# Teriparatide and Raloxifene Reduce the Risk of New Adjacent Vertebral Fractures in Postmenopausal Women with Osteoporosis. Results from Two Randomized Controlled Trials

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# Teriparatide and Raloxifene Reduce the Risk of New Adjacent Vertebral Fractures in Postmenopausal Women with Osteoporosis

## Results from Two Randomized Controlled Trials

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*Investigation performed at Eli Lilly and Company, Indianapolis, Indiana*

**Background:** Vertebral fractures increase the risk of new vertebral fractures; however, we are not aware of any study addressing the risk of new vertebral fractures adjacent to existing vertebral fractures. Therefore, we sought to determine the influence of the number and severity of prevalent (preexisting) vertebral fractures on the risk of new adjacent vertebral fractures and to determine whether teriparatide (rhPTH [recombinant human parathyroid hormone] [1-34]) or raloxifene treatment reduces the incidence of adjacent vertebral fractures in postmenopausal women with osteoporosis.

**Methods:** Data from the Fracture Prevention Trial and the Multiple Outcomes of Raloxifene Evaluation trial were analyzed to determine the incidences of new adjacent and new nonadjacent vertebral fractures in the placebo groups and the effect of treatment with raloxifene and teriparatide on the incidence of new adjacent vertebral fractures as compared with that of new nonadjacent vertebral fractures.

**Results:** Of 1226 untreated postmenopausal women with one or more prevalent vertebral fractures at baseline, 196 (16.0%) had a total of 292 new vertebral fractures during the two-year follow-up period, with 108 (8.8%) of the 1226 women having at least one new fracture adjacent to a prevalent fracture. Of the 292 new vertebral fractures, 136 (47%) were adjacent to a previously existing vertebral fracture. The risk of a new adjacent vertebral fracture was 2.5-fold higher than the risk of a new nonadjacent vertebral fracture (4.03% compared with 1.59%). The incidence of new adjacent vertebral fractures increased with both the number and the severity of prevalent vertebral fractures. Teriparatide reduced the risk of any new, new adjacent, and new nonadjacent vertebral fractures by 72%, 75%, and 70%, respectively, compared with the rates in the placebo group. Similarly, compared with the placebo, raloxifene treatment reduced the risk of any new vertebral fracture, new adjacent vertebral fracture, and new nonadjacent vertebral fracture by 54%, 54%, and 53%, respectively.

**Conclusions:** In untreated postmenopausal women with osteoporosis, nearly half of the incident vertebral fractures occur adjacent to an existing vertebral fracture. Both teriparatide and raloxifene can significantly reduce the occurrence of new adjacent and nonadjacent vertebral fractures.

**Level of Evidence:** Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Vertebral fractures are the earliest and most common type of osteoporotic fracture in postmenopausal women[1,2]. Approximately 30% of women sustain a vertebral fracture by the age of seventy-five years, and 50% sustain a vertebral fracture by the age of eighty-five years[3]. Lindsay et al. reported that a new vertebral fracture developed, during the first year of observation, in 1.9%, 4.6%, and 12.5% of osteoporotic women with zero, one, and two or more prevalent (preexisting) vertebral fractures, respectively[4]. Both the number and the severity of prevalent vertebral fractures independently predict the risk of

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**TABLE I Baseline Characteristics of Women in the Placebo Groups with One or More Prevalent Vertebral Fractures in the Fracture Prevention Trial and the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial***

| | Age *(yr)* | Height *(cm)* | Bone Mineral Density (T-Score) in Lumbar Spine | No. of Prevalent Vertebral Fractures | Semiquantitative Score |
|---|---|---|---|---|---|
| Fracture Prevention Trial (n = 398) | 69.1 ± 6.8 | 157.3 ± 6.3 | −2.5 ± 1.5 | 2.6 ± 1.7 | 1.9 ± 0.7 |
| MORE (n = 828) | 68.5 ± 6.2 | 158.4 ± 6.7 | −2.8 ± 1.2 | 2.0 ± 1.6 | 1.7 ± 0.8 |
| Combined (n = 1226†) | 68.7 ± 6.4 | 158.0 ± 6.6 | −2.7 ± 1.3 | 2.2 ± 1.6 | 1.8 ± 0.8 |

*The values are given as the mean and standard deviation. †Representing 39% of the total number of patients treated with a placebo in the two trials.

new vertebral fractures and of new moderate or severe vertebral fractures[5,6]. In addition, both community-based studies and clinical trials have shown an uneven distribution of fractures across the spine, with the peak fracture prevalence and incidence occurring at the midthoracic region (T7-T8) and thoracolumbar junction (T12-L1)[3,7-9].

Understanding the factors that influence where and when a new vertebral fracture occurs is critical for developing effective interventions. The large epidemiologic studies cited above have shown a strong relationship between a prevalent vertebral fracture and the risk of a future vertebral fracture in general. However, little is known about the effect of an existing vertebral fracture on the risk of a new fracture in a vertebral body immediately adjacent to the prevalent fracture (a new adjacent fracture) compared with the risk of a new nonadjacent vertebral fracture. One area in which this issue is very important is vertebral augmentation with either vertebroplasty or kyphoplasty, as some investigators have shown the risk of vertebral fracture to be increased in vertebrae adjacent to those that have been augmented, with the increase in the risk observed particularly in the first six months following the procedure[10-13]. Furthermore, adjacent-level fractures have been associated with leakage of cement into the intervertebral disc space[10,14-16]. However, many investigations of this phenomenon have not been well controlled, making it difficult to determine if adjacent fractures are the result of the vertebral augmentation procedure or the natural progression of osteoporosis[17,18].

Current osteoporosis therapies have been shown to reduce the risk of vertebral fractures in postmenopausal women, but little is known about the ability of these therapies to influence the risk of new adjacent vertebral fractures.

To address these issues, we conducted a secondary analysis of data from the Fracture Prevention Trial[19] and the Multiple Outcomes of Raloxifene Evaluation (MORE) trial[20]. We examined the relationship between prevalent vertebral fracture and the incidences of new adjacent and new nonadjacent vertebral fractures in women enrolled to receive a placebo or daily teriparatide (rhPTH [recombinant human parathyroid hormone] [1-34]) or raloxifene. We determined the influence of the number and severity of the prevalent vertebral fracture(s) on the risk of new adjacent vertebral fractures. We also examined the effects of teriparatide and raloxifene treatment on the incidence of new adjacent vertebral fractures as compared with that of new nonadjacent vertebral fractures.

## Materials and Methods

### *Design Overview*

The present analyses were conducted with use of data on 398 women from the placebo group and 793 women from the pooled teriparatide groups (dosages of 20 and 40 μg/day) from the Fracture Prevention Trial (ClinicalTrials.gov identifier: NCT00670501) and two-year data on 828 women from the placebo group and 1714 women from the pooled raloxifene groups (dosages of 60 and 120 mg/day) from the MORE trial (ClinicalTrials.gov identifier: NCT00670319). The results of these trials have been previously published[19,20].

### *Setting and Participants*

All patients included in these analyses had at least one prevalent vertebral fracture at baseline. Women in the Fracture Prevention Trial were able to walk, had undergone menopause at least five years previously, and had at least one moderate or two mild atraumatic vertebral fractures at baseline[19]. An additional entry criterion for the women who had fewer than two moderate vertebral fractures was a bone mineral density of the lumbar spine or proximal part of the femur of at least one standard deviation below the mean value in healthy young (twenty to thirty-five-year-old) white women (i.e., a T-score of ≤−1). Women in the MORE trial were up to eighty years of age, had undergone menopause at least two years previously, had osteoporosis, and had a bone mineral density at the lumbar spine or femoral neck of at least 2.5 standard deviations below the mean for normal young women or had at least one moderate or two mild vertebral fractures determined by lateral spine radiography[20]. In both trials, institutional review board approval was obtained at each study center, all study participants provided written informed consent, and all study methods were conducted in accordance with the Declaration of Helsinki.

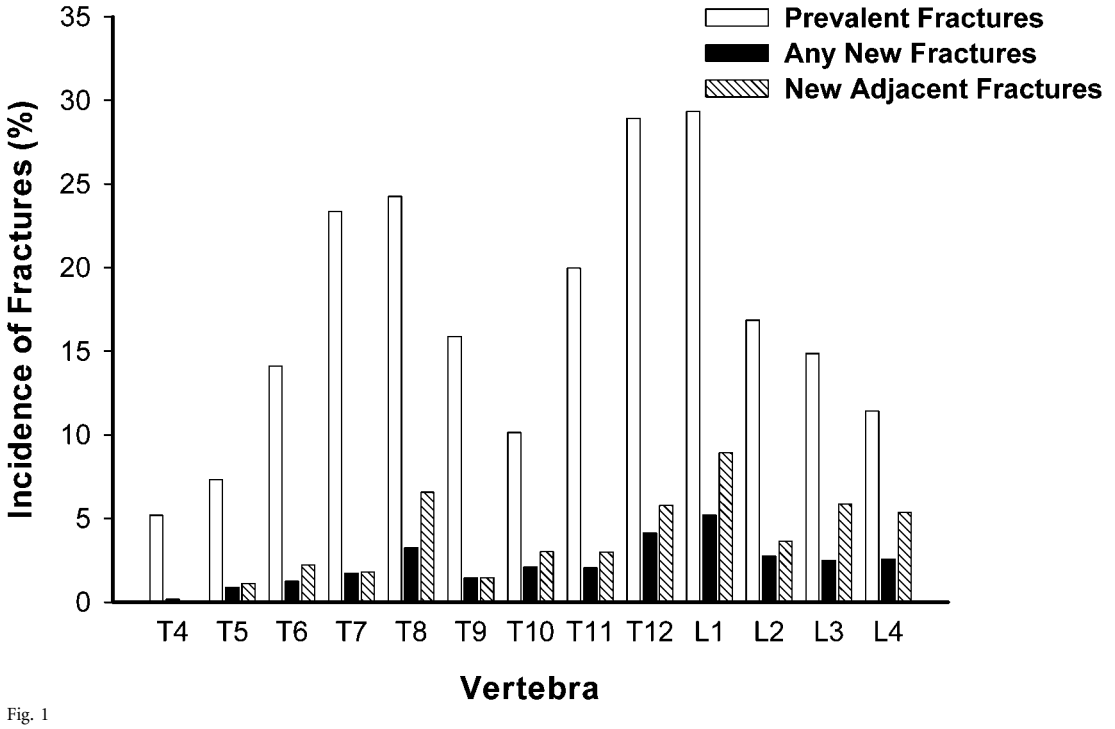


Fig. 1
Distribution of vertebral fractures in the placebo group.

*Randomization and Interventions*

The Fracture Prevention Trial was a prospective, randomized, double-blind study in which 20 or 40 μg of teriparatide, or a placebo, was given daily by subcutaneous injection into the thigh or abdomen for nineteen months to 1637 postmenopausal women with osteoporosis[19]. The MORE trial was a multicenter, randomized, double-blind study in which oral raloxifene (60 or 120 mg) or a placebo was taken daily by 7705 postmenopausal women with osteoporosis[20]. All participants received daily calcium supplements (500 mg in the MORE trial and 1000 mg in the Fracture Prevention Trial) and vitamin D (400 to 600 IU in the MORE trial and 400 to 1200 IU in the Fracture Prevention Trial).

*Outcomes and Follow-up*

Lateral spine radiographs were made at baseline and at two, three, and four years in the MORE trial and at baseline and at the study end point (at a median of twenty-one months) in the Fracture Prevention Trial. The radiographs were assessed at a central site (the Osteoporosis and Arthritis Research Center, University of California at San Francisco, San Francisco, California), and vertebral fractures were graded with use of a semiquantitative vertebral deformity scoring technique[21]. The interrater reliability (kappa statistic) of two independent observers using the semiquantitative method was 0.74 for prevalent fractures and 0.80 for incident fractures[21]. Vertebrae were assigned a semiquantitative score of 0 if no fracture was present, 1 if there was a mild deformity (approximately 20% to 25% compression), 2 if there was a moderate deformity (approximately 25% to 40% compression), and 3 if there was a severe deformity (more than approximately 40% compression). The location of the vertebral fracture, the severity grade (mild, moderate, or severe, with the highest grade used if the patient had more than one fracture), and the number of vertebral fractures (one, two, or three or more) were derived from this vertebral fracture assessment and were used in subsequent analyses. Vertebrae exhibiting abnormalities such as scoliosis, fusion, or other anomalies were excluded from the analysis.

Because the radiographs in the Fracture Prevention Trial were made after a median of twenty-one months, the two-year MORE trial results were used in the current analysis to facilitate pooling of the data from these two trials. In the MORE trial, radiographs were first assessed with use of the visual (semiquantitative) scoring system described above. If neither a prevalent nor an incident fracture was identified, no further analysis was performed. When a fracture was observed at baseline or the end point, a second radiologist confirmed whether a fracture was present and performed a quantitative morphometric analysis of each vertebra. The interrater reliability of the two independent observers using the quantitative morphometric method was not established. For the quantitative morphometric analysis, a fracture was defined as a decrease in the anterior, middle, or posterior vertebral height of 20%, with a minimum change of 4 mm. At baseline, adjacent vertebrae were referenced for comparison. A fracture was reported if the semiquantitative grade of at least one vertebra was >0 and the results of at least two of the three techniques were in agreement.

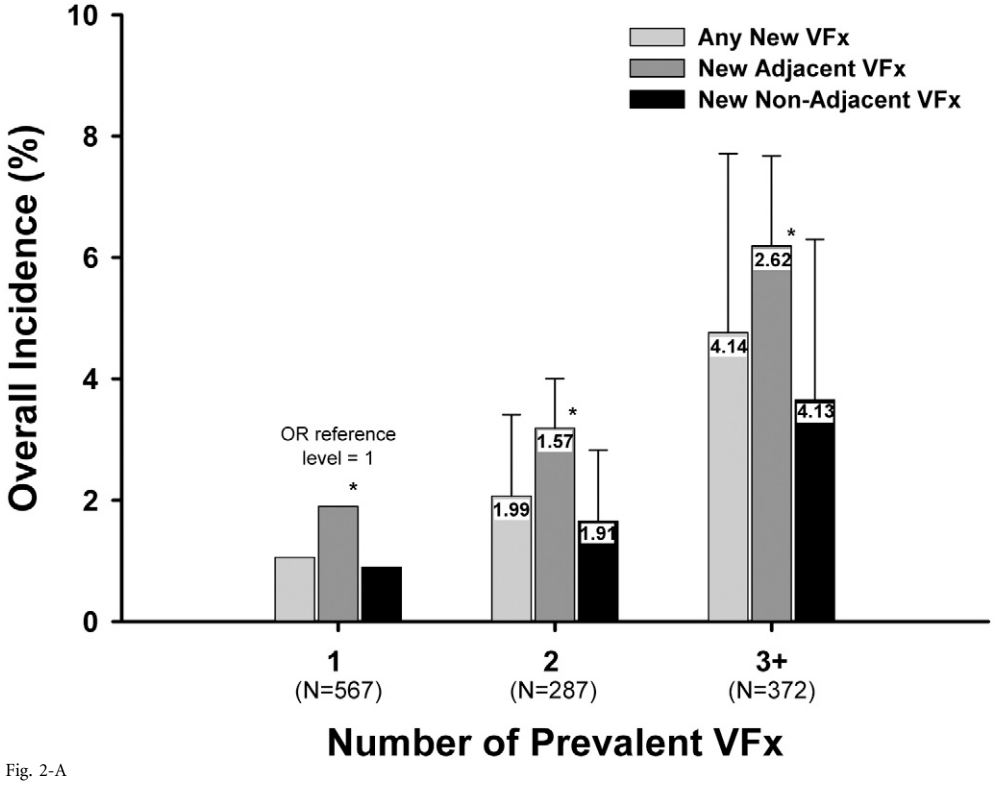


Fig. 2-A

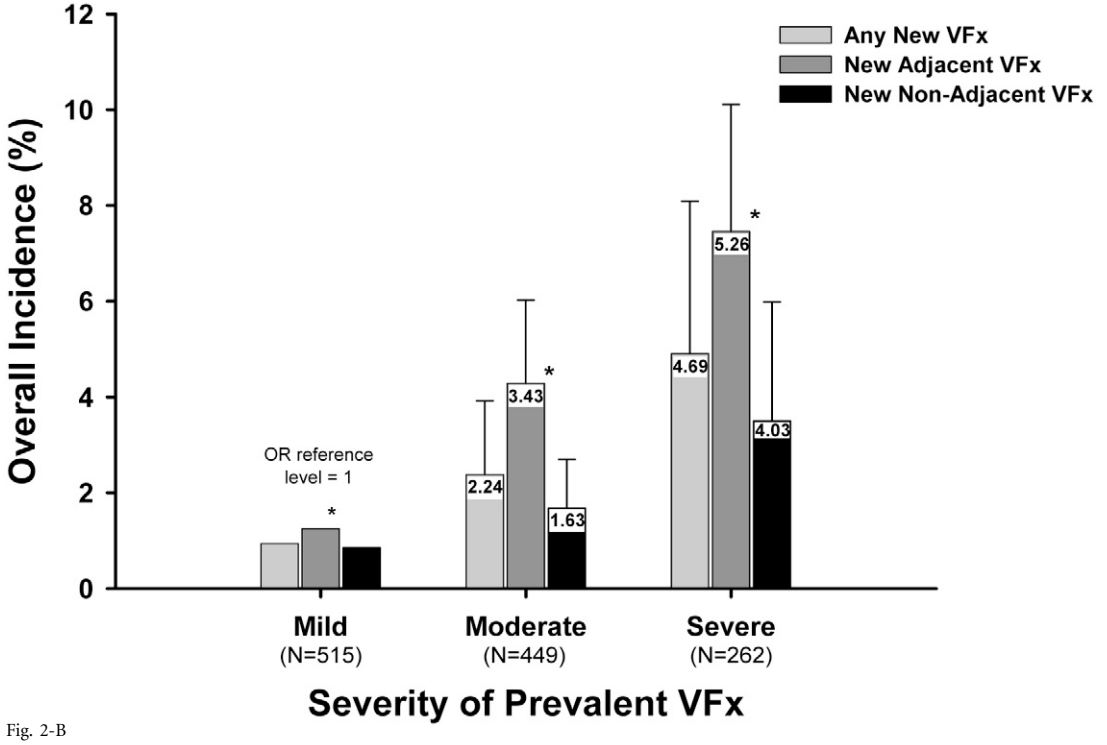


Fig. 2-B

Incidences of any new, new adjacent, and new nonadjacent vertebral fractures (VFx) according to the number (Fig. 2-A) and severity (Fig. 2-B) of the prevalent vertebral fracture. N = the number of patients, and the numbers in the bars represent the odds ratios. The odds ratios were adjusted for age and bone mineral density in the lumbar spine in the logistic regression analysis. *$p < 0.05$ compared with the incidence of nonadjacent fracture. See text for an explanation of how the overall incidence was calculated.

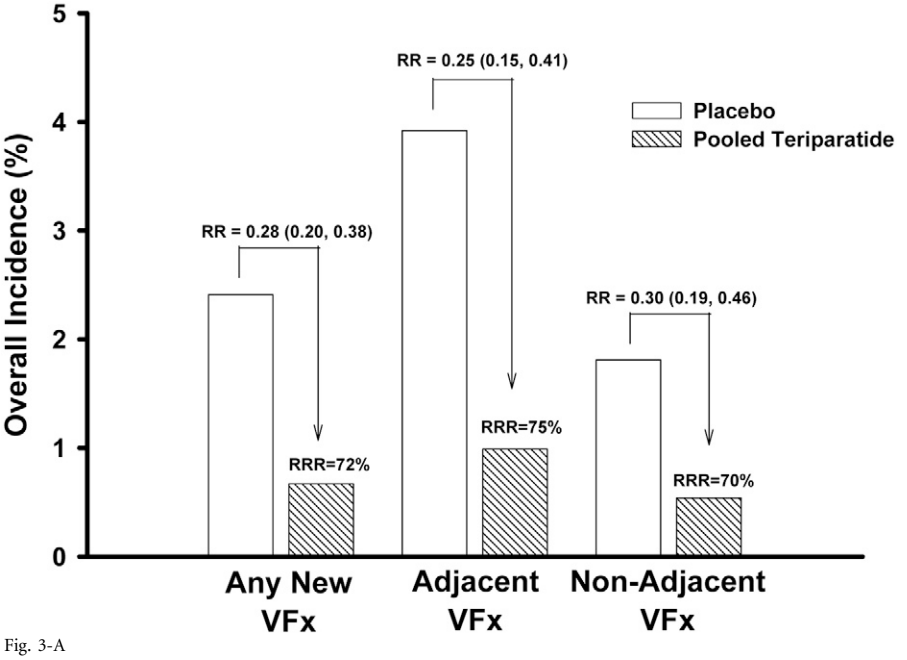


Fig. 3-A

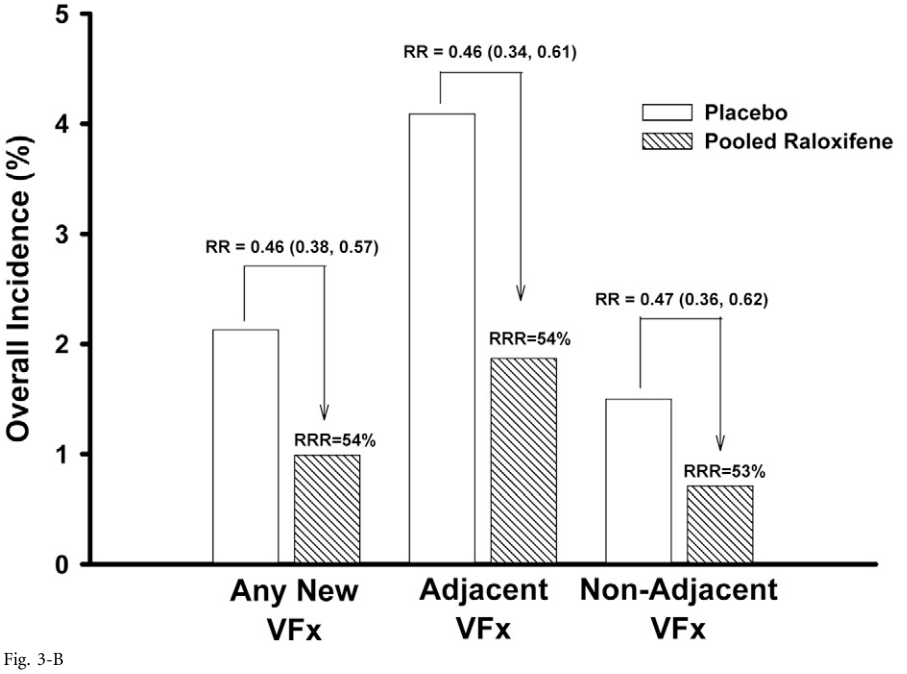


Fig. 3-B

Effect of teriparatide (Fig. 3-A) and raloxifene (Fig. 3-B) treatment on the incidences of any new, new adjacent, and new nonadjacent vertebral fractures (VFx) in women with one or more prevalent vertebral fractures at baseline. RR = relative risk (the ratio of the fracture risk in the treatment group to that in the placebo group), and RRR = relative risk reduction (1 minus the relative risk). The 95% confidence intervals are given in the parentheses after the relative risk values. See text for an explanation of how the overall incidence was calculated.

*Statistical Analyses*

Data for the 1226 women in the placebo groups (with 2712 prevalent vertebral fractures) were analyzed to determine the distribution of prevalent vertebral fractures as well as new adjacent and nonadjacent vertebral fractures by location across vertebral levels. The appropriateness of data-pooling was examined by evaluating, with use of a two-sample t test, the difference in baseline characteristics between the two trials. The

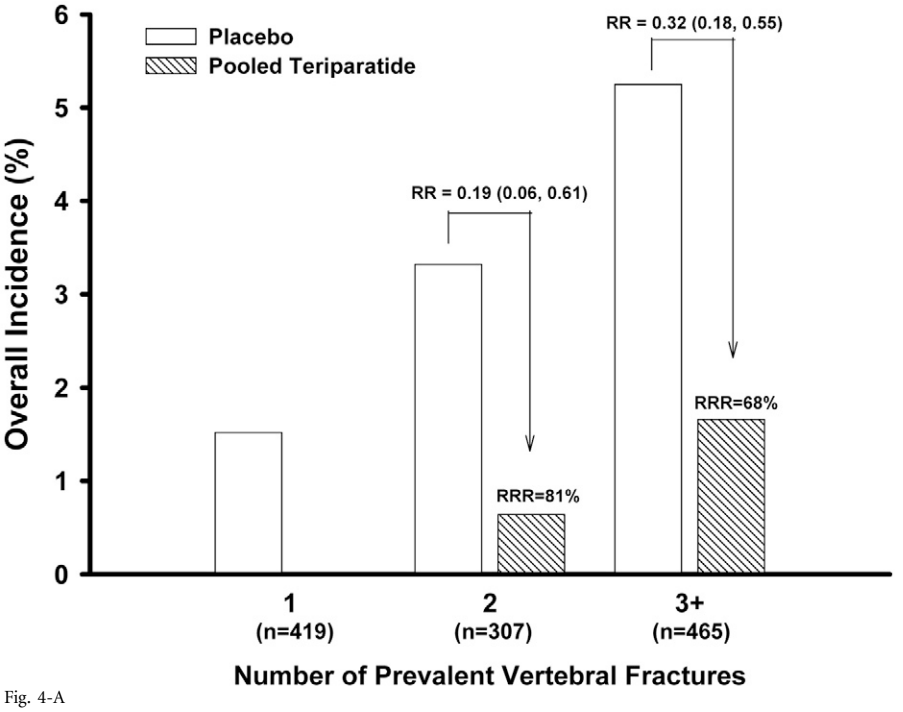


Fig. 4-A

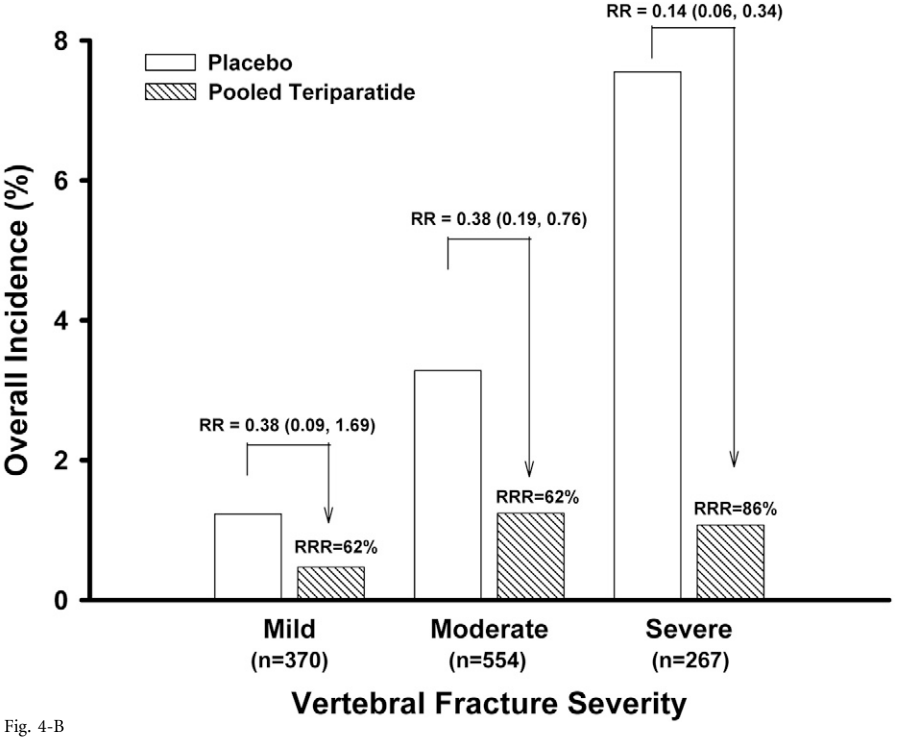


Fig. 4-B

Effect of teriparatide treatment on the incidences of new adjacent vertebral fractures according to the number (Fig. 4-A) and severity (Fig. 4-B) of the prevalent vertebral fracture. Note that no new adjacent vertebral fractures were observed in teriparatide-treated patients with one prevalent vertebral fracture at baseline. RR = relative risk (the ratio of the fracture risk in the treatment group compared with that in the placebo group), and RRR = relative risk reduction (1 minus the relative risk). The 95% confidence intervals are given in the parentheses after the relative risk values. See text for an explanation of how the overall incidence was calculated.

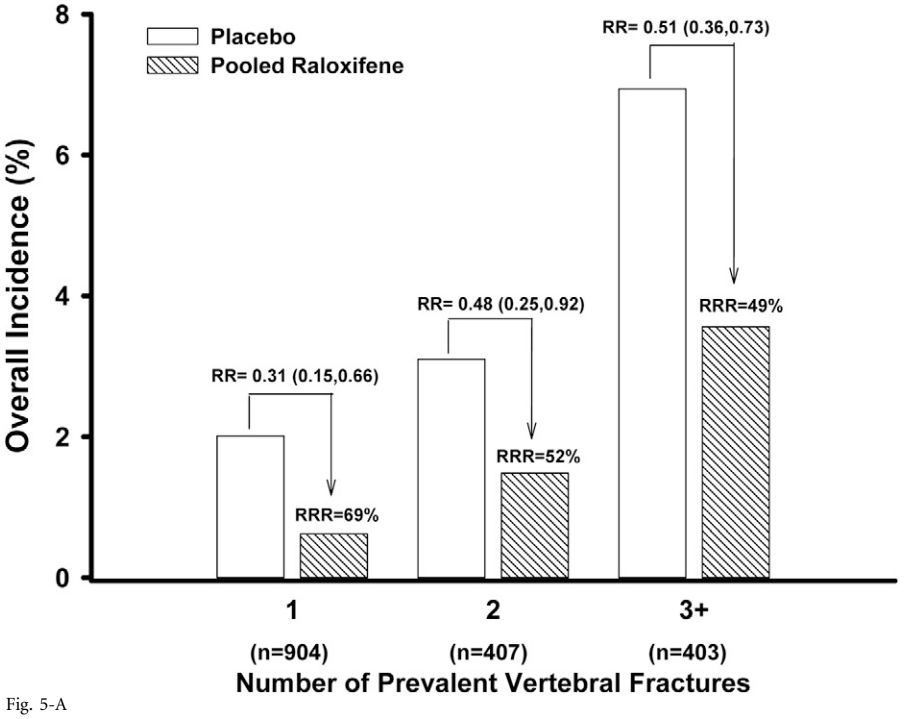


Fig. 5-A

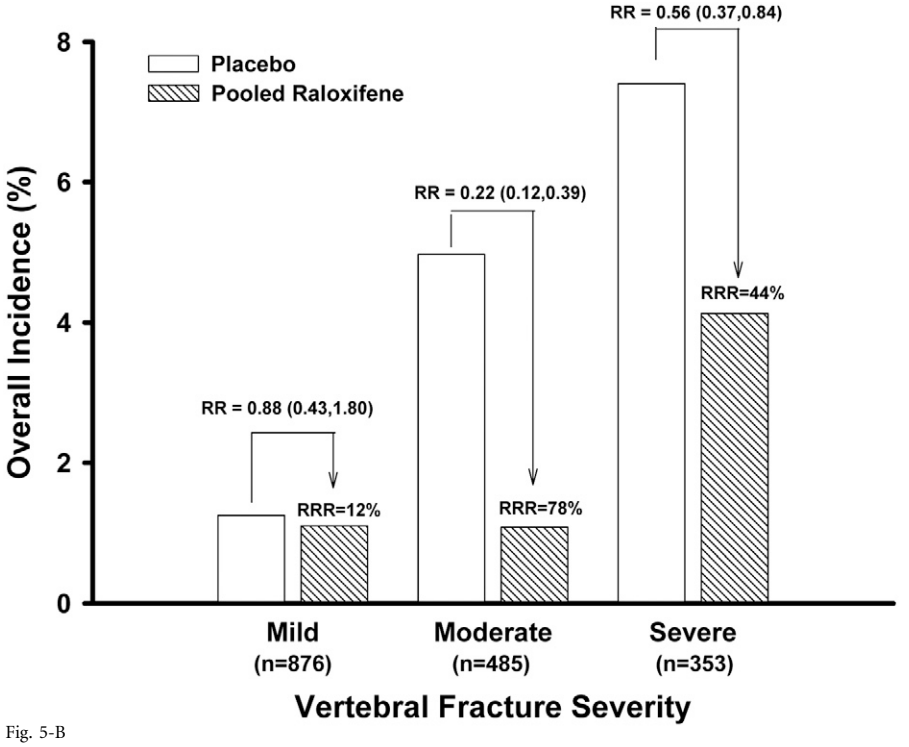


Fig. 5-B

Effect of raloxifene treatment on the incidences of new adjacent vertebral fractures according to the number (Fig. 5-A) and severity (Fig. 5-B) of the prevalent vertebral fracture. RR = relative risk (the ratio of the fracture risk in the treatment group compared with that in the placebo group), and RRR = relative risk reduction (1 minus the relative risk). The 95% confidence intervals are given in the parentheses after the relative risk values. See text for an explanation of how the overall incidence was calculated.

risk of new adjacent vertebral fractures and the risk of new nonadjacent vertebral fractures were determined after stratifying by the number and severity of prevalent vertebral fractures, and these risks were compared by means of logistic regression analysis. The risk of new adjacent vertebral fractures was calculated as the ratio of the number of new adjacent vertebral fractures to the number of adjacent nonfractured vertebrae. Similarly, the risk of new nonadjacent vertebral fractures was calculated as the ratio of the number of new nonadjacent vertebral fractures to the number of nonadjacent nonfractured vertebrae. The incidence of any new fracture (adjacent or nonadjacent) was determined as the ratio of the total number of new vertebral fractures (adjacent and nonadjacent) to the total number of nonfractured vertebrae (adjacent and nonadjacent). The effects of teriparatide and raloxifene on the risks of new adjacent and new nonadjacent vertebral fractures, stratified by the number and severity of the prevalent vertebral fractures, was determined with the Mantel-Haenszel method; the data for 793 women from the pooled teriparatide groups (dosages of 20 and 40 μg/day) from the Fracture Prevention Trial were compared with the data for 398 women from the placebo group from that trial, and the data for 1714 women from the pooled raloxifene groups (dosages of 60 and 120 mg/day) from the MORE trial were compared with the data for 828 women from the placebo group from that trial. Because the reduction in fracture risk was similar for the two doses in each study, the dose groups were combined to increase the statistical power of the analyses.

*Source of Funding*
Data analysis was performed by Eli Lilly.

## Results

The clinical profile of the patients included in the analyses was typical for postmenopausal women at high risk for fracture; 39% of the total number of patients treated with a placebo (73% of those in the Fracture Prevention Trial and 32% of those in the MORE trial) were included in the present analysis. There were no differences between the two trials with regard to the baseline characteristics of the subjects who had one or more prevalent vertebral fractures at baseline (Table I).

The distribution of prevalent vertebral fractures was bimodal, with peaks at the midthoracic and thoracolumbar regions of the spine. The pattern of new adjacent fractures was consistent with the pattern of prevalent fractures across the spine (Fig. 1).

Of 1226 women with at least one prevalent vertebral fracture at baseline, 196 (16.0%) sustained a total of 292 new vertebral fractures over two years. Of the 567 women with one prevalent fracture at baseline, fifty-four (9.5%) sustained a new vertebral fracture over two years. In comparison, of the 659 women with two or more vertebral fractures at baseline, 142 (21.5%) sustained a new vertebral fracture over two years. Of the 196 women who sustained a new fracture, 108 (55%) had at least one new fracture adjacent to a prevalent fracture. Of the 292 new vertebral fractures, 136 (47%) were adjacent to a prevalent fracture.

When we analyzed fracture rates on a vertebral body level rather than on the patient level, the overall incidences of any new, new adjacent, and new nonadjacent fractures were 2.22%, 4.03%, and 1.59%, respectively. The risk of a new adjacent vertebral fracture was 2.5-fold greater than the risk of a new nonadjacent vertebral fracture (relative risk, 2.53; 95% confidence interval, 2.02 to 3.18).

An increased number of prevalent vertebral fractures was associated with increased risks of any new, new adjacent, and new nonadjacent vertebral fractures (Fig. 2-A). The incidence of new adjacent vertebral fractures was significantly ($p < 0.05$) higher than the incidence of new nonadjacent fractures, irrespective of the number of prevalent fractures at baseline. Similarly, an increased severity of the prevalent vertebral fracture was associated with increased incidences of any new, new adjacent, and new nonadjacent vertebral fractures (Fig. 2-B). The incidence of new adjacent fractures was significantly ($p < 0.05$) higher than the incidence of new nonadjacent fractures in each severity category.

### *Effects of Treatment*

Compared with the placebo, teriparatide treatment reduced the risks of any new, new adjacent, and new nonadjacent vertebral fractures by 72%, 75%, and 70%, respectively (Fig. 3-A). Similarly, compared with the placebo, raloxifene treatment reduced the risks of any new, new adjacent, and new nonadjacent vertebral fractures by 54%, 54%, and 53%, respectively (Fig. 3-B). Compared with the placebo, teriparatide reduced the risk of a new adjacent fracture by 81% in women with two prevalent fractures at baseline and by 68% in those with three or more prevalent fractures at baseline (Fig. 4-A). Compared with the placebo, teriparatide treatment reduced the risk of a new adjacent vertebral fracture by 62% in women with a mild or moderate prevalent fracture and by 86% in women with a severe prevalent vertebral fracture (Fig. 4-B). Similarly, compared with the placebo, raloxifene reduced the risk of a new adjacent fracture by 69% in women with one prevalent fracture at baseline, by 52% in women with two such fractures, and by 49% in those with three or more prevalent fractures (Fig. 5-A). Raloxifene reduced the risk of a new adjacent fracture by 12% in women with a mild prevalent fracture, by 78% in those with a moderate prevalent fracture, and by 44% in those with a severe prevalent fracture (Fig. 5-B).

## Discussion

In this study, we characterized the incidence of new adjacent vertebral fractures as compared with that of new nonadjacent vertebral fractures in untreated postmenopausal women with osteoporosis and one or more prevalent vertebral fractures. We then determined the effects of teriparatide and raloxifene treatment on the incidences of any new, new adjacent, and new nonadjacent vertebral fractures in postmenopausal osteoporotic women with one or more prevalent vertebral fractures.

The distribution of prevalent vertebral fractures along the spine in the current study was similar to the distributions in previously reported community-based studies[3,7,8,22] and clinical trials[9], with a peak prevalence at the midthoracic and

thoracolumbar regions. Not surprisingly, given this distribution of prevalent fractures, the distribution of new adjacent vertebral fractures followed a similar pattern, with the highest incidences at T8 and L1. We confirmed previous findings that the risk of any new fracture increases with an increasing number and severity of prevalent fractures, and we extended those observations, showing that the risk of a new adjacent fracture follows a similar pattern. The impact of the severity of the prevalent fracture was particularly profound, as the individuals with a severe prevalent fracture at baseline had a 5.3-fold increase in the risk of a new adjacent fracture compared with those who had a mild prevalent fracture at baseline. In this study, 16% of the women sustained at least one new vertebral fracture, a rate that is comparable with that reported previously for women with similar demographic and risk factors[4].

Because morbidity is related to both the number and the severity of prevalent vertebral fractures, it is important to better understand the possible mechanisms underlying vertebral fractures. There are several possible reasons why the incidence of new adjacent fractures is higher than the incidence of new nonadjacent fractures in individuals who have had a prevalent vertebral fracture. First, given that fractures do not occur uniformly along the spine, it follows that, if the prevalent fracture is located in a "high-incidence" region, then the next fracture would be likely to be in this region as well. To further explore this issue, one would need to analyze the risk of a new fracture while taking into account the underlying probability of a fracture at each vertebral level, which we did not do in the present study. Second, it may be that the presence of a vertebral fracture alters the local biomechanics in terms of how loads are transferred along the spine. For instance, an anterior wedge fracture causes an anterior shift of the center of gravity of the upper body, altering the force distribution across the end plate and increasing pressure in the intervertebral disc[23]. Finally, a fractured vertebra may eventually stiffen as the cancellous bone compresses on itself, which also leads to altered load transfer to the adjacent vertebrae. It is likely that a combination of these factors contributes to the increased incidence of adjacent-level fractures.

Previous studies have shown that teriparatide and raloxifene reduce the risk of vertebral fractures[19], even in those with severe and multiple vertebral fractures at baseline[6]. In our study, both teriparatide and raloxifene were found to have reduced the incidence of new adjacent vertebral fractures (by 75% and 54%, respectively), indicating that both therapies can prevent fractures even in the unfavorable biomechanical situation of an adjacent fracture. The specific mechanisms by which teriparatide and raloxifene reduce the occurrence of these fractures are not known. However, both drugs increase bone mineral density, which is strongly associated with whole vertebral strength[24]. Furthermore, finite element analyses have indicated that teriparatide treatment increases the compressive strength of the vertebral body and, in particular, of the vertebral trabecular centrum[25].

One of the motivations for the current analysis was the observation, in several studies, of an increased incidence of fractures in vertebrae adjacent to those that had been augmented with cement during either vertebroplasty or kyphoplasty, with the increased risk observed particularly in the first few months following the procedure[10-13]. However, because those studies generally did not include an untreated control group, it has been difficult to know definitively whether fractures following vertebral augmentation are attributable to the procedure or to the natural progression of skeletal fragility in this population. Our data indicate that a new vertebral fracture occurs in 16% of women and a new adjacent-level fracture occurs in 9% of women over a two-year period following a prevalent fracture. In comparison, studies of vertebroplasty and kyphoplasty have demonstrated new-fracture incidences of 12% to 69%, with higher rates in those with steroid-induced osteoporosis[26-31]. A recent meta-analysis of 168 studies revealed that a new fracture occurred in 17.9% of patients treated with vertebroplasty and 14.1% of those treated with kyphoplasty, although the meta-analysis did not specify the rates of adjacent-level fractures compared with those of nonadjacent-level fractures[32]. In studies that did delineate these rates, 66% to 76% of new fractures were adjacent to existing fractures[10,30,33], incidences that are higher than the 47% rate found in the current study.

Although tempting and important, it is difficult to make direct comparisons between our study and previous reports of fracture incidence following vertebroplasty and kyphoplasty. First, it is not clear whether the populations are comparable with regard to disease severity and consequent risk of future fracture. Also, an important distinction between our study and those of vertebral augmentation is that we identified vertebral fractures on the basis of radiographic criteria, whereas the authors of studies of kyphoplasty and vertebroplasty have generally reported on clinically symptomatic fractures. As it is estimated that only about one-third of radiographically determined vertebral fractures present as clinically symptomatic fractures[32], the difference in the incidence of new fractures in untreated postmenopausal women compared with the incidence in those treated with vertebral augmentation may be even greater than indicated here since surveillance radiographs were not made in many of the vertebroplasty series. Finally, although we used the term "untreated" in this study, all subjects did receive calcium and vitamin-D supplementation, which may reduce the rate of new fractures compared with the rate in individuals with no supplementation. It is unclear whether individuals undergoing vertebroplasty or kyphoplasty procedures receive calcium and vitamin-D supplementation or other anti-osteoporotic therapy.

In summary, we confirmed that new vertebral fractures are common in women with prevalent fractures, and we extended this observation to show that approximately half of new fractures are adjacent to existing fractures. Although not directly comparable, our data suggest that new fractures, particularly adjacent-level fractures, are more common in patients treated with vertebroplasty and kyphoplasty than they are in postmenopausal women receiving calcium and vitamin-D supplementation. To our knowledge, teriparatide and raloxi-

fene are the first treatments to demonstrate effects in terms of reducing the incidence of adjacent-level vertebral fractures. ■

NOTE: The authors thank the investigators of the Fracture Prevention Trial and the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.

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## References

**1.** Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med. 1989;149:2445-8.

**2.** Melton LJ 3rd, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL. Epidemiology of vertebral fractures in women. Am J Epidemiol. 1989;129:1000-11.

**3.** Melton LJ 3rd, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL. Prevalence and incidence of vertebral deformities. Osteoporos Int. 1993;3:113-9.

**4.** Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320-3.

**5.** Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, Adachi JD. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone. 2003;33:522-32.

**6.** Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. J Clin Endocrinol Metab. 2005;90:1583-7.

**7.** Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res. 1992;7:221-7.

**8.** Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone. 1993;14 Suppl 1:S89-97.

**9.** Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, Grauer A, Cahall D, Watts NB; Improving Measurements of Persistence on Actonel Treatment (IMPACT) Investigators. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2007;92:1296-304. Erratum in: J Clin Endocrinol Metab. 2007; 92:2285.

**10.** Uppin AA, Hirsch JA, Centenera LV, Pfiefer BA, Pazianos AG, Choi IS. Occurrence of new vertebral body fracture after percutaneous vertebroplasty in patients with osteoporosis. Radiology. 2003;226:119-24.

**11.** Kallmes DF, Jensen ME. Percutaneous vertebroplasty. Radiology. 2003;229: 27-36.

**12.** Trout AT, Kallmes DF, Kaufmann TJ. New fractures after vertebroplasty: adjacent fractures occur significantly sooner. AJNR Am J Neuroradiol. 2006;27:217-23.

**13.** Trout AT, Kallmes DF, Lane JI, Layton KF, Marx WF. Subsequent vertebral fractures after vertebroplasty: association with intraosseous clefts. AJNR Am J Neuroradiol. 2006;27:1586-91.

**14.** Baroud G, Vant C, Wilcox R. Long-term effects of vertebroplasty: adjacent vertebral fractures. J Long Term Eff Med Implants. 2006;16:265-80.

**15.** Kim SH, Kang HS, Choi JA, Ahn JM. Risk factors of new compression fractures in adjacent vertebrae after percutaneous vertebroplasty. Acta Radiol. 2004;45: 440-5.

**16.** Lin EP, Ekholm S, Hiwatashi A, Westesson PL. Vertebroplasty: cement leakage into the disc increases the risk of new fracture of adjacent vertebral body. AJNR Am J Neuroradiol. 2004;25:175-80.

**17.** Trout AT, Kallmes DF. Does vertebroplasty cause incident vertebral fractures? A review of available data. AJNR Am J Neuroradiol. 2006;27:1397-403.

**18.** Villarraga ML, Bellezza AJ, Harrigan TP, Cripton PA, Kurtz SM, Edidin AA. The biomechanical effects of kyphoplasty on treated and adjacent nontreated vertebral bodies. J Spinal Disord Tech. 2005;18:84-91.

**19.** Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41.

**20.** Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Glüer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282:637-45.

**21.** Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137-48.

**22.** Samelson EJ, Hannan MT, Zhang Y, Genant HK, Felson DT, Kiel DP. Incidence and risk factors for vertebral fracture in women and men: 25-year follow-up results from the population-based Framingham study. J Bone Miner Res. 2006;21: 1207-14.

**23.** Rohlmann A, Zander T, Bergmann G. Spinal loads after osteoporotic vertebral fractures treated by vertebroplasty or kyphoplasty. Eur Spine J. 2006;15: 1255-64.

**24.** Moro M, Hecker AT, Bouxsein ML, Myers ER. Failure load of thoracic vertebrae correlates with lumbar bone mineral density measured by DXA. Calcif Tissue Int. 1995;56:206-9.

**25.** Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res. 2007;22:149-57.

**26.** Majd ME, Farley S, Holt RT. Preliminary outcomes and efficacy of the first 360 consecutive kyphoplasties for the treatment of painful osteoporotic vertebral compression fractures. Spine J. 2005;5:244-55.

**27.** Lee WS, Sung KH, Jeong HT, Sung YS, Hyun YI, Choi JY, Lee KS, Ok CS, Choi YW. Risk factors of developing new symptomatic vertebral compression fractures after percutaneous vertebroplasty in osteoporotic patients. Eur Spine J. 2006;15: 1777-83.

**28.** Deen HG, Aranda-Michel J, Reimer R, Miller DA, Putzke JD. Balloon kyphoplasty for vertebral compression fractures in solid organ transplant recipients: results of treatment and comparison with primary osteoporotic vertebral compression fractures. Spine J. 2006;6:494-9.

**29.** Harrop JS, Prpa B, Reinhardt MK, Lieberman I. Primary and secondary osteoporosis' incidence of subsequent vertebral compression fractures after kyphoplasty. Spine. 2004;29:2120-5.

**30.** Komemushi A, Tanigawa N, Kariya S, Kojima H, Shomura Y, Komemushi S, Sawada S. Percutaneous vertebroplasty for osteoporotic compression fracture: multivariate study of predictors of new vertebral body fracture. Cardiovasc Intervent Radiol. 2006;29:580-5.

**31.** Hiwatashi A, Westesson PL. Patients with osteoporosis on steroid medication tend to sustain subsequent fractures. AJNR Am J Neuroradiol. 2007;28:1055-7.

**32.** Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J. 2008;8:488-97.

**33.** Fribourg D, Tang C, Sra P, Delamarter R, Bae H. Incidence of subsequent vertebral fracture after kyphoplasty. Spine. 2004;29:2270-7.