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Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures

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Abstract
Summary In this meta-analysis of the control arms of four phase 3 trials, mild vertebral fractures were a significant risk factor for future vertebral fractures but not for non-vertebral fracture.
Introduction A prior vertebral fracture is a risk factor for future fracture that is commonly used as an eligibility criterion for treatment and in the assessment of fracture probability. The aim of this study was to determine the prognostic significance of a morphometric fracture according to the severity of fracture.
Methods We examined the control (placebo) treated arms of four phase 3 trials. Vertebral fracture status was graded at baseline in 7,623 women, and fracture outcomes were documented over the subsequent 20,000 patient-years. Fracture outcomes were characterised as a further vertebral fracture, a non-vertebral fracture or a clinical fracture (non-vertebral plus clinical vertebral fracture). The relative risk of fracture was computed from the merged β coefficients of each trial weighted according to the variance.
Results Mild vertebral fractures were a significant risk factor for vertebral fractures [risk ratio (RR)=2.17; 95 % CI=1.70–2.76] but were not associated with an increased risk of non-vertebral fractures (RR=1.08; 95 % CI=0.86–1.36). Moderate/severe vertebral fractures were associated with a high risk of vertebral fractures (RR=4.23; 95 % CI=3.58–5.00) and a moderate though significant increase in non-vertebral fracture risk (RR=1.64; 95 % CI=1.38–1.94).
Conclusions Prior moderate/severe morphometric vertebral fractures are a strong and significant risk factor for future fracture. The presence of a mild vertebral fracture is of no significant prognostic value for non-vertebral fractures. These findings should temper the use of morphometric fractures in the assessment of risk and the design of phase 3 studies.

Keywords Fracture risk · Meta-analysis · Vertebral morphometry

Introduction

Vertebral fractures occupy a dominant position in osteoporosis. The spine is a classic site of fragility fracture and vertebral fractures are associated with low bone mineral density (BMD) [1, 2]. The majority of phase 3 studies in osteoporosis have recruited individuals with a prior spine fracture and the principal outcome event has been the effect of intervention on the risk of vertebral fracture. Vertebral fractures also have a prominent role in assessment and treatment guidelines. For example, many authorities recommend that a prior spine fracture is an eligibility criterion for intervention or reimbursement [3–6].

Despite this central position, the incidence and morbidity from vertebral fractures are not well documented, in part related to the difficulties in defining vertebral fracture and because of the non-specific nature of the morbidity occasioned by the disorder (e.g. back pain). In addition, the diagnosis is made on the appearance or shape of the vertebral body on X-rays. The deformities that result from osteoporotic fracture are usually classified as a crush fracture (involving compression of the entire vertebral body), a wedge fracture (in which there is anterior or posterior height loss) and biconcavity (where there is relative maintenance of the anterior and posterior heights with central compression of the end-plate regions). A number of morphometric approaches have been developed to quantify the shape of the vertebral body from radiographs of the lateral spine [7–10], and this

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has helped in defining the prevalence and incidence of vertebral fracture. A widely used clinical semi-quantitative system is to classify vertebral fractures as mild (20–25 % height loss), moderate (25–40 % height loss) or severe (>40 % height loss) [11].

A further problem in describing the epidemiology of vertebral fracture is that not all fractures come to clinical attention [12–14]. Estimates for the proportion of vertebral deformities that reach the attention of primary care attention vary, however, in different countries [12, 15, 16]. In register studies, the discharge rate for hospitalised vertebral fractures is closely correlated with the discharge rate for hip fracture [14]. In Sweden, approximately 23 % of vertebral deformities come to clinical attention in women, and a somewhat higher proportion in men [16]. A similar proportion has been observed in the placebo wing of multinational intervention studies [17].

Thus, a vertebral fracture may variously be symptomatic or asymptomatic, mild, moderate or severe. Overall, vertebral fractures carry a significantly increased risk of a further fracture. Meta-analyses suggest that the risk is approximately twofold increased [18]. The aim of the present study was to assess the prognostic significance of vertebral fracture according to the degree of vertebral deformity. The hypothesis to be tested was that mild morphometric vertebral fractures carried the same prognostic significance as moderate or severe vertebral for future fracture outcomes.

Methods

We studied four phase 3 trials that examined the effects of intervention in postmenopausal women. Two studies examined the effect of strontium ranelate and the others, the effects of raloxifene and bazedoxifene. The trials have been published in full [19–22]. For this report, we studied all women that were allocated to the placebo arms of these studies. Details relevant to this analysis are summarised below.

The SOTI study

Spinal Osteoporosis Therapeutic Intervention (SOTI) study was a randomized, double-blind, placebo-controlled trial that recruited 1,649 postmenopausal women with low bone mineral density and at least one vertebral fracture to receive 2 g of oral strontium ranelate daily or placebo for 3 years [19]. Calcium and vitamin D supplements were given to both groups before and during the study. Women were enrolled at 72 centres in 11 European countries and Australia. Women were eligible for the study if they were at least 50 years old, had been postmenopausal for at least 5 years, had at least one fracture confirmed by spinal radiography (after minimal trauma) and had a lumbar spine bone mineral density of 0.840 g/cm^2 or less (measured with Hologic instruments). The primary endpoint was the effect of strontium ranelate on the risk of vertebral fracture at 3 years.

The TROPOS study

The treatment of peripheral osteoporosis (TROPOS) study was a randomized, double-blind, placebo-controlled clinical trial designed to assess the effectiveness of strontium ranelate in preventing non-vertebral fractures in postmenopausal women with osteoporosis [20]. Ambulatory postmenopausal women were recruited at 75 centres in 11 European countries and in Australia. Women were eligible for study if they had a femoral neck BMD <0.600 g/cm^2 (measured with Hologic instruments), corresponding to a T-score<−2.5 SD according to the centralised normative data and were >74 years of age, or aged between 70 and 74 years but with one additional fracture risk factor for fracture (i.e. history of osteoporotic fracture after menopause, residence in a retirement home, frequent falls or a maternal history of osteoporotic fractures of the hip, spine or wrist). Women received 2 g of oral strontium ranelate daily or placebo for 3 years. Calcium and vitamin D supplements were given to both groups before and during the study. The primary endpoint was the incidence of non-vertebral fractures.

Bazedoxifene

This trial was a 3-year multinational, double-blind, randomized, placebo- and raloxifene-controlled study including 7,492 osteoporotic women aged 55 years or more (mean age=66 years) [21]. The primary analysis was over a 3-year exposure. Postmenopausal women were recruited either on the basis of low BMD (T-score≤−2.5 SD at the lumbar spine or femoral neck) or a prior vertebral fracture. Patients were randomised to four treatment groups: Two groups received bazedoxifene (20 or 40 mg daily; n=1,886 and 1,872, respectively), a third group received raloxifene (60 mg daily) and a placebo group (n=1,885). All patients took calcium (1,200 mg daily) and vitamin D (400–800 IU daily). The primary endpoint of the 3-year study was to evaluate the efficacy of bazedoxifene compared with placebo on the risk of radiographically confirmed new vertebral fractures in postmenopausal women with osteoporosis after 36 months of therapy. A secondary endpoint was the effect of bazedoxifene on non-vertebral fracture and clinical vertebral fractures. The prognostic significance of vertebral fractures at baseline has been published separately [23].

The MORE study

The pivotal study of raloxifene was the Multiple Outcomes of Raloxifene Evaluation (MORE) study [22]. MORE was a

multicentre, randomised, blinded, placebo-controlled trial that examined the effect of raloxifene in postmenopausal osteoporosis. The trial recruited 7,705 women aged 31 to 80 years in 25 countries who had been postmenopausal for at least 2 years and who met World Health Organization criteria for having osteoporosis. Study group 1 included those in whom the femoral neck or lumbar spine bone mineral density T-score was below −2.5 SD. Study group 2 included women who had low bone mineral density and one or more moderate or severe vertebral fractures, or two or more mild vertebral fractures, or who had at least two moderate fractures regardless of their bone mineral density. The study had up to 36 months of follow-up for efficacy. Within each substudy, women were randomly assigned to raloxifene 60 mg daily, raloxifene 120 mg daily or to placebo. In addition, all women received supplemental calcium (500 mg daily) and cholecalciferol (400 to 600 IU daily). The primary endpoint was the effects of raloxifene on the incidence of morphometric vertebral fracture. Secondary endpoints included the effects of raloxifene on non-vertebral fractures.

Assessment of prior vertebral fracture

Within each study, a prior vertebral fracture was assessed from lateral X-rays of the thoracic and lumbar spine by semi-quantitative (SQ) visual assessment of each vertebra, from T4 to L4. The semi-quantitative grading scale was as follows: grade 0 (none), normal; grade 1 (mild), a decrease in the height of any vertebra of 20 to 25 %; grade 2 (moderate), a decrease of 25 to 40 %; and grade 3 (severe), a decrease of 40 % or more [11, 24].

The data base provided the maximum SQ grade of each enrolled patient. For example, the allocation of a score of 2 indicates that at least one moderate fracture was detected at screening. Maximum scores were given as 0, 1, 2 or 3.

For strontium ranelate and bazedoxifene, a history of a previous fracture of any kind was documented in all patients. Fractures other than prior vertebral fractures were not documented in MORE.

Assessment of outcome fractures

A new vertebral fracture was defined by a change in the score of a vertebra from grade 0 at baseline to a subsequent grade of 1 or more. A second quantitative assessment was also performed: Anterior, middle and posterior vertebral heights were measured for each vertebra, from T4 to L4. A new fracture was defined by a decrease in height of at least 15 % on a vertebra graded 0 at baseline and with a grade on the semi-quantitative scale of 1, 2 or 3 [25]. A fracture was considered to be a clinical fracture if there was associated acute back pain, a decrease in body height of at least 1 cm, or both and supported by additional radiographs. Clinical vertebral fracture outcomes were excluded from the analysis of morphometric vertebral fracture outcome, except in the case of bazedoxifene.

Non-vertebral fractures were confirmed by a radiologic evaluation or from a hospital report. For the purposes of this report, we excluded fractures of the skull, hands, feet and ankle which are characteristically not associated with osteoporosis [26, 27]. We also excluded from analysis patients who sustained a pathological fracture due to secondary carcinoma.

For the purposes of the present study, the primary outcomes were as follows: vertebral fractures assessed by morphometry and, secondly, non-vertebral fractures at sites susceptible to osteoporosis as previously described. In addition, we assessed all clinical fractures comprising non-vertebral fractures as described above plus clinical vertebral fractures.

Measurement of BMD

BMD was measured at the femoral neck. For the studies with strontium ranelate, the measurements were made using Hologic equipment and BMD results were converted to a T-score using the US normative database from the National Health and Nutrition Examination Survey III [28]. For the MORE study, BMD was supplied as a T-score using the US normative database from NHANES III. To accommodate different equipment manufacturers, conversion standards [29] were used. For the study of bazedoxifene, a machine-specific Z-score was calculated by age which removed the systematic differences among machine manufacturers.

Statistical methods

We assessed the relative risk of outcome fractures according to the maximum SQ grade for each treatment modality (i.e. the two trials for strontium ranelate were merged as detailed elsewhere [30]). Relative risk was assessed with and without adjustment or BMD. Summary relative risks were derived.

The risk of fracture was estimated by Poisson regression applied to each cohort separately. Covariates included time since start of follow-up, current age, prior fracture and BMD. We additionally excluded BMD from the model. The results of each cohort were weighted according to the variance and merged to determine the weighted means and standard deviations. The risk ratio (RR) of those with a prior fracture versus those without a prior fracture was equal to e^{mean}.

Results

Patient characteristics at baseline are shown in Table 1. A total of 7,623 women were available for analysis of which all but 144 had a BMD measurement at the femoral neck at baseline. The age range was 40–96 years. Fifty-five percent of women had no vertebral deformity at study entry. Of those

with a vertebral fracture, 46, 36 and 18 % were characterised as having a mild, moderate or severe fracture, respectively.

Patients in the MORE study were followed up for up to 3.9 years (mean 2.6 years). For the SOTI/TROPOS studies, the follow-up interval was up to 4.6 years (mean 2.8 years). For women allocated to the placebo arm of the bazedoxifene study, the follow-up was up to 3.3 years (mean 2.6 years). The total follow-up was 20,149 patient-years. Fracture outcomes are shown in Table 2.

A mild vertebral fracture at the baseline was associated with a significant increase in the risk of a further incident vertebral fracture categorised using either a morphometric or clinical definition (Table 3). The risk was increased approximately twofold to threefold. Moderate or severe vertebral fractures at baseline were associated with a much higher relative risk—approximately fourfold. These findings persisted with adjustment for femoral neck BMD. The separation of moderate/severe vertebral fractures indicated a progressive increase in risk with the grade of vertebral fracture at baseline (Fig. 1). Severe vertebral fractures at the baseline were associated with a sixfold increase in risk of a new vertebral fracture (RR=6.12; 95 % CI=5.00–7.49).

In contrast, the risk of non-vertebral fractures was not significantly increased in the presence of a prior mild vertebral fracture. Moderate/severe prior vertebral fractures were associated, however with a significant increase in the risk of a further non-vertebral fracture in placebo treated patients. The increase in risk was modest (RR=1.64; 95 % CI=1.38–1.94) in comparison with the risk of a clinical vertebral fracture (RR=7.24; 95 % CI=5.47–9.57) or a morphometric vertebral fracture (RR=4.23; 95 % CI=3.58–5.00). These findings were independent of BMD. As in the case of vertebral fracture outcomes, the risk of non-vertebral fracture increased progressively according to the grade of prior vertebral fracture.

It should be noted that the outcome variable of clinical vertebral fractures by definition excluded other clinical fractures. When these were added to the outcome (i.e. clinical vertebral fracture and non-vertebral fracture), the associations persisted though the hazard ratios were higher (Table 3). The impact of a mild vertebral fracture in predicting all clinical fractures was significantly increased, though the effect size was modest with or without adjustment for the femoral neck BMD (RR=1.24 and 1.26, respectively). Some patients with a moderate or severe vertebral fracture would also have sustained a prior non-vertebral fracture. When a prior non-vertebral fracture was adjusted for in the analysis (possible in the case of strontium ranelate and bazedoxifene), our findings did not materially differ in that the risk of non-vertebral fractures was not increased in the presence of a prior mild vertebral fracture (RR=1.00; 95 % confidence interval 0.74–1.35). Overall, a morphometric fracture (irrespective of grade) was associated with a twofold increase in the risk of a further clinical fracture (non-vertebral+clinical vertebral fracture) (RR=2.02; 95 % CI=1.77–2.30 and RR=2.00; 95 % CI=1.75–2.28 when adjusted for BMD).

There was no significant interaction with age. Thus, the risk of outcome fractures as a function of grade of baseline vertebral fracture was not dependent on age.

Table 1 Characteristics of placebo-treated patients at trial entry

	Intervention			
	Strontium ranelate	Raloxifene	Bazedoxifene	Combined
Number of women	3,176	2,563	1,884	7,623
Age (years)±SD	74.8±6.4	66.6±7.1	66.5±6.8	70.0±7.8
Previous fracture history[a]	1,158	NR	317	
Vertebral fracture				
Grade 0	1,803	1,631	827	4,208
Grade 1	243	422	864	1,568
Grade 2	750	314	189	1,240
Grade 3	380	196	4	609
Femoral neck T-score (SD)	−3.05±0.68	−2.34±0.56	−1.8±0.9	

[a] Excludes morphometric vertebral fracture determined at baseline

NR not recorded

Table 2 Number of patients with one or more outcome fracture

Outcome fracture	Intervention			
	Strontium ranelate	Raloxifene	Bazedoxifene	Combined
Morphometric vertebral	514	192	59	765
Non-vertebral fractures	357	240	99	696
All clinical (vertebral+non-vertebral)	551	310	111	972
Clinical vertebral	239	81	14	334

Discussion

The present meta-analysis confirms previous reports of individual studies that the grade of a prior vertebral fracture is an important determinant of the risk of a further fracture [31]. The data are also consistent with prior meta-analyses [18, 32]. The present study adds information on the significance

Table 3 Relative risk and 95 % confidence intervals for outcome fractures according to grade of baseline vertebral fracture

Outcome fracture	None		Mild		Moderate/severe	
	RR	95%CI	RR	95%CI	RR	95%CI
Unadjusted						
Morphometric vertebral	1	–	2.17	1.70–2.76	4.23	3.58–5.00
Non-vertebral fractures	1	–	1.08	0.86–1.36	1.64	1.38–1.94
All clinical (vertebral+non-vertebral)	1	–	1.24	1.01–1.52	2.50	2.17–2.89
Clinical vertebral	1	–	2.50	1.62–3.85	7.24	5.47–9.57
Adjusted for BMD						
Morphometric vertebral	1	–	2.22	1.74–2.84	4.11	3.47–4.86
Non-vertebral fractures	1	–	1.09	0.86–1.37	1.57	1.32–1.86
All clinical (vertebral+non-vertebral)	1	–	1.26	1.02–1.55	2.50	2.37–2.64
Clinical vertebral	1	–	2.59	1.68–4.00	7.17	5.42–9.49

of the grade of prior vertebral fracture on different fracture outcomes. Whereas the grade of prior vertebral fracture is an important determinant of future fracture risk, its significance is site-specific. Thus, a prior vertebral fracture had a greater prognostic significance for further vertebral fractures than for non-vertebral fracture outcomes [33–39]. Of particular importance, a mild vertebral fracture was not associated with an increase in the risk of a non-vertebral fracture.

The latter findings have implications for the design of phase 3 studies of efficacy where a desired primary or secondary outcome measure is the effect of an intervention on non-vertebral fractures. The present study indicates that the inclusion of patients with only a mild vertebral fracture adds no more power to a study than the inclusion of a patient without any prior fracture. Although several studies have shown that the number of prior vertebral fractures is associated with an increase in non-vertebral fracture risk [40–42] and that multiple mild vertebral fractures may be associated with lower BMD [42], whether the inclusion of patients with two or more mild vertebral fractures has significance for non-vertebral fracture risk is not known.

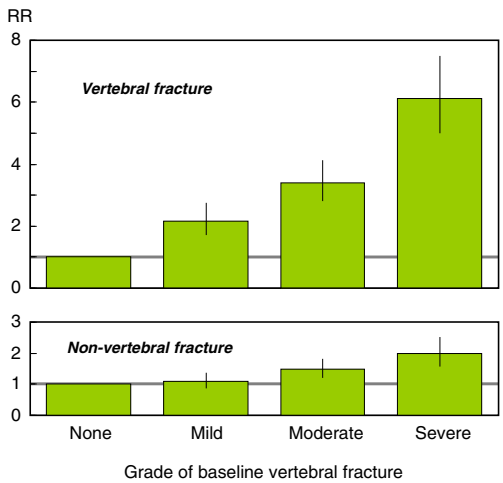

Fig. 1 Relative risk (+95 % confidence intervals) of a morphometric vertebral fracture and a non-vertebral fracture in women according to the grade of prior vertebral fracture

The present study also has some implications for FRAX®. The FRAX tool inputs a history of a prior fragility fracture and computes that the risk of a subsequent hip or major fracture is approximately increased twofold, based on the large meta-analysis used to populate the FRAX model [32]. In men and women combined, the risk ratio ranges from 1.83 to 2.03 depending upon age. However, FRAX is blind to the site of prior fracture or the number of prior fractures or, in the case of vertebral fracture, the severity of the deformity all of which impact on fracture risk assessment. In the case of a prior mild vertebral fracture, the risk of a clinical fracture is less than that assumed by FRAX (RR 1.24; 95 % confidence interval 1.01–1.52; Table 3). In the presence of a moderate or severe fracture, the risk is higher than that assumed by FRAX (RR 2.50; 95 % confidence interval 2.17–2.89). The underestimate and overestimate on the risk of fracture means that on average, the risk of a clinical fracture is very close to that used in the FRAX model (RR=2.00; 95 % CI=1.75–2.28) when adjusted for BMD. The ultimate effect of the underestimate and overestimate on the 10-year probability of fracture is not known. This would require knowledge of the impact of the grade of vertebral fracture on the death hazard. This is not known, though symptomatic vertebral fractures appear to be associated with a higher mortality risk than asymptomatic vertebral fractures [43]. These considerations suggest, however, that there is not a special case to be made for the interpretation of a prior vertebral fracture (compared to prior fractures at other sites), but FRAX is likely to overestimate fracture probability in the case of a mild prior vertebral facture and, conversely, underestimate fracture probability in the case of a moderate or severe prior vertebral facture.

There are a number of important caveats to consider. The first is that our findings are confined to a female population and the results may differ quantitatively in men. For example,

there is evidence that prior forearm fracture in men has a different prognostic significance than in women [44]. A limitation of the present study relates to the documentation of prior fractures. In the case of vertebral fractures, the data that we used are related to the patient as a unit. Thus, the categorisation of a patient as having a moderate vertebral fracture indicated that at least one moderate fracture was detected at screening. The patient may have had several moderate and/or mild fractures. Thus, the accuracy of the categorisation is imperfect. In addition, some patients categorised by prior vertebral fractures would have a history of a prior fracture at a non-vertebral site. Where possible (in women studied with strontium or bazedoxifene), adjustment for prior non-vertebral fractures did not alter our principal findings.

We conclude that prior moderate and severe morphometric vertebral fractures are a strong and significant risk factor for future fracture, particularly for vertebral fracture. The presence of a mild vertebral fracture is, in contrast, of no significant prognostic value for non-vertebral fracture outcomes. These findings should be considered in the design of phase 3 studies where the endpoint includes the effect of intervention on non-vertebral fracture risk. The interpretation of FRAX should take account of the severity of vertebral deformity.

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