Effects of Raloxifene on Serum Lipids and Coagulation Factors in Healthy Postmenopausal Women

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Context.—Raloxifene is a selective estrogen receptor modulator that has estrogen-agonistic effects on bone and estrogen-antagonistic effects on breast and uterus.

Objective.—To identify the effects of raloxifene on markers of cardiovascular risk in postmenopausal women, and to compare them with those induced by hormone replacement therapy (HRT).

Design.—Double-blind, randomized, parallel trial.

Setting.—Eight sites in the United States.

Participants.—390 healthy postmenopausal women recruited by advertisement.

Intervention.—Participants were randomized to receive 1 of 4 treatments: raloxifene, 60 mg/d; raloxifene, 120 mg/d; HRT (conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d); or placebo.

Main Outcome Measures.—Change and percent change from baseline of lipid levels and coagulation parameters after 3 months and 6 months of treatment.

Results.—At the last visit completed, compared with placebo, both dosages of raloxifene significantly lowered low-density lipoprotein cholesterol (LDL-C) by 12% (P < .001), similar to the 14% reduction with HRT (P < .001). Both dosages of raloxifene significantly lowered lipoprotein(a) by 7% to 8% (P < .001), less than the 19% decrease with HRT (P < .001). Raloxifene increased high-density lipoprotein-2 cholesterol (HDL2-C) by 15% to 17% (P < .001), unlike HRT, which had no effect. Neither treatment changed fibrinopeptide A or prothrombin fragment 1 and 2.

Conclusions.—Raloxifene favorably alters biochemical markers of cardiovascular risk by decreasing LDL-C, fibrinogen, and lipoprotein(a), and by increasing HDL2-C without raising triglycerides. In contrast to HRT, raloxifene had no effect on HDL-C and PAI-1, and a lesser effect on HDL2-C and lipoprotein(a). Further clinical trials are necessary to determine whether these favorable biochemical effects are associated with protection against cardiovascular disease.

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For editorial comment see p 1483.

Since estrogen is clearly not an ideal treatment, drugs have been sought that have an estrogenic effect in some tissues, such as bone and cardiovascular system, but not in others, such as breast and endometrium. This tissue selectivity is biologically possible because the conformation of a drug-estradiol receptor complex determines the particular DNA response elements to which it can bind. Drugs that have these tissue-specific effects have been termed selective estrogen receptor modulators. Potentially, with these agents the benefits of estrogen could be derived without the accompanying risks. One such drug, tamoxifen, used initially to prevent the recurrence of breast cancer, caused considerable excitement when it was found to protect against osteoporosis and cardiovascular disease. Unfortunately, it was later found to increase the incidence of endometrial cancer.

Raloxifene, a benzothiophene derivative that binds to the estrogen receptor, is likewise a selective estrogen receptor modulator. The raloxifene-estrogen receptor complex does not bind to the estrogen-response element. Instead, it binds to a unique area of DNA called the raloxifene-response element, to produce estrogen-agonistic effects in some tissues and estrogen-antagonistic effects in others. Raloxifene appears to have an estrogen-antagonistic effect on breast tissue. Raloxifene inhibits estrogen-
dependent proliferation of human MCF-7 breast cancer cells in vitro and inhibits the development of carcinogen-induced mammary tumors in rats. Raloxifene also has a estrogen-agonistic effect on the uterus, producing minimal endometrial stimulation in ovariectomized rats. In contrast, raloxifene has estrogen-agonistic effects on bone and cholesterol. Raloxifene treatment lowered serum cholesterol levels of ovariectomized rats and rabbits, and preserved bone density of ovariectomized rats. The hypolipemic effect required binding to the estrogen receptor.

Short-term clinical studies in humans have demonstrated that raloxifene, at high dosages of 200 mg/d and 600 mg/d for 2 months, significantly decreased low-density lipoprotein cholesterol (LDL-C) by approximately 9% to 12%. This was comparable to the 11% decline seen with conjugated equine estrogen, 0.625 mg/d. Therefore, raloxifene, like estrogen, has the potential to reduce cardiovascular risk in postmenopausal women. If this potential is realized, it will be an important finding. Raloxifene may be widely used in the future, since it has been recently shown to increase the bone mineral density of healthy postmenopausal women.

The present study was performed to identify the effects of lower dosages of raloxifene, 60 mg/d and 120 mg/d, on important cardiovascular intermediate end points. These include LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and fibrinogen. In addition, potentially important cardiovascular risk markers such as high-density lipoprotein-2 cholesterol (HDL 2-C), lipoprotein(a) (Lp(a)), apolipoproteins A-I and B, prothrombin fragment 1 and 2 (F 1+2), fibrinopeptide A (FPA), and plasminogen activator inhibitor-1 (PAI-1) were also measured.

METHODS

Subjects
Healthy postmenopausal women with an intact uterus were eligible if they were aged 45 to 72 years and had had amenorrhea for at least 12 months. Women who had undergone hysterectomy were also eligible if they were aged 50 to 72 years. Postmenopausal status in all subjects was verified by a follicle-stimulating hormone level of at least 30 mIU/mL (30 IU/L) and a serum estradiol level of at most 40 pg/mL (147 pmol/L). Body mass index was required to be between 18.5 and 31 kg/m2 and stable within 15% for the previous 2 years. Subjects were excluded if they did not qualify for therapy according to the prescribing information for conjugated equine estrogen and medroxyprogesterone acetate; had a history of breast cancer or any estrogen-dependent neoplasia; had any other cancer within the previous 5 years (except for excised superficial skin lesions); had any history of deep venous thrombosis, thromboembolic disorders, or cerebral vascular accident; or had acute coronary disease or unstable angina in the previous year. In addition, women treated with hypolipidemic drugs, warfarin, androgen, systemic corticosteroids, estrogen, or progesterin within 3 months of entry were excluded. Women were also excluded if they had intolerable postmenopausal symptoms, uterine bleeding, diabetes mellitus, or other endocrinopathy requiring drug therapy (except if biochemically euthyroid while receiving thyroid hormone replacement); if they had impaired liver or kidney function; if they abused alcohol or other drugs; or if they had ever participated in another raloxifene trial; or if they had participated in any investigational trial within the previous month.

Study Design
This prospective, double-blind, placebo-controlled, randomized parallel study was conducted at 8 sites in the United States. The study was approved by the ethical review boards at each site and all subjects gave written informed consent. Subjects were recruited by advertisement, and typically were reimbursed for their expenses. We chose a sample size that had 80% power to detect the smallest change in the mean LDL-C level that we considered to be clinically significant, which was a 6% change vs placebo, using a 2-sided significance level of .05. We used an SD of 0.48 mmol/L (19 mg/dL) for LDL-C, based on prior placebo-controlled trials evaluating estrogen in healthy postmenopausal women. This indicated that we would need 76 subjects to complete each treatment arm. Assuming a 15% dropout rate seen with similar studies, we calculated that we would need to enroll approximately 90 subjects per treatment arm (a total of at least 360).

Three hundred ninety subjects were found to be eligible and were randomly assigned using a random number table generated by a computer program (Clinpro/LBL; Clinical Systems Inc, Garden City, NY) and a block size of 8, to 1 of 4 therapy groups: (1) raloxifene hydrochloride, 60 mg/d; (2) raloxifene hydrochloride, 120 mg/d; (3) hormone replacement therapy (HRT), 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate given in a continuous combined fashion; or (4) placebo. All treatments were given for 6 months, taken as 2 tablets and 2 capsules of blinded study medication each morning. The study medication and placebo were formulated in identical tablets and capsules. Compliance was ascertained by pill counts performed at every visit, and expressed as the ratio of (number of pills dispensed – number of pills returned)/total days of therapy. Subjects were considered compliant if they took more than 70% of their expected study medication and did not miss more than 6 days of treatment in any 2-week period. Subjects were instructed not to significantly change their diet during the study. This was assessed by dietary questionnaires completed at baseline and end point. Subjects fasted for at least 12 hours prior to each of 10 visits: 1 visit for screening, 3 visits in the week prior to randomization to obtain baseline measurements, 3 visits during the 12th week of treatment, and 3 visits during the 24th week of treatment. Three visits were scheduled at each time point to provide multiple measures. This was done to minimize the effects of day-to-day variation in lipid levels. Serum lipids were measured on all 3 days during each 7-day interval, and coagulation markers were measured on 2 of those 3 days.

Laboratory Methods
Lipoproteins—Sample Collection.—Fasting serum for lipid analyses was obtained on 3 different days within a 7-day time period at baseline, 12 weeks, and 24 weeks. Blood was centrifuged within 30 minutes of collection at 3000 g for 10 minutes at 4°C and the plasma was frozen. Samples were then shipped to a central laboratory (Covance, Indianapolis, Ind) where they were stored at -70°C for up to 1 year. Two analytical runs of each assay were performed, with all the samples for a given subject contained in the same batch. All serum samples drawn in the same week that were free of hemolysis and not visibly lipemic were pooled prior to lipid analysis.

Analyses.—High-density lipoprotein and high-density lipoprotein-3 (HDL 3-C) were sequentially separated by precipitation with dextran sulfate and magnesium chloride. Cholesterol and triglycerides were measured with enzymatic reagents (Boehringer-Mannheim, Indianapolis). LDL-C was calculated using the Friedewald equation: LDL-C = (total cholesterol – HDL-C) – (triglycerides × 0.20). Eight subjects were excluded from the LDL-C analysis because of triglyceride values greater than 4.4 mmol/L (380 mg/dL). Lipoprotein(a) was quantified by an automated immunonephelometric analysis (IncStar Corp, Stillwater, Minn.). Apolipoproteins A-I and B were quantified using rate nephelometry. The intra-assay and interassay

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coefficients of variation, respectively, for these assays were 1.4% and 4.3% for HDL-C, 1.2% and 9.6% for HDL-C, 1.1% and 12.6% for triglycerides, 2.6% and 5.6% for Lp(a), 2.5% and 4.8% for apolipoprotein A-I, and 1.7% and 3.7% for apolipoprotein B.

Coagulation Factors.—Sample Collection.—Fasting serum for measurement of coagulation factors was obtained on 2 different days within a 7-day time period at baseline, 12 weeks, and 24 weeks. Blood was drawn by technicians extensively trained in nontraumatic phlebotomy technique to minimize ex vivo coagulation activation. To assess the quality of phlebotomy, blood samples obtained at screening were assayed on a continuing basis for FPA, the coagulation activation marker most sensitive to traumatic phlebotomy. Specimens with FPA levels greater than 50 ng/mL were believed to result from traumatic phlebotomy (9 [3.6%] of 258 screening samples), based on the values previously reported in postmenopausal women. Results were reported back to each site to facilitate improvements in phlebotomy technique.

Following phlebotomy, blood was transferred to tubes (SCAT-1; Hematologic Technologies Inc, Burlington, Vt), containing anticoagulants with final concentrations of EDTA, 4.5 mmol/L; aprotonin, 0.15 kallikrein inhibition units per liter (KIU/L); and D-Phe-Pro-Arg chloromethyl ketone, 20 µmol/L, a potent serine protease inhibitor. Blood was centrifuged within 30 minutes of collection at 3000g for 10 minutes at 4°C, and the plasma was frozen. Samples were shipped to a central laboratory (Cooper-3000, Massachusetts General Hospital, Boston, Mass), containing anticoagulants with final concentrations of EDTA, 4.5 mmol/L; aprotonin, 0.15 kallikrein inhibition units per liter (KIU/L); and D-Phe-Pro-Arg chloromethyl ketone, 20 µmol/L, a potent serine protease inhibitor. Blood was centrifuged within 30 minutes of collection at 3000g for 10 minutes at 4°C, and the plasma was frozen. Samples were shipped to a central laboratory (Cooper-3000, Massachusetts General Hospital, Boston, Mass). The intra-assay and interassay coefficients of variation, respectively, for these assays were 1.4% and 4.3% for coefficients of variation, respectively, for these assays were 0.7% to 1.7% and 1.9% to 2.5% for fibrinogen; 4.1% to 18.3% and 7.1% to 23.7% for PAI-1; 4.8% to 5.2% and 6.7% to 12.6% for F1+2; and 8.6% to 12.3% and 14.3% to 20% for FPA.

Analyses.—Fibrinogen was measured by the Clauss clotting technique with an automated coagulation analyzer (MLA Electra 1600C; Medical Laboratory Automation, Pleasantville, NY) that uses a photometric clot detection technique. Plasminogen activator inhibitor-1 activity in plasma was determined using an amidolytic assay kit (Spectrolyse PL; Biopool, Umea, Sweden). Prothrombin fragment 1 and 2 was measured by enzyme immunoassay (Enzymnost F1+2; Behringwerke AG, Marburg, Germany). Fibrinogen was assayed by a competitive enzyme immunoassay in plasma extracted with bentonite to remove fibrinogen (Asnieres, France). The intra-assay and interassay coefficients of variation, respectively, for these assays were 0.7% to 1.7% and 1.9% to 2.5% for fibrinogen; 4.1% to 18.3% and 7.1% to 23.7% for PAI-1; 4.8% to 5.2% and 6.7% to 12.6% for F1+2; and 8.6% to 12.3% and 14.3% to 20% for FPA.

Statistical Methods

The primary analysis was change and percent change from baseline to end point for all lipid and coagulation markers using a 2-way analysis of variance (ANOVA) with treatment and investigators as fixed effects in the model, since no treatment-by-investigator interaction (for all 8 investigators) was found in any of the variables. End point refers to the last visit completed, which was either a 3-month or 6-month visit. All analyses were performed using data from all randomly assigned subjects according to the intent-to-treat principle of last-observation-carried-forward, in which subjects were assigned to the therapy actually received. Thus, analyses were performed in all subjects who had a baseline and at least 1 postbaseline result. Most of the lipid and coagulation data were skewed and in some cases heterogeneity of variances was observed. Therefore, ANOVA was performed on appropriate power-transformed or rank-transformed data. For absolute changes from baseline, two-thirds power transformations were used for HDL-C, LDL-C, triglycerides, Lp(a), apolipoprotein A-I, and F1+2; and rank transformations were used for apolipoprotein B, HDL-C, FPA, fibrinogen, and PAI-1. For percent changes from baseline, two-thirds power transformations were used for HDL-C, triglycerides, apolipoprotein A-I, and F1+2; and rank transformations were used for LDL-C, HDL-C, Lp(a), apolipoprotein B, FPA, and PAI-1; and no transformations were used for fibrinogen. Medians are presented as descriptive statistics of the variable. The SEs for the medians were calculated using the d-delete jackknife method.

To determine if differences in the years after menopause among the groups could account for any of the treatment differences, an analysis of covariance was performed using years after menopause as a covariate. To determine if differences in the proportions of hysterectomies among the groups could account for any of the treatment differences, hysterectomy status was used as an effect in the ANOVA.

Adverse events were analyzed using the Cochran-Mantel-Haenszel technique, stratified by investigators. All dietary variables were analyzed for changes from baseline to end point using rank-transformed ANOVA.

RESULTS

Patient Characteristics

Of 541 women who underwent screening procedures, 390 were found to be eligible and were randomized (98 to pla-

Table 1.—Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 98)</th>
<th>Raloxifene, 60 mg/d (n = 95)</th>
<th>Raloxifene, 120 mg/d (n = 101)</th>
<th>HRT* (n = 96)</th>
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<tr>
<td>Age, y</td>
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<td>59 ± 7</td>
<td>59 ± 6</td>
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<td>6</td>
<td>4</td>
<td>3</td>
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<td>3</td>
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<td>1</td>
<td>5</td>
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<td>25 ± 3</td>
<td>26 ± 3</td>
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<tr>
<td>Years after menopause†</td>
<td>10 ± 7</td>
<td>11 ± 7</td>
<td>10 ± 7</td>
<td>13 ± 9</td>
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<td>Hysterectomy, %</td>
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<td>31</td>
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<td>Current smoker, %</td>
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<td>20</td>
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<td>123 ± 18</td>
<td>128 ± 20</td>
<td>127 ± 16</td>
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<tr>
<td>Diastolic blood pressure, mm Hgt</td>
<td>77 ± 10</td>
<td>75 ± 10</td>
<td>77 ± 10</td>
<td>78 ± 11</td>
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</table>

*HRT indicates hormone replacement therapy (conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d) given in a continuous combined fashion.
†Plus-minus values are means ± SDs.
‡P = .03.

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raloxifene and HRT was not significant.

with the 2 raloxifene dosages (22 g) were not significantly different among therapy groups. At baseline, the mean daily dietary intakes of total joules (7531 J [1800 cal]), protein (81 g), fat (58 g), carbohydrates (243 g), sucrose (10 g), cholesterol (232 mg), and dietary fiber (22 g) were not significantly different among the groups. There were no significant differences among the groups in any of the dietary variables over the course of the study. Systolic and diastolic blood pressure, weight, and heart rate did not significantly change in any of the 4 treatment groups. Study drug compliance was 84% at 3 months and 94% at 6 months, which did not significantly differ among therapy groups.

Lipoproteins

At baseline, there were no significant differences in lipoprotein levels among treatment groups. As shown in Figures 1 and 2, the effect of treatment was evident by 3 months, with little additional change at 6 months, implying short-term stability of these changes. There were no significant differences between the 2 dosages of raloxifene tested. The levels of all measured lipids, except for Lp(a), did not change more than 1% during the 6-month treatment with placebo. This stability of the control group over time may have been achieved by obtaining multiple blood specimens, as well as the subjects' success in maintaining a constant diet. Both of these factors would serve to minimize the effects of biological variation of lipid levels. At end point (ie, the last visit completed), the following statistically significant comparisons with placebo were noted (Table 2), and were not different when the analysis was restricted to only those subjects who completed this 6-month study; low-density lipoprotein cholesterol levels were lowered by 12% with the 2 raloxifene dosages (P < .001 for both) and were lowered by 14% with HRT (P < .001). The difference between raloxifene and HRT was not significant.

Figure 1.—Median percentage changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high-density lipoprotein-2 cholesterol (HDL-C2), and triglyceride levels in healthy postmenopausal women during a 6-month treatment regimen with raloxifene, 60 mg/d; raloxifene, 120 mg/d; hormone replacement therapy (HRT) (conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d); or placebo. Bars show SEs for the median changes. Asterisk indicates P < .001 for comparison with placebo value; dagger, P < .05 for comparison with placebo value.

Figure 2.—Median percentage changes in apolipoproteins A-I and A-II, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) levels in healthy postmenopausal women during a 6-month treatment regimen with raloxifene, 60 mg/d; raloxifene, 120 mg/d; hormone replacement therapy (HRT) (conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d); or placebo. Bars show SEs for the median changes. Asterisk indicates P < .001 for comparison with placebo value; dagger, P < .05 for comparison with placebo value.
High-density lipoprotein cholesterol levels were unchanged by raloxifene, but were increased by 10% with HRT (P < .001). High-density lipoprotein-2 cholesterol levels were increased by 15% and 17% for the 2 raloxifene dosages (P = .009 and P = .005, respectively), and were increased by 33% (P < .001) for HRT. Hormone replacement therapy raised HDL-C levels significantly more (P < .001) than did either dosage of raloxifene. High-density lipoprotein-3 cholesterol levels were not significantly changed by any treatment.

Triglyceride levels were not changed by either raloxifene dosage, but were increased by 20% with HRT (P < .001). Apolipoprotein A-I levels were increased by 5% with raloxifene, 120 mg/d (P < .001) and were increased by 12% with HRT (P < .001). Hormone replacement therapy raised apolipoprotein A-I significantly more (P < .001) than did either dosage of raloxifene. Apolipoprotein B levels were reduced by 9% with both raloxifene dosages (P < .001 for both), but were not changed by HRT.

Lipoprotein(a) levels were lowered by 7% and 8% for the 2 raloxifene dosages (P = .04 and P = .02, respectively) and were lowered by 19% with HRT (P < .001). Hormone replacement therapy reduced Lp(a) levels significantly more (P < .001) than did either dosage of raloxifene. Apolipoprotein B levels were reduced by 9% with both raloxifene dosages (P < .001 for both), but were not changed by HRT.

Coagulation Factors

At baseline, there were no significant differences in coagulation factor levels between treatment groups. At end point, the following statistically significant comparisons with placebo were noted (Table 3), and were not different when the analysis was restricted to only those subjects who completed this 6-month study: fibrinogen levels were lowered by 10% and 12% for the 2 raloxifene dosages (P < .001), but were unchanged by HRT. There was no correlation between the percent change in fibrinogen and any of the lipoproteins measured. Plasminogen activator inhibitor-1 levels were not changed by either raloxifene dosage, but were reduced by 19% with HRT (P < .001). Fibrinopeptide A and F1+2 levels were not significantly changed by raloxifene or HRT.

Adverse Events

The most commonly noted adverse events were vaginal bleeding, breast tenderness, and hot flashes (Table 4). Hot flashes were the most common adverse event in the raloxifene groups, with the highest incidence (22%) occurring at the 120-mg dosages. In contrast, vaginal bleeding was the most common adverse event in the HRT group (45%), and occurred significantly (P < .001) more often than in the placebo or raloxifene groups. Significantly more patients in the HRT group discontinued the study, primarily because of vaginal bleeding (P < .001). In contrast, there were few discontinuations because of hot flashes in the raloxifene groups. There were no other adverse events that had a statistically significant higher incidence in the raloxifene groups compared with the placebo group.

COMMENT

This study demonstrates that raloxifene, a selective estrogen receptor modulator, favorably alters several markers of cardiovascular risk in healthy postmenopausal women. Specifically, raloxifene reduced the levels of LDL-C, fibrinogen, and Lp(a); did not raise triglyceride levels; and raised HDL-C levels. However, in contrast with HRT, raloxifene had no effect on HDL-C and PAI-1 levels and a lesser effect on HDL-C and Lp(a) levels. There were no significant differences between the 2 dosages tested. The changes seen with HRT are similar to those previously reported.\(^\text{29}\)

The decrease in LDL-C by raloxifene would be expected to reduce the risk of coronary artery disease. Epidemiological studies have found that the levels of LDL-C are related to risk of coronary artery disease among both men and women. Moreover, clinical trials that lowered LDL-C levels in women have been found to reduce the incidence of a...
second cardiac event. One such trial of a lipid-lowering agent found that a 30% reduction in LDL-C levels in women was associated with a 46% reduction in cardiovascular events.70 This suggests that the 12% reduction in LDL-C levels observed in this study, if sustained over time, might lower the incidence of heart disease by as much as 18%. The 7% reduction in Lp(a) levels may reduce this risk even more.

The decline in fibrinogen levels induced by raloxifene treatment may also serve to lower cardiovascular risk. Fibrinogen levels have been found to be an independent risk factor for heart disease, with a reduction of 0.5% for every 0.01-g/L decrease in fibrinogen levels.71 We may hypothesize that the 0.42-g/L reduction in fibrinogen induced by raloxifene in this study could therefore translate into an additional 21% reduction in cardiovascular events. This is speculative, since, to our knowledge, there is no evidence to date from a clinical trial that shows that lowering the fibrinogen level of an individual will reduce her cardiovascular risk.

Although there are similarities between the effects of raloxifene and estrogen on lipid and coagulation factors, there are differences as well. This indicates that the serum levels of these factors are controlled by processes that operate by independent mechanisms. Some of these processes appear to be alterable by estrogen only, some by raloxifene only, and some by both. This independence of mechanisms is consistent with the observation that the magnitudes of the changes in LDL, HDL, and triglyceride levels induced by estrogen treatment are not significantly correlated within individual subjects.75 One noteworthy difference between estrogen and raloxifene is in their effect on HDL-C, HDL2-C, and apolipoprotein A-I levels, which were only marginally increased by raloxifene. Therefore, raloxifene does not appear to have full agonistic activity against the target(s) that estrogen modulates to increase HDL. In contrast, the lowering of LDL-C represents an estrogen-agonistic effect of raloxifene and is similar in magnitude to the estrogen effect. This is consistent with the in vitro observation that raloxifene lowers LDL-C by binding to the estrogen receptor.76

The effect of raloxifene on markers of cardiovascular risk bore a greater resemblance to the pattern previously reported for tamoxifen77-79 (Table 5). Since these data are not derived from the same clinical trial, the percentage changes seen may not be directly comparable among the different treatment groups. However, these trials were all performed in similar groups of healthy postmenopausal women, and illustrate that the raloxifene and tamoxifen effects on HDL-C, HDL2-C, and apolipoprotein A-I levels are only marginally increased by raloxifene. Therefore, raloxifene does not appear to have full agonistic activity against the target(s) that estrogen modulates to increase HDL. In contrast, the lowering of LDL-C represents an estrogen-agonistic effect of raloxifene and is similar in magnitude to the estrogen effect. This is consistent with the in vitro observation that raloxifene lowers LDL-C by binding to the estrogen receptor.76
clinical trial were found to have a significantly lower incidence of fatal myocardial infarction (odds ratio, 0.97; 95% confidence interval, 0.80-1.17). In another such controlled clinical trial, women randomized to tamoxifen treatment had fewer hospital admissions for cardiac disease (relative risk, 0.68; 95% confidence interval, 0.47-1.58). A third such trial found a trend toward fewer cardiovascular deaths in women given tamoxifen, but this did not reach statistical significance (relative risk, 0.85; 95% confidence interval, 0.47-1.58).

With the exception of hot flashes, raloxifene was found to be free of any significant adverse effects. Most important, raloxifene did not cause vaginal bleeding. The incidence of vaginal bleeding in the most half of HRT subjects experienced vaginal bleeding and approximately a third of HRT subjects experienced breast tenderness. Both of those symptoms caused many participants randomized to HRT to drop out of the study, and they also cause many women who have been prescribed HRT to stop taking it. Although the incidence of hot flashes was 6% and 12% higher for the 2 dosages of raloxifene compared with placebo, it did not cause subjects to discontinue their participation. It therefore appears that long-term compliance could be greater for treatment with raloxifene than is currently the case with HRT.

In summary, raloxifene at both dosages favorably altered a number of lipid and coagulation markers of cardiovascular risk. For the most part, the direction of the response paralleled that of HRT, although not necessarily of the same magnitude. The pattern of response bore a greater similarity to tamoxifen than to HRT. Because of these beneficial effects on biochemical markers of cardiovascular risk, it can be speculated that raloxifene, used at either 60 mg/d or 120 mg/d, might substantially reduce the risk of heart disease in postmenopausal women. Conclusive proof would require a clinical trial with cardiovascular events as the definitive end point.

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