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ORIGINAL ARTICLE

Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies

Steven Boonen · Roland F. Laan · Ian P. Barton
Nelson B. Watts

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Abstract Most osteoporosis treatments have proven efficacy in reducing the risk of vertebral fractures, whereas evidence is less straightforward for prevention of non-vertebral fractures. Conclusions as to the efficacy of a treatment should be based primarily on analyses of the intention to treat (ITT) population rather than on exploratory subgroup analyses; however, non-vertebral anti-fracture efficacy has been largely derived by post-hoc subgroup analyses. This review and meta-analysis was performed to assess non-vertebral anti-fracture efficacy of several osteoporosis therapies, including a more stringent assessment of the ITT populations. Data on non-vertebral anti-fracture efficacy, a defined endpoint of the ITT analyses and confirmed by radiographs, were obtained from randomized, placebo-controlled, phase III clinical trials of at least 3-year duration. Meta-analyses were performed for the two bisphosphonates, alendronate and risedronate. Relative risks (RR), 95% confidence intervals (CI) and statistical significance for active treatment compared with placebo were calculated. Eleven clinical trials met the criteria for review, three of which showed statistically significant ($P \leq 0.05$) non-vertebral anti-fracture efficacy in the ITT population: two trials with risedronate and one trial with strontium. A meta-analysis showed significant reductions in the relative risk of non-vertebral fracture for both alendronate (RR = 0.86; 95% CI: 0.76–0.97, $P = 0.012$) and risedronate (RR = 0.81; 95% CI: 0.71–0.92, $P = 0.001$). Risedronate and strontium ranelate were the only treatments to show non-vertebral anti-fracture efficacy in this robust assessment of anti-fracture efficacy of osteoporosis therapy using ITT populations in trials of 3 years or more in duration. Risedronate was the only agent shown to demonstrate efficacy in more than one trial. Meta-analysis showed that both alendronate and risedronate provide non-vertebral anti-fracture efficacy.

Keywords Alendronate · Ibandronate · Non-vertebral fracture · Raloxifene · Risedronate · Strontium ranelate

S. Boonen (✉)
Division of Geriatric Medicine,
Center for Metabolic Bone Diseases,
Catholic University of Leuven, Herestraat 49,
3000 Leuven, Belgium
E-mail: steven.boonen@uz.kuleuven.ac.be
Tel.: +32-16-3448 22

R. F. Laan
Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

I. P. Barton
Procter and Gamble Pharmaceuticals, Egham, UK

N. B. Watts
College of Medicine, University of Cincinnati,
Cincinnati, OH, USA

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality [1]. Although vertebral fractures are the most common osteoporotic fracture, non-vertebral fractures, particularly hip fractures, are associated with high levels of morbidity and mortality. Indeed, approximately 20% of patients with hip fracture do not survive for more than a year from diagnosis, and over 50% never completely regain their prefracture status [2].

A number of pharmacologic agents are approved for the treatment of osteoporosis. Although these agents have documented efficacy in reducing the risk of vertebral fracture, it is highly desirable from a clinical standpoint that treatments should also reduce the risk of non-vertebral fractures. However, few available therapies have unequivocal clinical data supporting their efficacy in preventing non-vertebral fracture [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

The gold standard for demonstration of anti-fracture efficacy in osteoporosis trials is the primary predetermined analysis of the intention to treat (ITT) population; this is highlighted by the requirement of fracture prevention efficacy in trials of at least 3-year duration for registration of new therapies [15, 16]. The majority of these trials have focused on the prevention of vertebral fracture, with assessment of efficacy in the prevention of non-vertebral fracture relying largely on the analysis of subgroups. The use of subgroup analyses to demonstrate efficacy of a new treatment is not in line with recognized scientific standards and should be interpreted with caution. Indeed, the guidelines from the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use explicitly state that such analyses should be used in an exploratory manner only and that conclusions as to the efficacy of a treatment should not be based on such analyses alone [17].

Meta-analyses provide a framework to formally evaluate quantitatively the treatment effect from at least two trials. However, the Committee for Proprietary Medicinal Products (CPMP) guidance document on meta-analyses states that a meta-analysis involving trials that are not convincing in their own right is inferior to one robust trial supported by smaller trials [18]. Pre-specification of the objective of the intended analyses, search strategy, inclusion and exclusion criteria and statistical methods are important components when planning a meta-analysis. Such analyses can combine summary statistics from individual trials or individual patient data, with the latter allowing a more comprehensive evaluation [19]. From a statistical point of view, it is important to evaluate the possibility of a qualitative trial-by-treatment interaction and be aware that differential exposure to study medication across different trials can have an effect on outcome.

Recently, a number of meta-analyses have been published documenting the efficacies of currently available osteoporosis treatments in the prevention of fracture [20, 21, 22, 23, 24, 25, 26, 27]. In the absence of results from head-to-head trials of osteoporosis treatments, such an approach combines data in a surrogate attempt to formulate a statistical summary statement. However, some meta-analyses have ignored key registration trials [24], and others have used those meta-analyses inappropriately to compare efficacy between treatments [28].

The aim of this study was to evaluate the non-vertebral anti-fracture efficacy data of available treatments for osteoporosis as assessed by 3-year clinical trials of ITT populations that met the regulatory registration criteria laid down for osteoporosis treatments. In addition, a meta-analysis was performed for the two bisphosphonates, alendronate and risedronate.

Materials and methods

Review

Data sources

Journal manuscripts describing the key phase III trials for all currently available osteoporosis treatments were identified through Medline (1966 to March 2004), EMBASE (1984 to March 2004) and BIOL (1996 to March 2004) literature searches. BIOL was used in order to identify abstracts from scientific meetings that may not have been published as manuscripts. Key terms used in the search were osteoporosis, fracture, clinical trial, clinical study and human. Duplicate sources were removed, and the articles were hand-searched by two people, independently.

Inclusion criteria

Only data from phase III, randomized, placebo-controlled clinical trials of osteoporosis treatments of at least 3-year duration were included. All incident non-vertebral fractures were confirmed by radiographs. Data were derived for each trial based on the number of patients in the ITT populations for active and placebo treatment groups. Consistent with regulatory agency guidelines, the incidence of patients with new fractures was analyzed using the patient as the sampling unit (not the number of fractures) [15, 16]. The treatment effect was summarized for each trial [i.e., relative risk (RR), 95% confidence interval (CI) and *P* value]. An analysis was also undertaken to assess treatment efficacy over a range of disease severity as determined by placebo fracture incidence. Subgroup analyses were not included.

Definition of non-vertebral fracture

Definition of non-vertebral fractures differed between trials as shown in Table 1.

Meta-analysis

Data from trials with alendronate and risedronate were included in the meta-analysis. A time to first fracture assessment was not evaluated since individual patient data for alendronate were unavailable. Relative risks, 95% confidence intervals (CI) and statistical significance for active treatment versus placebo were calculated for each individual trial. Pooled estimates for each treatment were computed using Cochrane-Mantel-Haenszel statistics, thus allowing the analysis to be stratified by individual trials. The statistical analyses were performed using PC SAS v8.2.

Table 1 Definition of non-vertebral fracture between trials

Reference	Treatment	Definition of non-vertebral fracture
[3]	Alendronate	Excluded fractures on the basis of trauma
[4, 5]	Alendronate	Excluded pathogenic fractures or fractures due to trauma sufficient to fracture a normal bone in most young adults. Prior to unblinding, subgroups of clinical fractures were defined as non-vertebral fractures
[11]	Calcitonin	Fractures were recorded and verified by hospital records
[12, 13]	Ibandronate	Excluded fractures of the hand, feet, face and skull
[14]	Raloxifene	Excluded traumatic fractures (i.e., resulting from traffic collision, a beating or having been struck by falling or moving objects). Excluded pathologic fractures and those involving the fingers, toes and skulls
[6, 7, 8]	Risedronate	Included non-spine osteoporosis-related fractures recorded at six skeletal sites regardless of trauma: clavicle, hip, humerus, leg, pelvis and wrist
[9, 10]	Strontium	Excluded fractures of the skull, face, finger, toe and coccyx

Results

Review

Eleven trials fulfilled the analysis criteria: three with alendronate [3, 4, 5], one with calcitonin [11]; one with ibandronate [12], one with raloxifene [14], three with risedronate [6, 7, 8] and two with strontium ranelate [9, 10]. A summary of the patient characteristics, including calcium and vitamin D intake and fracture status at study entry for each of the trials included in this review, is shown in Table 2. The average patient was aged 69 years, with a BMI of 25 kg/m^2, taking 1,000 mg supplementation of calcium and 500 IU of vitamin D (Table 2).

Table 3 shows that statistically significant reductions in the risk of non-vertebral fracture ($P \leq 0.05$) were observed in the ITT population of three trials, risedronate in two trials [6 8] and strontium ranelate in one [10]. Across all 11 trials, treatment efficacy did not appear to be related to the severity of osteoporosis (Fig. 1); that is, efficacy was demonstrated in some trials with a relatively low incidence of non-vertebral fractures in the control group and not demonstrated in other trials where the placebo incidence was high.

Meta-analysis

A meta-analysis of alendronate and risedronate trials was initiated to further explore the efficacies of these two bisphosphonates in preventing non-vertebral fracture. Pooled data were assessed from the six trials that met the analysis criteria. A funnel plot showed no obvious sign

Table 2 Patient characteristics of trials included in the review. *BMI* body mass index

Drug/trial	Age (years)[a]	BMI (kg/m^2)[a]	Height (cm)[a]	Calcium supplement (mg)	Vitamin D supplement (IU)	Prior vertebral fracture
Alendronate						
Libermann	64	24	-	500	-	21%
FIT VFA	71	26	159	500	250	100%
FIT CFA	68	25	160	500	250	0%
Risedronate						
VERT-MN	71	26	156	1,000	500	98%
VERT-NA	69	26	158	1,000	500	78%
HIP	78	25	156	1,000	500	30%
Raloxifene						
MORE	66	25	-	500	400–600	37%
Strontium						
TROPOS	77	-	-	1,000	400–800	34%
SOTI	69	26	-	1,000	400–800	100%
Ibandronate						
BONE	69	-	160	500	400	94%
Calcitonin (200 IU)						
PROOF	69	25	-	1,000	400	79%
Median	69	25	158.5	1,000	500	78%

[a]Mean. - Not known

Table 3 Non-vertebral fracture incidence by treatment. RR (95% CI) = relative risk and 95% CI; ARR = absolute risk reduction

Drug/trial	Fracture incidence		Treatment effect		
Total*n*	Placebo *n* (%)	Active *n* (%)	RR (95% CI)	*P* value	ARR
Alendronate					
Liberman: 0–3 years(n = 994)	397 (10.7%)	597 (8.5%)	0.79 (0.52, 1.22)	Not available	2.2%
FIT VFA: 0–3 years (n = *2,027*)	1,005 (14.7%)	1,022 (11.9%)	0.80 (0.63, 1.01)	P = 0.063	2.8%
FIT CFA: 0–4 years (n = 4,432)	2,218 (13.3%)	2,214 (11.8%)	0.88 (0.74, 1.04)	P = 0.130	1.5%
Risedronate					
VERT-MN: 0–3 years (n = 812)	406 (16.0%)	406 (10.9%)	0.67 (0.44, 1.04)	P = 0.063	5.1%
VERT-NA: 0–3 years (n = 1,627)	815 (8.4%)	812 (5.2%)	0.60 (0.39, 0.94)	P = 0.020	3.2%
HIP: 0–3 years (n = 9,331)	3,134 (11.2%)	6,197 (9.4%)	0.80 (0.70, 1.00)	P = 0.030	1.8%
Raloxifene					
MORE: 0–3 years (n = 6,828)	2,292 (9.3%)	4,536 (8.5%)	0.90 (0.80, 1.10)	Not available	0.8%
Strontium					
TROPOS: 0–3 years (n = 4,932)	2479 (12.9%)	2453 (11.2%)	0.84 (0.71, 1.00)	P = 0.040	1.7%
SOTI: 0–3 years (n = 1442)	723 (16.9%)	719 (15.6%)	0.90 (0.69, 1.17)	Not available	1.3%
Ibandronate					
BONE: 0–3 years (n = 2,929)	975 (8.2%)	2.5 mg/day 977 (9.1%)	1.11 (0.83, 1.48)	Not available	−0.9%
		20 mg/int 977 (8.9%)	1.09 (0.81, 1.45)	Not available	−0.7%
Calcitonin (200 IU)					
Proof: 0–5 years (n = 620)	305 (15.7%)	315 (14.6%)	0.88 (0.59, 1.32)	Not available	1.1%

The*n* (%) is based on the number of ITT patients included and the percent who were estimated to have sustained at least one incident non-vertebral fracture according to the published manuscript; RR (95% CI) for ibandronate (i.e., BONE trial) is estimated

of heterogeneity, indicating that pooling of these data was appropriate (Fig. 2).

Analysis of the pooled data showed that both alendronate and risedronate significantly reduced the relative risk of non-vertebral fracture (P = 0.012 and P = 0.001, respectively). The estimated risk reduction values were 0.86 (95% CI 0.76, 0.97) for alendronate and 0.81 (95% CI 0.71, 0.92) for risedronate (Table 4).

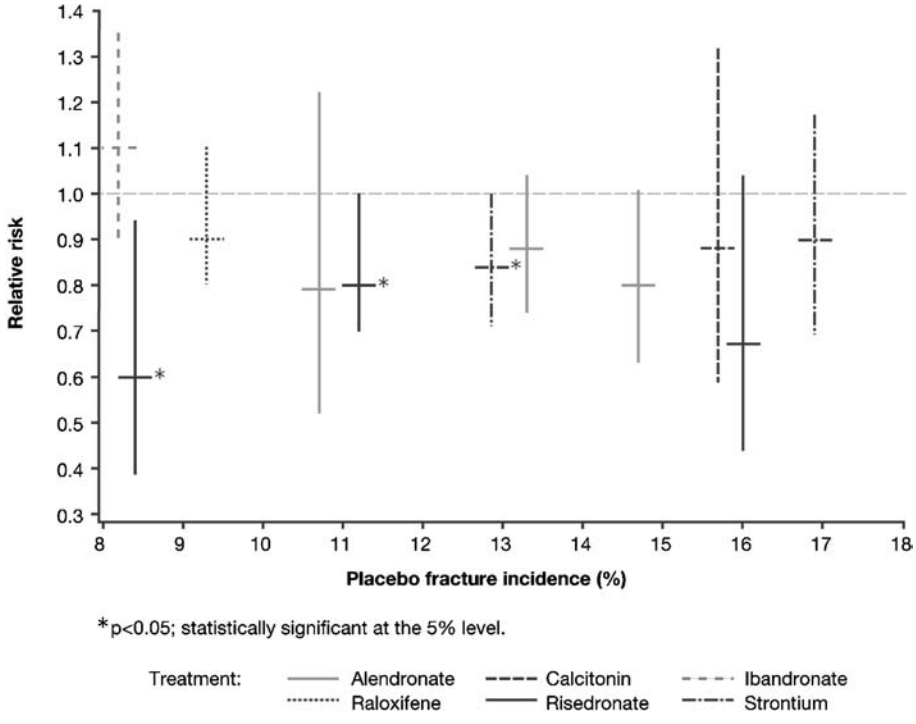

Fig. 1 Non-vertebral anti-fracture efficacy by placebo incidence

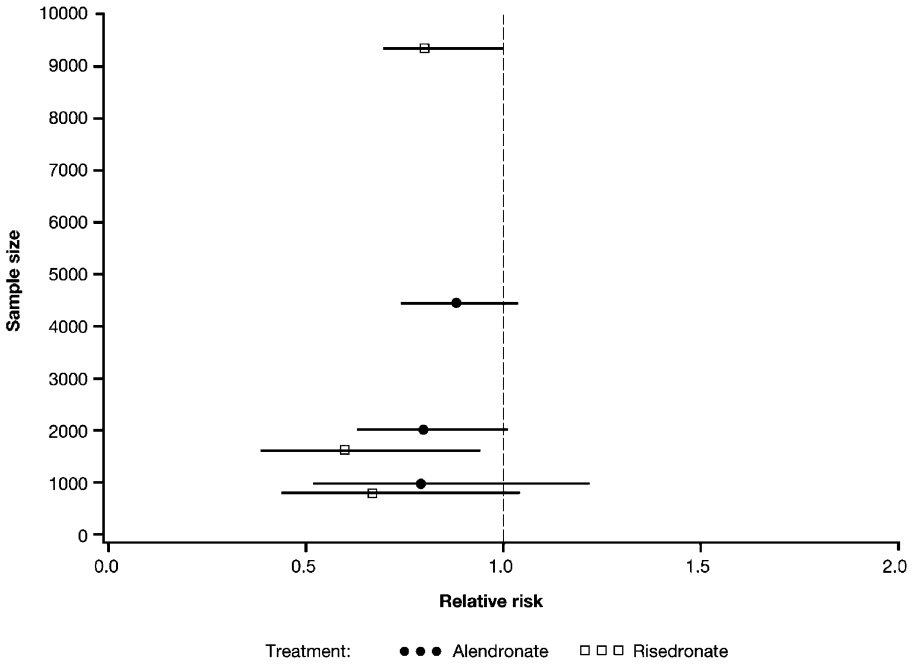

Fig. 2 *Funnel plot* of six trials with alendronate and risedronate

Discussion

This paper provides both a review of non-vertebral anti-fracture efficacy from phase III registration trials of 3-year duration and a meta-analysis of those treatments that reported non-vertebral fracture incidence in the respective trials. Risedronate exhibited efficacy in two trials of patients with differing severities of disease ($P \leq 0.03$) [6, 8], and strontium ranelate demonstrated efficacy in one trial ($P = 0.04$) [10]. Additionally, a meta-analysis of the pooled data of alendronate and risedronate showed that both treatments significantly reduced the risk of non-vertebral fracture ($P = 0.012$ and $P = 0.001$, respectively).

An assessment of fracture incidence from the placebo arms of the trials contributes to an understanding of the effects of osteoporosis treatment on non-vertebral fracture risk reduction. Non-vertebral fracture incidence in the placebo-treated patients of the risedronate trials spanned a wide range (8.4 to 16.0%) [6, 7, 8]. Risedronate therapy showed significant efficacy compared with the placebo treatment arm across this range of disease severity. In the alendronate trials, the incidence of non-vertebral fracture in the placebo arms ranged from 10.7 to 14.7% [3, 4, 5]. In the individual trials, alendronate treatment was not significant at reducing the incidence of non-vertebral fracture when compared with the placebo groups. The lowest incidence of fracture in placebo arms (8.2%) was found in the BONE trial with ibandronate [12]. The incidence of non-vertebral fracture for both doses of ibandronate examined in this study (2.5 mg/day = 9.1% and 20 mg/intermittently = 8.9%) was similar and was not significantly different compared with placebo (8.2%). In the strontium ranelate trial a significant reduction in non-vertebral fracture ($P = 0.04$) was reported, with a fracture incidence of 12.9% in the placebo population [10].

Table 4 Non-vertebral fracture incidence by treatment, pooled meta-analysis. RR (95% CI) = relative risk and 95% confidence interval

Drug/trial	Treatment effect per publications RR (95% CI)	*P* value	Our estimated treatment effect RR (95% CI)	*P* value
Alendronate				
Liberman: 0–3 years	0.79 (0.52, 1.22)	Not available	0.79 (0.52, 1.19)	$P = 0.256$
FIT VFA: 0–3 years	0.80 (0.63, 1.01)	$P = 0.063$	0.81 (0.65, 1.01)	$P = 0.065$
FIT CFA: 0–4 years	0.88(0.74, 1.04)	$P = 0.130$	0.89 (0.76, 1.04)	$P = 0.140$
Pooled estimate (Trial-by-Trt:$P = 0.740$)	-	-	0.86 (0.76, 0.97)	$P = 0.012$
Risedronate				
VERT-MN: 0–3 years	0.67 (0.44, 1.04)	$P = 0.063$	0.71 (0.47, 1.06)	$P = 0.089$
VERT-NA: 0–3 years	0.60 (0.39, 0.94)	$P = 0.020$	0.64 (0.42, 0.97)	$P = 0.036$
HIP: 0–3 years	0.80 (0.70, 1.00)	$P = 0.030$	0.85 (0.74, 0.98)	$P = 0.028$
Pooled estimate (Trial-by-Trt:$P = 0.347$)	-	-	0.81 (0.71, 0.92)	$P = 0.001$

Findings from a previous meta-analysis by Cranney et al. [24] have subsequently been inappropriately used for an "evidence-based comparison of anti-resorptive agents for the treatment of osteoporosis" [28], suggesting that alendronate was superior to risedronate for prevention of non-vertebral fractures. This suggestion was based on apparent differences in the point estimates of the fracture risk reductions for these two agents. In the meta-analysis by Cranney et al., risedronate and alendronate were both found to demonstrate efficacy in preventing non-vertebral fracture [20, 24]. However, examination of the methodology used in this study revealed several differences compared with our study. In particular, data from the Fracture Intervention Trial (FIT) [5], one of the largest trials and included in our analysis, were excluded from the analysis by Cranney et al.[24]. The omission of this pivotal trial is inconsistent with the authors' inclusion of other large trials of calcitonin [11] and raloxifene [14] into the pooled analysis. As indicated, the findings from this analysis with the non-inclusion of the FIT data have subsequently been used as a basis for further analyses in the literature [28]. Karpf et al. [29] performed a meta-analysis of alendronate using individual patient data from five studies, which also did not include FIT, concluding that alendronate was effective in reducing the risk of non-vertebral fractures.

The results of our meta-analysis are not intended as a comparison between alendronate and risedronate. Instead, it is intended that these data provide assessments of non-vertebral fracture risk reduction based on RR proportions from phase III pivotal fracture trial programs using the ITT population. There is increasing evidence that the BMD-fracture risk relationship is not a linear one, and that it is affected differently by different agents [30, 31]. Therefore, BMD endpoint trials cannot substitute for fracture endpoint trials and do not allow a formal comparison of the magnitude of the treatment effects of different osteoporosis agents. To date, alendronate and risedronate have not been studied in head-to-head comparative trials with fracture endpoints. In the absence of head-to-head trials, the use of meta-analyses to compare treatments is common; however, meta-analyses cannot substitute for direct comparative fracture trials either. Even in the presence of discrete CIs, between-trial comparisons of treatment effects are unreliable due to differences in study populations' sensitivity to treatment effect [20]. In the context of osteoporosis treatment with alendronate or risedronate, the CIs around the magnitude of treatment effect overlap in their effects on both vertebral and non-vertebral fractures. Differences in the point estimates should therefore not be interpreted as indicating true underlying differences in the magnitude of the effect. Indeed, Cranney et al. cautioned against inferring that the effect of one bisphosphonate is greater than the other, based on their recent meta-analysis [20].

Several limitations of our study should be highlighted. This analysis is based on published data; access to internal data was not available from most studies. Moreover, with meta-analyses it is not possible to match patient cohorts precisely, either in terms of demography or disease severity. The trials included here also differed in their location and definition of non-vertebral fractures as well as the inclusion/exclusion of fractures caused by trauma. Similarly, the incidence of fracture within placebo groups varied from trial to trial. By placing a 3-year limit on the inclusion of data, the analysis has also omitted positive data for several treatments. For example, both parathyroid hormone (PTH) and alendronate have been shown to significantly reduce the risk of non-vertebral fracture compared with placebo ($P = 0.02$ and $P = 0.021$, respectively) at time points outside the scope of this paper [32, 33]. Additionally, by excluding all but ITT population data, this analysis does not reveal the efficacy of individual treatments in preventing non-vertebral fracture in study sub-populations [5, 12, 34]. However, these efficacy subgroup analyses only included a small proportion of the ITT population. For example, the reduction in relative risk of new non-vertebral fractures with raloxifene in patients with two or more pre-existing vertebral fractures was derived from a subgroup representing approximately 20% of the ITT population [34]. It should also be noted that of the 11 trials included in our study, only two trials were specifically designed to evaluate non-vertebral fracture efficacy as the primary endpoint [8, 10].

The ITT principle is based on two components: the patient population and the handling of the data. Compliance with this principle would require that all randomized patients (regardless of failure to satisfy major entry criteria, failure to take at least one dose of study medication and the lack of any data post randomization) be included with complete follow-up for all study outcomes [17]. In practice this ideal may be difficult to achieve. As highlighted by statisticians and epidemiologists [35, 36, 37], the impact of missing data can have an effect on the analyses. Phillips and Wright respectively provide real-life and simulation data showing that an imbalance caused by missing data between treatment groups can bias the results [35, 37].

During the review of the 11 trials included in this research, it was clear that there was no universal approach to reporting the reasons for withdrawal, and more importantly, to reporting how many patients had complete outcome data (e.g., the calcitonin, ibandronate, risedronate and raloxifene trials summarized the number of withdrawals; the alendronate trials summarized the number of patients who did not have follow-up radiographs; the strontium trials summarized the number of patients who had complete follow-up at 3 years). Taking these limitations into account, we believe inferences from this review are valid and meaningful, as there was no relationship between treatment and missing outcome (e.g., within each trial the loss-to-follow-up was similar across treatment groups), and all the analyses used time-to-first event methodology, which can take into account censored observations, thus retaining all

patients regardless of withdrawal. The authors recommend that in the event of violating the ITT principle in its strictest sense, sensitivity analyses should be performed and summarized in the literature so the impact of loss-to-follow-up to the estimation of the treatment effect can be fully appreciated.

The efficacy of each individual pharmacological agent is likely to differ, and the suitability of a particular therapy should be judged on a case-by-case basis. Given the chronic nature of osteoporosis and therefore the requirement for long-term treatment efficacy, the use of such limits in this analysis is appropriate to the condition. Indeed, the availability of proven long-term fracture efficacy in randomized controlled trials provide the most robust assessments of drug efficacy, which are ultimately of benefit to clinicians and, in turn, patients [38].

Conclusions

Only risedronate and strontium ranelate have been shown to reduce the risk of non-vertebral fractures in the ITT populations from randomized trials of at least 3-year duration. Of these, only risedronate has been shown to provide non-vertebral anti-fracture efficacy in more than one study. Meta-analyses of both risedronate and alendronate showed the two bisphosphonates to be efficacious in preventing non-vertebral fracture. The use of data only from ITT populations, while likely resulting in conservative estimates of the overall reduction in relative risk of fracture, ultimately gives the most reliable overall estimate of treatment efficacy.

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