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Effects of raloxifene on lipid and lipoprotein levels in postmenopausal osteoporotic women with and without hypertriglyceridemia

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Abstract

This post hoc analysis reports the effects of raloxifene on lipids and lipoproteins in 2659 women with either normal (≤150 mg/dL) or high (>150 mg/dL) triglyceride levels from a substudy of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. In both triglyceride subgroups, raloxifene significantly improved low-density lipoprotein cholesterol, total cholesterol, non–high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, apolipoprotein A-I, and fibrinogen compared with placebo ($P < .05$). After raloxifene treatment, women with high triglycerides experienced an equal or more robust reduction in cholesterol, lipoprotein parameters, and ratios of total cholesterol to HDL-C and non–HDL-C to HDL-C than was observed in women with normal triglycerides ($P < .05$). Mean levels of low-density lipoprotein cholesterol and apolipoprotein B were reduced by 16.5% and 15.8%, respectively, in women with high triglycerides, and by 12.7% and 11.3%, respectively, in women with normal triglycerides. These findings further substantiate that raloxifene improves concentrations of both cholesterol and β-lipoprotein. The subgroup of women with high triglycerides, who have elevated cardiovascular risk, appear to derive at least equal, if not greater, overall effect on lipid and lipoprotein lowering with raloxifene.

1. Introduction

Cardiovascular disease has been the largest cause of morbidity and mortality in postmenopausal women in the Western world for several decades, with mortality rates in women remaining higher than in men, despite the availability of several efficacious therapies [1]. Triglyceride-rich lipoproteins play a prominent role in atherogenesis, especially in women [2-4], even after adjustments for other lipid and nonlipid risk factors [5,6]. Women with elevated triglycerides have a more highly atherogenic dyslipidemia as seen by elevations in very low-density lipoprotein (VLDL), intermediate-density lipoprotein, low-density lipoprotein (LDL), and remnant particles, all of which may be involved in plaque deposition [7-9]. With increasing triglyceride levels, LDL-C is less predictive of coronary heart disease. Instead, non–high-density lipoprotein cholesterol (HDL-C) better estimates the concentration of all atherogenic lipoproteins [VLDL cholesterol + LDL-C + intermediate-density lipoprotein], namely, those containing apolipoprotein B [7-9]. Although apolipoprotein B measurement is the most accurate way of determining the atherogenic lipoprotein pool size, it is less available and more costly to use in clinical practice than the calculated value of non–HDL-C, which has been adopted as a surrogate end point for treatment guidelines [7]. The revised National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines recommend that all patients with triglyceride values of more than 150 mg/dL be targeted for more intense intervention, as elevated triglycerides pose additional cardiovascular risk [7]. Reducing LDL-C to this goal is the primary therapeutic target for treating hypertriglyceridemia, with a secondary target for non–HDL-C to be ≤30 points higher than the LDL-C goal in these individuals [7].

Elevated triglycerides may promote atherogenesis through changes in the concentration and corresponding composition of LDL particles. Higher triglyceride levels increase the LDL particle concentration through increased

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hepatic production of VLDL particles, which subsequently form LDL particles. In addition, hepatic lipase acts to reduce LDL particle size, resulting in the formation of smaller, denser LDL particles, which can more readily penetrate endothelial barriers, be oxidized by reactive oxygen species, and are less vulnerable to removal by hepatic LDL receptors [8-10]. The LDL particles that pass through the endothelial barrier are subjected to oxidative forces and macrophage ingestion, which produces foam cells and leads to plaque formation. Elevated triglyceride levels also promote an increase in the production of remnant chylomicrons, VLDL, and intermediate-density lipoproteins, which are all capable of endothelial invasion and macrophage ingestion, thereby conveying added atherogenic risk. Beyond the changes in β-lipoproteins, elevated triglycerides are associated with increased fibrinogen and small dense HDL particle production [6,8,9].

Almost all oral estrogen and estrogen/progestin preparations at standard doses induce some degree of hypertriglyceridemia [11,12]. Estrogen-induced hypertriglyceridemia was suggested to be the most plausible explanation for the failure of estrogen to reduce cardiovascular events in the Women's Health Initiative study [13]. In contrast to estrogen, raloxifene does not adversely affect clinically relevant triglyceride concentrations, although some women with triglyceride levels of more than 500 mg/dL, who have a further elevation with estrogen therapy, may respond similarly with raloxifene [14,15].

Raloxifene, a selective estrogen receptor modulator, is currently approved for the prevention and treatment of postmenopausal osteoporosis [14]. In a retrospective cardiovascular safety analysis from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene was associated with a neutral effect on cardiovascular events in the overall population of postmenopausal women with osteoporosis [16]. Raloxifene has been shown to have a neutral to favorable effect on multiple atherogenic and inflammatory cardiovascular risk markers [14-19].

Because of the added risk imposed with elevated triglyceride levels, this current post hoc analysis compared the effects of raloxifene on serum lipoproteins in women with and without elevated triglyceride concentrations at baseline (defined as triglycerides of >150 and ≤ 150 mg/dL, respectively). Further analyses determined the efficacy of raloxifene in lowering LDL-C, non–HDL-C, and apolipoprotein B, and in improving other lipoproteins and markers of cardiovascular risk in women with and without hypertriglyceridemia.

2. Materials and methods

The 4-year, randomized, double-blind, placebo-controlled MORE trial was designed to evaluate the effects of raloxifene therapy on vertebral fractures and overall safety in 7705 postmenopausal women with osteoporosis. The effect of long-term raloxifene treatment on serum lipids and other laboratory markers of cardiovascular risk in postmenopausal women with osteoporosis was a secondary study outcome. At the time of enrollment, women were postmenopausal for 2 years or more and had osteoporosis, documented with either existing vertebral fractures or baseline bone mineral density measurement of -2.5 SD or less from the normal peak bone mass for healthy premenopausal women. The ethical review board at each site approved the study, and all women signed an informed consent before entering the study. Trial design and lipid results have been published in more detail in previous publications [15,16]. Total cholesterol was measured in the fasting state in all women enrolled in the MORE trial at baseline, and serum lipoproteins, triglycerides, and fibrinogen were measured in a subset of 2738 women at baseline and at 6, 12, 24, and 36 months. The current analysis included 2659 women who had baseline values for both LDL-C and triglycerides, and at least 1 postbaseline LDL-C value.

The primary objective of this analysis was to evaluate and compare the effects of raloxifene (combined 60 and 120 mg/d doses) vs placebo on fasting LDL-C concentrations in subgroups of osteoporotic postmenopausal women, with and without hypertriglyceridemia. Hypertriglyceridemia was defined as triglyceride levels of 150 mg/dL or more, based on the NCEP-ATP III recommendations [7]. As secondary objectives of the analysis, the effects of raloxifene and placebo on the concentrations of other lipoproteins and apolipoproteins (such as non–HDL-C, apolipoprotein B, and various lipoprotein ratios) as well as fibrinogen were compared in these subgroups. In addition, the overall safety of raloxifene was assessed in these 2 subgroups of women. Comparisons were performed between treatment groups for serious adverse events with more than 2% of occurrence, and for serious or nonserious adverse events related to hypertriglyceridemia.

2.1. Measurement of serum lipoproteins and fibrinogen

Blood samples were obtained after a 12-hour fast, and serum was isolated during each clinic visit. Samples were assayed for lipoproteins and apolipoproteins at a central laboratory [15]. Total cholesterol and triglycerides were measured with enzymatic reagents (Roche Diagnostics, Indianapolis, IN). High-density lipoprotein cholesterol was sequentially separated by precipitation with dextran sulfate and magnesium chloride. The supernatant was assayed for HDL-C using the method described for total cholesterol. Low-density lipoprotein cholesterol was calculated from the Friedewald [20] equation using the measured values of total cholesterol, triglycerides, and HDL-C. Non–HDL-C was determined for each subject by calculating the difference between the concentrations of total cholesterol and HDL-C. Apolipoprotein A-I and apolipoprotein B were quantified by rate nephelometry using the Beckman IMMAGE Immunochemistry System (Beckman Instruments, Brea, CA). Fibrinogen was measured by the Clauss clotting technique with an automated coagulation analyzer (MLA Electra 1600 C; Medical Laboratory Automation, Pleasantville, NY) that uses a photometric clot detection technique [18].

Table 1
Baseline characteristics of postmenopausal women with osteoporosis with high and normal baseline triglyceride levels

Baseline characteristic	High triglycerides		Normal triglycerides	
	Placebo (n = 159)	Raloxifene (n = 287)	Placebo (n = 735)	Raloxifene (n = 1478)
Age (y)	67.9	67.6	67.4	67.3
White (%)	97.5	97.6	97.7	97.6
Smoking (%)	12.1	17.6	17.3	17.0
Alcohol >3 drinks per week (%)	10.7	17.5	19.8	17.9
Years postmenopausal*	20.5	20.6	19.7	19.3
Hysterectomy (%)*	34.6	27.9	21.0	19.2
Body mass index (kg/m^2)*	26.9	26.7	24.7	24.8
Systolic blood pressure (mm Hg)*	142.2	142.0	137.6	137.9
Diastolic blood pressure (mm Hg)*	81.7	81.5	79.6	79.3
Hypertension (%)[a,*]	67.9	67.9	53.5	52.5
Hypercholesterolemia (%)[b,*]	79.2	79.8	66.8	67.9
Diabetes (%)*	8.9	9.2	2.6	3.1
Cardiovascular risk score ≥4 (%)[c]	25.2	27.5	13.1	14.6
Prior cardiovascular event (%)	4.4	4.5	3.4	3.1
Lipid-lowering medications (%)*	10.7	15.7	5.0	6.9
Aspirin use (%)	20.1	22.6	18.8	17.8
Antihypertension medication (%)	35.8	37.6	23.7	22.9

[a] Systolic blood pressure of more than 140 mm Hg, or diastolic blood pressure of more than 85 mm Hg, or taking antihypertension medication.
[b] Low-density lipoprotein cholesterol of more than 140 mg/dL or taking lipid-lowering medication.
[c] Women with 4 or more risk points were considered to be at increased risk of cardiovascular events [16,39].
* $P < .05$ between high-triglyceride and normal-triglyceride subgroups.

2.2. Statistical analysis

Procedures in SAS version 8.02 (SAS Institute, Cary, NC) were used to perform all statistical analyses. Unless otherwise specified, the interactions were tested at a significance level of .1, and other hypotheses were tested at significance level of .05. All tests were 2-sided, and no adjustments were made for multiplicities. Analyses were performed using an intention-to-treat principle. Women with a baseline LDL-C and triglyceride concentration and any postbaseline LDL-C measurement were included in the analyses. Women were classified into normal or high-triglyceride subsets depending on their baseline triglyceride concentration. Women with baseline triglyceride levels of 150 mg/dL or more were allotted to the high-triglyceride subset, whereas those with baseline triglyceride levels of less than 150 mg/dL were in the normal triglyceride subset. Pooled raloxifene doses (60 and 120 mg/d) were analyzed, as there is no statistically significant difference in the lipid-lowering effect between the 2 doses [15,16]. For all serum lipid and lipoprotein measurements, change from baseline as well as percentage of change from baseline was calculated. For each parameter, mixed-models, repeated-measures analysis on change from baseline to all time points was used to account for the possible correlation between repeated measurements made on an individual over time. The independent variables were baseline triglycerides status (high/normal), treatment (placebo/raloxifene), time (6 months and 1, 2, and 3 years) and all interactions. Contrasts for treatment effect, effect of baseline triglycerides status, as well as the interaction between treatment and baseline triglycerides status at 3 years were tested. Other within-group and between-group tests were based on the least squares means from the above model. As baseline triglyceride levels varied between triglyceride subgroups, an analysis was performed with adjustments for these differences. This analysis produced similar results as the unadjusted analysis and, therefore, only the unadjusted analysis was reported. All categorical variables were compared by χ^2 test or Fisher exact test. Continuous baseline characteristics and baseline serum markers were compared using a 2-way analysis of variance model. Serious adverse events related to cardiovascular disease, common adverse events with more than 2% of occurrence, and adverse events (serious or nonserious) related to hypertriglyceridemia were compared across treatment groups.

A post hoc power calculation was performed for the change in LDL-C from baseline to 3 years. With an SD of 30 mg/dL and the available sample size in this database, there was more than 90% power to detect a difference of 15 mg/dL in the change in LDL-C between placebo and raloxifene within the triglyceride subgroups at a significance level of .05. With an SD of 30 mg/dL and the available sample size in this database, there was more than 80% power to detect a difference of 5.5 mg/dL in the change in LDL-C between triglyceride subgroups at a significance level of .05.

3. Results

3.1. Baseline characteristics

Most baseline characteristics were significantly different between women with high triglycerides and those with normal triglycerides (Table 1), although no differences were seen between treatment arms in women within each triglyceride subgroup. Women with high triglycerides had significantly higher body mass indices, systolic and

Table 2
Mean baseline lipoprotein and fibrinogen levels in postmenopausal women with osteoporosis with high and normal baseline triglyceride levels

Baseline serum cardiovascular risk marker	High triglycerides		Normal triglycerides	
	Placebo (n = 159)	Raloxifene (n = 287)	Placebo (n = 735)	Raloxifene (n = 1478)
Triglycerides (mg/dL)**	208.4	201.0*	91.7	88.5*
LDL-C (mg/dL)**	165.8	167.4	155.6	156.9
Total cholesterol (mg/dL)**	253.9	255.2	235.5	236.6
Non–HDL-C − LDL-C**	41.5	39.8*	18.4	17.7*
Apolipoprotein B (mg/dL)**	175.3	175.6	144.8	145.5
HDL-C (mg/dL)**	47.0	47.9	61.5	62.0
Apolipoprotein A-I (mg/dL)**	145.1	145.8	157.6	158.2
Total cholesterol/HDL-C**	5.6	5.6	4.0	4.0
Non–HDL-C/HDL-C**	4.6	4.6	3.0	3.0
Non–HDL-C (mg/dL)**	207.2	207.3	174.0	174.6
Fibrinogen (g/dL)**	3.5	3.4	3.3	3.4

* $P < .05$ between raloxifene and placebo within each triglyceride subgroup.
** $P < .01$ between high and normal triglyceride subgroups.

diastolic blood pressures, and cardiovascular risk scores [16] compared with women with normal triglycerides. Correspondingly, women with high triglycerides at baseline were more likely to have diagnoses of diabetes mellitus, hypercholesterolemia or hypertension, and more likely to use β-blockers, diuretics, and lipid-lowering medications than women with normal triglycerides. The overall attrition rate was 17.3%, with no significant differences in attrition between the 4 groups. Compliance, defined as the proportion of women taking at least 80% of the study medication, was greater than 80% in all 4 groups at all time intervals. The compliance rates in the high triglyceride-raloxifene group were 81% to 82% during years 2 and 3, which were slightly lower than that seen in the other groups (87%-91%).

Women with baseline hypertriglyceridemia had higher concentrations of total cholesterol, LDL-C, apolipoprotein B, and non–HDL-C levels, but lower HDL-C and apolipoprotein A-I levels, than women with normal triglycerides (Table 2). In addition, the ratios of non–HDL-C to HDL-C, total cholesterol to HDL-C, and the calculated difference (non–HDL-C minus LDL-C) were greater in women with hypertriglyceridemia than in women with normal triglycerides at baseline. Within each triglyceride subgroup, baseline triglyceride levels were slightly higher in placebo-treated women compared with raloxifene-treated women ($P < .05$), although the levels (3-7 mg/dL) were not clinically different.

3.2. Effects of raloxifene on lipoprotein and apolipoprotein levels

After 3 years of treatment, women with high baseline triglyceride levels still had higher levels of total cholesterol, LDL-C, non–HDL-C, apolipoprotein B, and triglycerides and lower levels of apolipoprotein A-I ($P < .01$) compared with women with normal baseline triglyceride levels (Table 3, Figs. 1 and 2), whereas HDL-C and fibrinogen levels were similar between triglyceride subgroups ($P > .1$), regardless of treatment. However, compared with placebo, raloxifene significantly improved LDL-C, non–HDL-C, total cholesterol, apolipoprotein A-I, apolipoprotein B, and fibrinogen in both triglyceride subgroups (Table 3, Figs. 1 and 2). Both triglyceride subgroups had similar improve-

Table 3
Serum cardiovascular markers at 3 years: mean absolute value and mean percentage of change from baseline

	High triglycerides		Normal triglycerides	
	Placebo (n = 159)	Raloxifene (n = 287)	Placebo (n = 735)	Raloxifene (n = 1478)
Total cholesterol (mg/dL)*	243.9	224.8	234.4	219.3
	−2.5%	−10.4%	0.9%	−6.4%
HDL-C (mg/dL)	49.2	51.3	65.0	65.1
	5.0%	8.1%	6.3%	6.0%
Apolipoprotein A-I (mg/dL)*	143.5	150.6	155.2	159.2
	1.9%	4.3%	0.2%	2.2%
Total cholesterol/ HDL-C*	5.2	4.6	3.8	3.5
	−4.5%	−15.3%	−3.3%	−10.0%
Non–HDL-C/HDL-C	4.2	3.6	2.8	2.5
	−5.1%	−18.9%	−4.0%	−13.3%
Triglycerides (mg/dL)*†	188.9	191.0	91.7	96.5
	−7.5%	−2.9%	3.1%	11.9%
Fibrinogen (g/dL)*	3.4	2.9	3.3	2.9
	2.9%	−12.1%	6.7%	−8.9%

* $P < .05$ in the mean absolute value between raloxifene and placebo, within each triglyceride subgroup.
† $P < .05$ in the mean percentage of change between raloxifene and placebo, within each triglyceride subgroup.

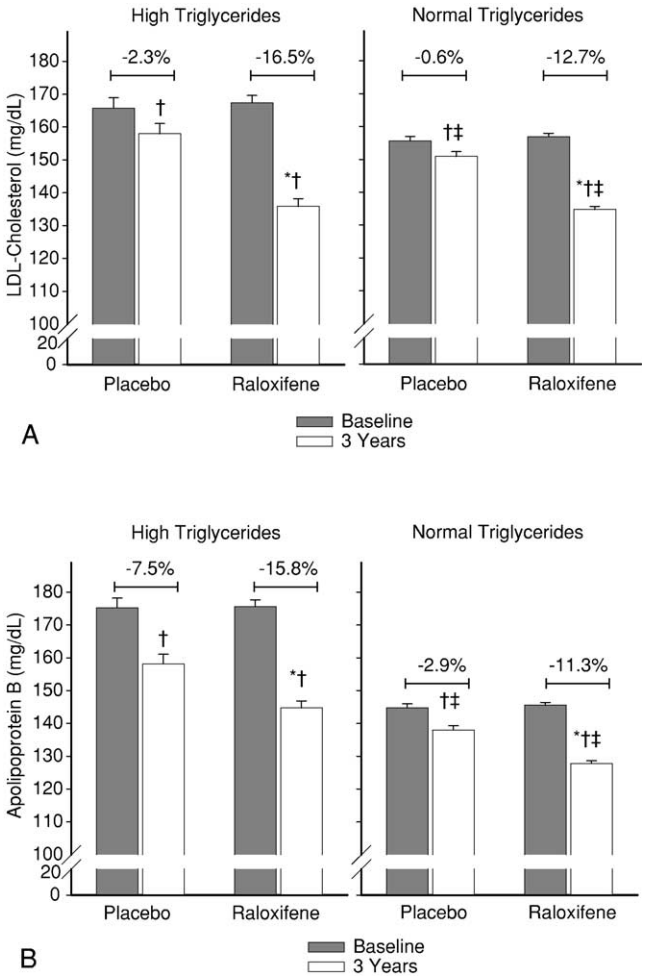

Fig. 1. LDL-C (A) and apolipoprotein B (B) values (mean ± SE) at baseline and after 3 years of treatment in postmenopausal women with high (>150 mg/dL) and normal (≤150 mg/dL) triglyceride levels at baseline. *$P < .01$ between placebo and raloxifene groups, within each triglyceride subgroup. super †$P < .01$ compared with baseline. ‡$P < .01$ between the high and normal triglyceride subgroups, within each treatment group at 3 years.

ments in lipid parameters with raloxifene (interaction $P > .1$). However, women with higher triglycerides and baseline lipid parameters had a greater reduction in the absolute concentrations than women with normal triglycerides (Figs. 1 and 2). At 3 years, mean LDL-C levels were similar between women with normal baseline triglycerides (134.8 mg/dL) and those with elevated baseline triglycerides (135.9 mg/dL, Fig. 1A). Low-density lipoprotein cholesterol concentrations, as well as other lipoprotein constituents, were modified beginning at 6 months of raloxifene treatment, reaching a plateau level at this time, and the changes persisted through the end of the study, without further decreases (Fig. 3).

At baseline, few women in the placebo and raloxifene groups (6% and 8%, respectively) used lipid-lowering medications, whereas at the end of the study, 13% and 11% of women in the placebo and raloxifene groups, respectively, were taking lipid-lowering medications. In addition, a greater proportion of women in the high-triglyceride subgroup (14%) was treated with lipid-lowering medication at study entry compared with women in the normal-triglyceride subgroup (6%).

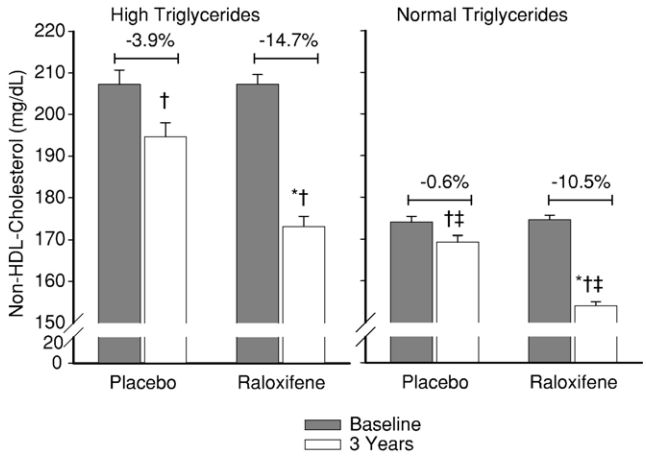

Fig. 2. Non–HDL-C values (mean ± SE) at baseline and after 3 years of treatment in postmenopausal women with high (>150 mg/dL) and normal (≤150 mg/dL) triglyceride levels at baseline. *$P < .01$ between placebo and raloxifene groups, within each triglyceride subgroup. †$P < .01$ compared with baseline. ‡$P < .01$ between the high and normal triglyceride subgroups, within each treatment group at 3 years.

When women who took lipid-lowering medications were excluded from the analysis (data not shown), the outcomes were similar to those already reported herein for all women, irrespective of use of lipid-lowering agents, for all parameters except LDL-C. Among women who were not exposed to lipid-lowering medications, raloxifene had a more robust effect in reducing LDL-C in women with high baseline triglycerides (0.1% for placebo, −16.3% for raloxifene) compared with those with normal baseline

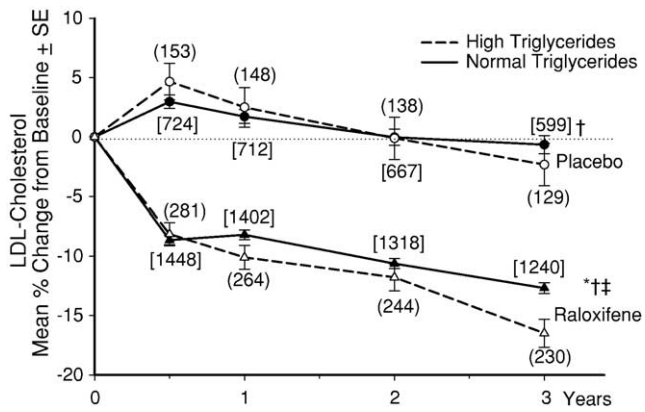

Fig. 3. Mean percentage change (±SE) in LDL-C concentrations from baseline to 3 years in postmenopausal women with high (>150 mg/dL) and normal (≤150 mg/dL) triglyceride levels at baseline. Numbers of women at each time point are denoted in parentheses for the high-triglyceride group and in brackets for the normal-triglyceride group. At 3 years, *$P < .0001$ between placebo and raloxifene within each triglyceride subgroup, †$P < .005$ from baseline for placebo and raloxifene groups in both triglyceride subgroups, and ‡$P < .002$ between high- and normal-triglyceride subgroups in the raloxifene treatment group.

triglycerides (0.8% for placebo, −12.7% for raloxifene, interaction $P = .06$).

In both subgroups, raloxifene significantly improved the calculated ratios of total cholesterol to HDL-C and non–HDL-C to HDL-C (Table 3) compared with placebo at 3 years ($P < .001$). Women with high baseline triglycerides had more robust reductions in both ratios than women with normal triglycerides (interaction $P = .01$). At the end of 3 years, triglyceride levels in women with high baseline triglycerides (placebo, 189 mg/dL; raloxifene, 191 mg/dL) and women with normal baseline triglycerides (placebo, 92 mg/dL; raloxifene, 97 mg/dL) were clinically similar between treatment groups ($P > .05$ within each triglyceride subgroup). In addition, regardless of baseline triglyceride status (Table 3), raloxifene treatment equally reduced fibrinogen levels, did not alter HDL-C levels, and significantly increased apolipoprotein A-I levels ($P < .05$).

3.3. Adverse events

Raloxifene was generally well tolerated. Common adverse events (>2% occurrence) reported by women in the placebo group significantly more often than women in the raloxifene group included arthritis, hypercholesterolemia, insomnia, and weight loss ($P < .05$), whereas women in the raloxifene group reported flushing, muscle cramps, peripheral edema, and vertigo more often than those in the placebo group ($P < .05$). Compared with placebo, uterine polyps were reported less frequently after raloxifene treatment in women with high triglycerides, and more frequently in women with normal triglycerides ($P < .05$). The occurrence of venous thromboembolism was similar between women with normal and high triglycerides ($P > .2$) within the placebo and raloxifene groups. No adverse events of liver enzyme abnormalities, liver dysfunction, or pancreatitis were reported in raloxifene-treated women with hypertriglyceridemia.

4. Discussion

Scientific investigations over the last 40 years have validated the "cholesterol hypothesis" as being a significant contributor to cardiovascular disease progression. Low-density lipoprotein cholesterol measurement is the mainstay of assessing atherosclerotic load in clinical practice. However, the non–HDL-C concentration offers a best approximation of the total atherogenic lipoprotein burden because it reflects the entire cholesterol content for all atherogenic β-lipoproteins, namely, lipoprotein (a), chylomicrons, chylomicron remnants, VLDL, VLDL remnants, LDL, and intermediate-density lipoprotein [18,21]. Alternatively, information on the number of atherogenic β-lipoprotein molecules, namely, apolipoprotein B concentrations, has been shown to be the best predictors of major coronary events and coronary mortality in large, randomized, placebo-controlled clinical trials [22-24].

When triglycerides are elevated, the liver synthesizes large amounts of triglyceride-rich VLDLs, which are processed to atherogenic β-lipoprotein particles such as intermediate-density lipoproteins, remnant particles, and small dense LDLs, all of which are reflected in a higher non–HDL-C and serum apolipoprotein B measurements. Recognizing the importance of all β-lipoproteins, the NCEP-ATP III guidelines elevated the importance of the non–HDL-C as a risk factor and therapeutic target in the prevention and treatment of atherosclerosis, especially in patients with hypertriglyceridemia [7]. Recent clinical outcomes and angiographic trials provide clinical support for these new guidelines, as statins, bile acid sequestrants, fibrates, and niacin decrease apolipoprotein B and non–HDL-C levels and reduce the occurrence of clinical events [17,25]. The non–HDL-C goal does not abrogate from the need to achieve even greater LDL-C goals recently published by the NCEP-ATP III [26], but rather complements and further intensifies therapy for those patients with elevated triglyceride component in their lipid profile, who are at higher risk [27,28]. In the present analysis, we have calculated the non-HDL/HDL ratio as an estimate of the apolipoprotein B–apolipoprotein A-I ratio, which may be more concise than the LDL/HDL ratio, when apolipoproteins are not directly measured. Similarly, the (non-HDL − LDL) difference may give an estimate of the other atherogenic apolipoprotein B–containing lipoproteins, excluding LDL-C.

In this analysis from the MORE study, raloxifene improves both cholesterol concentrations and β-lipoprotein number in women with and without baseline hypertriglyceridemia. Compared with women with normal triglycerides, women with elevated triglycerides have concurrent and comparable reductions in LDL-C, apolipoprotein B, and the non–HDL-C after raloxifene treatment, which may help to reduce their higher vascular burden, given their more atherogenic lipid milieu. Interestingly, the reduction in total cholesterol, LDL-C, apolipoprotein B, and non–HDL-C seemed more robust in the subgroup of women with elevated triglycerides at baseline who were not taking lipid-lowering medication. Given that hyperlipidemia is undertreated in American women, this added effect of raloxifene could be significant. These observed differences in lipid reductions cannot be attributed to population differences in study attrition or medication compliance rates. Although the compliance in the raloxifene-treated high-triglyceride subgroup was slightly lower than that in the other 3 groups, the decrease in LDL-C in this group was still significant compared with placebo. This observed relative decrease in LDL-C may be underestimated.

In this analysis, the reductions in LDL-C observed at 3 years with raloxifene treatment ranged between 13% and 17% from baseline. According to the "doubling rule of 6%," doubling the dose of statins decreases LDL-C by an additional 6% [29], so the observed LDL-C reductions with raloxifene compare favorably to a potential reduction seen with 2 doublings of a statin dose. Furthermore, a recent study

has found that coadministration of raloxifene 60 mg/d and simvastatin 10 mg/d resulted in greater reductions in LDL-C than that seen with either drug alone [30]. Although the magnitude of the LDL-C–lowering effects of raloxifene is interesting, the effects of raloxifene in coadministration with statins on cardiovascular event rates are presently unknown.

In this study, decreases in LDL-C with raloxifene treatment reached a plateau at 6 months, which is consistent with the time course of lipid-lowering effects seen with both the 60 and 120 mg/d doses of raloxifene in other trials [18] and suggests an LDL-C–lowering effect for raloxifene. The likely mechanism by which raloxifene reduces LDL-C involves enhanced LDL particle removal via up-regulation of hepatic LDL receptors [31]. In women with hypertriglyceridemia, raloxifene therapy is associated with an overall improvement in atherogenic particle number and cholesterol load of the atherogenic lipoproteins, as measured by reductions in the apolipoprotein B and the LDL-C and non–HDL-C components, respectively [15]. Because only 19 women in the MORE trial had marked hypertriglyceridemia (>500 mg/dL) at baseline, the numbers were too small for any statistical evaluation of increased or sustained hypertriglyceridemia with raloxifene compared with placebo [15]. In a recent study of 12 women with a documented history of oral estrogen-induced hypertriglyceridemia (≥300 mg/dL), 3 women experienced marked hypertriglyceridemia (≥1000 mg/dL) after 2 weeks of raloxifene therapy [32]. Therefore, some women with a history of developing increased triglyceride levels (>500 mg/dL) with oral estrogen or estrogen plus progestin therapy may experience increased triglyceride levels with raloxifene therapy, and all women with such a history should have serum triglycerides monitored when taking raloxifene [14,32].

Typically, hypertriglyceridemia is associated with reduced levels of HDL-C, and this was also observed at baseline in the MORE cohort. During reverse transport, the HDL particle exchanges cholesterol for triglyceride from triglyceride-rich β-lipoproteins, resulting in a triglyceride-rich, cholesterol-poor HDL particle, which then undergoes lipolysis via hepatic lipase and becomes a small dense HDL particle [31]. In epidemiologic trials of drug-naive, insulin-resistant patients, increased concentrations of small HDL particles have not been correlated with cardioprotection [33]. Raloxifene had no significant effect on HDL-C levels, but did increase apolipoprotein A-I concentrations. Previous trials have shown that raloxifene increases the HDL_2 subfraction.

In contrast to raloxifene, oral estrogen therapy does not consistently lower apolipoprotein B levels to the extent that it lowers LDL-C [12,18], likely due to estrogen-induced hypertriglyceridemia. Induction of triglyceride synthesis by oral estrogen therapy increases production of β-lipoproteins (both remnant lipoproteins and small dense LDL particles) and may reduce LDL size, which may lead to a paradoxical decrease in the LDL-C level. Estrogen increases HDL-C levels, but the main effect is in the HDL_2 and HDL_3 subfractions [12,34-36]. Unless apolipoproteins are measured, the lipid changes may be misinterpreted, and atherogenicity may actually be increased rather than decreased during estrogen therapy.

It is possible that the improvement in lipoprotein population after raloxifene therapy may lead to a reduction in cardiovascular risk. In addition to the effects on lipids and lipoproteins, raloxifene also produces favorable changes in markers of endothelial function, such as increasing the activity or production of nitric oxide, and reducing the expression of intercellular cell adhesion molecules and vascular cell adhesion molecules. Raloxifene was shown to decrease the activity and content of matrix metalloproteinase-9 within carotid lesions, which may affect plaque stability [37-39]. In addition to these effects on the vascular wall, improvements in other cardiovascular risk markers, such as reduction in fibrinogen and homocysteine, are seen with raloxifene [18,19]. In this analysis, raloxifene was equally effective in reducing fibrinogen levels regardless of triglyceride subgroup.

This post hoc analysis, which was not a prespecified hypothesis in the original MORE study protocol, has additional limitations. The present results are limited to postmenopausal women with osteoporosis enrolled in a clinical trial and cannot be generalized to the overall population. Furthermore, the women in this analysis had moderately elevated triglycerides, such as that seen in type 2 dyslipidemia, which is the most commonly seen in populations ingesting the Western diet. Too few cardiovascular events occurred in this clinical trial to comparatively assess the effects of raloxifene on cardiovascular outcomes in women with and without hypertriglyceridemia. These results should not be extrapolated to women with extreme hypertriglyceridemia (>500 mg/dL) at baseline because only 18 women (placebo, n = 6; raloxifene, n = 12) in the MORE trial had such baseline triglyceride levels, and there was insufficient statistical power to test whether raloxifene treatment had any effect on LDL-C, non–HDL-C, and apolipoprotein B levels in these women. Women with severe hypertriglyceridemia (>500 mg/dL) who have further triglyceride elevations in response to estrogen therapy may develop a similar response if given raloxifene, so additional triglyceride monitoring should be performed in these women when raloxifene therapy is initiated [14,15].

In conclusion, this post hoc analysis shows that, in postmenopausal women with osteoporosis, with normal or moderately elevated triglyceride levels at baseline, raloxifene reduces both atherogenic lipoprotein cholesterol and lipoprotein particle concentrations to reach current NCEP-ATP III guidelines [26]. Furthermore, women with elevated triglycerides derive at least an equal lipid-lowering benefit compared with women with normal triglycerides, as seen by changes in LDL-C, apolipoprotein B, total cholesterol, non–HDL-C, and ratios of total cholesterol to HDL-C, and of non–HDL-C to HDL-C.

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References

[1] American Heart Association. 2002 Heart and stroke statistical update. Available at: www.americanheart.org.
[2] Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213-9.
[3] Lloyd-Jones DM, O'Donnell CJ, D'Agostino RB, et al. Applicability of cholesterol-lowering primary prevention trials to a general population: the Framingham Heart Study. Arch Intern Med 2001;161:949-54.
[4] Assmann G, Schulte H, Funke H, et al. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J 1998;19(Suppl M):M8-M14.
[5] Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998;81:7B-12B.
[6] Austin MA. Plasma triglyceride and coronary heart disease. Arterioscler Thromb 1991;11:2-14.
[7] Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[8] Havel RJ, Rapaport E. Management of primary hyperlipidemia. N Engl J Med 1995;332:1491-8.
[9] Krauss RM. Atherogenicity of triglyceride-rich lipoproteins. Am J Cardiol 1998;81:13B-7B.
[10] Dayspring TD. Coronary heart disease in women: triglycerides and lipoprotein biology. J Gend Specif Med 2002;5:27-33.
[11] Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13.
[12] Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. Fertil Steril 2001;76:13-24.
[13] Kuller LH. Hormone replacement therapy and risk of cardiovascular disease: implications of the results of the Women's Health Initiative. Arterioscler Thromb Vasc Biol 2003;23:11-6.
[14] Evista package insert. Indianapolis (Ind): Eli Lilly and Company; 2001.
[15] Mosca L, Harper K, Sarkar S, et al. Effect of raloxifene on serum triglycerides in postmenopausal women: influence of predisposing factors for hypertriglyceridemia. Clin Ther 2001;23:1552-65.
[16] Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002;287:847-57.
[17] Moriarty PM. Using both "relative risk reduction" and "number needed to treat" in evaluating primary and secondary clinical trials of lipid reduction. Am J Cardiol 2001;87:1206-8.
[18] Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998;279:1445-51.
[19] Walsh BW, Paul S, Wild RA, et al. The effects of hormone replacement therapy and raloxifene on C-reactive protein and homocysteine in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab 2000;85:214-8.
[20] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
[21] Davis RA. Cell and molecular biology of the assembly and secretion of apolipoprotein B–containing lipoproteins by the liver. Biochim Biophys Acta 1999;1440:1-31.
[22] Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026-33.
[23] Gotto Jr AM, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation 2000;101:477-84.
[24] Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453-60.
[25] Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA 1996;276:875-81.
[26] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 2004;44:720-32.
[27] Cui Y, Blumenthal RS, Flaws JA, et al. Non–high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 2001;161:1413-9.
[28] Grundy SM. Low-density lipoprotein, non–high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. Circulation 2002;106:2526-9.
[29] Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999;341:498-511.
[30] Insull W, Davidson MH, Kulkarni PM, et al. Effects of raloxifene and low-dose simvastatin coadministration on plasma lipids in postmenopausal women with primary hypercholesterolemia. Metabolism 2005;54:939-46.
[31] Gotto Jr AM. Contemporary diagnosis and management of lipid disorders. Newtown (Pa): Handbooks in Health Care; 1999.
[32] Carr MC, Knopp RH, Brunzell JD, et al. Effect of raloxifene on serum triglycerides in women with a history of hypertriglyceridemia while on oral estrogen therapy. Diabetes Care 2005;28:1555-61.
[33] Asztalos BF, Collins D, Cupples LA, et al. Value of high density lipoprotein (HDL) subpopulations in predicting recurrent cardiovascular events in the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol 2005;25:2185-91.
[34] Knopp RH, Zhu X, Bonet B. Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. Atherosclerosis 1994;110(Suppl):S83-S91.
[35] Wakatsuki A, Ikenoue N, Izumiya C, et al. Effect of estrogen and simvastatin on low-density lipoprotein subclasses in hypercholesterolemic postmenopausal women. Obstet Gynecol 1998;92:367-72.
[36] Wakatsuki A, Ikenoue N, Okatani Y, et al. Estrogen-induced small low density lipoprotein particles may be atherogenic in postmenopausal women. J Am Coll Cardiol 2000;37:425-30.
[37] Baetta R, Comparato C, Altana C, et al. Raloxifene reduces macrophage accumulation and matrix metalloproteinase expression in carotid lesions of ovariectomized, cholesterol-fed rabbits. Circulation 2001;104:II-67.
[38] Simoncini T, Genazzani AR. Raloxifene acutely stimulates nitric oxide release from human endothelial cells via an activation of endothelial nitric oxide synthase. J Clin Endocrinol Metab 2000;85:2966-9.
[39] Colacurci N, Manzella D, Fornaro F, et al. Endothelial function and menopause: effects of raloxifene administration. J Clin Endocrinol Metab 2003;88:2135-40.