotic patients with one prevalent fracture at baseline. We restricted our analysis to agents that are currently available in Europe for the treatment of postmenopausal osteoporosis. We used the reported data to calculate ARRs and NNT for each trial for vertebral and hip fracture

over 3 years (**Tables 1 and 2, Figure 1**). We chose these two outcomes since they are the most common sites for osteoporotic fracture. We selected hip fracture, as opposed to "nonvertebral" fracture, which was reported in some of the studies, since these outcomes were composites of fractures at different sites (hip, wrist, and/or ankle) with differing definitions according to the clinical trial.

Antiresorptive agents

NNT to prevent vertebral fracture

Pivotal vertebral fracture data for the bisphosphonate alendronate were reported by the Fracture Intervention Trial (FIT) research group in 1996 [18]. This first report from the FIT investigators included postmenopausal women aged between 55 and 81 years with at least one prevalent vertebral fracture and a femoral neck T-score of <– 2.1. Later reports from the FIT trial did not meet our selection criteria. The rate of vertebral fracture in FIT was 15% in the placebo group versus 8% in the alendronate group. There was a 7% ARR for alendronate 10 mg/day for vertebral fracture over 3 years versus placebo, which leads to an NNT of 15 (**Table 1**).

More recently, the bisphosphonate ibandronate was assessed in the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North American and Europe (BONE) [19]. in 2946 osteoporotic postmenopausal women. The BONE participants were aged between 55 and 80 years and had at least one prevalent vertebral fracture, and with an average lumbar spine T-score of –2.8. Over 3 years, the rate of vertebral fracture was 4.7% with oral ibandronate 2.5 mg/day versus 9.6% with placebo (P=0.0001), which translates into an NNT of 21 (**Table 1**).

The data for the other once-daily bisphosphonate in **Table 1**, risedronate, come from Vertebral Efficacy with Risedronate Therapy–North America (VERT-NA) [20], which was carried out in a similar population of patients aged <85 years with at least one vertebral fracture, and with an average lumbar spine T-score of –2.4. The parallel multinational study (VERT-MN) did not meet our selection criteria. The 3-year event rate for vertebral fracture was 16.3% in the placebo group versus 11.3% in the

risedronate group (*P*=0.003). The ARR for vertebral fracture over 3 years with risedronate 5 mg/day was 5.0% compared with placebo, which gives an NNT of 20.

The bisphosphonates are currently being prescribed in longer-acting formulations, leading to once-weekly, once-monthly, or even once-yearly regimens. Despite this, there are few pivotal trials with these long-acting formulations, since most authorizations are based on bridging trials, which generally use surrogate end points as evidence of efficacy, as opposed to reduction in fracture (bone mineral density or biochemical markers of bone turnover) [21,22]. There is therefore only one pivotal trial of a long-acting formulation of zoledronate in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial [23]. Osteoporotic women were included in HORIZON if they were aged between 65 and 89 years and had a femoral neck T-score of <–2.5 with one or no prevalent vertebral fracture, or <–1.5 if they had more than one prevalent vertebral fracture. The HORIZON participants received a single 15-minute infusion of 5 mg zoledronic acid every 12 months. There was a substantial difference in event rates between zoledronate (3.3%) and placebo (10.9%) over 3 years (**Table 1**). Responder analysis gives an ARR of 7.6% and an NNT of 14, which is compatible with the other bisphosphonates.

The antifracture efficacy of the selective estrogen receptor modulator (SERM) raloxifene was explored in the Multiple Outcomes of Raloxifene Evaluation (MORE) in postmenopausal osteoporotic women aged <80 years [24]. In MORE participants with at least one prevalent vertebral fracture, treatment with raloxifene 60 mg/day reduced the rate of fracture over 3 years versus placebo (14.7% versus 21.2%) (**Table 1**). These data correspond to an ARR of 6.5% and an NNT for vertebral fracture of 16 for raloxifene at 60 mg/day.

NNT to prevent hip fracture

There are three pivotal studies of antiresorptive treatments that give NNT values, all of which are bisphosphonates (**Table 2**). In the FIT study, the rate of hip fracture was reported for postmenopausal osteoporotic women aged between 55 and 81 years with at least one prevalent vertebral fracture; their femoral neck T-score was <–2.1 [18]. The rate of hip fracture over 3 years was 1.0% with alendronate 10 mg/day versus

2.1% with placebo. The substantial 52% RRR should be considered alongside a 1.1% ARR and an NNT for hip fracture of 91.

The same ARR (1.1%) and NNT (91) values were found for hip fracture over 3 years for risedronate and zoledronate in the Hip Intervention Program (HIP) [25] and HORIZON [23] studies, respectively (**Table 2**). In HIP, administration of risedronate 2.5 or 5 mg/day to postmenopausal osteoporotic women (aged 70 to 79 years; femoral neck T-score <–4) led to a 2.8% rate of hip fracture versus 3.9% in the placebo group. The event rates in HORIZON were slightly lower, at 1.4% with zolendronate acid versus 2.5% with placebo. The HORIZON population comprised postmenopausal osteoporotic women aged between 65 and 89 years with a femoral neck T-score of <–2.5 with one or no prevalent vertebral fracture, or <–1.5 if they had more than one prevalent vertebral fracture [23].

Bone-forming agents

NNT to prevent vertebral fracture

There are only two bone-forming agents for which there are pivotal trials yielding data for responder analysis, strontium ranelate and teriparatide (**Table 1**). The antifracture efficacy of strontium ranelate was examined in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial for vertebral fracture [26]. The patients in this trial were aged >50 years; they had diagnosed postmenopausal osteoporosis with at least one prevalent vertebral fracture and in average with a femoral neck T-score of –2.8 and lumbar spine T-score of –3.5. The event rate for vertebral fracture over 3 years in women receiving 2 g/day strontium ranelate was 20.9% versus 32.8% in the placebo group. These data translate into an 11.9% ARR and an NNT of 9 [26].

The randomized, double-blind, pivotal phase 3 trial for registration of teriparatide lasted for a median duration of 21 months [27]. This study was performed in a population aged >50 years with at least one prevalent vertebral fracture and a femoral neck or lumbar spine T-score of <–1. The event rates for vertebral fracture were 5.0%

for teriparatide 20 µg/day over 21 months and 14% with placebo, leading to an ARR of 9% and an NNT of 12 [27].

NNT to prevent hip fracture

There is one pivotal trial in the prevention of peripheral fracture with strontium ranelate (**Table 2**). The Treatment of Peripheral Osteoporosis (TROPOS) trial [28] included an analysis of postmenopausal osteoporotic women aged 74 years or older with a femoral neck T-score ≤–2.4. In this population, the event rate for hip fracture in patients receiving strontium ranelate 2 g/day was 4.3% versus 6.4% in the placebo group, leading to an ARR of 2.1% [28]. The NNT with strontium ranelate 2 g/day to prevent one hip fracture is therefore 48.

To our knowledge, there is no pivotal study showing a reduction in rates of hip fracture with the other bone-forming agent teriparatide.

Discussion

The use of NNT to assess antifracture efficacy has been endorsed by international and national guidelines [15,17,29]. It translates the relatively complex results of clinical trials into a single accessible number, and allows comparison of the amount of effort needed to prevent the same event in comparable populations with other treatment options, which can aid in treatment decisions in daily clinical practice. It provides useful information about the efficacy of treatment, incorporating the effects of treatment and no treatment (placebo) into a single number. In limiting our meta-analytical approach to the selection of studies to pivotal phase 3 studies lasting 3 years on agents currently available in Europe for the treatment of postmenopausal osteoporosis, we hope to have simplified the comparison of antifracture efficacy within the class.

NNT values were also found over the longer-term, according to data available for 5 years' treatment in osteoporosis. To date, among all the antiosteoporotic agents, only strontium ranelate has a prespecified analysis of efficacy against vertebral and

nonvertebral fracture over 5 years [30]. This long-term extension of the TROPOS trial for strontium ranelate 2 g/day reported an NNT of 21 for the prevention of one new osteoporotic fracture at any site (vertebral or nonvertebral) over 5 years in osteoporotic women with baseline lumbar and femoral neck T-scores <–2.4 [30]. This study demonstrated that strontium ranelate has antiosteoporotic efficacy in preventing vertebral and nonvertebral fractures (including hip) over 5-year follow-up. While these data are impressive and confirm the long-term anti-fracture efficacy of this agent, it is difficult to compare with other NNT values with other treatments for osteoporosis, due to the paucity of comparable data in terms of study design, duration, and population.

Another factor to take into consideration when considering anti-fracture efficacy in the clinical setting is adherence to treatment. Indeed, poor adherence to treatment can substantially increase the NNT to prevent an outcome. This issue was addressed in a recent report on the impact of low versus high adherence to bisphosphonate treatment on NNT in osteoporosis [31]. The NNT values in this report (ranging from >100 to well into the thousands) are systematically higher than the values in our paper, because even 80% adherence can increase the NNT relative to a clinical trial setting. This underlines the importance of selection of agents with good acceptability to improve patient compliance with treatment.

Our analysis is not without its limitations. Confining the study to pivotal phase 3 trials used as part of the European regulatory processes may have eliminated those with better or worse NNT values from our analysis, as well as agents in development that have not yet received approval for clinical use. Another limitation is possible differences in the baseline characteristics of the populations concerned. However, our aim was to clarify the comparison of absolute risk reduction in the management of osteoporosis in real clinical practice and simplify the selection of trials. The similarity of the values we found within the bisphosphonate class may support our analysis.

Our simplified approach shows that all of the currently available antiosteoporotic agents have acceptable NNT values for efficacy in preventing vertebral fracture, ranging from NNT=9 for strontium ranelate 2 g/day over 3 years to NNT=21 for ibandronate 2.5 mg/day. The NNT values for the prevention of hip fracture are higher, as would be expected by the increased risk of these patients, and range from NNT=48 for strontium ranelate 2 g/day to NNT=91 for bisphosphonates. On the basis of our

analysis, it appears that bone-forming agents such as strontium ranelate have the lowest NNT for the prevention of both vertebral and hip fracture. With this analysis, we have demonstrated that pharmacological treatment of osteoporosis is worthwhile in the prevention of fracture, and that the antiosteoporotic class is not entirely homogeneous in terms of NNT.

Box 1. Risk, absolute risk, and number needed to treat**.**

Adapted and modified from Barratt et al [9].

Event rate: The number of patients experiencing an event (e.g., vertebral fracture) over a fixed period of time, as a proportion of the number of patients in the whole population.

Relative risk reduction (RRR): The percentage difference in the event rates between two groups (e.g., percentage reduction in vertebral fracture rate in patients receiving treatment versus those receiving placebo), usually expressed as a proportion of the event rate in the untreated (placebo) group.

Absolute risk reduction (ARR): The arithmetic difference between events rates in two groups (e.g., difference in vertebral fracture rates in patients receiving treatment and in those receiving placebo).

Number needed to treat (NNT): The number of patients needed to treat over a fixed period of time to prevent one event (e.g., vertebral fracture) occurring, calculated as the reciprocal of the ARR (NNT=1/ARR).

Table 1 Absolute risk reduction (ARR) and number needed to treat (NNT) for vertebral fracture over 3 years with various antiosteoporotic treatments calculated from the results of randomized, double-blind, pivotal phase 3 trials versus placebo.

	Study	Number of patients (placebo/active treatment)	Mean BMD (T-score or absolute value)		ARR	NNT	*P*†
			Placebo	Active treatment			
Antiresorptive agents							
Alendronate	FIT [18]	965/981	FN BMD 0.56 g/cm^2	FN BMD 0.57 g/cm^2	7.0%	15	<0.001
Ibandronate	BONE [19]	975/977	LS T-score –2.8 FN T-score –2.0	LS T-score –2.8 FN T-score –2.0	4.9%	21	<0.0001
Risedronate	VERT-NA [20]	820/821	LS BMD 0.83 g/cm^2 FN BMD 0.60 g/cm^2	LS BMD 0.83 g/cm^2 FN BMD 0.59 g/cm^2	5.0%	20	0.003
Zoledronate	HORIZON [23]	3861/3875	LS BMD 0.79 g/cm^2 FN BMD 0.53 g/cm^2	LS BMD 0.79 g/cm^2 FN BMD 0.53 g/cm^2	7.6%	14	<0.001
Raloxifene	MORE [24]	770/769	LS BMD 0.75 g/cm^2 FN BMD 0.57 g/cm^2	LS BMD 0.75 g/cm^2 FN BMD 0.57 g/cm^2	6.5%	16	<0.001
Bone-forming agents							
Strontium ranelate	SOTI [26]	719/723	LS BMD 0.72 g/cm^2 FN BMD 0.59 g/cm^2	LS BMD 0.73 g/cm^2 FN BMD 0.59 g/cm^2	11.9%	9	<0.001
Teriparatide*	Neer et al [27]	448/444	LS BMD 0.82 g/cm^2 FN BMD 0.64 g/cm^2	LS BMD 0.82 g/cm^2 FN BMD 0.64 g/cm^2	9.0%*	12*	<0.001

*Assessment over 21 months. †Significance of difference in event rates (treatment versus placebo). BMD, bone mineral density; FN, femoral neck; LS, lumbar spine.
FIT, Fracture Intervention Trial; BONE, Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe; VERT-NA, Vertebral Efficacy with Risedronate Therapy–North America; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; MORE, Multiple Outcomes of Raloxifene Evaluation; SOTI, Spinal Osteoporosis Therapeutic intervention.

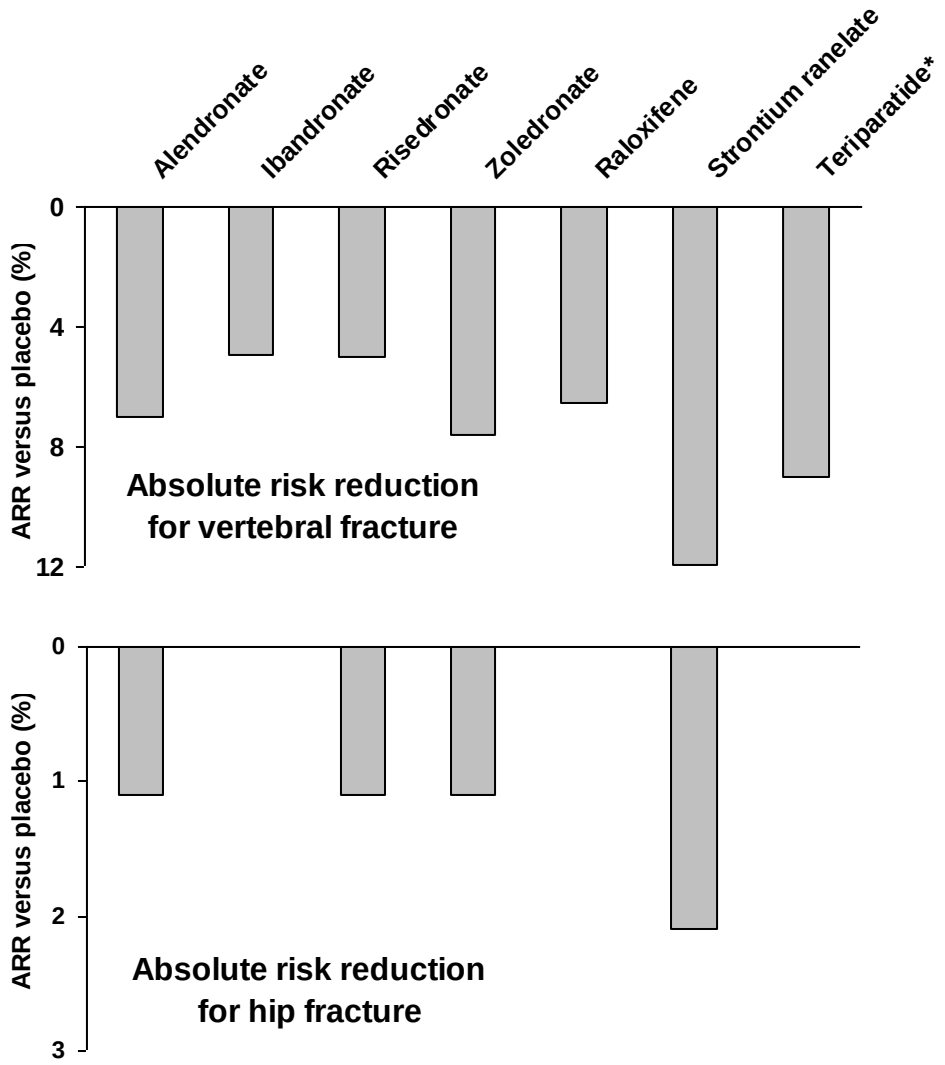
Table 2 Absolute risk reduction (ARR) and number needed to treat (NNT) for hip fracture over 3 years with various antiosteoporotic treatments calculated from the results of randomized, double-blind, pivotal phase 3 trials versus placebo.

	Study	Number of patients (placebo/active treatment)	Mean BMD (T-score or absolute value)		ARR	NNT	*P**
			Placebo	Active treatment			
Antiresorptive agents							
Alendronate	FIT [18]	1005/1022	LS BMD 0.79 g/cm^2 FN BMD 0.56 g/cm^2	LS BMD 0.79 g/cm^2 FN BMD 0.57 g/cm^2	1.1%	91	0.047
Risedronate	HIP [25]	3134/6197	FN T-score –3.7	FN T-score –3.7	1.1%	91	0.02
Zoledronate	HORIZON [23]	2853/2822	LS BMD 0.79 g/cm^2 FN BMD 0.53 g/cm^2	LS BMD 0.79 g/cm^2 FN BMD 0.53 g/cm^2	1.1%	91	0.002
Bone-forming agent							
Strontium ranelate	TROPOS [28]	995/982	LS T-score –3.2 FN T-score –3.6	LS T-score –3.2 FN T-score –3.6	2.1%	48	0.046

*Significance of difference in event rates (treatment versus placebo). Data for ibandronate, raloxifene, and teriparatide not available. BMD, bone mineral density; FN, femoral neck; LS, lumbar spine.
HIP, Hip Intervention Program; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; TROPOS, Treatment of Peripheral Osteoporosis; FIT, Fracture Intervention Trial.

Figure 1. Absolute risk reduction (ARR) with various antiosteoporotic therapies versus placebo for vertebral fracture (top) and hip fracture (bottom) over 3 years in postmenopausal osteoporotic women.

*Assessment over 18 to 21 months. Hip fracture data for ibandronate, raloxifene, and teriparatide not available.



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