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## EFFECTS OF RALOXIFENE ON BONE MINERAL DENSITY, SERUM CHOLESTEROL CONCENTRATIONS, AND UTERINE ENDOMETRIUM IN POSTMENOPAUSAL WOMEN

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### ABSTRACT

**Background** Long-term estrogen therapy can reduce the risk of osteoporotic fracture and cardiovascular disease in postmenopausal women. At present, however, these beneficial effects are not separable from undesirable stimulation of breast and endometrial tissues.

**Methods** We studied the effect of raloxifene, a nonsteroidal benzothiophene, on bone mineral density, serum lipid concentrations, and endometrial thickness in 601 postmenopausal women. The women were randomly assigned to receive 30, 60, or 150 mg of raloxifene or placebo daily for 24 months.

**Results** The women receiving each dose of raloxifene had significant increases from base-line values in bone mineral density of the lumbar spine, hip, and total body, whereas those receiving placebo had decreases in bone mineral density. For example, at 24 months, the mean ( $\pm$ SE) difference in the change in bone mineral density between the women receiving 60 mg of raloxifene per day and those receiving placebo was  $2.4 \pm 0.4$  percent for the lumbar spine,  $2.4 \pm 0.4$  percent for the total hip, and  $2.0 \pm 0.4$  percent for the total body ( $P < 0.001$  for all comparisons). Serum concentrations of total cholesterol and low-density lipoprotein cholesterol decreased in all the raloxifene groups, whereas serum concentrations of high-density lipoprotein cholesterol and triglycerides did not change. Endometrial thickness was similar in the raloxifene and placebo groups at all times during the study. The proportion of women receiving raloxifene who reported hot flashes or vaginal bleeding was not different from that of the women receiving placebo.

**Conclusions** Daily therapy with raloxifene increases bone mineral density, lowers serum concentrations of total and low-density lipoprotein cholesterol, and does not stimulate the endometrium. (N Engl J Med 1997;337:1641-7.)

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THE incidence of osteoporosis and of cardiovascular disease increases in women after menopause. These increases can be prevented by estrogen therapy, but this treatment is associated with an increased risk of endometrial cancer,<sup>1</sup> which may persist despite the addition of a progestin,<sup>2</sup> and perhaps also with an increased risk of breast cancer.<sup>3</sup> Thus, a therapy that could prevent postmenopausal bone loss and lower serum cholesterol concentrations without stimulating reproductive tissues would be desirable.

Raloxifene is a nonsteroidal benzothiophene that inhibits the growth of estrogen-receptor-dependent, dimethylbenzanthracene-induced mammary tumors and reduces the occurrence of nitrosomethylurea-induced mammary tumors in rats. It has been classified as a selective estrogen-receptor modulator on the basis of studies in which it prevented bone loss and lowered serum cholesterol concentrations without stimulating the endometrium.<sup>4-7</sup> In preliminary clinical studies, administration of raloxifene in doses ranging from 50 to 600 mg per day decreased bone turnover as assessed by biochemical markers, and lowered serum cholesterol concentrations without increasing serum triglyceride concentrations or causing endometrial proliferation.<sup>8,9</sup> These tissue-specific estrogen-agonist or -antagonist actions of raloxifene may be related in part to a novel pathway for estrogen-receptor-mediated gene activation.<sup>10</sup> We report here the 24-month interim results of a long-term multicenter, placebo-controlled, double-blind study

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**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY SUBJECTS.\*

CHARACTERISTIC	PLACEBO	RALOXIFENE		
		30 mg	60 mg	150 mg
No. of subjects	150	152	152	147
Age (yr)	55±4	55±3	55±3	55±3
Years since menopause	4±2	5±2	5±2	5±2
Body-mass index†	25.4±3.8	26.1±4.4	25.9±4.1	25.7±4.1
Lumbar-spine bone mineral density (g/cm <sup>2</sup> )	0.94±0.11	0.93±0.11	0.94±0.12	0.94±0.10
Serum total cholesterol (mg/dl)‡	235	239	238	241
Prior estrogen therapy (%)	15	16	19	19
Prior hysterectomy (%)	9	13	13	13

\*Plus-minus values are means ±SD.

†The body-mass index was defined as the weight in kilograms divided by the square of the height in meters.

‡Median serum cholesterol concentrations are shown. To convert cholesterol values to millimoles per liter, multiply by 0.026.

examining the effect of raloxifene on regional and total-body bone mineral density, bone turnover, serum lipid concentrations, and endometrial thickness in 601 healthy postmenopausal women.

## METHODS

### Study Subjects

This study was conducted in Austria, Belgium, Denmark, France, Germany, Italy, the Netherlands, and the United Kingdom. Most of the women were recruited with the use of lists of social-security numbers or registered voters. Women were eligible to participate if they were 45 to 60 years of age, were within two to eight years of menopause, and had a lumbar-spine bone mineral density between 2.5 SD below and 2.0 SD above the mean value for normal premenopausal women (0.78 g per square centimeter and 1.27 g per square centimeter, respectively). The enrollment criteria were designed to include both women with low and those with normal bone mineral density. Women were excluded if they had a history of estrogen-dependent tumors (except in situ uterine tumors cured by hysterectomy), had had cancer within the previous five years (except excised skin cancers), had taken androgen, estrogen, calcitonin, or glucocorticoids within the previous six months, had ever taken a bisphosphonate or fluoride (except for dental prophylaxis), were taking antiepileptic medications, were taking pharmacologic doses of vitamin D or lipid-lowering drugs, had a history of thromboembolic disorders or of diabetes mellitus or other endocrine disorders requiring therapy (except thyroid hormone replacement), had abnormal renal function (serum creatinine, >2.0 mg per deciliter [177 μmol per liter]) or hepatic function, had serious postmenopausal symptoms or abnormal uterine bleeding, consumed an excess of alcohol (>4 drinks per day), or abused drugs. The protocol was approved by the human-studies review board at each center. All the women gave written informed consent to their participation in the study in accordance with the ethical principles stated in the Declaration of Helsinki.

### Treatment Protocol and Follow-up Studies

The women were assigned to therapy with 30, 60, or 150 mg of raloxifene per day or placebo on the basis of a randomized

block design. All the women were also given a daily supplement of 400 to 600 mg of elemental calcium. Study visits occurred every 3 months for 24 months in this ongoing study. Serum lipids and biochemical markers of bone turnover were measured at each visit. Bone mineral density of the spine and hip and endometrial thickness were measured every six months. Total-body bone mineral density was determined every 12 months. The women were questioned at each visit about the occurrence and severity of adverse events.

### Analytic Procedures

Bone mineral density of the lumbar spine and total hip was measured by dual-energy x-ray absorptiometry with a Hologic QDR-1000 or QDR-2000 densitometer (Hologic, Waltham, Mass.). At one study site, total-body bone mineral density was measured with a Hologic QDR-2000 densitometer. Scan quality was reviewed, without knowledge of group assignment, at a central facility (QAC Herlev, Hovegard, Denmark), which provided correction factors to adjust for changes in the performance of the densitometer over time.

Biochemical markers of bone turnover, including serum osteocalcin (measured by ELSA-OSTEO assay, CIS Biointernational, Gif-sur-Yvette, France),<sup>11</sup> serum bone-specific alkaline phosphatase (Ostase, Hybritech, San Diego, Calif.),<sup>12</sup> and the ratio of urinary type I collagen C-telopeptide to creatinine (CrossLaps Osteometer Biotech, Herlev, Denmark),<sup>13</sup> were measured at a single laboratory (Hôpital Edouard Herriot, Lyons, France). Serum lipids, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, were measured at a central laboratory (SciCor, Geneva) in samples obtained after an overnight fast. The double-layer thickness of the uterine endometrium was determined by transvaginal ultrasonography.

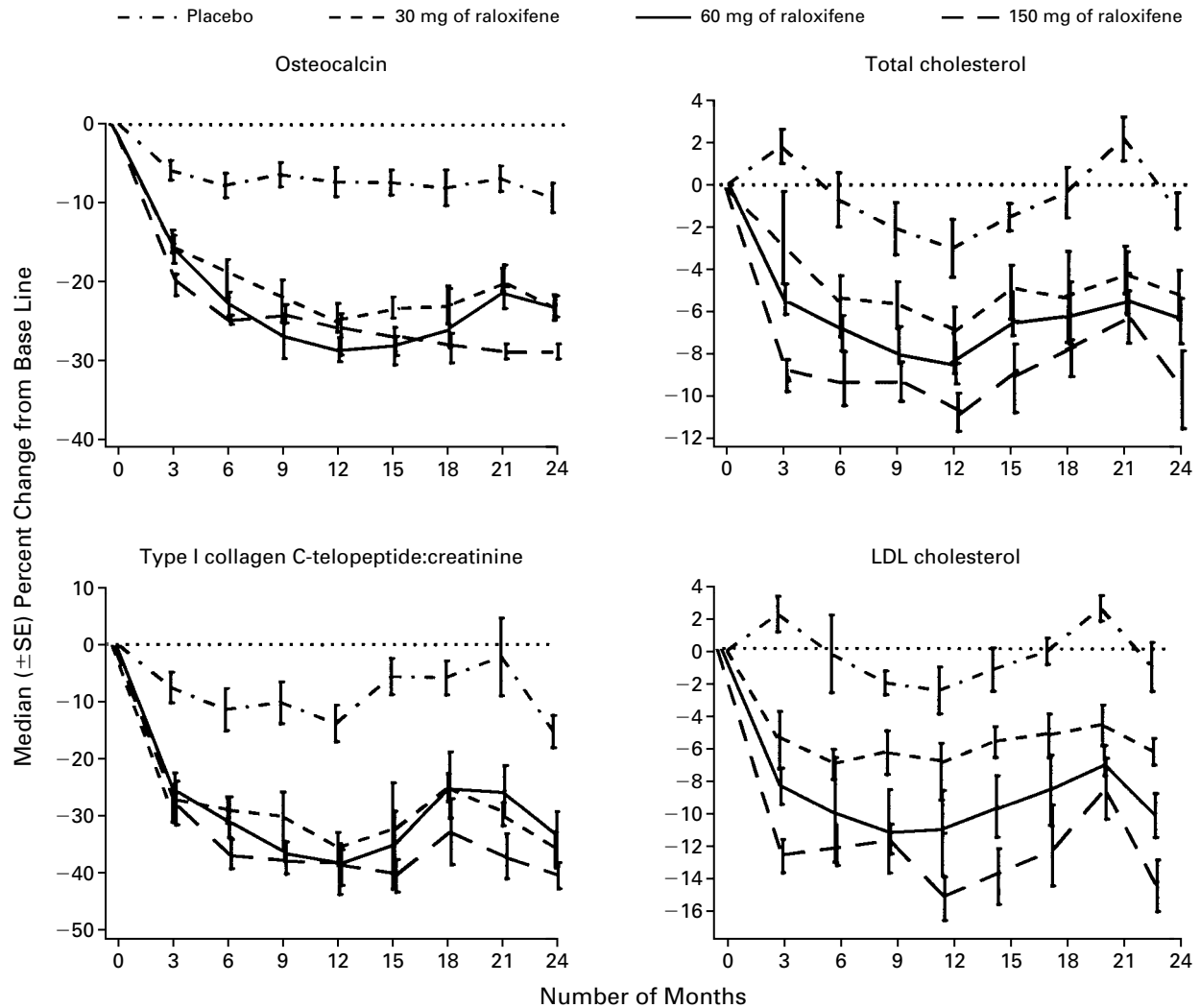
### Statistical Analysis

All analyses were performed on an intention-to-treat basis. The data set comprised all the women who had at least one follow-up visit after randomization. For the women who withdrew from the study before the 24-month visit, their last values were carried forward to subsequent visits. The change and percent change in bone mineral density from base line to months 6, 12, 18, and 24 were analyzed with an analysis of variance that included a term for therapy and country. Initially, a term for interaction between therapy and country was included and tested for significance at the 0.10 level. Since this interaction was rarely significant, the term was deleted from all models. Least-squares analysis was used to test each pairwise comparison at the 0.03 two-sided level of significance for bone-mineral-density end points, reflecting adjustment for one interim analysis.<sup>14</sup>

The results reflecting the changes and percent changes in the concentrations of biochemical markers of bone turnover and serum lipids and the changes and percent changes in endometrial thickness were skewed (by the Shapiro-Wilks test). Therefore, the measurements were ranked and then analyzed by the above method. Standard errors for median changes in bone-marker and serum lipid concentrations and in endometrial thickness were estimated by using the d-delete jackknife method and two-sided statistical tests.<sup>15,16</sup>

## RESULTS

The base-line characteristics of the women in the raloxifene and placebo groups were similar (Table 1). Almost all (99 percent) were white. The women's mean lumbar-spine bone mineral density was 0.94 g per square centimeter, approximately 1.0 SD below peak bone mass. Despite the inclusion of women with normal bone mineral density, nearly 55

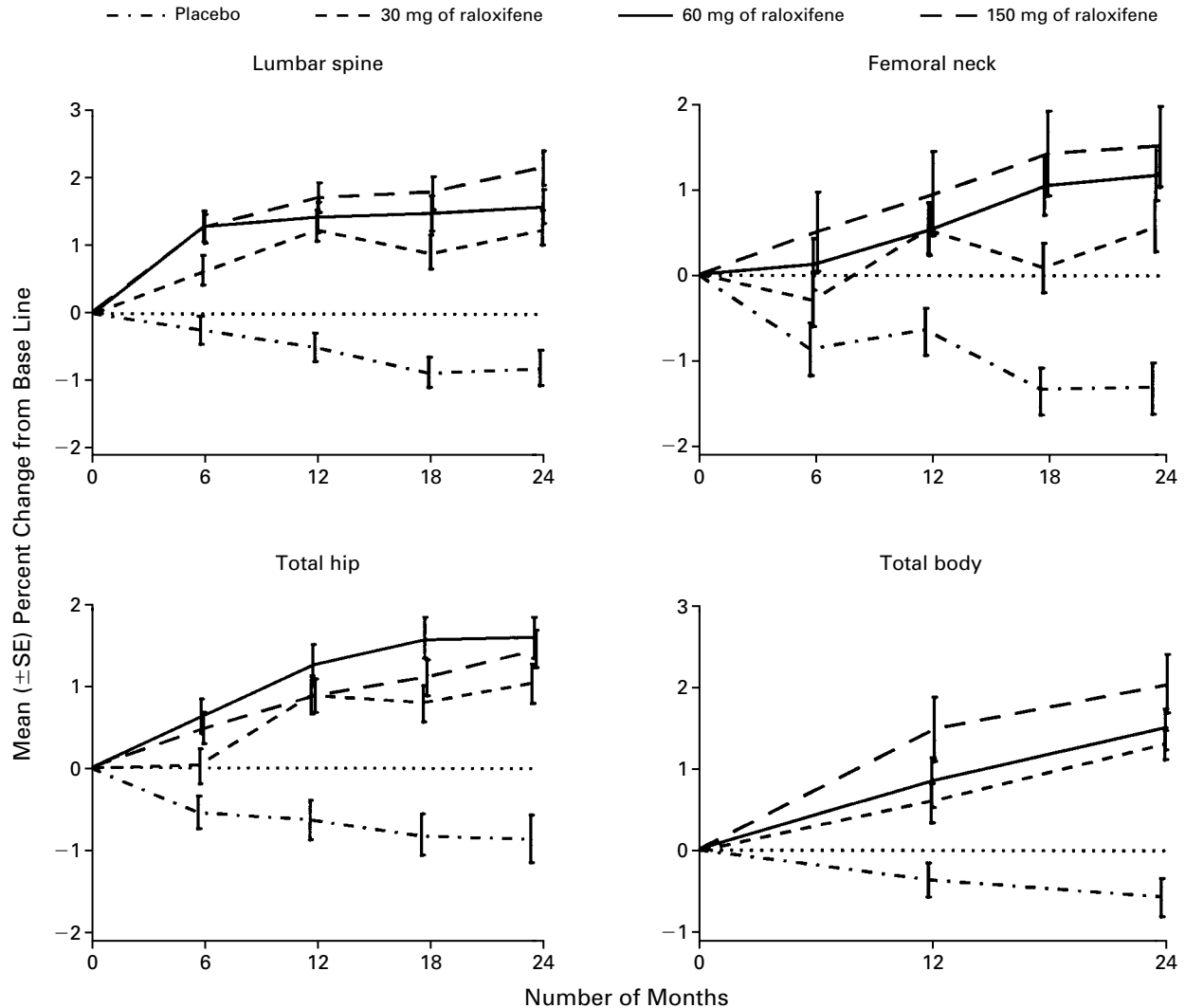


**Figure 1.** Median Percent Change in Serum Total and LDL Cholesterol Concentrations, Serum Osteocalcin Concentrations, and Ratios of Urinary Type I Collagen C-Telopeptide to Creatinine in Postmenopausal Women Treated with Raloxifene or Placebo for Two Years. Standard errors of the median changes were estimated by the d-delete jackknife method.

percent of the study participants had low bone mineral density (osteopenia) according to the criteria of the World Health Organization. During the 24-month study period, 149 of the women (25 percent) dropped out of the study. There were no differences among therapy groups with respect to the number of women who dropped out.

In the placebo group, serum concentrations of bone-specific alkaline phosphatase (data not shown) and osteocalcin and the ratio of urinary type I collagen C-telopeptide to creatinine decreased slightly over a period of 24 months (Fig. 1). As compared with the placebo group, each of the raloxifene groups had a statistically significant decrease in the concentrations of the three markers of bone turnover. The serum osteocalcin concentrations and the

ratio of urinary type I collagen C-telopeptide to creatinine decreased during the first six to nine months of treatment and remained stable thereafter. Serum concentrations of bone-specific alkaline phosphatase decreased during the first 12 months and did not change thereafter (data not shown). The median ( $\pm$ SE) base-line serum concentrations of osteocalcin and bone-specific alkaline phosphatase and the median urinary type I collagen C-telopeptide:creatinine ratio ( $24.6 \pm 0.4$   $\mu$ g per liter,  $13.1 \pm 0.1$   $\mu$ g per liter, and  $292.5 \pm 6.5$   $\mu$ g per millimole of creatinine, respectively) were similar to mean values reported for other postmenopausal French women.<sup>11,17</sup> After 24 months, the median serum concentrations of bone-specific alkaline phosphatase and osteocalcin and the median ratio of urinary type I collagen C-telopep-



**Figure 2.** Mean Percent Change in Bone Mineral Density in Postmenopausal Women Given Raloxifene or Placebo for Two Years.

tide to creatinine had declined by 23.1 percent, 15.0 percent, and 34.0 percent, respectively, in the group that received 60 mg of raloxifene per day. At that time, the median serum concentrations of bone-specific alkaline phosphatase and osteocalcin and the median urinary type I collagen C-telopeptide:creatinine ratio were similar to the values in premenopausal women.<sup>11,17</sup>

Bone mineral density increased significantly in the lumbar spine, total hip, femoral neck, and total body with all doses of raloxifene (Fig. 2 and Table 2), whereas there was loss of bone at each site in the women given placebo. For example, the mean ( $\pm$ SE) difference in the change in bone mineral density between the group that received 60 mg of raloxifene per day and the placebo group was  $2.4 \pm 0.4$  percent for

the lumbar spine,  $2.4 \pm 0.4$  percent for the total hip, and  $2.0 \pm 0.4$  percent for the total body ( $P < 0.001$  for all comparisons).

The increase in bone mineral density at most sites was greatest in the group that received 150 mg of raloxifene per day; however, in the total hip the greatest increase was in the 60-mg group. A subgroup analysis demonstrated that the increases in bone mineral density in the lumbar spine and hip during therapy were similar regardless of the initial bone mineral density, base-line serum osteocalcin concentration or ratio of urinary type I collagen C-telopeptide to creatinine, age, body-mass index, or history of estrogen or thiazide therapy.

Serum concentrations of total and LDL cholesterol decreased significantly in each of the raloxifene

groups as compared with the placebo group (Table 3). The concentrations decreased during the first three months of therapy and did not change thereafter (Fig. 1). There were no significant changes in median serum concentrations of HDL cholesterol, nor were there any significant changes in median concentrations of serum triglycerides among the groups during therapy.

A total of 444 women each had a measurement of endometrial thickness at base line and at least once thereafter. The median base-line thickness ranged from 1.9 to 2.0 mm in each group. There was no difference in endometrial thickness among the four groups at any time during the study.

Raloxifene was well tolerated. There were no significant differences among the four groups in the proportion of women reporting any adverse event or in the proportion leaving the study because of an adverse event. In particular, there was no significant difference in the proportion of women reporting breast pain between the group that received 60 mg of raloxifene per day and the placebo group (3.3 percent and 2.0 percent, respectively). There were no significant differences between the 60-mg group and the placebo group with respect to the proportions of women reporting hot flashes (26.3 percent and 22.7 percent, respectively) or the proportions leaving the study because of hot flashes. In addition, there was no significant difference between the 60-mg and placebo groups in the proportions of women with an intact uterus reporting vaginal bleeding (3.0 percent [4 of 132 women] and 2.2 percent [3 of 137 women], respectively). None of the women receiving 60 mg of raloxifene per day who reported bleeding had an endometrial thickness greater than 5 mm.

## DISCUSSION

Therapy with raloxifene for 24 months in postmenopausal women increases bone mineral density, decreases bone turnover as assessed by biochemical markers, and lowers serum concentrations of total and LDL cholesterol without stimulating the endometrium. This profile is clinically favorable and is distinct from that observed during therapy with estrogen or tamoxifen.

The decreases in the bone mineral density of the total body, total hip, and lumbar spine in the placebo group (0.6 percent, 0.8 percent, and 0.8 percent, respectively) were smaller than those in another recent study in early postmenopausal women (1.8 percent, 1.4 percent, and 1.8 percent, respectively), but calcium supplementation was not provided in the latter study.<sup>18</sup> The effect of therapy with raloxifene on total-body bone mineral density (the differences between the changes with raloxifene and those with placebo ranged from 1.8 percent to 2.5 percent after 24 months) was similar to that with conjugated

**TABLE 2.** MEAN PERCENT CHANGES FROM BASE LINE IN BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN GIVEN RALOXIFENE OR PLACEBO FOR TWO YEARS.\*

SITE	PLACEBO	RALOXIFENE†		
		30 mg	60 mg	150 mg
Lumbar spine	-0.8±0.3	1.3±0.3	1.6±0.3	2.2±0.3
Hip	-0.8±0.3	1.0±0.2	1.6±0.2	1.5±0.2
Femoral neck	-1.3±0.3	0.6±0.3	1.2±0.3	1.5±0.5
Total body	-0.6±0.2	1.2±0.2	1.4±0.2	1.9±0.4

\*Plus-minus values are means ±SE.

†All values are significantly different from those for placebo ( $P<0.03$ ).

**TABLE 3.** MEDIAN PERCENT CHANGES FROM BASE LINE IN SERUM LIPID CONCENTRATIONS IN POSTMENOPAUSAL WOMEN GIVEN RALOXIFENE OR PLACEBO FOR TWO YEARS.\*

SERUM LIPID	PLACEBO	RALOXIFENE		
		30 mg	60 mg	150 mg
Cholesterol				
Total	-1.2±0.8	-5.2±1.2†	-6.4±1.1†	-9.7±1.8†
LDL	-1.0±1.5	-6.2±0.8†	-10.1±1.4†	-14.1±1.6†
HDL	-4.7±1.0	-3.1±1.5	-3.7±0.8	-4.5±0.9
Triglycerides	0.0±2.1	0.0±5.5	3.2±3.1	0.5±4.1

\*Plus-minus values are medians ±SE. Standard errors were estimated by the d-delete jackknife method.

†Value is significantly different from that for placebo ( $P<0.05$ ).

equine estrogens and medroxyprogesterone acetate (2.9 percent) or 5 mg of alendronate per day (2.4 percent) in that trial.<sup>18</sup> The increase in total-body bone mineral density and content is consistent with the positive effect of raloxifene on total-body calcium balance.<sup>19</sup> In the total hip, the therapy effect with raloxifene, with differences from placebo ranging from 1.8 percent to 2.3 percent, was also similar to that with conjugated equine estrogens and medroxyprogesterone acetate or alendronate — each 3.3 percent<sup>18</sup> — and compares favorably with changes in bone mineral density during therapy with nasal calcitonin,<sup>20</sup> cyclic etidronate,<sup>21</sup> or tamoxifen.<sup>22,23</sup> However, the effect on the bone mineral density of the lumbar spine, with differences from placebo ranging from 2.1 percent to 3.0 percent, was lower than that with conjugated equine estrogens and medroxyprogesterone acetate (5.2 percent) or alendronate (5.8 percent) after 24 months.<sup>18</sup>

The increases in bone mineral density of the lumbar spine, total hip, and total body were quantitatively similar during the first 24 months of raloxifene therapy, suggesting important effects on cortical as well as on trabecular bone. In contrast, treatment

with other antiresorptive agents usually results in a greater increase in lumbar-spine bone mineral density. The overall reduction in markers of both bone resorption and formation, with a steady state achieved after 12 months of therapy, is consistent with an antiresorptive effect of raloxifene on bone tissue.

Therapy with raloxifene resulted in significant reductions in serum concentrations of total and LDL cholesterol that were similar to the changes that occur during estrogen-replacement therapy.<sup>24</sup> There was no change in serum concentrations of HDL cholesterol or triglycerides during therapy with raloxifene, whereas both increase in women receiving estrogen-replacement therapy.<sup>24</sup> The changes in the lipid profile resulting from raloxifene therapy may be clinically favorable.<sup>25-27</sup> Taken together with preclinical findings in cholesterol-fed rabbits in which therapy with raloxifene reduced aortic accumulation of cholesterol,<sup>28</sup> these results suggest that raloxifene may have a favorable effect on the incidence of cardiovascular disease.

Nearly 400 women in this study had measurements of endometrial thickness by transvaginal ultrasonography every six months. Using this technique, we found no significant difference in endometrial thickness between any of the therapy and placebo groups at any time. The findings are consistent with preclinical data<sup>6</sup> as well as with findings from biopsies performed during short-term treatment,<sup>29</sup> and are important, given the propensity of tamoxifen to cause endometrial hyperplasia, polyps, and endometrial cancer.<sup>30,31</sup>

In conclusion, during 24 months of therapy, raloxifene at doses of 30, 60, and 150 mg per day increased bone mineral density, decreased bone turnover, and lowered serum concentrations of total and LDL cholesterol without endometrial stimulation in early postmenopausal women. This clinical profile suggests that raloxifene may be useful in the prevention of osteoporosis and cardiovascular disease in postmenopausal women. In addition, raloxifene can be administered without progestins. On the other hand, raloxifene does not appear to be useful therapy for hot flashes. Although it had no effect on the incidence of hot flashes in this study, in other trials of raloxifene hot flashes did occur slightly but significantly more often in raloxifene-treated women (Lilly Research Laboratories: unpublished data).

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Drs. Delmas and Christiansen have served or are now serving as scientific advisors to numerous pharmaceutical companies that make products involved in the treatment of osteoporosis.

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## APPENDIX

In addition to Drs. Delmas and Christiansen, the following also were principal investigators: J. Huber, Vienna, Austria; J.P. Devogelaer, Brussels, Belgium; J. Happ, Frankfurt, Germany; J. Semler, Berlin, Germany; C. Gennari, Siena, Italy; M. Brandi, Florence, Italy; S. Papapoulos, Leiden, the Netherlands; J.I. Puyenbroek, Amsterdam; and I. Smith, Corley, Lancashire, United Kingdom.

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