

Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene

Results From a 3-Year Randomized Clinical Trial

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RALOXIFENE HYDROCHLORIDE IS a nonsteroidal benzothio-
phene that binds to estrogen
receptors and inhibits bone re-
sorption without stimulating the uterine
endometrium in postmenopausal
women.¹ However, the effect of raloxi-
fene on the risk of fracture is not known.
Observational studies in postmeno-
pausal women have suggested that long-
term estrogen therapy reduces the inci-

For editorial comment see p 687.

Context Raloxifene hydrochloride, a selective estrogen receptor modulator, prevents bone loss in postmenopausal women, but whether it reduces fracture risk in these women is not known.

Objective To determine the effect of raloxifene therapy on risk of vertebral and non-vertebral fractures.

Design The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a multi-center, randomized, blinded, placebo-controlled trial.

Setting and Participants A total of 7705 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. The study began in 1994 and had up to 36 months of follow-up for primary efficacy measurements and nonserious adverse events and up to 40 months of follow-up for serious adverse events.

Interventions Participants were randomized to 60 mg/d or 120 mg/d of raloxifene or to identically appearing placebo pills; in addition, all women received supplemental calcium and cholecalciferol.

Main Outcome Measures Incident vertebral fracture was determined radiographically at baseline and at scheduled 24- and 36-month visits. Nonvertebral fracture was ascertained by interview at 6-month-interim visits. Bone mineral density was determined annually by dual-energy x-ray absorptiometry.

Results At 36 months of the evaluable radiographs in 6828 women, 503 (7.4%) had at least 1 new vertebral fracture, including 10.1% of women receiving placebo, 6.6% of those receiving 60 mg/d of raloxifene, and 5.4% of those receiving 120 mg/d of raloxifene. Risk of vertebral fracture was reduced in both study groups receiving raloxifene (for 60-mg/d group: relative risk [RR], 0.7; 95% confidence interval [CI], 0.5-0.8; for 120-mg/d group: RR, 0.5; 95% CI, 0.4-0.7). Frequency of vertebral fracture was reduced both in women who did and did not have prevalent fracture. Risk of nonvertebral fracture for raloxifene vs placebo did not differ significantly (RR, 0.9; 95% CI, 0.8-1.1 for both raloxifene groups combined). Compared with placebo, raloxifene increased bone mineral density in the femoral neck by 2.1% (60 mg) and 2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) $P < 0.001$ for all comparisons). Women receiving raloxifene had increased risk of venous thromboembolus vs placebo (RR, 3.1; 95% CI, 1.5-6.2). Raloxifene did not cause vaginal bleeding or breast pain and was associated with a lower incidence of breast cancer.

Conclusions In postmenopausal women with osteoporosis, raloxifene increases bone mineral density in the spine and femoral neck and reduces risk of vertebral fracture.

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dence of fracture,^{2,3} but the efficacy of estrogen in reducing fractures has been demonstrated in only 1 small prospective study.⁴ In addition, in the US Breast Cancer Prevention Trial,⁵ tamoxifen ci-

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trate, another selective estrogen receptor modulator, appeared to have a favorable effect on the incidence of fractures. The Multiple Outcomes of Raloxifene Evaluation (MORE) study was undertaken in 1994 primarily to examine the effect of raloxifene on the skeleton. We report herein the results of measurements of bone mineral density and assessment for fractures from a planned 36-month interim analysis.

METHODS

Subjects

We studied 7705 women who were at least 2 years postmenopausal and had no severe or long-term disabling conditions but who had osteoporosis, defined as low bone mineral density or radiographically apparent vertebral fractures. Subject recruitment and follow-up are summarized in FIGURE 1. The women were divided into 2 study groups and then were randomized to receive either placebo or 1 of 2 dosage amounts of raloxifene. Study group 1 included those whose femoral neck or lumbar spine bone mineral density *t* score was below -2.5 . Study group 2 included women who had low bone mineral density and 1 or more moderate or severe vertebral fractures or 2 or more mild vertebral fractures or who had at least 2 moderate frac-

tures, regardless of their bone mineral density. A mild vertebral fracture corresponds to a 20% to 25% reduction in height and a moderate vertebral fracture corresponds to a 25% to 40% reduction from expected vertebral height.^{6,7}

Women were excluded if they had experienced bone disease other than osteoporosis, substantial postmenopausal symptoms or abnormal uterine bleeding, endometrial carcinoma, a history of or suspected breast carcinoma at any time, or a history of nonskin cancer in the previous 5 years; taken an androgen, calcitonin, or bisphosphonate within the previous 6 months; been taking oral estrogen within the previous 2 months; been receiving fluoride therapy for more than 3 months during the previous 2 years; undergone systemic glucocorticoid therapy for more than 1 month within the past year; taken antiseizure drugs or pharmacologic doses of cholecalciferol; had a history of thromboembolic disorders within the last 10 years (except in association with an injury; experienced endocrine disorders requiring therapy (except for type 2 diabetes or hypothyroidism); had serum creatinine levels above 225 $\mu\text{mol/L}$ (2.5 mg/dL); had active renal lithiasis, abnormal hepatic function, or untreated malabsorption; or consumed more than 4 al-

coholic drinks per day. In addition, we excluded women with pathologic fractures, those from whom satisfactory thoracic and lumbar radiographs could not be obtained, and those with fewer than 2 lumbar and 4 thoracic vertebrae that were evaluable. The women were enrolled at 180 centers in 25 countries. Approximately half the study subjects were recruited by a centralized campaign in the United States and Canada that used both print and radio advertisements. Women responding to campaign advertisements were screened by telephone. Qualifying women were referred to study sites for further evaluation. The other half of the study subjects were enrolled at sites that may have used their own institutional or other databases to identify and contact potential subjects. The protocol was approved by the human studies review board at each center, and informed consent was obtained.

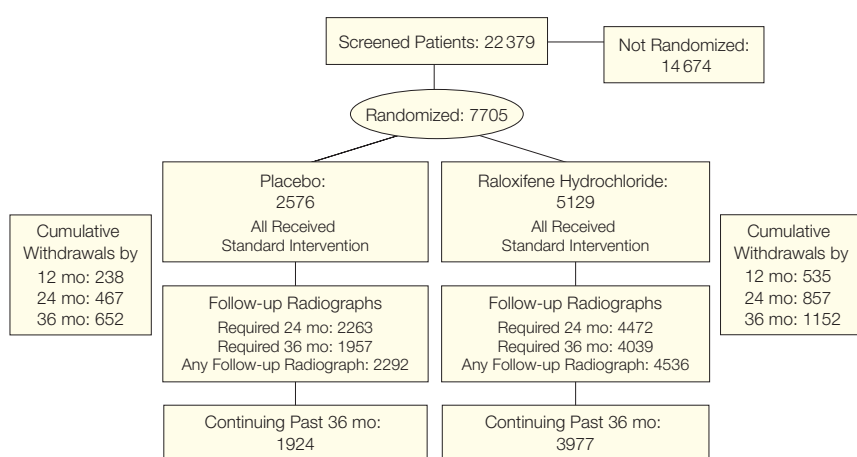
Treatment

Within each substudy, women were randomly assigned to treatment groups and were asked to take daily 1 of 3 types of identically appearing pills: placebo or 60 mg or 120 mg of raloxifene. Randomization was performed by the Eli Lilly Clinical Trials Materials Group, Indianapolis, Ind. This clinical trials group was also responsible for packaging the study drug materials but was not involved in either study design or patient monitoring. Study drug assignments were generated randomly. Upon entry into the study, all women received daily supplements of 500 mg of calcium and 400 to 600 IU of cholecalciferol.

Assessment of Vertebral Fracture

Participants underwent vertebral radiography at baseline, 24 months, and 36 months. When symptoms of vertebral fracture occurred, women underwent radiography at interim 6-month visits. When possible, radiographies were performed on women who had terminated from the study early. All vertebral radiographs were assessed at a central site by radiologists blinded to treatment group assignment. To establish eligibility for

Figure 1. Study Recruitment and Follow-up



Prior to randomization, patients were stratified to 1 of 2 study groups at the time of radiographic screening: 5064 were assigned to study group 1 if they had no vertebral fractures and 2641 were assigned to study group 2 if they had vertebral fractures.

study group 2, the baseline radiographs were scored using a semiquantitative scale^{6,7} for each vertebra (T4-L4). The grading scores were set as 0 for none, 1 for mild, 2 for moderate, and 3 for severe fractures. After 36 months, a radiologist blinded to treatment group assignment graded the baseline and end point radiographs using the same semiquantitative scale.^{6,7} An incident fracture was defined as a grade change of at least 1. If no fractures were detected after the review of baseline and end point radiographs, the analysis stopped for that patient. For fractures observed at baseline or end point, a second radiologist determined whether a fracture was present for each vertebra and also performed quantitative morphometry (with an incident fracture defined as a decrease in anterior, mid, or posterior vertebral height of at least 20% and at least 4 mm). Vertebral fractures were scored when they were confirmed by at least 2 of the 3 types of determinations from 2 independent semiquantitative readings and 1 quantitative assessment. A new vertebral fracture was defined as an incident fracture of a vertebra that was not fractured at baseline. We defined clinical vertebral fractures as incident fractures found at interim 6-month visits through additional unscheduled radiographies performed because of back pain suggestive of fractures. When incident fractures were adjudicated from these nonscheduled radiographs, they were counted as a clinical fracture as well as an incident fracture.

Nonvertebral fractures were determined by direct questioning every 6 months at each clinic visit. Fractures resulting from a traffic collision, a beating, or having been struck by a falling or moving object were considered traumatic and were excluded from the analysis. In addition, pathologic fractures and those involving the fingers, toes, and skull were excluded.

Assessment of Bone Mineral Density

Spine and femoral neck bone mineral density were measured annually by dual-energy x-ray absorptiometry. A central reading facility provided cor-

rection factors to adjust for intersite differences and changes in the performance of the densitometers over time.^{7,8}

Participants were required to discontinue the study if at 1 year they had experienced a bone mineral density decrease of at least 7% in their lumbar spine or 10% in their femoral neck; if at 2 years they had experienced a lumbar spine decrease of at least 11% or femoral neck decrease of at least 14%; or if at any time during the study, they had experienced more than 2 incident vertebral fractures.

Assessment of Adverse Events

Mammography was performed at baseline, was optional at 1 year, but was required after 2 and 3 years. Transvaginal ultrasonography was performed at baseline, annually at 17 large clinical centers, and in others if clinically indicated. A total of 1781 women had a baseline and at least 1 postbaseline transvaginal ultrasonography. All women were questioned about the adverse effects of treatment at each visit; all serious adverse effects reported for up to 40 months of follow-up and all nonserious adverse effects reported for up to 36 months of follow-up were analyzed regardless of the investigators' assessments of causality. Adverse events that resulted in death, hospitalization, cancer, permanent disability, or threat to life were classified as serious. *The Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART)*⁹ dictionary was used to categorize reported adverse events. We report all categories of adverse events for which frequency was different ($P < .05$) between the placebo and combined raloxifene groups and for which the incidence was at least 2% in any group.

Biochemical Assessment of Physiologic Functions and Bone Turnover

Hematologic, renal, and hepatic function was tested periodically during the study. Markers of bone turnover, including serum osteocalcin (ELSAOSTEO, CIS Biointernational, Gifsur Yvette, France)¹⁰ and the urinary type I collagen C-

telopeptide excretion, corrected for urinary creatinine excretion (CrossLaps, Osteometer A/S, Herlev, Denmark),¹¹ were measured in 2622 women who were enrolled at some sites in North America, Europe, and South America.

Statistical Analysis

The primary end points in each substudy were the effects of raloxifene on incident vertebral fractures and bone mineral density; a secondary end point was any nonvertebral fracture. The sample size provided a greater than 90% power (2-tailed t test, $P < .05$ significance level) to detect a 40% reduction in vertebral fractures between pooled raloxifene doses and placebo. Power calculations were based on the assumptions that after 3 years, the cumulative incidence of osteoporotic vertebral fractures among women receiving placebo would be 7.2% for those free of vertebral fracture at baseline and 19.5% for those with 1 or more fractures at baseline. On the basis of observed incidence of vertebral fractures in the placebo group, the study's power was slightly greater than predicted.

We included only women who had incident fractures in vertebrae that were not fractured at baseline. We examined 12 categories of nonvertebral fracture: humerus, wrist, hip, patella, tibia/fibula, ankle, metatarsal, rib/sternum, clavicle, scapula, sacrum, and pelvis. Using log-rank tests, we compared the time to first occurrence of nonvertebral fracture between the raloxifene and placebo groups. Adverse effects were analyzed using χ^2 tests. All analyses were performed as intention to treat (ie, participants were classified according to their substudy group and treatment assignment regardless of compliance). Missing postbaseline data were imputed by carrying forward the last observation. All comparisons were 2 sided and were performed at a $P = .05$ level of significance. No adjustments were made for multiple comparisons. The number needed to treat was calculated as the reciprocal of the difference in vertebral fracture incidence between treatment and placebo.

RESULTS

The 7705 women enrolled in the study ranged in age from 31 to 80 years (mean, 67 years). Almost all (95.7%) were white. There were no statistically significant differences in baseline characteristics (TABLE 1). Compared with the women in study group

1, women in study group 2 (see "Methods" section for study group assignment criteria) were older and had lower bone mineral density at baseline. We found no difference in adherence to treatment among the groups: 92% of the women took more than 80% of the study medication.

Vertebral Fracture

Baseline and follow-up radiographs were available for 6828 women (89%); the study groups were similar in percentage of women having available radiographs. Of these women, 88% had radiography performed at the 36-month visit; for the others, the last postbaseline radiograph was used. We found no difference in baseline characteristics between these women and the 877 women who discontinued treatment and had had no follow-up radiographs. After 36 months, 503 (7.4%) of the 6828 women had 1 or more new vertebral fractures. Overall and in each study group, women receiving raloxifene had fewer new vertebral fractures (TABLE 2) regardless of whether the women had existing fractures at the beginning of the study (FIGURE 2). Overall, we found no difference in the rate of vertebral fracture incidence between the 2 raloxifene-treated groups; however, in study group 2, we saw a lower incidence of fractures in the women given 120 mg of raloxifene compared with women given 60 mg of raloxifene (10.7% vs 14.7%, respectively; $P = .02$). Twenty-two women in study group 1 and 95 women in study group 2 had 2 or more new vertebral fractures (relative risk [RR], 0.2; 95% confidence interval [CI], 0.1-0.6; and RR, 0.5; 95% CI, 0.3-0.7, respectively, for pooled raloxifene groups vs placebo). The reduction in fracture risk for the subset of 65 women with clinical vertebral fractures was similar to those discovered by routine radiographic assessment (RR, 0.4; 95% CI, 0.3-0.7, for pooled raloxifene groups vs placebo). The reduction in vertebral fracture risk associated with raloxifene treatment was similar in each of the following subgroups: tertiles of age, tertiles of baseline femoral neck or lumbar spine bone mineral density, prior hysterectomy vs not, and prior hormone replacement therapy vs none.

Nonvertebral Fracture

When assessed at 36 months, 240 women (9.3%) receiving placebo reported at least 1 nonvertebral fracture compared with 437 women (8.5%) in the

Table 1. Characteristics of 6828 Postmenopausal Women*

Characteristics	Study Group 1†		Study Group 2†	
	Placebo (n = 1522)	Raloxifene (n = 3002)	Placebo (n = 770)	Raloxifene (n = 1534)
Age, y	65 (7)	65 (7)	69 (6)	68 (7)
No. of years since menopause	18 (8)	17 (8)	21 (8)	21 (8)
Body mass index, kg/m ²	25.0 (3.9)	25.0 (3.9)	25.8 (3.9)	25.8 (4.2)
Femoral neck BMD, g/cm ²				
Hologic densitometry (n = 4347)	0.584 (0.061)	0.585 (0.059)	0.565 (0.074)	0.569 (0.071)
Lunar densitometry (n = 1965)	0.719 (0.069)	0.720 (0.073)	0.707 (0.088)	0.702 (0.084)
Norland densitometry (n = 476)	0.666 (0.058)	0.663 (0.061)	0.645 (0.091)	0.615 (0.092)
Lumbar spine BMD, g/cm ²				
Hologic densitometry (n = 4347)	0.768 (0.114)	0.774 (0.111)	0.748 (0.142)	0.745 (0.126)
Lunar densitometry (n = 1976)	0.886 (0.144)	0.883 (0.135)	0.845 (0.146)	0.842 (0.142)
Norland densitometry (n = 477)	0.753 (0.129)	0.768 (0.125)	0.747 (0.139)	0.742 (0.144)
Women with existing vertebral fracture, %				
0	89.9	88.7	11.6	10.0
1	8.3	9.6	40.5	40.4
≥2	1.7	1.7	47.9	49.6
Previously received estrogen therapy, %	29.4	29.4	26.6	26.6
Previously had hysterectomy, %	21.2	22.8	23.9	21.6
Current smoker, %	15.3	15.5	16.0	16.4

*BMD indicates bone mineral density (unadjusted value). Data are presented as mean (SD) unless otherwise indicated. Approximately 10% of the women in each study group showed a different number of vertebral fractures under a more stringent radiographic assessment protocol. Data are from women who completed the study and who had evaluable radiographs at 36 months.

†Study group 1 included women whose femoral neck or lumbar spine bone mineral density *t* score was below -2.5 . Study group 2 included women who had low bone mineral density, 1 or more moderate or severe vertebral fractures, or 2 or more mild vertebral fractures or who had at least 2 moderate fractures, regardless of their bone mineral density.

Table 2. New Vertebral Fracture in 6828 Postmenopausal Women Receiving Placebo or Raloxifene Hydrochloride Therapy for Osteoporosis*

	Placebo	Raloxifene, 60 mg/d	Raloxifene, 120 mg/d
Study group 1			
No. of women	1522	1490	1512
Women with ≥1 vertebral fracture, No. (%)	68 (4.5)	35 (2.3)	42 (2.8)
RR (95% CI)	...	0.5 (0.4-0.8)	0.5 (0.4-0.9)
No. of women needed to treat†	...	46	59
Study group 2			
No. of women	770	769	765
Women with ≥1 vertebral fracture, No. (%)	163 (21.2)	113 (14.7)	82 (10.7)
RR (95% CI)	...	0.7 (0.6-0.9)	0.5 (0.4-0.7)
No. of women needed to treat†	...	16	10
No. of women in both study groups	2292	2259	2277
Total with ≥1 vertebral fracture, No. (%)	231 (10.1)	148 (6.6)	124 (5.4)
Total RR (95% CI)	...	0.7 (0.5-0.8)	0.6 (0.4-0.7)

*RR indicates relative risk; CI, confidence interval. Data are from women who completed the study and who had evaluable radiographs at 36 months.

†For 3 years to prevent 1 incident vertebral fracture.

pooled raloxifene groups (RR, 0.9; 95% CI, 0.8-1.1) (TABLE 3 and FIGURE 3). The analyses of individual fracture sites for pooled raloxifene groups and placebo showed 237 wrist, 62 ankle, and 58 hip fractures. Among all 12 categories of non-vertebral fractures, only the ankle fracture risk reduction was statistically significant (Figure 3).

Bone Mineral Density and Bone Turnover

Compared with bone mineral density in the placebo group, bone mineral density increased after 36 months by 2.1% and 2.6% at the femoral neck and spine in the 60-mg raloxifene group and by 2.4% and 2.7% at the femoral neck and spine in the 120-mg raloxifene group, respectively ($P < .001$, all comparisons) (FIGURE 4). In the raloxifene groups, bone density of the hip peaked at 24 months, and spinal density remained constant between 2 and 3 years. A total of 94 women (3.6%) assigned to the placebo group, 28 (1.1%) assigned to the 60 mg of raloxifene group, and 22 (0.9%) assigned to the 120 mg of raloxifene group withdrew from the study for having multiple fractures or for excessive bone mineral density loss, a predefined study end point ($P < .001$ for each raloxifene dose vs placebo).

The median baseline serum osteocalcin concentration was 24.1 $\mu\text{g/L}$, and urinary excretion of C-telopeptide was 248 $\mu\text{g/mmol}$ of creatinine. After 36 months, the serum osteocalcin concentrations decreased by a median of 8.6%, 26.3%, and 31.1%, and the urinary C-telopeptide excretion decreased by 8.1%, 34.0%, and 31.5% in the placebo, the 60 mg of raloxifene, and the 120 mg of raloxifene groups, respectively ($P < .001$ for each raloxifene dose vs placebo).

Adverse Effects

After 36 months, 24.2% of the women had serious adverse effects regardless of treatment group. Venous thromboembolic events, including deep vein thrombophlebitis and pulmonary embolism, were the only serious adverse effects believed to be causally related to raloxifene treatment; by 40 months, venous

thromboembolic events had been reported by 8 (0.3%), 25 (1.0%), and 24 (1.0%) of all patients in the placebo, the 60 mg of raloxifene, and the 120 mg of raloxifene groups, respectively (RR, 3.1; 95% CI, 1.5-6.2 for both raloxifene groups combined vs placebo).

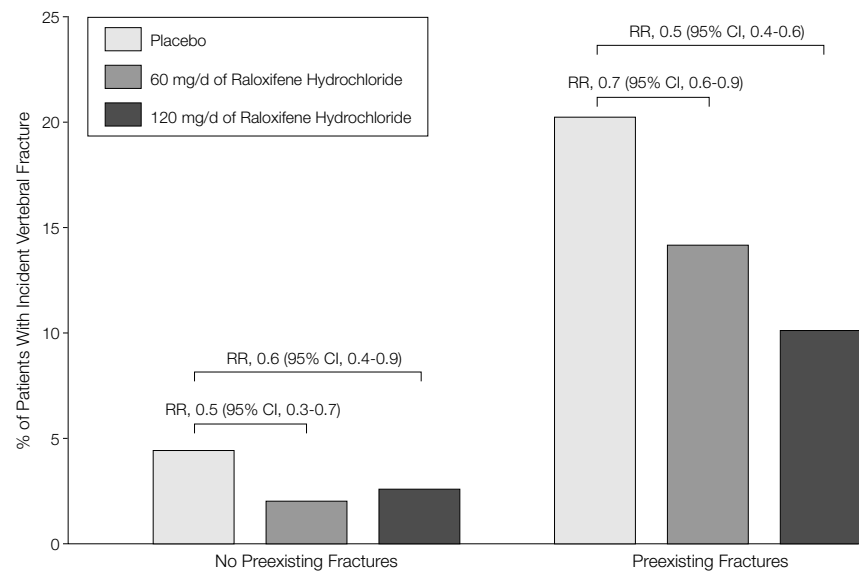
Breast cancer was less frequent in the women receiving raloxifene. By 40 months, 54 women had a confirmed diagnosis of breast cancer (RR, 0.3; 95% CI, 0.2-0.6 for both raloxifene groups combined vs placebo). Ten women had endometrial cancers: 4 in the placebo group, 4 in the 60 mg of raloxifene group, and 2 in the 120 mg of raloxifene group.

A total of 83 adverse effects occurred in at least 2% of the women in any treatment group. TABLE 4 lists only

those adverse events experienced by at least 2% of the women in each group and those for which the numbers and percentages of women experiencing adverse events in the combined raloxifene groups differed from the placebo group ($P < .05$). Vaginal bleeding was reported by 62 (3.1%), 67 (3.4%), and 56 (2.8%) of women in the placebo, the 60 mg of raloxifene, and the 120 mg of raloxifene groups, respectively. In addition, the proportion of women reporting breast pain did not differ among groups (data not shown).

A total of 754 women (9.8%) withdrew from the study due to an adverse event: 527 women (10.3%) in the raloxifene groups and 227 women (8.8%) in the placebo group ($P = .04$). Hot

Figure 2. Reduction in New Vertebral Fractures Among 6828 Women Who Completed the Study



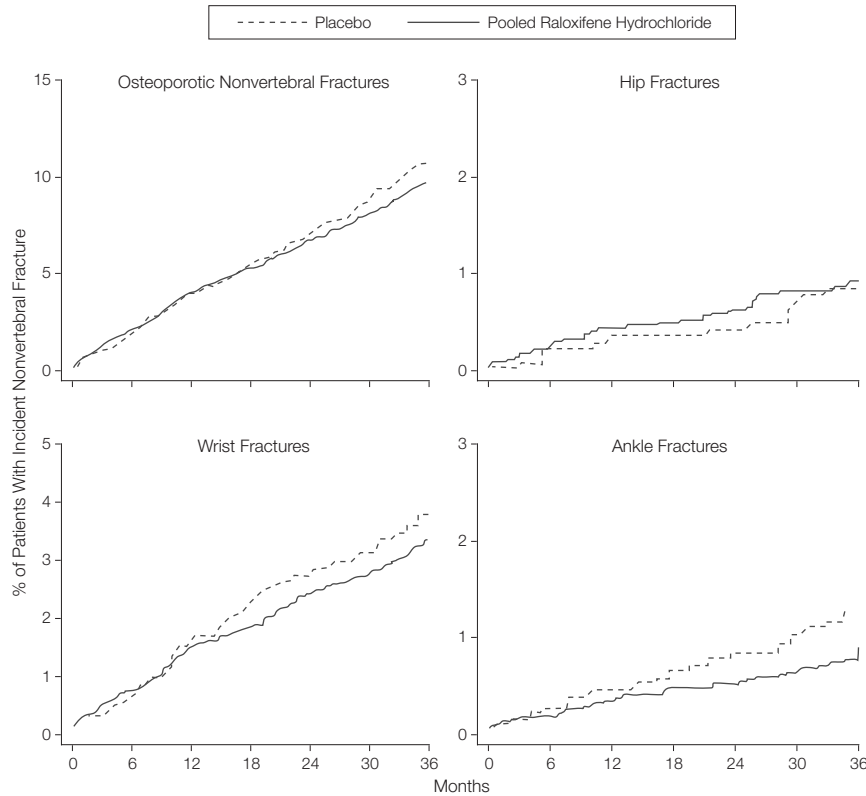
Women did or did not have vertebral fracture at the beginning of study. RR indicates relative risk; CI, confidence interval.

Table 3. Nonvertebral Fractures in 4536 Women Receiving Raloxifene Hydrochloride Therapy and 2292 Women Receiving Placebo

	No. (%) of Women		Relative Risk (95% CI)*
	Placebo	Raloxifene	
Nonvertebral fracture	240 (9.3)	437 (8.5)	0.9 (0.8-1.1)
Wrist fracture	86 (3.3)	151 (2.9)	0.9 (0.6-1.1)
Ankle fracture	28 (1.1)	34 (0.7)	0.6 (0.4-1.0)
Hip fracture	18 (0.7)	40 (0.8)	1.1 (0.6-1.9)

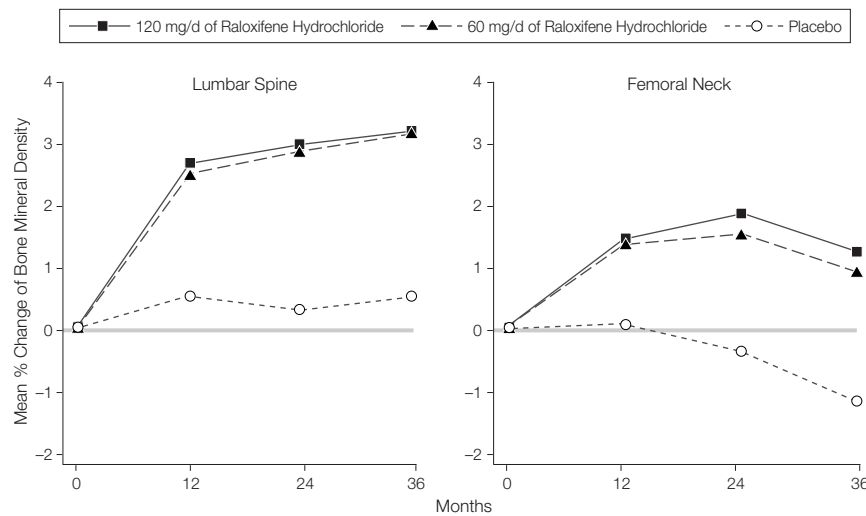
*CI indicates confidence interval.

Figure 3. Occurrence of First Nonvertebral Fracture Since Start of Study



This represents 2292 women who received placebo and 4536 women who received raloxifene therapy for osteoporosis. For osteoporotic nonvertebral fractures, $P = .24$; hip fractures, $P = .71$; wrist fractures, $P = .34$; and ankle fractures, $P < .05$. Percentages are calculated from survival distribution using the product limit (Kaplan-Meier) method.

Figure 4. Percentage Change in Bone Mineral Density in Lumbar Spine and Femoral Neck



Data represent 1490 women receiving 60 mg/d of raloxifene, 1512 women receiving 120 mg/d of raloxifene, and 1522 women receiving placebo.

flashes were the most common non-serious adverse event, prompting withdrawal in 0.1%, 0.7%, and 0.5% of the women in the placebo, the 60 mg of raloxifene, and the 120 mg of raloxifene groups, respectively.

There were no clinically important changes in hemologic, renal, or hepatic function laboratory assessments.

COMMENT

The risk for vertebral fractures, detected clinically or by radiography, was decreased by 30% to 50% among women treated with raloxifene for 36 months. The reduction compared with placebo was statistically significant for women both with and without vertebral fractures at baseline. The decreased risk was marginally greater in the women with prevalent vertebral fractures who were in the 120 mg of raloxifene group compared with those who were in the 60 mg of raloxifene group.

These results are comparable with those found in prospective trials of other antiresorptive drugs, including a trial of bisphosphonate alendronate¹²⁻¹⁴ and a small trial with transdermal estrogen.⁴ Radiographic deformities, whether clinically apparent or not, have been associated with substantial increases in back pain and back-related disability.¹⁵ A recent trial of another selective estrogen receptor modulator, tamoxifen, suggested a decrease in the risk of clinical osteoporotic fractures by 19%.⁵

Similar to previous studies of raloxifene in early postmenopausal women without osteoporosis,¹ we found about a 2% to 3% increase in spine and hip bone mineral density after 2 and 3 years of raloxifene treatment compared with those who were in the placebo group. We found a moderate reduction in biochemical markers of bone turnover and the median levels in the raloxifene groups were similar to the mean levels found in premenopausal women.^{15,16} Thus, although the effects we saw on bone density and biochemical markers were about half those observed in women treated with alendronate,¹¹ the reduction in vertebral fracture risk was similar. Our study supports previous

observations that the effect of fracture reduction is not clearly related to the increase in bone mineral density,^{16,17} suggesting that other factors also contribute to prevention of fractures. Indeed, lower bone turnover in elderly women is associated with decreased risk of hip fracture independent of bone density.^{16,17}

We did not observe a significant reduction in nonspine fractures after 3 years. However, the cumulative incidence curves for nonvertebral fractures begin to diverge after about 2 years. Although this trend was not significant at 3 years, the MORE study is continuing for another year to assess the effects of 4 years of raloxifene treatment.

Only a few other agents have been tested for their effects on nonvertebral fractures, and few studies have been primarily designed to evaluate the effect of treatment on a specific nonvertebral fracture such as the hip.^{18,19} A combination of calcium and cholecalciferol has been shown to significantly reduce the risk of nonvertebral fractures in elderly women¹⁸ and elderly men.^{18,19} In the MORE trial, all women received calcium and cholecalciferol supplements, which might have attenuated the risk of fractures in both placebo and raloxifene groups. Among 13 388 women at high risk of breast cancer, a median of 4.5 years of treatment with tamoxifen produced a nonsignificant trend for reduction in risk of hip and wrist fractures.⁵ In the Heart and Estrogen/Progestin Replacement Study (HERS) of 2705 women with heart disease, those receiving estrogen and progestin for an average of 4 years did not show a reduction in nonvertebral fractures compared with those receiving a placebo.²⁰ The Fracture Intervention Trial¹² reported that 2027 women with vertebral fractures who were treated with alendronate had a reduced risk of nonvertebral fractures. However, in a parallel 4-year study of 4272 women who had no vertebral fracture, the reduction in risk of nonvertebral fracture with alendronate was not statistically significant. A subset of women with femoral neck *t* scores below -2.5 showed a statistically sig-

nificant reduction (RR, 0.6, 95% CI, 0.5-0.8) in the risk of vertebral and nonvertebral fracture, but the study did not report this subgroup's risk for nonvertebral fracture only.¹⁴ Based on the observed rate of fractures in the placebo group, our study had 80%, 38%, and 12% power to detect a 20% reduction in risk (placebo vs pooled raloxifene groups) in total nonspine, wrist, and hip fractures, respectively. However, there was a greater number of women removed from the placebo group because of rapid bone loss or multiple vertebral fractures during the trial. Because these women were at high risk of nonvertebral fractures, their removal may have decreased the ability to detect a statistically significant effect.

The women receiving raloxifene had an increased incidence of venous thromboembolic events compared with the women receiving placebo. Overall, the RR for venous thromboembolic events was approximately 3, which is comparable to that reported for postmenopausal women receiving estrogen therapy in observational studies,²¹⁻²³ for those in a prospective trial of estrogen therapy,²⁰ and for those receiving tamoxifen for prevention of breast cancer.⁵ Breast cancer was statistically significantly less frequent in the women receiving raloxifene, an effect similar to that reported for tamoxifen in the Breast Cancer Prevention Trial.⁵

During surveillance of the uterus by ultrasonography, about 1 in 12 of the women studied were found to have at least trace amounts of fluid in the endometrial cavity. In previous studies, endometrial fluid was detected in 6% to 12% of asymptomatic postmenopausal women in the absence of associated pathology.^{24,25} Of the women found to have endometrial fluid, 52 (31%) had undergone an endometrial biopsy; none of the women treated with raloxifene were found to have endometrial hyperplasia or endometrial carcinoma. Thus, raloxifene-associated endometrial fluid accumulation appears to be clinically unimportant. The study was not designed or powered to examine effects of raloxifene on endometrial cancer. The adverse events of leg cramps and peripheral edema were also reported more frequently in the women given raloxifene; these symptoms have also been reported in women receiving estrogen replacement therapy.²⁶

We conclude that 3 years of raloxifene treatment preserves bone density, reduces bone turnover, and reduces the incidence of vertebral fractures in postmenopausal women with osteoporosis.

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Table 4. Adverse Events With Incidence of at Least 2% and Differing Significantly for Women Receiving Raloxifene Hydrochloride Than for Women Receiving Placebo

Adverse Events	No. (%)			P Value*
	Placebo (n = 2576)	Raloxifene, 60 mg/d (n = 2557)	Raloxifene, 120 mg/d (n = 2572)	
	Raloxifene			
Influenza syndrome	293 (11.4)	346 (13.5)	345 (13.4)	.01
Hot flashes	165 (6.4)	249 (9.7)	269 (11.6)†	<.001
Leg cramps	96 (3.7)	178 (7.0)	178 (6.9)	<.001
Peripheral edema	114 (4.4)	134 (5.2)	168 (6.5)	<.01
Endometrial cavity fluid‡	43 (5.7)	60 (8.1)	66 (8.7)	.02
	Placebo			
Hypertension	231 (9.0)	177 (6.9)	194 (7.5)	.01
Hypercholesterolemia	121 (4.7)	55 (2.2)	50 (1.9)	<.001
Hematuria	55 (2.1)	35 (1.4)	33 (1.3)	<.01

*Combined raloxifene groups vs placebo.

†Only hot flashes differed significantly between 60 mg and 120 mg dosages of raloxifene.

‡Among 2262 women who had transvaginal ultrasonography.

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