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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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 nonvertebral fractures.

Design The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a multicenter, 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 identical-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.
study group 2, the baseline radiographs were scored using a semiquantitative scale 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 endpoint radiographs using the same semiquantitative scale. An incident fracture was defined as a grade change of at least 1. If no fractures were detected after the review of baseline and endpoint 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 correction factors to adjust for intersite differences and changes in the performance of the densitometers over time. 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, 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) 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) and the urinary type I collagen C-telopeptide excretion, corrected for urinary creatinine excretion (CrossLaps, Os-tometer–VS, Herlev, Denmark), 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 sub-study 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 chi-square 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.
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 59 hip fractures. Among all 12 categories of nonvertebral 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 due to adverse events in the combined raloxifene groups, respectively (P<.05). Vaginal bleeding was 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 events 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 flashes 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).
observations that the effect of fracture reduction is not clearly related to the increase in bone mineral density, 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.

We did not observe a significant reduction in nonspine fractures after 3 years. However, the cumulative incidence curves for nonvertebral fractures then 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. A combination of calcium and cholecalciferol has been shown to significantly reduce the risk of nonvertebral fractures in elderly women and elderly men. 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. In the Heart and Estrogen/Progestin Replacement Study (HERS) of 2,705 women with heart disease, those receiving estrogen and progesterin for an average of 4 years did not show a reduction in nonvertebral fractures compared with those receiving a placebo. The Fracture Intervention Trial 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 4,272 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 significant 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. 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, for those in a prospective trial of estrogen therapy, and for those receiving tamoxifen for prevention of breast cancer. 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.

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

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n = 2,576)</th>
<th>Raloxifene, 60 mg/d (n = 2,576)</th>
<th>Raloxifene, 120 mg/d (n = 2,576)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza syndrome</td>
<td>293 (11.4)</td>
<td>346 (13.3)</td>
<td>345 (13.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>165 (6.4)</td>
<td>249 (9.7)</td>
<td>269 (11.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>96 (3.7)</td>
<td>178 (7.0)</td>
<td>178 (6.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>114 (4.4)</td>
<td>134 (5.3)</td>
<td>168 (6.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Endometrial cavity fluid†</td>
<td>43 (1.7)</td>
<td>60 (1.8)</td>
<td>66 (8.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>231 (9.0)</td>
<td>177 (6.9)</td>
<td>194 (7.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>121 (4.7)</td>
<td>55 (2.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>55 (2.1)</td>
<td>35 (1.4)</td>
<td>33 (1.3)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*Combined raloxifene groups vs placebo.
†Only hot flashes differed significantly between 60 mg and 120 mg dosages of raloxifene.
‡Among 2,262 women who had transvaginal ultrasonography.

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. 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.

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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EFFECT OF RALOXIFENE ON FRACTURE RISK


