Simvastatin, Transdermal Patch, and Oral Estrogen-Progestogen Preparation in Early-Postmenopausal Hypercholesterolemic Women: A Randomized, Placebo-Controlled Clinical Trial

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Hormone replacement therapy (HRT) seems to have a favorable influence on the plasma lipid profile. Only a few investigations have examined the effects of HRT versus hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors. We compared the relative effects of different hypolipidemic strategies on lipoproteins and coagulative parameters in women with recent-onset spontaneous menopause. In this 24-week, placebo-controlled trial, 60 consecutive healthy women aged ≥ 45 years, with amenorrhea from 6 to 60 months (mean, 1.9 ± 1.4 years), serum follicle stimulating hormone (FSH) greater than 40 U/L, and slight to moderate hypercholesterolemia (low-density lipoprotein-cholesterol [LDL-C] 160 to 250 mg/dL, high-density lipoprotein-cholesterol [HDL-C] < 75 mg/dL, and triglycerides < 200 mg/dL) were enrolled and randomized to dietetic advice (placebo group), simvastatin 10 mg, 0.625 mg of conjugated equine estrogen (CEE), or 50 μg estrogen transdermal patch (ETP). In the latter 2 cases, the progestative nomegestrol was added to estrogens (days 17 to 28 of the cicle). Lipoprotein parameters were evaluated after separating very–low-density lipoproteins (VLDLs) by ultracentrifugation, while fasting glucose and insulin, homocysteine, and hemocoagulative parameters were determined in plasma. Fifty-four patients completed the trial. Total cholesterol (TC) and LDL-C significantly decrased in the simvastatin (−62 mg/dL [−20%] and −72 mg/dL [−30%], respectively), CEE (−42 mg/dL [−13%] and −45 mg/dL [−18%]), and ETP (−30 mg/dL [−10%] and −26 mg/dL [−11%]) groups compared to baseline, but only simvastatin showed an effect significantly superior to diet alone. Apolipoprotein (Apo) B was decreased by simvastatin (−25%, *P* < .001) and by CEE (−10%, *P* < .05); again, simvastatin was more effective than either diet or ETP. Triglyceride concentration and VLDL-C were unmodified by treatments. HDL-C and Apo A-I significantly increased in the simvastatin group (+18% and +8%, respectively), while HDL-C was unmodified by both HRT regimens and Apo A-I was reduced by ETP treatment (−17%); lipoprotein[a] (Lp[a]) was decreased by both HRTs (−38%, *P* < .05, and −22%, *P* = .07, for CEE and ETP, respectively). Among coagulative parameters, plasminogen activator inhibitor-1 (PAI-1) was significantly reduced by CEE (−29%, *P* < .05) but not ETP treatment (+16%, *P* = not significant), while fibrinogen, antithrombin, and homocysteine were unaffected by therapy. Thus, HRT, particularly CEE, seems well tolerated and moderately effective in improving the lipid pattern and, perhaps, the coagulative/fibrinolytic balance in postmenopausal hypercholesterolemic women; it may represent a therapeutic option in slightly dyslipidemic subjects. Statins are preferred in case of more severe disease.

CARDIOVASCULAR RISK increases progressively after menopause,[1] and coronary heart disease (CHD) represents the leading cause of death in postmenopausal women.[2] Observational investigations suggested that hormonal replacement therapy (HRT) could reduce the incidence of CHD events,[3] even if recent randomized controlled trials have cast some doubts on the issue.[4,5] These conflicting results gave rise to divergent indications: HRT has been both proposed as a first-line intervention in climacteric women (primary CHD prevention)[6] and precluded in those with established cardiovascular disease (secondary CHD prevention).[7]

HRT seems to favorably modify the lipid pattern, increasing high-density lipoprotein-cholesterol (HDL-C) and reducing low-density lipoprotein-cholesterol (LDL-C) and lipoprotein [a] (Lp[a]) plasma levels.[8,9] In addition, it may improve arterial vasomotion[10] and affect several coagulative variables or molecules known to influence thrombosis (eg, homocysteine)[11]; while some factors change in an unfavorable direction (eg, increases in factor VII), others may show an apparently favorable modification (eg, decreases in fibrinogen and plasminogen activator inhibitor-1 [PAI-1]), conditioning the reciprocal balance of coagulation and fibrinolytic pathways[12] and the risk for venous thromboembolism.[4,8] These effects depend on the type, dosage, and way of administration of the drug, but also on the utilization of either isolated estrogen (unopposed HRT) or estrogen associated with progestative agents, which, if these partly counteract some of the beneficial actions of estrogen, tend also to moderate the unfavorable hyperstimulus on endometrium and mammary gland (opposed HRT).[13] HRT may prove particularly useful in dyslipidemic women[14-16] given the unfavorable lipid concentrations that follow menopause.[17,18] However, only a few investigations have compared the effects of HRT with those of hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) inhibitors in postmenopausal hypercholesterolemic women.[19-23] They included subjects with a broad age range and in menopause for many years. These trials also lasted only a few weeks, and thus do not reflect the usual context in which HRT is proposed (perimenopause).

The current study is a 6-month, randomized trial, designed to compare the relative effects of 2 HRT strategies (transdermal and oral estrogen with a progestative agent), a statin (simvastatin), or diet alone on lipid and thrombotic cardiovascular risk parameters in dyslipidemic women with recent-onset spon-

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Table 1. Characteristics of the 54 Hypercholesterolemic Women at Baseline and After 24 Weeks of Treatment With Diet Alone, Simvastatin, ETP, or CEE

	Treatment Group			
	Diet	Simvastatin	ETP	CEE
No. of subjects	14	14	13	13
Age (yr)	53.4 ± 3.2	52.7 ± 3.9	51.7 ± 2.1	52.0 ± 2.9
Last menses (yr)	2.1 ± 1.8	1.9 ± 1.5	1.6 ± 0.9	2.1 ± 1.2
No. with hypertension	3 (21%)	2 (14%)	2 (15%)	4 (31%)
No. of smokers	3 (21%)	3 (21%)	5 (38%)	4 (31%)
FSH (IU/L)	89 ± 27	66 ± 20	77 ± 17	67 ± 21
β-Estradiol (pmol/L)				
Before treatment	25 ± 11	26 ± 20	22 ± 20	23 ± 27
On treatment (24 weeks)	18 ± 18	37 ± 50	63 ± 28*	61 ± 77
Estrone (pmol/L)				
Before treatment	29 ± 21	25 ± 14	31 ± 18	30 ± 33
On treatment (24 weeks)	19 ± 11	22 ± 11	30 ± 14	98 ± 74*
BMI (kg/m^2)				
Before treatment	25.3 ± 1.6	25.4 ± 3.3	26.6 ± 3.1	26.1 ± 4.5
On treatment (24 weeks)	25.1 ± 2.2	25.0 ± 2.7	25.8 ± 2.8	25.5 ± 4.4
SBP (mm Hg)				
Before treatment	135 ± 16	137 ± 24	128 ± 15	132 ± 13
On treatment (24 weeks)	136 ± 15	131 ± 22	125 ± 11	127 ± 17
DBP (mm Hg)				
Before treatment	85 ± 7	86 ± 10	80 ± 10	85 ± 8
On treatment (24 weeks)	83 ± 11	82 ± 14	80 ± 10	82 ± 11

NOTE. Values are mean ± SD unless otherwise indicated.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*$P < .05$ for within-group comparison (baseline *v* 24 weeks of treatment).

taneous menopause, providing a follow-up of sufficient duration.

MATERIALS AND METHODS

Patient Population and Entry Criteria

Women aged more than 45 years with absence of menses for at least 6 months but no more than 5 years and having a serum follicle-stimulating hormone (FSH) level above 40 IU/L were screened for this study. Subjects also had to be moderately hypercholesterolemic, with fasting total cholesterol (TC) greater than 240 mg/dL and LDL-C between 160 and 250 mg/dL, plasma triglycerides less than 200 mg/dL, and HDL-C less than 75 mg/dL.

Subjects who had undergone surgical oophorectomy or hysterectomy were not elegible. Other exclusion criteria were as follows: personal history of estrogen-related cancer, venous thromboembolism, or cardiovascular disease (ie, cerebrovascular accidents, unstable angina, or myocardial infarction); severe climacteric symptoms (hot flashes); hyperlipidemia secondary to systemic disease, familial hypercholesterolemia, or other severe dyslipidemia defined by LDL-C greater than 250 mg/dL; diabetes; hypertension (both uncontrolled or treated with β-blockers and diuretics); and obesity (body mass index [BMI] $>$ 30 kg/m^2). Patients who had received HRT or hypocholesterolemic agents in the past were required to suspend treatment at least 12 weeks before starting the run-in period.

All subjects gave their written informed consent; the protocol was approved by the Ethics Committee of the Ferrara University Hospital.

Study Protocol

This investigation was conducted in a parallel, randomized manner, and lasted 24 weeks. Sixty subjects initially met the enrollment criteria but only 54 completed the study. After a 4-week run-in period, in which all women underwent a clinical interview and a physical examination and were checked for plasma lipids and hematochemical safety parameters, the subjects were randomly allocated to 4 groups by telephone from an outer officer. To ensure an equal distribution of women among groups, a random number sequence was developed in blocks of 12 treatment assignments. The placebo group was given general dietetic advice according to the recommendations of the European Atherosclerosis Society,[6] while interventional groups were given both dietetic advice and simvastatin 10 mg, or 0.625 mg of conjugated equine estrogen (CEE), or 50 μg estrogen transdermal patch (ETP). In estrogen-treated cases, the progestative nomegestrol acetate was added in a cyclic pattern (days 17 to 28 of the cycle).

After randomization, patients were seen at times 8, 16, and 24 weeks. They were asked to keep a record of any deviation from the prescribed treatment, and of the occurrence of bleeding. Compliance was tested by pill and patch count. At each visit, diaries were checked, BMI calculated, blood pressure measured, and the presence of menopausal symptoms assessed.

Laboratory Investigations

Hematochemical determinations were performed at randomization and after 8, 16, and 24 weeks. Lipoprotein parameters were evaluated after a ultracentrifugation step at $d = 1.006$ g/mL, while glucose, insulin, homocysteine, and hemocoagulative parameters were determined in plasma.

Following an overnight fast of at least 12 hours, blood samples were drawn from an antecubital vein; safety biochemical parameters were checked. After centrifuging at low speed (2,000 rpm), serum was separated. Very–low-density lipoproteins (VLDLs) were then isolated by single-spin preparative ultracentrifugation (UC) at $d = 1.006$ g/dL with a Beckman T100 instrument (100,000 rpm, 4 hours at 4°C; Beckman Instruments, Fullerton, CA). TC, VLDL-C, HDL-C, and triglycerides were assayed by standard enzymatic-colorimetric meth-

ods. VLDL-C was determined in the $d < 1.006$ UC-fraction, while HDL-C in the $d > 1.006$ UC-fraction (in the latter case after selective precipitation of apo lipoprotein [Apo] B–containing lipoprotein with phosphotungstic acid in the presence of Mg^{2+}).[24] LDL-C was calculated by subtracting HDL-C to cholesterol in the $d > 1.006$ UC-fraction. Apo A-I and Apo B were determined by immunoturbidimetry, while lipoprotein[a] (Lp[a]) was evaluated using an enzyme-linked immunosorbent assay (ELISA) procedure with polyclonal anti-Apo[a] antibody. Among coagulative parameters, fibrinogen was assayed in plasma by the Clauss method,[25] antithrombin III by colorimetric assay, PAI-I by an ELISA double-antibody sandwich technique, and homocysteine by high-performance liquid chromatography (HPLC) and fluorometric detection.[26] β-estradiol and estrone determinations were performed by radioimmunoassay. Chemical analyses were determined in duplicate and the study laboratory was involved in a quality-control program.

Statistical Analysis

Systat software (Systat Inc, Evanston, IL) was used for all statistical analyses. Data are means ± SD or means and 95% confidence intervals (CI). Lipid and coagulative parameters in transdermal estrogen, oral estrogen, simvastatin, and placebo groups were compared at baseline through one-way analysis of variance (ANOVA). Repeated-measure ANOVA with 1 grouping (time) was used to compare values before and after treatment; multiple comparisons within and among treatments were adjusted according to the Bonferroni method. The distributions of Lp[a], triglyceride, and fibrinogen concentrations were skewed, with relatively more low values. Because of this, analyses were conducted on log-transformed data for the latter parameters; means and standard deviations were transformed back into their raw units for reporting. All P values are 2-tailed. Linear regression analysis was used to examine the relationships between lipoprotein or coagulative/fibrinolytic parameters and plasma estrogen concentration.

RESULTS

Sixty women were enrolled out of a population of 380 free-living subjects who attended a single Menopause Centre in the town of Ferrara, in northeastern Italy. They were middle-class, caucasian women with a mean age of 52.6 ± 3.2 years. All but 6 completed the 24-week treatment period with satisfactory compliance (> 90% of prescriptions consumed, by pill or patch count). One subject in the diet group, 1 in the simvastatin group, and 2 in the ETP group withdrew their consent from the trial; 1 subject in the CEE group moved to another town and was lost to follow-up, while an additional woman in the same group had menorrhagia and stopped her treatment; these patients were not replaced.

Table 1 shows the basal characteristics of the 4 groups; women did not differ significantly by age, BMI, blood pressure levels, or prevalence of hypertension and smoking. On average, they had been in menopause for 1.9 years, according to their last menses, and had similar FSH, β-estradiol, and estrone plasma levels. After treatment, estrone rose in the CEE group and β-estradiol levels increased in the ETP subjects (Table 1). We found a significant direct correlation between basal BMI and estrone concentration ($r = 0.352$, $P < .05$), a well-known phenomenon explained by the aromatization capacity of adipose tissue. Blood pressure slightly diminished with both statin and HRT treatment, but the effect was not statistically significant (Table 1). In the simvastatin, CEE, and ETP (but not diet) groups, TC significantly decreased compared to baseline (−62 mg/dL [−20%], −42 mg/dL [−13%], −30 mg/dL [−10%], respectively) while LDL-C was mainly responsible for the effect (simvastatin, −72 mg/dL [−30%]; CEE, −45 mg/dL [−18%]; ETP, −26 mg/dL [−11%]) and simvastatin-treatment was significantly superior to diet alone or ETP in mediating these effects ($P < .05$) (Table 2 and Fig 1).

Table 2. Plasma Lipid-Protein Variables at Baseline and Mean Change After 24 Weeks of Treatment in the Different Subgroups of Patients

Variable and Treatment Group	Before Treatment	On Treatment (24 weeks) Mean Change (95% CI)*	*P* Value†
TC (mg/dL)			
Diet	281 ± 39	+2 (−9 to +14)	
Simvastatin	297 ± 36	−62 (−92 to −32)[c]	<.05
ETP	291 ± 18	−30 (−54 to −5)[a]	
CEE	302 ± 37	−42 (−63 to −21)[b]	
LDL-C (mg/dL)			
Diet	215 ± 37	+2 (−13 to +17)	
Simvastatin	231 ± 28	−72 (−101 to −44)[c]	<.05
ETP	224 ± 24	−26 (−51 to −1)[a]	
CEE	240 ± 33	−45 (−63 to −26)[c]	
VLDL-C (mg/dL)			
Diet	7 ± 4	+3 (−1 to +6)	
Simvastatin	11 ± 8	+1 (−2 to +4)	NS
ETP	14 ± 13	−2 (−7 to +4)	
CEE	16 ± 10	−2 (−9 to +5)	
Triglycerides (mg/dL)			
Diet	104 ± 22	+26 (−1 to +50)	
Simvastatin	125 ± 56	−9 (−40 to +21)	NS
ETP	151 ± 86	−30 (−80 to +20)	
CEE	158 ± 50	−4 (−40 to +31)	
HDL-C (mg/dL)			
Diet	58 ± 16	−3 (−15 to +8)	
Simvastatin	56 ± 19	+9 (+3 to +15)[b]	NS
ETP	54 ± 21	−2 (−13 to +9)	
CEE	46 ± 12	+5 (−6 to +15)	
Apo A-I (mg/dL)			
Diet	177 ± 29	−17 (−39 to +5)	
Simvastatin	167 ± 48	+11 (−8 to +30)	<.05
ETP	172 ± 42	−30 (−46 to −14)[b]	
CEE	162 ± 28	0 (−32 to +32)	
Apo B (mg/dL)			
Diet	126 ± 24	+4 (−4 to +11)	
Simvastatin	132 ± 24	−35 (−49 to −20)[c]	<.05
ETP	127 ± 24	−5 (−14 to +5)	
CEE	149 ± 33	−17 (−31 to −4)[a]	
Lp[a] (mg/dL)			
Diet	28 ± 31	+2 (−1 to +5)	
Simvastatin	26 ± 27	+2 (−2 to +6)	.08
ETP	32 ± 38	−5 (−11 to 1)	
CEE	22 ± 22	−4 (−6 to −2)[a]	

*Mean change from pretreatment value to the completion of the study (time = 24 weeks) and 95% confidence interval. Data are significant when both lower and upper confidence limits are simultaneously negative or positive.

[a] $P < .05$,

[b] $P < .01$,

[c] $P < .001$.

†P values are for among-group comparisons, by analysis of variance.

Abbreviation: NS, not significant.

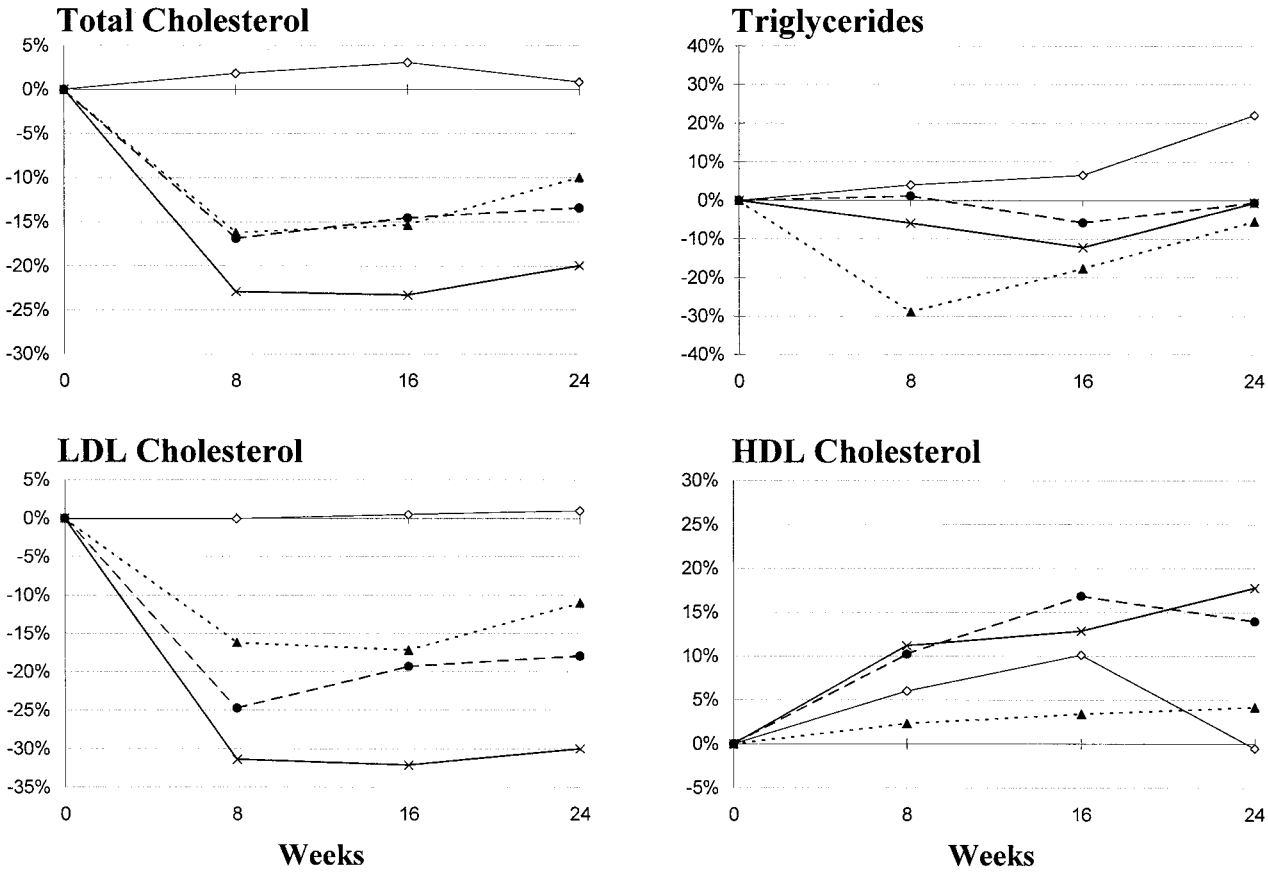

Fig 1. TC, Triglycerides, LDL-C, and HDL-C percent modification in the 4 treatment groups. (◇) Diet, (×) Simvastatin, (▲) ETP, (●) CEE.

Apo B was decreased by all drugs (marginally in the ETP group), and simvastatin was more effective than either diet or CEE therapy ($P < .05$) (Table 2 and Fig 2). Triglyceride and VLDL-C concentrations were unaffected by any treatments, while HDL-C increased in the simvastatin group (+18%, $P < .01$), nonsignificantly increased in the CEE patients, and decreased slightly in the ETP group, where apo A-I was significantly reduced (−30 mg/dL [−17%], $P < .01$) (Table 2 and Fig 2). The LDL-C/HDL-C ratio, a widely used atherogenic index, was lowered by simvastatin from the moderate- to low-risk category (4.53 ± 1.28 to 2.68 ± 0.90, −39%, $P < .001$) and to some extent also by CEE (5.55 ± 1.57 to 4.16 ± 1.27, −22%, $P < .05$), while the apo B/apo A-I ratio increased with ETP (+17%, $P < .05$) and diminished with simvastatin (−29%, $P < .001$). Lp[a] decreased both in the CEE (−38%, $P < .05$) and ETP (−22%, $P = .07$) groups.

Among coagulative parameters, PAI-1 was significantly decreased in the CEE group (−19 ng/mL [−29%]), but fibrinogen and homocysteine were unaffected by any of the treatments (Table 3 and Fig 2).

Among non–statin-treated subjects, the percentage estrone plasma increase correlated significantly with percentage LDL-C and PAI-1 decrease ($r = -0.526$, $P < .01$, and −0.394, $P < .05$, respectively), while the percentage β-estradiol modification correlated directly with changes in HDL-C percentage ($r = .508$, $P < .01$); inclusion of simvastatin-treated women in the analysis blunted the results.

DISCUSSION

This study addresses the question of cardiovascular risk modification, and particularly lipid pattern improvement, in postmenopausal women. Dyslipidemia is a frequent occurrence in climacteric women,[18] but its significance and optimum treatment are still matters of debate.

On the whole, the results of our study are in agreement with those obtained by others in unselected postmenopausal women.[14-16] HRT treatment was associated with a significant increase in estrogen plasma levels (mainly estradiol in ETP women and estrone in CEE patients, according to the predominant hormone introduced and its hepatic metabolism)[27]; correlations between lipid and hormonal parameters, even if weakened by the strong influence of statin treatment, are indicative of a graduate effect of HRT.

In our hypercholesterolemic population, TC, LDL-C, and Apo B were reduced by all treatments, but simvastatin was the most effective agent; HDL-C and Apo A-I did not increase. Also, total triglycerides and VLDL-C were unmodified by simvastatin or HRT, while Lp[a] was significantly reduced by CEE and marginally by ETP. Among the coagulative/fibrino-

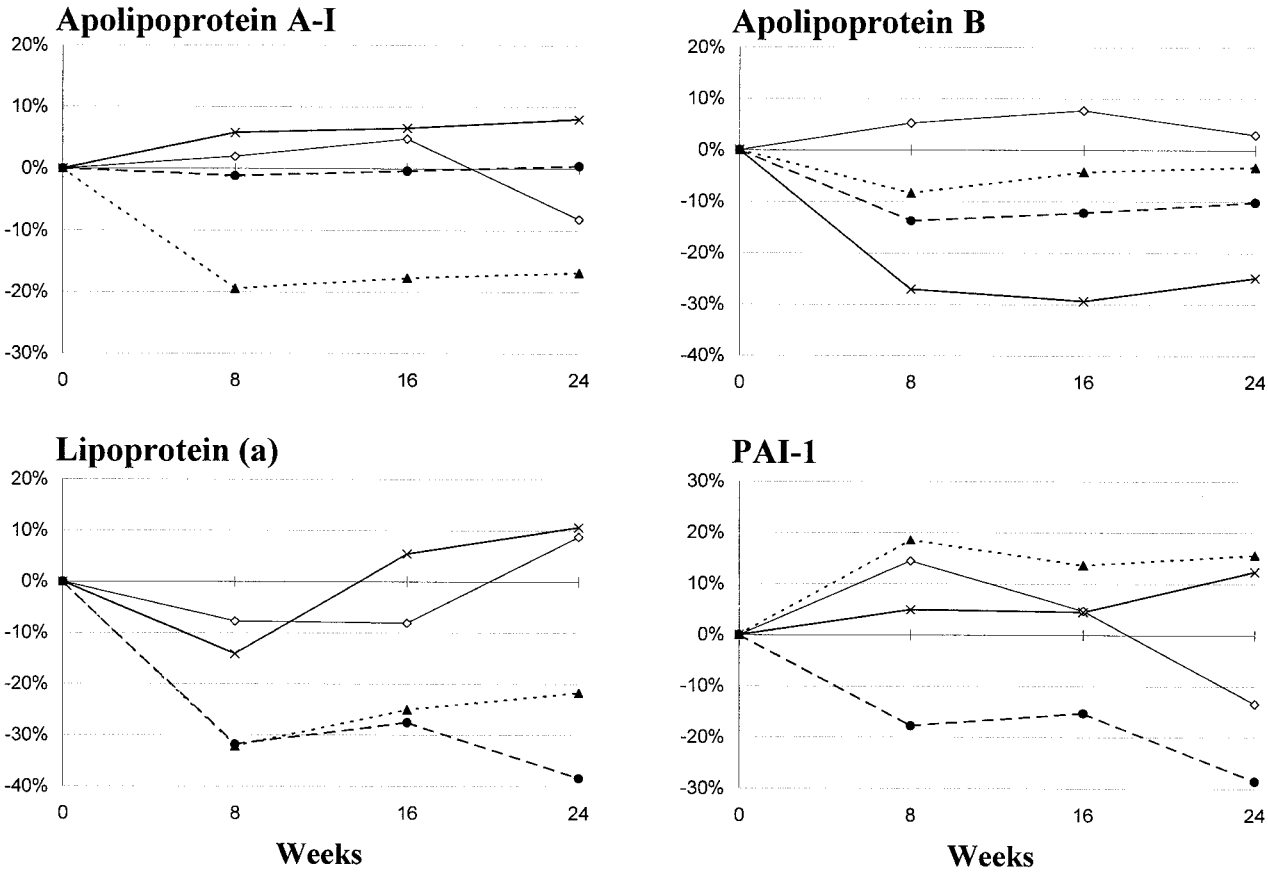

Fig 2. Apo A-I, Apo B, Lp[a], and PAI-1 percent modification in the 4 treatment groups. (◇) Diet, (×) Simvastatin, (▲) ETP, (●) CEE.

lytic and related parametrs, oral estrogen formulation decreased PAI-1, but not fibrinogen or homocysteine.

Several investigations found that estrogen replacement therapy, even if associated with progestogens (opposed HRT), may improve lipid-protein pattern. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial is particularly remarkable for number of women enrolled (687 subjects) and design (randomized, placebo-controlled); its results are evident from the sixth month to the end of the trial. They show that unopposed CEE or CEE in addition to either medroxyprogesterone acetate (both cyclic and continuous) or micronized progesterone, is associated with a significant reduction of TC (by 4% to 8%) and LDL-C (by 10% to 14%), and with a small, variable rise of HDL-C (less apparent with CEE + medroxyprogesterone acetate).[8,28] Likewise, in a subgroup of patients, Lp[a] levels were significantly reduced by estrogen treatment (with or without progestogen regimens) by 15% to 30%.[29] The women in the PEPI trial were older (mean age, 56 ± 4 years), with long-lasting menopause (1 to 10 years), and slightly overweight; one third had undergone hysterectomy. Further, dyslipidemia was not an enrollment criterium.

Our study, on the contrary, focuses on overtly dyslipidemic postmenopausal women, with recent-onset menopause (on average by 1.9 years), and compares 2 widely used HRT regimens and a hypocholesterolemic treatment based on HMG-CoA reductase inhibitors, which currently represents the standard treatment of hypercholesterolemia.[30] CEE and ETP are inexpensive, easily available, and fairly well tolerated; the metabolic actions of CEE seem to be more evident than that of ETP, due to a first-passage hepatic effect, but we maintain that avalaible data are questionable.[27,31] As part of a necessarily opposed HRT, we added nomegestrol acetate to oral or transdermal estrogen; it represents a progestogen of the latest generation, whose effect on the lipid pattern may be neutral or at least less harmful than other 19-nortestosterone congeners.[32] In general, the latter are more androgenic than 17-α-hydroxyprogesterone compounds, and may induce a decrease in HDLs and an increase in LDL plasma levels, but a high degree of heterogeneity does exist.[33] In hypercholesterolemic postmenopausal women, medroxyprogesterone acetate (MPA; a 17-α-hydroxyprogesterone derivative) in conjunction with CEE showed favorable lipid effects,[20-22] similar to normocholesterolemic women.[4,8] On the other hand, in a comparable dyslipidemic population, norethisterone (a 19-nor progestogen) sequentially combined with 17-β-estradiol also showed a beneficial effect on the lipid pattern.[16]

Only few recent studies have focused on the relative benefit of HRT versus HMG-CoA inhibitors; these investigations differ from ours with respect to a higher mean age of participants and time from last menses, grade of hypercholesterolemia, and

Table 3. Hemocoagulative Parameters and Homocysteine at Baseline and Mean Change (95% CI) After 24 Weeks of Treatment in the Different Subgroups of Patients

Variable and Treatment Group	Before Treatment	On Treatment (24 weeks) Mean Change (95% CI)*	*P* Value†
Fibrinogen (mg/dL)			
Diet	324 ± 58	+30 (−66 to +7)	
Simvastatin	339 ± 83	−16 (−49 to +17)	NS
ETP	355 ± 83	−6 (−61 to +50)	
CEE	366 ± 87	+2 (−39 to +43)	
PAI-1 (ng/mL)			
Diet	44 ± 35	−12 (−30 to +6)	
Simvastatin	35 ± 14	+1 (−11 to +13)	NS
ETP	33 ± 14	+7 (−4 to +18)	
CEE	46 ± 24	−18 (−33 to −3)[a]	
Antithrombin III (activity %)			
Diet	110 ± 8	+8 (+2 to +13)[b]	
Simvastatin	109 ± 13	+4 (−3 to +11)	NS
ETP	111 ± 10	+2 (−5 to +9)	
CEE	114 ± 11	+1 (−5 to +7)	
Homocysteine (μmol/L)			
Diet	11.2 ± 3.2	−0.1 (−1.7 to +1.6)	
Simvastatin	9.9 ± 1.7	+0.5 (−1.6 to 2.5)	NS
ETP	11.3 ± 3.8	+1.2 (−2.7 to 5.0)	
CEE	8.8 ± 3.2	+1.5 (−1.3 to 4.3)	

*Mean change from pretreatment value to the completion of the study (time = 24 weeks) and 95% confidence interval. Data are significant when both lower and upper confidence limits are simultaneously negative or positive: [a]$P < .05$, [b]$P < .01$.

†*P* values are for among-group comparisons, by analysis of variance

type and dosage of drugs; in addition, they did not include a group of estrogen-patch users. Accordingly, the results are somewhat different. Davidson et al randomized 76 nonhypocholesterolemic women (on average 60 years of age and 230 mg/dL TC) to pravastatin 20 mg/d and/or unopposed CEE 0.625 mg/d or placebo for 16 weeks[19]; LDL-C, estimated by Friedewald's formula,[34] was decreased by 13.5% in the CEE group and by 25.4% in the pravastatin group. Our results, obtained by an indirect measure of LDL-C, are more striking even in presence of opposed HRT: both CEE and ETP significantly reduced LDL-C (−18% and −11%, respectively), while simvastatin was particularly effective (−30%). In a randomized, cross-over trial, Darling et al treated 58 postmenopausal women (aged 61 ± 6 years) with opposed HRT (CEE until 1.25 mg/d + MPA) or simvastatin 10 mg/d. They observed a 24% reduction of Friedewald's calculated LDL-C (−36% with simvastatin), a slight nonsignificant increase in triglycerides and HDL-C, and a 27% reduction of Lp[a].[20] We similarly found a significant, favorable Lp[a] decrease with opposed CEE (−38%) and a borderline decrease with ETP (−22%, $P = .07$), while simvastatin had a neutral effect.

Another cross-over study by Sbarouni et al[21] analyzed the effects of CEE 0.625 mg/d plus consecutive MPA 2.5 mg/d versus simvastatin 20 mg/d or combination therapy in 16 hypercholesterolemic postmenopausal women (aged 66 ± 4 years) with documented coronary artery disease. The reduction of calculated LDL-C by HRT was 20% (−45% and −46% with simvastatin and combination treatment); HDL-C and Apo B were unaffected by hormonal treatment (the latter was reduced by 39% with simvastatin), while Apo A-I was significantly increased by 11% and Lp[a] decreased by 23%. According to our data, Apo B decreased by 25% at 6 months, while opposed CEE was associated with a 10% reduction ($P < .05$) and ETP with a nonsignificant 3% reduction compared to controls. Surprisingly, Apo A-I decreased in the ETP group of our study (−17%); this effect is probably related to the oral progestogen. In a previous investigation, we found that oral MPA and ETP determined a reduction in HDL-C[13]; in the present study, HDL-C reduction was apparent but nonsignificant, while Apo A-I reduction may indicate the presence of larger, less-dense, protein-poor buoyant HDL particles, perhaps of the HDL_2 class,[31] which has antiatherogenic properties.

In our study, we could not find any adverse effect of HRT on triglyceride-rich lipoproteins (TRLs); both total triglycerides and VLDL-C levels did not appear to change with any treatment. It is possible that estrogens facilitate the synthesis and metabolism of TRLs,[35] but progestogens may conteract these actions,[36] at least in women with normal basal triglycerides. We maintain that nomegestrol acetate suppressed VLDL synthesis, contributing to a reduction of circulating LDLs.

We must note that neither simvastatin 10 mg nor HRT could normalized LDL-C in our postmenopausal hypercholesterolemic women. If we refer to 195 mg/dL of TC concentration (or 115 mg LDL-C) as ideal treatment goals,[6] only 2 simvastatin-treated subjects (14%) and no women on HRT reached the target; on the other hand, less stringent goals of at least 240 mg/dL for TC or 160 mg/dL for LDL-C[37] were obtained by 64% of statin-treated women and by only 29% of HTP-and CEE-treated subjects.

Regarding the hemostatic/fibrinolytic balance, there are indications that the plasma levels of homocysteine, an emerging cardiovascular risk factor, increase after menopause.[38] However, it is doubtful whether HRT diminishes[11] or not[39] homocysteine concentrations, while simvastatin seems generally ineffective[40,41]; we did not notice any HRT or statin effect. A potential reduction of antithrombin III and of fibrinogen levels has been described with estrogen utilization[42]; the former may prove unfavorable and the latter beneficial to thrombotic risk. We did not find any difference in antithrombin III and fibrinogen plasma levels among women treated with HRT or simvastatin and placebo, while we confirmed a reduction in PAI-1 with CEE. High levels of PAI-1 were noted in postmenopausal women[43] and may partly account for the increased risk of atherosclerosis[44]; a reduction could be advantageous and is in agreement with other recent observations.[45] Koh et al, in a randomized study investigating vascular reactivity in slightly hypercholesterolemic postmenopausal women treated with unopposed CEE, simvastatin, and a combination of the two, described a reduction of PAI-1 level[23] similar to our findings. These authors also failed to find any effect mediated by simvastatin.

In conclusion, the recent publications of the Heart and Estrogen/Progestin Replacement (HERS) trial[4] and of the Women's Estrogen for Stroke Trial (WEST),[46] 2 secondary cardiovascular prevention studies with negative results, have cast suspicion on the possible benefit that HRT may confer in established atherosclero-

sis. A similar distrust as been raised by an angiographic study, the Estrogen Replacement and Atherosclerosis (ERA) trial,[5] which did not find regression or stabilization of established atherosclerotic coronary lesions with HRT. On the other hand, statin treatment seems beneficial in cardiovascular prevention, irrespective of sex and age.[30] The "hard" cardiovascular endpoints (total and cardiovascular mortality, acute myocardial infarction, and stroke incidence), therefore, tend to obscure the significance of the "surrogated" endpoints represented by cardiovascular risk factor, lipids above all. From a practical point of view, the aim of cardiovascular prevention in hypercholesterolemic women seems to be only scarcely met by HRT. Statin therapy should neither be neglected nor postponed because of concomitant HRT, even if a combination might be considered. It is also possible that other behavioral interventions (diet, physical exercise, etc)[47,48] may prove valuable in postmenopausal cardiovascular prevention, and contribute to better defining the utilization context and limits of HRT and/or statin treatment.

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