Risk of New Vertebral Fracture in the Year Following a Fracture

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Context Vertebral fractures significantly increase lifetime risk of future fractures, but risk of further vertebral fractures in the period immediately following a vertebral fracture has not been evaluated.

Objective To determine the incidence of further vertebral fracture in the year following a vertebral fracture.

Design and Setting Analysis of data from 4 large 3-year osteoporosis treatment trials conducted at 373 study centers in North America, Europe, Australia, and New Zealand from November 1993 to April 1998.

Subjects Postmenopausal women who had been randomized to a placebo group and for whom vertebral fracture status was known at entry (n=2725).

Main Outcome Measure Occurrence of radiographically identified vertebral fracture during the year following an incident vertebral fracture.

Results Subjects were a mean age of 74 years and had a mean of 28 years since menopause. The cumulative incidence of new vertebral fractures in the first year was 6.6%. Presence of 1 or more vertebral fractures at baseline increased risk of sustaining a vertebral fracture by 5-fold during the initial year of the study compared with the incidence in subjects without prevalent vertebral fractures at baseline (relative risk [RR], 5.1; 95% confidence interval [CI], 3.1-8.4; $P<.001$). Among the 381 participants who developed an incident vertebral fracture, the incidence of a new vertebral fracture in the subsequent year was 19.2% (95% CI, 13.6%-24.8%). This risk was also increased in the presence of prevalent vertebral fractures (RR, 9.3; 95% CI, 1.2-71.6; $P=.03$).

Conclusion Our data indicate that women who develop a vertebral fracture are at substantial risk for additional fracture within the next year.

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VERTEBRAL FRACTURES ARE A well-recognized consequence of postmenopausal bone loss and are the most common osteoporotic fractures.[1] It is estimated that less than one third of all vertebral fractures are clinically diagnosed.[2] However, all vertebral fractures, whether symptomatic or radiographically identified, are associated with increased mortality and morbidity, including back pain and decreased activity, with consequent increased days of bed rest.[3-5] Vertebral fractures are associated with increased risk of further vertebral fractures, with resulting height loss and kyphosis, as well as increased risk of nonvertebral fractures.[6-10] This increased risk remains after correction for bone mineral density (BMD), itself a potent risk factor for fracture.[6,10,11]

Since many vertebral fractures are found by chance and it is difficult to date these fractures, we do not know whether time from fracture modifies the risk conferred by the fracture. It has been suggested but not confirmed by data that the greatest risk of a second fracture exists during the time immediately following the initial fracture.[12] If true, this highlights the clinical importance of fracture identification as soon after the event as possible. To evaluate this issue, we analyzed data from women in the placebo groups of 4 large clinical trials conducted at 373 study centers in North America, Europe, Australia, and New Zealand to determine whether risk of vertebral fracture is increased in the period immediately following a vertebral fracture.

METHODS

The study population consisted of women who had been randomly assigned to a placebo group in 4 large 3-year clinical trials conducted from November 1993 to April 1998 evaluating the efficacy of risedronate, a bisphosphonate, for treatment of postmenopausal osteoporosis.[13-15] These women had either prevalent vertebral fractures (2 studies),[13,14] low femoral neck BMD, or risk factors for hip fracture.[15] All subjects received calcium supplementation (1000 mg/d). Women with serum 25-hydroxyvitamin D levels of less than 16 ng/mL (40 nmol/L)

at baseline also received vitamin D supplementation (up to 500 IU/d).

Lateral spine radiographs were obtained at baseline for evaluation of prevalent vertebral fractures and annually thereafter for incident vertebral fractures, as previously described.[13,14] The vertebral fracture analyses included all placebo subjects who had both baseline and postbaseline evaluable radiographs. Clinical vertebral fractures were recorded as adverse events and diagnosed by a physician.

Demographic and baseline characteristics were summarized using descriptive statistics for subjects receiving placebo. The incidence of new vertebral fractures, based on time to first incident fracture, was analyzed using survival analysis methods. The cumulative incidence was calculated using Kaplan-Meier estimates. A Cox regression model was used to compare risk of incident vertebral fracture in subjects with prevalent fracture compared with those without prevalent fracture; similar methods were used to investigate risk of additional vertebral fracture within 1 year of a vertebral fracture that occurred during the study. The effect of potential baseline covariates (age, weight, lumbar spine BMD, and vitamin D status) was investigated by adjusting for these covariates as continuous variables in the Cox regression model.

RESULTS

A total of 4356 subjects were randomly assigned to placebo study arms; of these, vertebral fracture status was known for 2725 (57%). The baseline characteristics of these subjects (98% white) are shown in TABLE 1 and were similar across studies. Because of differences in study design and recruitment among trials, baseline lumbar spine BMD values were available for 885 subjects (32%); the mean (SD) lumbar spine T score was −2.6 (1.3).

Over the course of the studies, vertebral fractures were observed in 381 of the 2725 women. The Kaplan-Meier estimate of the vertebral fracture incidence over 3 years was 16.9%. Of the 381 women who sustained vertebral frac-

tures, 23% had symptomatic vertebral fractures. Risk of sustaining a vertebral fracture increased with presence of prevalent fractures (relative risk [RR], 3.7; 95% confidence interval [CI], 2.8-4.9; P<.001). During the first year, the proportion of women who developed vertebral fractures was 6.6% (TABLE 2) and, again, risk increased with presence of prevalent vertebral fractures (RR, 5.1; 95% CI, 3.1-8.4; P<.001) (FIGURE 1A). In subjects with baseline BMD values, risk of incident vertebral fracture over 1 year increased significantly for each 1-SD decrease in baseline BMD value below the mean for a young, healthy population (RR, 1.6; 95% CI, 1.1-2.2; P=.007).

Among subjects in whom incident fractures were confirmed, occurrence of a second incident vertebral fracture within 1 year of the initial fracture was

19.2% overall (95% CI, 13.6%-24.8%) (TABLE 3). Risk also increased with prevalent vertebral fractures (RR, 9.3; 95% CI, 1.2-71.6; P=.03) (Figure 1B). Twenty-four percent of subjects with 2

Table 1. Baseline Characteristics of the Study Population (n = 2725)*

Age, y	74 (7.1)
Time since menopause, y	28 (9.5)
Weight, kg	63 (11.7)
Height, cm	157 (7.1)
Smoking status, No. (%)	
Never	1636 (60)
Current or previous	1089 (40)
Lumbar spine T score†	−2.6 (1.3)
Vertebral fractures at baseline, No. (%)	
0	1151 (42)
1	523 (19)
≥2	1051 (39)

*Data are presented as mean (SD) unless otherwise noted.
†The T score expresses bone mineral density in terms of the SD above or below the mean for healthy young adult women. Measurements were obtained for 885 subjects.
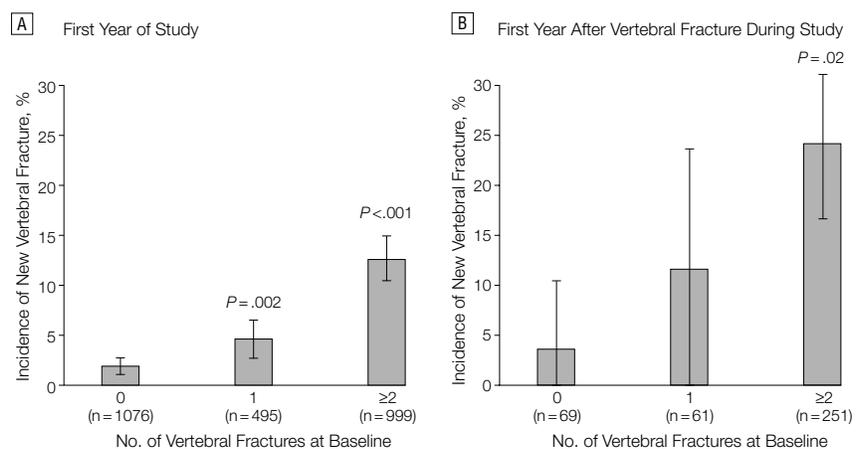
Table 2. Incidence of New Vertebral Fracture in First Year of Study

	Subjects With New Vertebral Fracture in First Year of Study, No. (%)*	Relative Risk (95% Confidence Interval)†	P Value†
Overall population (n = 2570)	163 (6.56)	. . .	. . .
Vertebral fractures at baseline, No. (%)			
0 (n = 1076)	20 (1.9)	. . .	. . .
1 (n = 495)	22 (4.6)	2.6 (1.4-4.9)	.002
≥1 (n = 1494)	143 (9.9)	5.1 (3.1-8.4)	<.001
≥2 (n = 999)	121 (12.5)	7.3 (4.4-12.3)	<.001

*Kaplan-Meier estimate of the survival function.
†Cox regression model; data are for comparison vs group with 0 baseline vertebral fractures. Ellipses indicate data not applicable.

Figure. Incidence of Vertebral Fracture by Number of Baseline Vertebral Fractures

Incidence is based on Kaplan-Meier estimates of the survival function. Error bars indicate 95% confidence intervals.

Table 3. Incidence of New Vertebral Fracture in Year Following Vertebral Fracture During Study

	Subjects With New Vertebral Fracture in Year Following Incident Vertebral Fracture, No. (%)*	Relative Risk (95% Confidence Interval)†	P Value†
Overall population (n = 381)	36 (19.18)	. . .	. . .
Vertebral fractures at baseline, No. (%)			
0 (n = 69)	1 (3.6)	. . .	. . .
1 (n = 61)	3 (11.5)	4.1 (0.4-38.5)	.22
≥1 (n = 312)	35 (21.9)	9.3 (1.2-71.6)	.03
≥2 (n = 251)	32 (24.0)	11.6 (1.5-90.1)	.02

*Kaplan-Meier estimate of the survival function.
†Cox regression model; data are for comparison vs group with 0 baseline vertebral fractures. Ellipses indicate data not applicable.

or more prevalent fractures at baseline had an incident vertebral fracture within 1 year of their first observed fracture. The RR did not change when adjusted for age, weight, or baseline vitamin D status.

COMMENT

Vertebral fractures are a serious and irreversible outcome of osteoporosis. Previous data have demonstrated that risk of vertebral fracture is increased among women in whom a prior vertebral fracture is identified. Our data are consistent with these reports, with the RR of new vertebral fracture increasing with the number of baseline vertebral fractures. The design of our clinical trials also allowed for identification of vertebral fractures on an annual basis (incident fractures). These incident vertebral fractures also increased risk of future vertebral fractures and this increased risk appeared to be greatest in the initial year following the fracture. Twenty-three percent of incident fractures were clinical events, similar to the relationship between clinical and radiological fractures observed previously.[2] Our finding that almost 20% of women will experience another fracture within 1 year of an incident vertebral fracture has important clinical implications. The increased fracture risk in the immediate period following a fracture demonstrates the urgency of identification and intervention for this segment of the population and was observed despite that all subjects received calcium and vitamin D.

The presence of prevalent fractures significantly enhanced risk after an incident fracture (4% with 0 vs 24% with ≥2). While BMD values were available only for a subset of the population, there was a 60% increase in risk of vertebral fracture during the first year of the study for each 1-SD decrease in baseline BMD value below the mean for a young, healthy population. Thus, the combination of low lumbar spine BMD and prevalent fractures is the best predictor of increased fracture risk in the immediate period after a fracture.

There are some limitations to our findings. First, clinical trial subjects may differ from patients commonly seen in clinical practice. The similarity of our findings to those already reported with regard to the effect of prevalent fractures in predicting future fractures suggests that our results may be generalized to the postmenopausal population with osteoporosis. As in observational studies, we do not know the timing of the fractures observed at baseline. Some may have been recent, which would lead to a higher-than-expected incidence in the first year and would be expected to diminish the differences we observed. Because we do not know the timing of the fractures that existed at baseline, our data do not allow us to evaluate an important clinical question: whether an incident fracture, compared with a history of fracture, leads to greater risk for fracture. Baseline BMD values were available for approximately one third of our subjects; thus, we cannot completely

correct for the effects of BMD. However, other studies have shown consistently that the effects of prevalent fractures are independent of BMD.[6,9,10]

We have confirmed that prevalent fractures increase risk of further vertebral fractures and have shown for the first time, to our knowledge, that incident vertebral fractures exacerbate this effect. Our finding that approximately 20% of women will experience another fracture within the first year of a vertebral fracture justifies a degree of urgency for clinicians in identifying and treating all patients who present with vertebral fractures. These data indicate that osteoporosis actually may be a quickly progressing disease once a fracture occurs. Further research should be carried out to determine whether an incident fracture, compared with a history of fracture, leads to greater future risk for fracture.

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If anything is sacred the human body is sacred.
—Walt Whitman (1819-1892)