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Effects of raloxifene and low-dose simvastatin coadministration on plasma lipids in postmenopausal women with primary hypercholesterolemia

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Abstract

Raloxifene and low-dose simvastatin can each reduce low-density lipoprotein (LDL) cholesterol without affecting high-density lipoprotein (HDL) cholesterol and triglycerides. The objective of this double-blind, 12-week study is to determine whether raloxifene and simvastatin coadministration gives added benefit beyond either monotherapy in affecting fasting lipoproteins and apolipoproteins. Ninety-five postmenopausal women with moderately elevated LDL cholesterol (mean, 146 mg/dL) were randomized to placebo, raloxifene 60 mg/d, simvastatin 10 mg/d, or raloxifene 60 mg/d coadministered with simvastatin 10 mg/d. Raloxifene, simvastatin, and coadministration therapy reduced mean LDL cholesterol by 10.5%, 23.3%, and 31.0% from baseline, respectively ($P < .003$ vs baseline; $P < .02$ vs placebo), and mean apolipoprotein B by 10.4%, 24.2%, and 30.0% from baseline, respectively ($P < .003$ vs baseline; $P < .02$ vs placebo). Each active treatment decreased non-HDL cholesterol compared with placebo ($P < .01$). Coadministration treatment was more effective than either monotherapy in reducing LDL cholesterol ($P < .05$). Coadministration treatment reduced mean apolipoprotein B ($P < .001$) and non-HDL cholesterol ($P < .001$) when compared with raloxifene, but was not significantly different when compared with simvastatin. Coadministration therapy increased HDL cholesterol and apolipoprotein A1 levels compared with placebo ($P < .02$). No significant effect on triglycerides, very low density lipoprotein cholesterol, and lipoprotein (a) occurred with any active treatment. Raloxifene, simvastatin, and the coadministration therapy were generally well tolerated with clinical adverse effects similar to placebo. No woman had clinically significant elevated liver function tests requiring drug discontinuation. Further data on safety and lipid-lowering effects are needed before raloxifene and statin coadministration may be considered as therapeutic interventions for treating postmenopausal women to achieve National Cholesterol Education Program–Adult Treatment Panel III treatment guidelines.

1. Introduction

Approximately 53% of deaths in women have been attributed to cardiovascular disease, and this figure has remained fairly constant over the last 20 years [1]. Appropriate identification and treatment of cardiovascular disease in early postmenopausal women can impart protection and prevent disease progression, which in turn will help improve on the associated morbidity and mortality.

Estrogen and estrogen plus progestin therapy had been thought to be cardioprotective based upon its positive effects on surrogate markers of cardiovascular disease [2] and on cardiovascular event reduction in observational studies [3,4]. However, due to findings from recent randomized, controlled trials such as the Women's Health Initiative, which found an increase in cardiovascular events [5-7], estrogen and estrogen plus progestin therapy has been removed from the National Cholesterol Education Program Adult Treatment Program III guidelines (NCEP-ATP III) [8,9], and the American Heart Association does not recommend its use for lipid lowering or cardioprotection [10].

Raloxifene, a selective estrogen receptor modulator, is approved for osteoporosis prevention and treatment in postmenopausal women. Raloxifene improves surrogate markers of cardiovascular disease, including LDL cholesterol, total cholesterol, non-HDL cholesterol, HDL_2-cholesterol, fibrinogen, homocysteine, and lipoprotein (a) [Lp(a)],

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and without increasing high-sensitivity C-reactive protein [11,12]. Cardiovascular events were assessed as secondary safety endpoints in the 4-year Multiple Outcomes of Raloxifene Evaluation osteoporosis treatment trial of postmenopausal women, and raloxifene treatment was associated with neutral effects on coronary or cerebrovascular events [13]. In a post hoc analysis, raloxifene therapy was associated with a significant 40% reduction in cardiovascular (both coronary and cerebrovascular) events in a subset of 1035 women determined retrospectively to have increased cardiovascular risk, based upon baseline data [13]. These findings require confirmation in trials with cardiovascular outcomes evaluated as a primary objective. The prospective, randomized, controlled Raloxifene Use in The Heart (RUTH) trial is currently investigating the effects of raloxifene on coronary events in 10 101 postmenopausal women with existing coronary heart disease (CHD) or at high risk for its occurrence [14].

The primary treatment for hyperlipidemia is statin therapy, which lowers LDL cholesterol. Only about half of all patients at high risk for cardiovascular disease can attain goals for LDL-cholesterol levels with available statin therapy [15]. Although statin use is initiated equally in high-risk patients of both sexes, women are less aggressively titrated with statin therapy than men, suggesting sex bias in the aggressive treatment of hyperlipidemia [16]. Other agents with beneficial effects on lipids could be coadministered with low-dose statins to lower cardiovascular disease risk and perhaps achieve NCEP-ATP III guideline goals in more women, without the adverse effects associated with higher statin doses, particularly for older postmenopausal women. This report shows the results of the first randomized, double-blind, placebo-controlled trial to assess the effects of raloxifene and simvastatin alone or in combination on lipid parameters in hypercholesterolemic postmenopausal women.

2. Methods

2.1. Study population

This study enrolled hypercholesterolemic (LDL cholesterol ≥ 130 and <190 mg/dL) postmenopausal women between 42 and 80 years of age who were postmenopausal for 2 years or more. Women were excluded if they had been treated with drugs for the purpose of lipid lowering within 3 months before study entry. Other exclusion criteria included history of breast cancer or estrogen-dependent neoplasia; history of deep vein thrombosis; prior history of CHD; uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 95 mm Hg); acute or chronic liver disease; abnormal renal function; abnormal uterine bleeding; treatment with androgens, estrogens, or progestins within 3 months before entry; and excessive alcohol consumption. The ethical review board at each site approved the study, and all women signed an informed consent before entering the study.

2.2. Study design

This was a randomized, double-blind, placebo-controlled study conducted at 4 clinic sites in the United States. Eligible women were randomized to 1 of 4 treatment groups: (1) placebo, (2) raloxifene HCl 60 mg/d, (3) simvastatin 10 mg/d, or (4) raloxifene HCl 60 mg/d plus simvastatin 10 mg/d. The treatment phase lasted 12 weeks. Participants were required to take both study drugs at the same time every day with their evening meal: 1 tablet (raloxifene HCl 60 mg or matching placebo) and 1 capsule (simvastatin 10 mg or matching placebo). Women were asked to maintain a consistent diet throughout the study. Consistency of diet among treatment groups was assessed by a Fat Intake Scale questionnaire administered at baseline and at endpoint [17]. Compliance was assessed by pill counts performed at postrandomization visits. Subjects were considered compliant if they took more than 80% of the prescribed study medication.

The primary objective of this study was to evaluate and compare the effects of 12 weeks' treatment with raloxifene HCl 60 mg/d (Evista, Eli Lilly and Company; Indianapolis, Ind) and simvastatin 10 mg/d (Zocor, Merck and Company, West Point, Pa) alone and when coadministered on fasting LDL cholesterol in postmenopausal women with hypercholesterolemia. Secondary objectives of the study were to determine the effects of raloxifene and simvastatin alone as well as in combination on other lipid measures and on general safety in postmenopausal women with hypercholesterolemia. Efficacy was evaluated by assessing the patient's serum lipoprotein and apolipoprotein concentrations at baseline and at every 4 weeks. Safety was evaluated at study entry by recording medical history and performing a physical examination. At subsequent visits, women were asked if they had experienced any adverse events. Liver function tests were performed at baseline and at weeks 4 and 12. Subjects whose LDL-cholesterol levels reached ≥ 195 mg/dL at any time during the study could be discontinued from the study at the discretion of the clinical investigator and referred for treatment with current standard of care for lipid management.

2.3. Measurement of serum lipids

Blood samples were obtained after a 12-hour fast and serum isolated during each clinic visit. Samples were assayed for lipoproteins and apolipoproteins at a central laboratory (Covance Laboratories, Indianapolis, Ind). Total cholesterol and triglycerides were measured with enzymatic reagents (Roche Diagnostics, Indianapolis, Ind). High-density lipoprotein cholesterol was sequentially separated by precipitation with dextran sulfate and magnesium chloride, and was assayed in the supernatant using the method described for total cholesterol. Non-HDL cholesterol for each subject was calculated as the difference between the total cholesterol and HDL-cholesterol concentrations. Very low density lipoprotein cholesterol was calculated using the following estimate: VLDL cholesterol = (triglyceride $\times$ 0.20). Low-density

lipoprotein cholesterol was measured directly by photometric analysis. Lipoprotein (a) levels were analyzed by an automated immunoprecipitin assay (Daisorin, Stillwater, Minn). Apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) were quantified by rate nephelometry using Beckman IMMAGE Immunochemistry System (Beckman Instruments, Brea, Calif). The interassay and intra-assay coefficients of variation, respectively, for these assays were 1.7% and 1.0% for cholesterol, 3.0% and 1.1% for triglycerides, 3.2% and 1.4% for HDL cholesterol, 2.7% and 1.1% for LDL cholesterol, 6.9% and 2.6% for Lp(a), 4.8% and 2.6% for ApoA1, and 3.7% and 2.0% for ApoB.

2.4. Statistical analysis

Analyses were performed using an intention-to-treat principle. All statistical analyses were performed using procedures in SAS (SAS Institute, Cary, NC). Hypotheses were tested at a significance level of .05. All tests were 2-sided and no adjustments were made for multiplicities. The analyses included women with baseline and any postbaseline measurements. Repeated measures analysis [18] was used for all measurements made on each individual and to account for any possible correlation between measurements made in an individual patient over time. To reduce the variability, the actual measurement at any visit was used as the analysis variable instead of the percent change. For LDL cholesterol (the primary efficacy variable), a repeated measures model was fitted with postbaseline measurement as the response, baseline measurement as the covariate, and therapy and investigator as fixed effects. In preliminary analyses, the fixed effects of visit, and the interaction of therapy and visit were not statistically significant and were not included in the model. Therefore, the treatment effects reported are based on the least square means for the entire study period instead of at any specific time point. Within-patient correlation over time was accounted for through repeated visit and a block diagonal matrix for the experimental error within each therapy with an autoregressive covariance structure. The same analysis model used for the primary efficacy variable of LDL cholesterol was used for all other lipids. Within- and between-treatments tests were conducted using least squares means. Within each treatment, the percentage mean change was calculated as 100 × (treatment least squares means − baseline mean of all patients) / (baseline mean of all patients). These were tested for significant differences from 0. The differences between treatments were evaluated via least squares means and contrasts. Treatment differences were also expressed as percent mean changes by dividing the least squares means differences and standard errors of differences by the overall baseline mean of all patients and multiplying by 100. As per protocol, patients from 1 investigator who enrolled fewer than 4 patients were pooled together with those from another investigator for the purpose of statistical analyses. Adverse events were analyzed using χ^2 test on all randomized patients.

3. Results

Of the 183 women screened at the qualifying clinic visit (Fig. 1), 95 were enrolled and randomized to the study treatments; placebo (N = 23), raloxifene (N = 24), simvastatin (N = 25), and raloxifene and simvastatin coadministration (N = 23). The primary reasons for

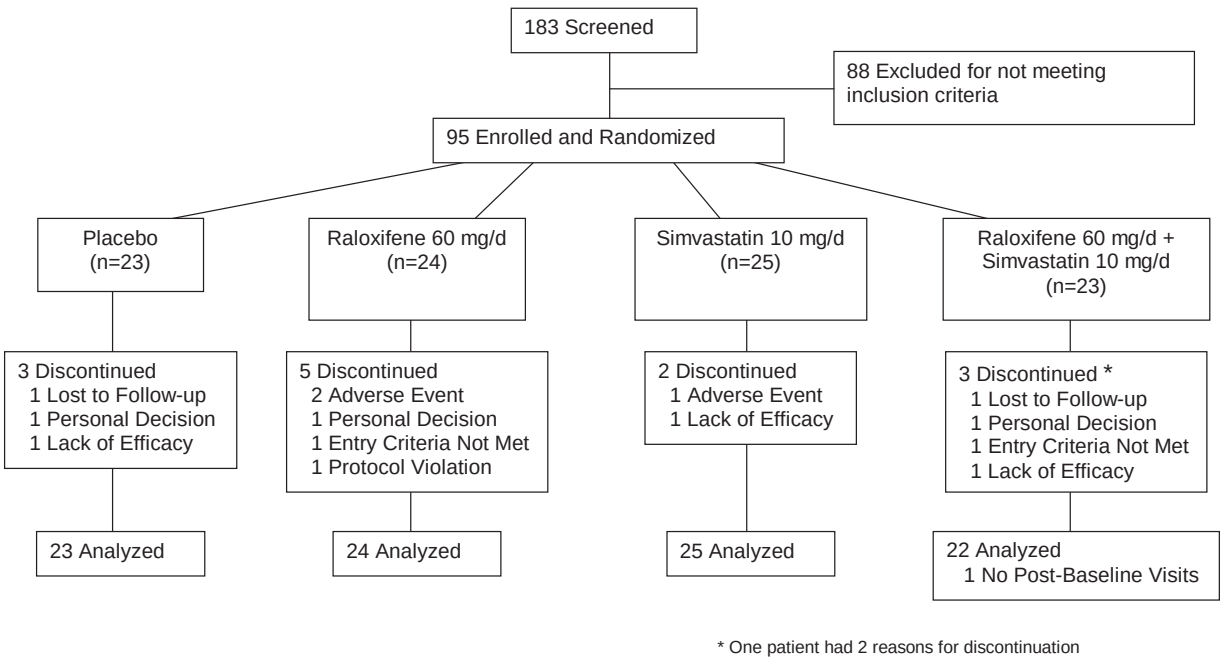

Fig. 1. Flow of patients.

Table 1
Subject characteristics at baseline

Characteristic[a]	Placebo (n = 23)	Raloxifene (n = 24)	Simvastatin (n = 25)	Raloxifene + simvastatin (n = 22)
Age, y	59 ± 9	61 ± 7	61 ± 8	58 ± 7
Ethnic origin (%)				
White	57	54	48	59
Hispanic	26	33	40	32
Body mass index (kg/m^2)	29 ± 6	29 ± 6	28 ± 5	27 ± 4
Weight (kg)	74 ± 17	75 ± 18	72 ± 11	69 ± 13
Years postmenopause	16 ± 10	14 ± 7	14 ± 10	10 ± 8
Systolic blood pressure, mm Hg	130 ± 17	127 ± 14	126 ± 15	123 ± 10
Diastolic blood pressure, mm Hg	78 ± 9	79 ± 9	75 ± 8	75 ± 9
Lipids[b]				
LDL cholesterol	147 ± 24	142 ± 26	147 ± 21	147 ± 29
HDL cholesterol	57 ± 17	55 ± 15	53 ± 16	53 ± 10
Non-HDL cholesterol	189 ± 30	192 ± 32	195 ± 24	191 ± 29
Total cholesterol	246 ± 32	246 ± 27	249 ± 25	244 ± 30
Triglycerides	153 ± 85	146 ± 70	149 ± 68	139 ± 72
VLDL cholesterol	31 ± 17	29 ± 14	30 ± 14	28 ± 15
Lp(a)	39 ± 51	24 ± 21	36 ± 36	43 ± 57
ApoA1	156 ± 23	153 ± 20	148 ± 27	150 ± 16
ApoB	159 ± 29	159 ± 22	171 ± 28	163 ± 25

[a] All values expressed as mean ± SD except where otherwise noted.
[b] Values expressed in milligrams per decaliter.

exclusion from the study were serum LDL-cholesterol levels beyond predefined limits and last menstrual period within the last 2 years. Study drug compliance was greater than 90% at all visits and did not differ significantly among treatment groups. One woman in the coadministration group had no postbaseline visit and therefore was not included in the efficacy analyses.

3.1. Baseline characteristics

Baseline characteristics did not significantly differ among treatment groups (Table 1). Overall, the women had a mean age of 60 years, were a mean 14 years postmenopausal, with a mean body mass index of 28 kg/m^2, and had normal blood-pressure readings. The majority of patients were white (54%), but an appreciable number of women were Hispanic (33%). There were no significant differences in baseline lipoprotein levels among the 4 treatment groups ($P \geq .340$). Diet fat intake scores were not significantly different among treatment groups at baseline or postbaseline.

3.2. Lipoprotein and apolipoprotein levels

During treatment, women in the placebo group had no significant change in any lipid parameter, except for a reduction in ApoA1 level. At study completion, LDL-cholesterol levels were (mean ± SE) 146 ± 5, 131 ± 5, 112 ± 4, and 101 ± 5 mg/dL for placebo, raloxifene, simvastatin, and coadministration therapy, respectively. These absolute mean values of LDL cholesterol corresponded to mean percent reductions from baseline of 0.2% with placebo, 10.5% with raloxifene, 23.3% with simvastatin, and 31% with coadministration therapy (Fig. 2). All 3 active treatments reduced LDL cholesterol compared with

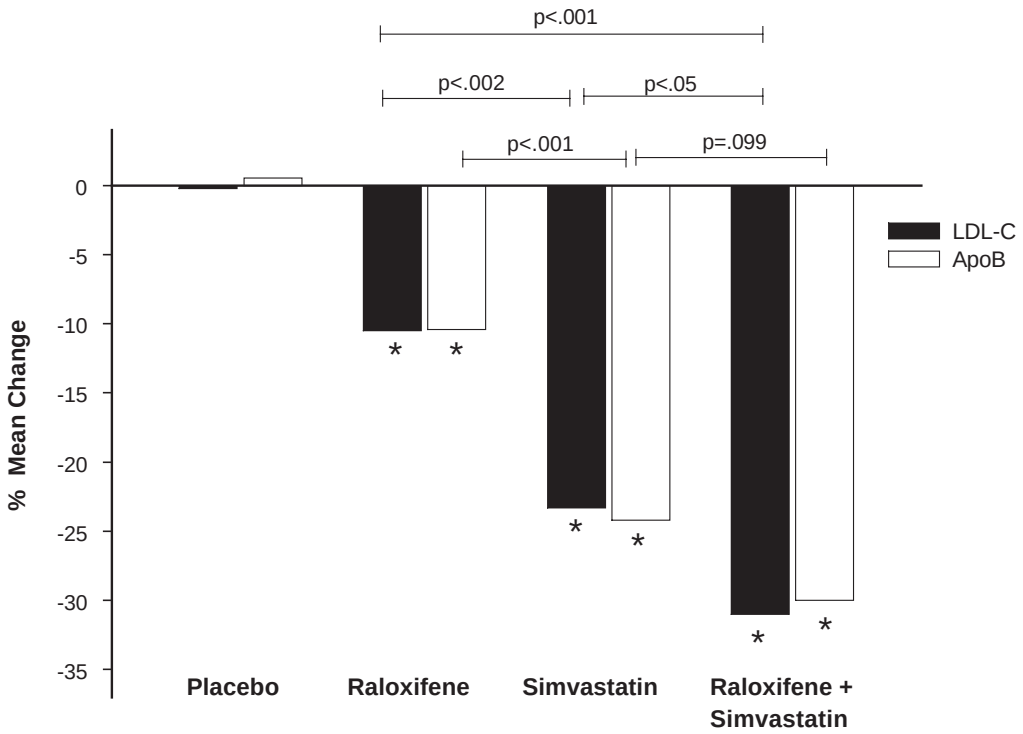

Fig. 2. Percentage change in mean LDL cholesterol and apoB from baseline with placebo, raloxifene, simvastatin, or coadministration therapy. Black bars indicate LDL cholesterol; white bars, apoB. *$P < .02$ vs placebo and $P < .003$ vs baseline.

Table 2
Lipid and lipoprotein percent changes from baseline

Variable[a]	Placebo (n = 23)	Raloxifene (n = 24)	Simvastatin (n = 25)	Raloxifene + simvastatin (n = 22)
Non-HDL cholesterol	1.0	−9.0[b]	−24.1[b,c]	−29.8[b,c]
Total cholesterol	1.4	−6.2[b]	−18.0[b,c]	−21.8[b,c]
Triglycerides	−8.5	−2.5	−11.5	−10.6
VLDL cholesterol	−8.6	−2.6	−11.7[d]	−10.6
Lp(a)	6.5	−5.6	−0.6	−0.1

[a] All values expressed as mean percent change from baseline, calculated as described in section 2.4.
[b] $P < .002$ vs baseline and $P < .01$ vs placebo.
[c] $P < .001$ vs raloxifene.
[d] $P < .05$ vs baseline.

baseline ($P < .003$) and placebo ($P < .02$). Simvastatin reduced LDL cholesterol to a greater extent than did raloxifene ($P < .002$). Coadministration therapy was superior to monotherapy with either simvastatin ($P < .05$) or raloxifene ($P < .001$) in reduction of LDL cholesterol. Mean ApoB was reduced from baseline by 10.4%, 24.2%, and 30.0% with raloxifene, simvastatin, and the coadministration therapy (Fig. 2), respectively ($P < .003$ vs baseline; $P < .02$ vs placebo). The reduction in ApoB levels was significantly greater with coadministration therapy when compared with raloxifene ($P < .001$) and reached borderline significance when compared with simvastatin ($P = .099$).

Non-HDL-cholesterol levels at study completion were (mean ± SE) 194 ± 5.9, 175 ± 4.0, 146 ± 5.1, and 135 ± 5.3 mg/dL for placebo, raloxifene, simvastatin, and coadministration therapy, respectively. Raloxifene, simvastatin, and coadministration therapy all lowered non-HDL cholesterol to a similar degree to that observed for LDL cholesterol ($P < .002$ compared with baseline; $P < .01$ compared with placebo; Table 2). Non-HDL cholesterol was reduced to a greater degree with coadministration therapy than with raloxifene ($P < .001$), but did not reach significance when compared with simvastatin ($P = .113$). Total cholesterol was significantly reduced from baseline (Table 2) in all 3 active treatment groups ($P < .002$) and was significantly different from placebo ($P < .01$). The reduction in total cholesterol from baseline with coadministration therapy was not statistically different than simvastatin, but was significantly greater compared with raloxifene (Table 2). None of the treatment groups had a reduction in HDL-cholesterol levels during the study (Fig. 3). Coadministration therapy increased HDL-cholesterol levels by 7.8%, which was significantly different from both baseline ($P < .003$) and placebo ($P < .02$). The variable "therapy" reached borderline significance in the HDL-cholesterol model ($P = .085$) and the coadministered treatment arm had higher HDL-cholesterol levels compared with either treatment alone ($P < .09$). Levels of ApoA1 were not altered significantly from baseline with any treatment regimen, except for a 3.4% reduction in the placebo group (Fig. 3) ($P < .04$). As with HDL cholesterol, the variable "therapy" reached borderline significance in the model for ApoA1 ($P = .089$). Coadministration therapy was associated with a 4.2% increase in ApoA1, which was significantly different from placebo ($P < .02$).

Triglycerides and VLDL-cholesterol levels were not adversely affected with any of the treatment groups compared with baseline (Table 2). In the simvastatin and coadministration treatment groups, the reduction in triglycerides reached borderline statistical significance from

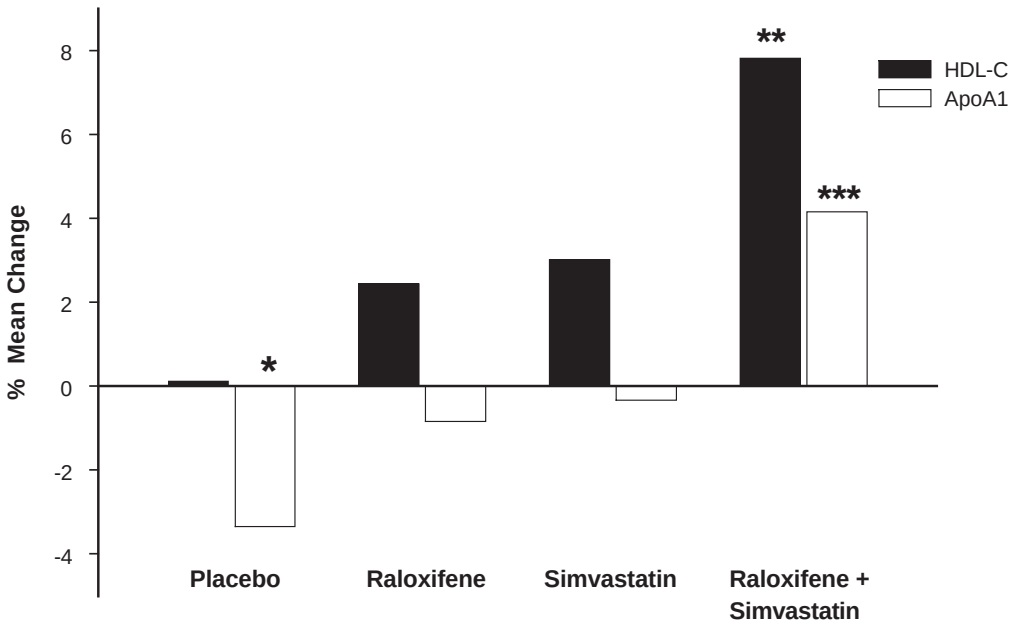

Fig. 3. Percentage change in mean HDL cholesterol and apoA1 from baseline with placebo, raloxifene, simvastatin, or coadministration therapy. Black bars indicate HDL cholesterol; white bars, apoA1. *$P < .05$ vs baseline, **$P < .003$ vs baseline and $P < .02$ vs placebo, ***$P < .02$ vs placebo.

baseline ($P < .06$), but the changes were not different from placebo. The reduction from baseline in VLDL-cholesterol levels was statistically significant in the simvastatin group, and the reduction with coadministration therapy reached borderline statistical significance ($P = .058$), but neither reduction was significantly different from placebo. Lipoprotein (a) was not significantly altered from baseline with any treatment during the study period (Table 2).

3.3. Adverse events

Raloxifene, simvastatin, and the coadministration therapy were generally well tolerated with no clinical evidence of adverse effects greater than placebo. The most commonly noted adverse events were headache (11.6%), pain not otherwise specified (10.5%), flu syndrome (6.3%), and infection (4.2%). There were no significant differences among the 4 treatment groups for any adverse events, including vasodilatation and leg cramps ($P \geq .296$). Overall, 13 (13.7%) women discontinued the study with similar frequencies in the 4 treatment groups. One woman in the simvastatin group had a serious adverse event (hospitalization related to gastritis/esophagitis), not related to the study drug, and continued in the study. Liver enzymes were monitored during the study, and there was no sustained elevated aspartate transaminase and alanine transaminase in any treatment group. One patient in the combination therapy group had an interim elevated ratio of aspartate transaminase/alanine transaminase, which resolved, was not attributed to therapy, and did not result in drug discontinuation.

4. Discussion

This is the first controlled clinical trial to evaluate the efficacy of coadministration of a selective estrogen receptor modulator, raloxifene, and a statin, simvastatin, on plasma lipoproteins and apolipoproteins in postmenopausal women. Raloxifene and simvastatin coadministration resulted in complementary and favorable changes in the levels of low-density and high-density lipoproteins and appeared to be well tolerated with no significant adverse effects. This study demonstrates an effect of coadministration therapy to decrease LDL cholesterol, non-HDL cholesterol, and ApoB, and indicates an increase in HDL cholesterol and ApoA1. The small size of the trial cohort limits the statistical power to detect treatment effects on the various plasma lipid components other than LDL cholesterol, but no trend to a less favorable lipid profile was seen with coadministration therapy. As only the 10 mg/d dose of statin was used, neither the efficacy nor safety in this study can be extrapolated to alternative or high doses of statins.

Raloxifene and simvastatin, alone and in coadministration, significantly reduced LDL-cholesterol, non-HDL-cholesterol, and ApoB levels. The observed LDL cholesterol decrease with coadministration therapy was close to the theoretical 33% decrease calculated from summing the effects seen with raloxifene and simvastatin individually. The additive effects in coadministration can be further evaluated using "doubling rule of 6%," [19] wherein doubling the statin dose typically results in an additional 6% reduction of LDL cholesterol. Raloxifene and simvastatin coadministration appeared to affect LDL cholesterol more than calculated using this doubling rule, which was established for statin drugs. The similar magnitude of effect on LDL cholesterol and ApoB also suggests no adverse effect on LDL-cholesterol particle size and is further substantiated by the overall improvements in non-HDL cholesterol, which is an estimate of the cholesterol content of all atherogenic lipoproteins.

All active drug treatments appeared to impart small but favorable increases in HDL cholesterol and ApoA1, with coadministration treatment having statistically significant effects, compared with placebo. The effect on HDL cholesterol appeared to be additive, with coadministration similar to that seen with LDL cholesterol. The increase in HDL cholesterol associated with raloxifene and simvastatin coadministration is comparable to those reported for low-dose statins when coadministered with 10 mg of ezetimibe, an inhibitor of cholesterol absorption [20]. The observed increase in HDL cholesterol parallels a similar increase in ApoA1, the major apolipoprotein of HDL cholesterol, suggesting again that particle size is not adversely affected.

Baseline mean triglyceride levels were within NCEP-ATP III guideline goals and, along with VLDL-cholesterol levels, were not adversely affected in any treatment group during the study. Lipoprotein (a) levels did not change significantly in any treatment group, although a wide variation at baseline may have obscured any subtle changes.

Raloxifene and simvastatin coadministration appeared to be generally well tolerated, although this study was not of sufficient size or duration to unequivocally evaluate safety. Few discontinuations were due to adverse events and the rates were not different among the 4 treatment groups. No significant adverse effects were attributed to the active treatments. The safety of raloxifene and simvastatin monotherapy has been previously reported [21,22]. The risk of myopathy/rhabdomyolysis, a serious adverse event associated with all statins, including simvastatin [23], appears to be both age- and dose-dependent with specific involvement of the cytochrome P450 metabolic pathway [24]. Thus, higher doses of simvastatin, or concomitant use of other drugs metabolized in this pathway, can further increase the risk of this serious adverse event [23]. No sulfate conjugates are found during raloxifene metabolism [25], indicating that raloxifene is not metabolized by cytochrome P450. Furthermore, raloxifene use has not been associated with myopathy/rhabdomyolysis in any large, randomized clinical trials [13,26-28]. In theory, for older postmenopausal women who may have a higher risk of statin-induced rhabdomyolysis, the possible risk of this adverse event may be decreased by using low-dose simvastatin with raloxifene, as compared with higher doses of simvastatin alone or combined with other lipid-altering drugs, which have been shown to increase

the risk of rhabdomyolysis [29-32]. Further data specifically evaluating the safety of raloxifene coadministration with multiple doses of statins are needed. The ongoing RUTH trial may further delineate the safety of coadministration, as approximately half of the participants reported using statins at baseline [33]. Venous thromboembolism is a serious adverse event associated with raloxifene use [34]. The present study was not large enough to assess the incidence of this event. Conversely, statins do not increase the rates of venous thromboembolism, and a subset analysis from clinical trials has shown that patients using statins have fewer events compared with placebo [35]. Whether statins and raloxifene coadministration can reduce the venous thromboembolism risk associated with raloxifene is unknown and requires further testing in a larger trial such as RUTH.

Current clinical practice favors increasingly intensive lipid management, particularly for secondary prevention and in other high-risk groups [8,9]. Approximately 75% of patients with CHD who qualify for drug therapy require LDL-cholesterol reductions of more than 30% [36], which often entails statin therapy at doses that can produce significant side effects [23]. In addition, a significant proportion of patients with hyperlipidemia cannot attain adequate lipid lowering using conventional treatments and dosing schedules. Coadministration of 2 lipid-altering agents to achieve NCEP-ATP III goals is an alternative to high-dose monotherapy. Although clinicians are familiar with using coadministration therapy to manage hypertension, coadministration of lipid-lowering agents in management of dyslipidemia has not been extensively used until recently. The rationale for coadministration therapy is based on well-established concepts [37-39]. Raloxifene and simvastatin have independent mechanisms of action and catabolism, complementary effects on the lipid profile, and long-term monotherapy studies have shown safety and efficacy, which are supported in this coadministration study. Several large-scale trials have shown that simvastatin reduces cardiovascular disease risk [40,41]. Raloxifene therapy was associated with a reduction in cardiovascular events in a subset of postmenopausal women with increased baseline cardiovascular risk [13], but this requires confirmation in trials with cardiovascular outcomes as a primary objective [14]. Whether raloxifene and simvastatin coadministration will further reduce cardiovascular risk beyond that seen with simvastatin alone is unknown. As both raloxifene and simvastatin have multiple pleiotropic effects on atherogenesis and inflammatory pathways, coadministration may be potentially beneficial against developing clinically evident cardiovascular disease [12,42]. Again, these hypotheses await the conclusion of the RUTH trial.

In conclusion, this study has demonstrated that raloxifene coadministered with simvastatin has favorable effects by lowering LDL cholesterol and raising HDL cholesterol more than either monotherapy. Raloxifene is currently indicated for the prevention and treatment of osteoporosis in postmenopausal women, and further evaluation would be needed before considering coadministration therapy for adjunct treatment of dyslipidemias. Whether these lipid effects translate to additional significant reductions in atherosclerotic morbidity and mortality remains to be determined and may be addressed in the ongoing RUTH trial [14,33]. Future research should determine the effects of raloxifene and simvastatin coadministration on other cardiovascular disease markers, on noncardiovascular endpoints, and on the safety profile with concurrent use of these 2 classes of drugs.

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