

ESTROGEN AND PROGESTIN COMPARED WITH SIMVASTATIN FOR HYPERCHOLESTEROLEMIA IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Background Postmenopausal estrogen therapy has favorable effects on serum lipoproteins in women with normal serum lipid levels, but the effect of combined estrogen and progestin therapy on lipoproteins in women with hypercholesterolemia has not been determined, nor has it been directly compared with the effect of conventional lipid-lowering therapy.

Methods In a randomized crossover trial, we studied 58 postmenopausal women with fasting serum total cholesterol levels greater than 250 mg per deciliter. Each woman received simvastatin (10 mg daily) for eight weeks and postmenopausal hormone therapy (up to 1.25 mg of conjugated equine estrogens daily, along with 5 mg of medroxyprogesterone acetate daily) for eight weeks, with an eight-week washout period between the two treatment phases.

Results At base line, the mean (\pm SD) cholesterol values were as follows: total cholesterol, 305 ± 39 mg per deciliter; high-density lipoprotein (HDL) cholesterol, 62 ± 19 mg per deciliter; and low-density lipoprotein (LDL) cholesterol, 217 ± 39 mg per deciliter. For total cholesterol, the mean decrease with hormone therapy was 14 percent (95 percent confidence interval, 11 to 16 percent) and the mean decrease with simvastatin was 26 percent (95 percent confidence interval, 23 to 29 percent). For LDL cholesterol, the mean decrease was 24 percent (95 percent confidence interval, 20 to 28 percent) with hormone therapy and 36 percent (95 percent confidence interval, 32 to 40 percent) with simvastatin. The effect of simvastatin was significantly greater than that of hormone therapy ($P < 0.001$). HDL cholesterol increased similarly with hormone therapy (mean increase, 7 percent; 95 percent confidence interval, 2 to 12 percent) and simvastatin (mean increase, 7 percent; 95 percent confidence interval, 4 to 10 percent). Triglyceride levels increased with hormone therapy (mean increase, 29 percent; 95 percent confidence interval, 15 to 42 percent) but decreased with simvastatin (mean decrease, 14 percent; 95 percent confidence interval, 8 to 20 percent). Lp(a) lipoprotein decreased with hormone therapy (mean decrease, 27 percent; 95 percent confidence interval, 20 to 34 percent), but not with simvastatin.

Conclusions In postmenopausal women with hypercholesterolemia, therapy with estrogen plus progestin has beneficial effects on lipoprotein levels. Hormone therapy may be an effective alternative to treatment with simvastatin, especially in women with normal triglyceride levels. (N Engl J Med 1997; 337:595-601.)

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CORONARY heart disease is the leading cause of death among women in industrialized countries and is an important cause of morbidity in later life. Studies of cardiovascular disease in women indicate that high-density lipoprotein (HDL) cholesterol is the most powerful serum lipid predictor of the risk of coronary heart disease in women, with higher levels being strongly protective.¹⁻³ Epidemiologic and pathophysiologic studies indicate that Lp(a) lipoprotein may also be a powerful, independent predictor of the risk of cardiovascular disease.^{4,5}

Intervention studies demonstrating a significant reduction in the incidence of cardiovascular events after the lowering of elevated total and low-density lipoprotein (LDL) cholesterol levels with drugs such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors support the current guidelines for the treatment of elevated cholesterol levels in the United States.⁶⁻⁸ However, for women the value of these guidelines, which are based on LDL cholesterol levels, is less well established. Not only is LDL cholesterol a less powerful predictor of the risk of coronary heart disease in women than is HDL cholesterol,⁹ but the intervention studies have also involved only limited numbers of women.

After menopause, women's lipoprotein profile becomes more atherogenic,^{10,11} but estrogen-replacement therapy has been shown to reverse some of these adverse changes in postmenopausal women with normal serum lipid levels.^{12,13} In addition, observational studies suggest that estrogen-replacement therapy reduces the risk of coronary events in postmenopausal women by up to 50 percent,^{14,15} with the greatest benefit occurring in women with established coronary heart disease.¹⁶ Approximately 25 to 50 percent of this reduction in risk has been attributed to changes in the levels of lipoproteins; the remaining cardioprotective effect is probably multifactorial, involving direct modification of the functions of the endothelium and vascular smooth muscle.

Thus, the use of estrogen as a specific therapy for hypercholesterolemia in postmenopausal women is

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soundly based yet has been little explored. Postmenopausal women with an intact uterus are prescribed concomitant progestin for protection of the endometrium, and there has been concern that the addition of progestin might attenuate the cardioprotective effects of estrogen, especially the effects on lipoproteins.

We conducted this randomized trial, therefore, to compare the effects of a combination of a commonly used estrogen and continuous (noncyclic) progestin (postmenopausal hormone therapy) with that of an HMG-CoA reductase inhibitor, simvastatin, on serum lipids and lipoproteins, including Lp(a) lipoprotein, in postmenopausal women with hypercholesterolemia. Our goal was to clarify the role of postmenopausal hormone therapy in the treatment of hyperlipidemia.

METHODS

Subjects

Women who were postmenopausal (defined as having had more than 12 months of amenorrhea and having a serum follicle-stimulating hormone level above 20 IU per liter), who had a fasting serum total cholesterol level above 250 mg per deciliter (6.5 mmol per liter), who had had a normal mammogram within the previous 2 years and a normal cervical smear within the past year, and who had not taken postmenopausal hormone therapy or lipid-lowering medication in the 8 weeks before enrollment were eligible for the study. Women with a history of estrogen-related cancer or confirmed thromboembolic disease, a previous cerebrovascular accident, uncontrolled hypertension (blood pressure, >180/100 mm Hg), unstable coronary artery disease (i.e., a myocardial infarction or unstable angina within the three months before enrollment), genital bleeding of undiagnosed cause, an alcohol intake greater than 30 g per day, or abnormal results on tests of liver function were excluded from the study. Women who were receiving anticonvulsant or anticoagulant therapy were also excluded, but the use of diuretic agents, beta-blockers, or thyroid supplements was acceptable if the dose was expected to remain stable for the duration of the study.

This study was approved by the Human Ethics Committee of the Austin and Repatriation Medical Centre, Melbourne. Participants were recruited from the regional population through newspaper articles and radio announcements over a 16-month period. Sixty-one women met the criteria for entry and gave written informed consent.

Protocol

At enrollment, all the women were given standard National Heart Foundation of Australia dietary advice¹⁷ by a trained nurse. Although they were encouraged to continue the recommended diet for the remainder of the study, there was no formal assessment of their compliance.

The experimental design was that of a randomized crossover study. The first treatment period (weeks 1 through 8), the washout period (weeks 9 through 16), and the second treatment period (weeks 17 through 24) were each eight weeks long. At the completion of the study, all subjects had received both simvastatin and postmenopausal hormone therapy, but in random order. The dose of simvastatin (Zocor, Merck Sharp & Dohme, Whitehouse Station, N.J.) was 10 mg daily. The hormone therapy consisted of 5 mg of medroxyprogesterone acetate daily (Provera, Upjohn, Kalamazoo, Mich.) and a dose of conjugated equine estrogens (Premarin, Wyeth-Ayerst, Philadelphia) that was adjusted to minimize side effects; subjects received 0.3 mg daily for the

first week, 0.625 mg daily for the second week, and 1.25 mg daily for the remaining six weeks.

Blood was sampled after a 12-hour fast. Blood was obtained up to five weeks before enrollment to measure serum lipids and lipoproteins, follicle-stimulating hormone, urea, creatinine and electrolytes, creatine kinase, and liver function. These were considered base-line (week 0) results. Blood was then sampled at weeks 4, 8, 16, 20, and 24 to measure lipids and lipoproteins and to monitor liver function and creatine kinase levels. Height and weight were measured at week 0, and weight was measured monthly. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Measurement of Lipids and Lipoproteins

Serum total cholesterol¹⁸ and triglycerides¹⁹ were measured enzymatically (Boehringer Mannheim, Indianapolis), with polyethylene glycol precipitation for the measurement of HDL cholesterol.²⁰ The LDL cholesterol level was calculated by the Friedewald formula²¹ when the triglyceride level was less than 400 mg per deciliter (4.5 mmol per liter).

Blood collected for Lp(a) lipoprotein analysis was immediately centrifuged and the separated serum stored at or below -20°C . The blood samples from each subject were stored together and analyzed in one batch after the subject had completed the study. Apolipoprotein A was measured with a solid-phase, two-site immunoradiometric assay (Merckodia, Uppsala, Sweden), as described by Leus et al.²² The coefficients of variation within and between assays were 3.1 percent and 6.7 percent, respectively. The assay was calibrated against a highly purified, commercial Lp(a) lipoprotein preparation.

Statistical Analysis

Base-line data (week 0) were summarized as means, standard deviations, ranges, and medians in order to describe the study subjects. The data on Lp(a) lipoprotein were not normally distributed; this was rectified with a square-root transformation, but because the statistical inferences after transformation were unchanged, raw results have been reported.

Data obtained before the initial treatment and at the end of the washout period (week 0 and week 16) were tested for differences between treatment groups with a two-sample t-test. The data were analyzed by repeated-measures analysis of covariance for crossover designs; the values of each variable before each treatment phase served as the covariate; that is, the week 0 measurement was the covariate for values measured at weeks 4 and 8, and the week 16 measurement was the covariate for the values at weeks 20 and 24. The least significant difference was used to assess pairwise differences when effects were significant. All P values are two-tailed.

Simple linear regression was used to assess the significance of the relation between quantitative variables. Blomqvist's method²³ was used to assess the significance of relations between the change in a variable and its base-line value.

RESULTS

Sixty-one women were enrolled in the study and underwent an evaluation of base-line characteristics (Table 1). Three women did not continue beyond the first treatment phase and were excluded from further analysis. Fifty-four women completed the study according to the protocol, and a further four women completed at least half of the second treatment phase (up to week 20). These four women were included in the final analysis on an intention-to-treat basis. The study population therefore consisted of a total of 58 women.

The groups did not differ significantly in any var-

TABLE 1. CLINICAL AND SERUM BIOCHEMICAL CHARACTERISTICS OF THE 61 WOMEN AT BASE LINE.*

CHARACTERISTIC	VALUE
Age	
Mean	61±6
Range	50–78
Yr since menopause	
Mean	11±6
Range	1–30
Follicle-stimulating hormone (IU/liter)	
Mean	94.9±35.4
Range	33.2–191.8
Body-mass index	
Mean	26.2±4.9
Range	17.4–38.3
Total cholesterol (mg/dl)	
Mean	305±39
Range	251–437
HDL cholesterol (mg/dl)	
Mean	62±19
Range	35–104
LDL cholesterol (mg/dl)	
Mean	217±39
Range	143–325
Triglycerides (mg/dl)	
Mean	159±71
Range	62–399
Lp(a) lipoprotein (mg/dl)	
Mean	38.0±44.2
Median	21.6
Range	0.7–196.4

*Plus-minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.0113.

ables at base line or at the end of the washout period (week 0 and week 16). The effects of the two treatments over the entire study period are summarized in Table 2, and the effects during phase 1 and phase 2 are shown in Table 3.

There was a statistically significant but small reduction in body-mass index after both treatments, with a greater reduction after hormone therapy ($P=0.04$). This small change in body-mass index was not a significant covariate for the changes in lipid and lipoprotein variables ($P>0.5$).

Both hormone therapy and simvastatin caused significant reductions in total cholesterol (of 14 percent and 26 percent, respectively) and LDL cholesterol (24 percent and 36 percent, respectively), but simvastatin was more effective than hormone therapy ($P<0.001$).

Both treatments caused a significant increase (7 percent) in HDL cholesterol, with no significant difference between the two ($P=0.12$). There was a significant linear regression between the change in the HDL cholesterol level and the base-line HDL cholesterol level with hormone therapy (slope, -0.12 ; $P=0.10$), but not with simvastatin ($P=0.34$); the slopes of the regression lines for the two treatment

groups were significantly different ($P=0.05$). The two treatments differed significantly in their effect on triglyceride levels ($P<0.001$), with simvastatin reducing these levels (by 14 percent) and hormone therapy increasing them (by 29 percent).

There was a significant 27 percent reduction in Lp(a) lipoprotein levels with hormone therapy (a decrease of 11 mg per deciliter), whereas simvastatin had no significant effect. There was a significant linear regression between the percentage change in serum Lp(a) lipoprotein and the base-line LDL cholesterol level with hormone therapy (slope, 6.75; $P=0.006$).

Thirty-eight women who had either established coronary heart disease (4 women) or one or more risk factors for coronary heart disease (hypertension, diabetes, current smoking, body-mass index >29 , or a first-degree relative under the age of 60 years with coronary heart disease) in addition to hypercholesterolemia (34 women) were identified after randomization and considered to be "at risk." A subgroup analysis was performed, and the results in this subgroup were similar to those in the overall study population. In particular, both hormone therapy and simvastatin caused significant increases in the HDL cholesterol level (hormone therapy: mean increase, 8 percent; 95 percent confidence interval, 1 to 15 percent; simvastatin: mean increase, 7 percent; 95 percent confidence interval, 3 to 11 percent), with no significant difference between the treatments ($P=0.40$), and both caused significant reductions in LDL cholesterol (hormone therapy: mean decrease, 22 percent; 95 percent confidence interval, 17 to 27 percent; simvastatin: mean decrease, 39 percent; 95 percent confidence interval, 36 to 43 percent); simvastatin was more effective ($P<0.001$). Again, after hormone therapy, significant linear regressions were observed between the change in the HDL cholesterol level and the base-line HDL cholesterol level (slope, -0.435 ; $P<0.001$) and between the percentage change in the serum Lp(a) lipoprotein level and the base-line LDL cholesterol level (slope, 16.55; $P<0.001$).

Tolerance

Both treatments were well tolerated, but all four women who withdrew from the study during the second treatment phase were receiving hormone therapy. One withdrew because of intractable diarrhea (week 20), one because of lethargy and nausea (week 20), one because of unacceptable vaginal bleeding (week 22), and the fourth because of severe mastalgia and abdominal cramps (week 20). Of the 53 women who had an intact uterus, 14 had vaginal bleeding while receiving hormone therapy and 13 had vaginal bleeding after its cessation. Other commonly reported side effects of hormone therapy included mastalgia (32 women) and bloating (9).

TABLE 2. EFFECTS OF POSTMENOPAUSAL HORMONE THERAPY AND SIMVASTATIN ON BODY-MASS INDEX AND ON SERUM LIPID AND LIPOPROTEIN CONCENTRATIONS IN 58 WOMEN.*

VARIABLE AND TREATMENT GROUP	BEFORE TREATMENT	DURING TREATMENT	P VALUE†	PERCENT CHANGE	
				mean (95% CI)‡	
Body-mass index					
Hormone therapy	26.1±5.1	26.0±4.9	0.04	-0.7	(-1.3 to 0.0)
Simvastatin	26.0±4.9	25.8±4.9		-0.5	(-1.0 to 0.0)
Total cholesterol (mg/dl)					
Hormone therapy	305±41	255±32	<0.001	-14	(-16 to -11)
Simvastatin	307±43	227±33		-26	(-29 to -23)
HDL cholesterol (mg/dl)					
Hormone therapy	63±17	67±16	0.12	+7	(+2 to +12)
Simvastatin	64±17	68±17		+7	(+4 to +10)
LDL cholesterol (mg/dl)					
Hormone therapy	212±40	154±29	<0.001	-24	(-28 to -20)
Simvastatin	211±40	134±32		-36	(-40 to -32)
Triglycerides (mg/dl)					
Hormone therapy	151±60	172±59	<0.001	+29	(+15 to +42)
Simvastatin	160±75	125±48		-14	(-20 to -8)
Lp(a) lipoprotein (mg/dl)					
Hormone therapy	34.5±38.6	23.8±25.3	<0.001	-27	(-34 to -20)
Simvastatin	34.9±39.2	33.7±37.6		+1	(-6 to +8)

*Fifty-four women completed the study without protocol violations; an additional four women completed at least half of the second treatment phase. Plus-minus values are unadjusted means ±SD. Values before treatment are those measured at base line or at the end of the washout period, and values during treatment are those measured at weeks 4 and 8 or 20 and 24. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.0113.

†P values are for the difference between the treatment groups, by analysis of covariance.

‡Values show the mean of the percentage change calculated for individual subjects from the pre-treatment value to the value at the completion of each treatment phase (i.e., from week 0 to week 8 or week 16 to week 24). CI denotes confidence interval.

TABLE 3. EFFECTS OF POSTMENOPAUSAL HORMONE THERAPY AND SIMVASTATIN ON BODY-MASS INDEX AND SERUM LIPID AND LIPOPROTEIN CONCENTRATIONS DURING PHASE 1 AND PHASE 2.*

VARIABLE	HORMONE THERAPY		SIMVASTATIN		P VALUE†	
	PHASE 1	PHASE 2	PHASE 1	PHASE 2	PHASE 1	PHASE 2
Body-mass index	26.0±5.1	25.9±4.9	25.8±5.2	25.9±4.7	0.363	0.621
Total cholesterol (mg/dl)	259±36	252±31	228±28	224±38	<0.001	<0.001
HDL cholesterol (mg/dl)	65±17	69±14	65±18	70±18	0.802	0.831
LDL cholesterol (mg/dl)	161±32	147±26	137±30	131±33	0.002	0.006
Triglycerides (mg/dl)	175±60	175±61	122±49	121±45	<0.001	<0.001
Lp(a) lipoprotein (mg/dl)	24.1±29.6	24.0±22.2	33.0±45.5	34.8±30.2	0.036	0.001

*The women received the treatments in random order. Values for phase 1 were measured at weeks 4 and 8 and those for phase 2 at weeks 20 and 24. Plus-minus values are unadjusted means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.0113.

†P values are for the difference between the treatment groups, by analysis of covariance.

There were no consistently reported side effects of simvastatin. Nine women had mild and reversible elevations in serum aminotransferase levels while taking simvastatin, one woman had a significant elevation of γ -glutamyltransferase (a tripling of the baseline value) that resolved when the medication was withdrawn, and one woman had a minor and reversible elevation of creatine kinase.

DISCUSSION

This study compared the effects of hormone therapy (estrogen plus progestin) with those of conventional lipid-lowering therapy (simvastatin) in postmenopausal women with hypercholesterolemia. Our data confirm the efficacy of high-dose oral conjugated estrogens combined with continuous medroxyprogesterone acetate in lowering elevated serum total and LDL cholesterol and Lp(a) lipoprotein levels and raising HDL cholesterol levels in such women. They also demonstrate that although many of the beneficial changes in the lipoprotein profile induced by postmenopausal hormone therapy and simvastatin are similar, the two treatments differ substantially with respect to their effects on serum triglycerides and Lp(a) lipoprotein.

Because screening cholesterol values were used to determine both eligibility for this study and base-line values, regression toward the mean could have resulted in an overstatement of the effects of the two therapies on lipid levels in phase 1. However, as Table 3 shows, the treatment effects were nearly the same in phase 1 and phase 2, suggesting little regression toward the mean in phase 1. This was confirmed when the size of the regression toward the mean for the total cholesterol levels was estimated to be 4.6 mg per deciliter (0.12 mmol per liter).²⁴ Furthermore, our subjects were recruited from the population of postmenopausal women with established hypercholesterolemia, a process that would further reduce the extent of any regression toward the mean.²⁵

Few studies designed specifically to investigate the effects of postmenopausal hormone therapy on lipoprotein levels in women with hyperlipidemia have been published,²⁶⁻²⁸ and only one other study has directly compared estrogen therapy with treatment with an HMG-CoA reductase inhibitor.²⁹ Our findings are qualitatively consistent with the published data, with the exception of the study by Tonstad et al.,²⁶ in which estradiol and cyclical norethindrone acetate were administered for 48 weeks. Although all the studies reported a significant reduction in total cholesterol (by 6 to 14 percent) and LDL cholesterol (by 14 to 27 percent), only the study by Tonstad et al. did not find an increase in HDL cholesterol and triglyceride levels, which increased by 6 to 25 percent and 10 to 30 percent, respectively, in the other studies. This lack of effect probably reflects the androgenicity of norethindrone acetate, especial-

ly if serum was sampled on the days this progestogen was taken,¹³ and is consistent with the results of norethindrone acetate use in women with normal lipid levels.³⁰

All quantitative differences between our data and the results of the published studies referred to above can be explained in terms of the addition of progestin, the androgenicity of the progestin administered, the timing of blood sampling in cyclic regimens, and the dose of estrogen. In general, the greater the dose of estrogen used, the greater the reduction in total and LDL cholesterol reported.²⁶⁻²⁹ This observation is unexpected, given that studies of unopposed estrogen in women with normal lipid levels have not demonstrated any such dose-dependent relation.¹² Furthermore, in comparing the studies of women with hyperlipidemia and those with normal lipid levels, one observes that equivalent doses of estrogen elevate HDL cholesterol more in women with hyperlipidemia than in those with normal lipid levels.^{12,26-29} These observations indicate that the lipoproteins respond differently to postmenopausal hormone therapy in women with hyperlipidemia than in normal women; this difference may partly explain the greater cardioprotective effect of postmenopausal hormone therapy in women with documented coronary heart disease than in healthy women.¹⁶

Simvastatin therapy resulted in a statistically greater reduction in both serum total and LDL cholesterol than did hormone therapy in our study, but the clinical importance of this difference remains unclear. Secondary-prevention studies reporting a decreased incidence of cardiovascular events in women have not shown that reducing total or LDL cholesterol is superior to increasing HDL cholesterol, and the evidence suggesting that the HDL cholesterol level is a more powerful predictor of the risk of coronary heart disease in women than the total or LDL cholesterol level is strong.^{1,3,9,31} Therefore, interventions aimed at increasing HDL cholesterol levels may prove to be of the greatest clinical benefit to women. We found no difference between the effects of hormone therapy and those of simvastatin in elevating HDL cholesterol levels in the study group as a whole; however, the effect of hormone therapy was significantly greater in the women with the lowest HDL cholesterol levels at base line. This relation was even stronger in the subgroup of women defined as clinically "at risk."

Our study highlights the differing effects of postmenopausal hormone therapy and simvastatin on serum triglycerides. Oral estrogen is known to increase serum triglyceride levels in a dose-dependent manner,^{12,13} whereas the addition of a progestin can moderate this increase.¹³ The increase in mean triglyceride levels with hormone therapy in our study is consistent with the estrogen-dominant combination used. It is noteworthy, however, that hormone ther-

apy did not increase serum triglyceride levels in 31 percent of the women and that the mean triglyceride level with hormone therapy increased just to the limit of the normal range. However, caution should clearly be used in administering oral hormone therapy to women with preexisting hypertriglyceridemia.

The clinical importance of estrogen-induced hypertriglyceridemia with respect to coronary heart disease is somewhat controversial. Postmenopausal estrogen therapy increases triglyceride levels primarily by increasing the production of large very-low-density lipoprotein (VLDL), most of which is then cleared directly by the liver rather than being converted to small (more atherogenic) VLDL or to LDL.¹² In addition, patients with hypertriglyceridemia, in whom the incidence of heart disease is increased, tend to have low HDL cholesterol concentrations,³² whereas estrogen-induced hypertriglyceridemia is associated with a concomitant increase in HDL cholesterol. Thus, the atherogenic potential of estrogen-induced hypertriglyceridemia may be of little concern.

The precise role of Lp(a) lipoprotein in atherosclerotic vascular disease has yet to be defined, but a body of circumstantial evidence links Lp(a) lipoprotein with the pathologic processes of thrombogenesis and atherogenesis and indicates that the Lp(a) lipoprotein level may be a powerful and independent predictor of the risk of coronary heart disease.^{4,5,33} Elevated LDL cholesterol levels in combination with increased Lp(a) lipoprotein levels have been associated with a significantly increased risk of atherosclerotic vascular disease.³⁴ Our results show that hormone therapy, unlike simvastatin treatment, resulted in a marked reduction in mean Lp(a) lipoprotein levels and that the reduction was greatest in those with the highest base-line LDL cholesterol levels. The lack of effect of simvastatin on Lp(a) lipoprotein in this study is consistent with previous reports.³⁵

In the other studies of hyperlipidemia and hormone therapy, only Tonstad et al.²⁶ measured Lp(a) lipoprotein. They documented a mean reduction of 18 percent and indicated that blood sampling was evenly distributed among the three phases of the cyclic therapy. Therefore, more samples were taken during unopposed estrogen therapy. This factor could explain the relative dilution of the effect of the hormone therapy, since greater reductions have been reported with norethindrone acetate alone (47 percent) than with unopposed estrogen (14 to 20 percent) or estrogen combined with medroxyprogesterone acetate (20 to 50 percent) in women with normal lipid levels.³⁶⁻⁴⁰ The study by Soma et al. indicates that the reductions in Lp(a) lipoprotein levels induced by hormone therapy are likely to be sustained with long-term therapy.⁴⁰

The incidence of side effects was much higher

during hormone therapy than during simvastatin therapy, but they were troublesome enough to lead to withdrawal in only four women. Side effects reflected the relatively high and fixed dose of estrogen used and the short duration of the study. Notably, our data demonstrated that postmenopausal hormone therapy does not result in weight gain in the short term. The small reduction in body-mass index noted over the study period was essentially the same for both treatment groups and had no significant effect on the lipoprotein variables.

In conclusion, we have documented the beneficial effects of high-dose conjugated estrogens combined with continuous medroxyprogesterone acetate therapy on the lipoprotein profile of postmenopausal women with hyperlipidemia. We have shown that although an HMG-CoA reductase inhibitor lowered total and LDL cholesterol levels more than did hormone therapy, there was no difference between the two therapies with respect to the increase in HDL cholesterol levels. We have demonstrated the unique effects of postmenopausal hormone therapy in lowering Lp(a) lipoprotein levels and have shown that this effect, like the HDL cholesterol-elevating effect of such therapy, appears to be strongest in women at greatest risk for cardiovascular disease. There is strong epidemiologic evidence of a cardioprotective effect of estrogen in healthy postmenopausal women (risk reduction, up to 50 percent) and an even stronger effect in women with documented coronary heart disease. For this reason, and because of the other benefits of postmenopausal hormone therapy — such as the prevention of osteoporosis, urogenital aging, and possibly dementia — we believe that individualized hormone therapy is strongly indicated as pharmacotherapy for hypercholesterolemia in postmenopausal women.

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REFERENCES

1. Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA* 1986;256:2835-8.
2. Jacobs DR Jr, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol* 1990;131:32-47.
3. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med* 1993; 153:2209-16.
4. Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM Jr. Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 1986;74:758-65.
5. Cremer P, Nagel D, Labrot B, et al. Lipoprotein Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and

- other risk factors: results from the prospective Gottingen Risk Incidence and Prevalence Study (GRIPS). *Eur J Clin Invest* 1994;24:444-53.
6. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
7. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
8. The Expert Panel. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-23.
9. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study. *Am Heart J* 1987;114:413-9.
10. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med* 1989;321:641-6.
11. Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. *Matutitas* 1990;12:321-31.
12. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnkar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991;325:1196-204.
13. Lobo RA. Clinical review 27: effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. *J Clin Endocrinol Metab* 1991;73:925-30.
14. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality in noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987;75:1102-9.
15. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991;325:756-62.
16. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease: effect on survival in postmenopausal women. *Arch Intern Med* 1990;150:2557-62.
17. Shrapnel WS, Calvert GD, Nestel PJ, Truswell AS. Diet and coronary heart disease: the National Heart Foundation of Australia. *Med J Aust* 1992;156:Suppl:S9-S16.
18. Deeg R, Ziegenhorn J. Kinetic enzymic method for automated determination of total cholesterol in serum. *Clin Chem* 1983;29:1798-802.
19. Nagele U, Hagele EO, Sauer G, et al. Reagent for the enzymatic determination of serum total triglycerides with improved lipolytic efficiency. *J Clin Chem Clin Biochem* 1984;22:165-74.
20. Demacher PNM, Hijmans AGM, Vos-Janssen HE, van't Laar A, Jansen AP. A study of the use of polyethylene glycol in estimating cholesterol in high-density lipoprotein. *Clin Chem* 1980;26:1775-9.
21. 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.
22. Leus FR, Leerink CB, Prins J, van Rijn HJM. Influence of apolipoprotein(a) phenotype on lipoprotein(a) quantification: evaluation of three methods. *Clin Biochem* 1994;27:449-55.
23. Blomqvist N. On the relation between change and initial value. *J Am Stat Assoc* 1977;72:746-9.
24. Cutter GR. Some examples for teaching regression toward the mean from a sampling viewpoint. *Am Stat* 1976;30:194-7.
25. Hayes RJ. Methods for assessing whether change depends on initial value. *Stat Med* 1988;7:915-27.
26. Tonstad S, Ose L, Gørbitz C, Djøseland O, Bard JM, Fruchart JC. Efficacy of sequential hormone replacement therapy in the treatment of hypercholesterolemia among postmenopausal women. *J Intern Med* 1995;238:39-47.
27. Denke MA. Effects of continuous combined hormone-replacement therapy on lipid levels in hypercholesterolemic postmenopausal women. *Am J Med* 1995;99:29-35.
28. Granfone A, Campos H, McNamara JR, et al. Effects of estrogen replacement on plasma lipoproteins and apolipoproteins in postmenopausal, dyslipidemic women. *Metabolism* 1992;41:1193-8.
29. Davidson MH, Testolin LM, Maki KC, von Duvillard S, Drennan KB. Effects of conjugated estrogens alone and combined with pravastatin for management of hypercholesterolemia in postmenopausal women. *J Am Coll Cardiol* 1996;27:412A. abstract.
30. Farish E, Fletcher CD, Dagen MM, et al. Lipoprotein and apolipoprotein levels in postmenopausal women on continuous oestrogen/progestogen therapy. *Br J Obstet Gynaecol* 1989;96:358-64.
31. Jacobs D, Blackburn H, Higgins M, et al. Report of the Conference on Low Blood Cholesterol: mortality associations. *Circulation* 1992;86:1046-60.
32. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb* 1991;11:2-14.
33. Coleman MP, Key TJA, Wang DY, et al. A prospective study of obesity, lipids, apolipoproteins and ischaemic heart disease in women. *Atherosclerosis* 1992;92:177-85.
34. Armstrong VW, Cremer P, Eberle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis: dependence on serum LDL levels. *Atherosclerosis* 1986;62:249-57.
35. The Simvastatin Pravastatin Study Group. Comparison of the efficacy, safety and tolerability of simvastatin and pravastatin for hypercholesterolemia. *Am J Cardiol* 1993;71:1408-14.
36. Farish E, Rolton HA, Barnes JF, Hart DM. Lipoprotein(a) concentrations in postmenopausal women taking norethisterone. *BMJ* 1991;303:694.
37. Sacks FM, McPherson R, Walsh BW. Effect of postmenopausal estrogen replacement on plasma Lp(a) lipoprotein concentrations. *Arch Intern Med* 1994;154:1106-10.
38. Kim CJ, Jang HC, Cho DH, Min YK. Effects of hormone replacement therapy on lipoprotein(a) and lipids in postmenopausal women. *Arterioscler Thromb* 1994;14:275-81.
39. Mendoza S, Velazquez E, Osona A, Hamer T, Glueck CJ. Postmenopausal cyclic estrogen-progestin therapy lowers lipoprotein(a). *J Lab Clin Med* 1994;123:837-41.
40. Soma MR, Osnago-Gadda I, Paoletti R, et al. The lowering of lipoprotein(a) induced by estrogen plus progesterone replacement therapy in postmenopausal women. *Arch Intern Med* 1993;153:1462-8.