

The Effect of Hormone Replacement Therapy Alone and in Combination With Simvastatin on Plasma Lipids of Hypercholesterolemic Postmenopausal Women With Coronary Artery Disease

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Objectives. This study sought to compare hormone replacement therapy (HRT), simvastatin and their combination in the management of hypercholesterolemia in postmenopausal women with coronary artery disease (CAD).

Background. Lipid-lowering therapy reduces mortality in hypercholesterolemic women with CAD. In postmenopausal women HRT seems to increase survival, particularly those with ischemic heart disease, and this is partly due to changes in lipid levels.

Methods. We studied 16 postmenopausal women with CAD and fasting total cholesterol <200 mg/dl and low-density lipoprotein (LDL) cholesterol <130 mg/dl. We compared HRT (0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate daily) with simvastatin (20 mg daily) and their combination in a randomized, crossover, placebo-controlled study. Each treatment period was 8 weeks long with a 4-week washout interval between treatments.

Results. Simvastatin, HRT and their combination significantly reduced total and LDL cholesterol by 35%, 13%, and 33% and 45%, 20%, and 46%, respectively, compared to placebo ($p < 0.001$). However, simvastatin and the combination was superior to HRT ($p < 0.001$), and none of our patients had total cholesterol

<180 mg/dl and LDL cholesterol <100 mg/dl on HRT alone. High-density lipoprotein cholesterol was not significantly affected by any of the active treatments, and triglycerides were lower during simvastatin therapy compared to placebo ($p < 0.01$). Apolipoprotein B was significantly reduced by simvastatin, alone and combined with HRT, by 39% and 35%, respectively, compared to placebo ($p < 0.001$). Alone and in combination with simvastatin, HRT significantly increased apolipoprotein A-I by 11% and 12%, respectively, compared to placebo ($p < 0.05$) and decreased lipoprotein (a) by 23% and 33%, respectively, compared to placebo ($p < 0.05$), whereas simvastatin had no significant effect on either of these parameters.

Conclusions. In hypercholesterolemic postmenopausal women with CAD, HRT exerts beneficial effects on plasma lipids but the levels currently recommended for secondary prevention are not achieved. Hormone replacement therapy combined with simvastatin is well tolerated and extremely effective, as the two therapies seem to be additive.

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Hormone replacement therapy (HRT)—administration of estrogen and progestins—reduces the risk of coronary events in postmenopausal women by up to 50% (1,2) and reduces cardiovascular and total mortality (3,4); the greatest benefit seems to occur in women with known coronary artery disease (CAD) (5-7). These data, however, derive from observational studies (8-11) and mainly concern estrogen administration alone. Part of estrogen's protective effect (25% to 50%) is due to beneficial changes of plasma lipids (12). After menopause a significant increase in total cholesterol, low-density lipoproteins (LDL) and lipoprotein (a) (Lp(a)) levels occurs whereas high-density lipoproteins (HDL) falls (13-17). These unfavor-

able changes are reversed by estrogen replacement. Unopposed estrogen lowers total cholesterol, LDL and Lp(a) and raises HDL levels in postmenopausal women with normal or elevated baseline lipid levels (18-20); however, the addition of progestins, obligatory in women with an intact uterus, may attenuate or negate the beneficial effects of estrogen, and this seems to vary with the degree of androgenic activity (21-23).

Treatment of hypercholesterolemia as primary prevention has been shown to be effective for men (24) and evidence is now also emerging for women (25). In addition, the majority of prospective observational studies have reported a positive association between CAD and total plasma cholesterol and an inverse relation between CAD and HDL cholesterol in women (26). Similarly, the 4 S (27), and the CARE (28), both secondary prevention studies, have shown significant reduction in coronary events and total mortality with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor in patients of both sexes.

Women with CAD and hypercholesterolemia, even mild,

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Abbreviations and Acronyms

CAD	= coronary artery disease
CARE	= Cholesterol and Recurrent Events Trial
4 S	= Scandinavian Simvastatin Survival Study
HDL	= high-density lipoprotein
HMG-CoA	= 3-hydroxy-3-methylglutaryl coenzyme A
HRT	= hormone replacement therapy
LDL	= low-density lipoprotein
Lpa	= lipoprotein (a)
NCEP	= National Cholesterol Education Program

should be treated aggressively with a lipid-lowering agent. These women should also be considered for long-term HRT unless there is a clear contraindication. Because HRT may improve the lipid profile, it may be recommended as initial or adjunct therapy in postmenopausal women with hypercholesterolemia and CAD.

This is the first randomized, crossover, placebo-controlled study to compare simvastatin with HRT and their combination. In a recent study, simvastatin was shown to be more effective in decreasing total and LDL cholesterol compared with HRT and equally effective in increasing HDL, but HRT uniquely lowered Lp(a) in hypercholesterolemic women (29). However, the combination of the two therapies was not studied; there was no placebo control in this study and the dose of HRT was higher than that commonly prescribed. There is only one report of the combined regimen being more effective than either treatment alone, but unopposed estrogen was used in this study (30) and this is a therapeutic option of limited value as it can only be recommended in women with a previous hysterectomy. In addition, both studies included women with and without CAD, whereas we focused on women with CAD as they are more likely to gain more from both HRT and lipid-lowering therapy.

Methods

Patients. Postmenopausal women, defined as having had more than 12 months of amenorrhea, with documented CAD were prospectively screened for participation in the study. Patients receiving HRT or lipid-lowering agents entered an initial 4-week-long washout period and subsequently followed a National Cholesterol Education Program (NCEP) Step II diet for 6 weeks. Patients with fasting serum total cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl and triglycerides <500 mg/dl after 6 weeks of NCEP Step II diet were included in the study. Women with a history of breast cancer or endometrial cancer or a strong family history of estrogen-related cancer were excluded from the study as were those with previous thromboembolic disease and liver disorders. All patients had a normal mammogram and a normal cervical smear within the last year as well as normal liver and thyroid function tests. All our patients had angiographically proved significant CAD with at least one >80% diameter stenosis of an epicardial vessel and positive exercise test, and were

clinically stable. Patients with myocardial infarction or unstable angina within a period of 3 months before enrollment, with severe uncontrolled hypertension, previous stroke or on anti-coagulants were excluded from the study.

The study protocol was approved by the institutional committee on human research and a written informed consent form was obtained from all patients.

Protocol. This was a randomized, placebo-controlled, crossover study. All patients were randomly assigned to placebo, continuous combined HRT with 0.625 mg of conjugated estrogens (Premarin, Wyeth Hellas, Athens, Greece) and 2.5 mg of medroxyprogesterone acetate (Provera, Upjohn, Athens, Greece), once daily, simvastatin 20 mg (Zocor, MSD, Athens, Greece), once daily, and the combination of HRT and simvastatin, in all 24 possible orders (Latin square). Each treatment period was 8-weeks long and the washout period between them was a 4-week interval. We had to enroll 24 patients according to the study design but we terminated the study early, due to significant results, at a prescheduled interim analysis when 16 women had completed the protocol.

All our patients remained on the same antianginal-antihypertensive regimen throughout the study period and the same occurred with the thyroid supplements. Likewise, the patients were advised to continue the NCEP diet during all treatment arms.

Blood was sampled, after a 12-h fast, at the end of each of the four treatment periods.

Measurement of lipid and lipoproteins. Serum total cholesterol, triglycerides and HDL were measured by photometry (Cobas Integra Analyzer, Roche, Swiss), with MgCl₂ and dextran sulfate precipitation of the plasma for the HDL measurement. The LDL cholesterol was calculated by the Friedewald formula because the triglyceride level was less than 400 mg/dl in all our patients. Apolipoprotein B, apolipoprotein A-I and Lp(a) were measured by nephelometry (Nephelometer Analyzer 100, Behring, Germany).

Statistical analysis. Results are expressed as mean value \pm SD. Lipoprotein(a) was not normally distributed and therefore median values are also presented. The effect of each treatment—simvastatin, HRT and the combination therapy—compared to placebo is examined with the Scheffe test. The effect of each drug, alone and combined, and the interaction term between simvastatin and HRT is analyzed with repeated measures two way analysis of variance. A p value <0.05 was considered significant. We used the statistical package Statistica, Version 4.3 F (1993 edition) by StatSoft Inc (Tulsa, Oklahoma).

Results

We studied 18 women, 66 ± 4 years of age (range 58 to 72). Fifteen patients had already undergone revascularization procedures, nine had percutaneous transluminal coronary angioplasty, five had coronary artery bypass grafting and one had both; the remaining three patients were on medical therapy.

Two of our patients did not complete the protocol; one did

Table 1. Baseline Values of Serum Lipids and Lipoprotein Levels of 16 Postmenopausal, Hypercholesterolemic Women With Coronary Artery Disease

Total cholesterol	269 ± 41 (206–332)
LDL	194 ± 38 (133–267)
HDL	49 ± 11 (35–69)
Triglycerides	127 ± 36 (77–192)
Apo B	164 ± 24 (116–199)
Apo A-I	164 ± 26 (126–213)
Lp(a)	37 ± 27 [29] (12–119)

Values are expressed as mean ± SD (range). For Lp(a), median values are also presented in brackets. Results are expressed in milligrams per deciliters. Apo A-I, Apo B = apolipoproteins A-I and B; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a).

not take the combination therapy (HRT and simvastatin) because she developed severe breast tenderness while on HRT alone and the other refused to take the placebo as she presented with angioplasty restenosis during the course of the study. Both these patients were excluded from final analysis. All treatments were well tolerated. Ten patients reported mastalgia while on HRT but only one of the 17 women who had an intact uterus suffered vaginal bleeding immediately after cessation of HRT, both alone and in combination with simvastatin.

Baseline values of lipid and lipoproteins are shown in Table 1 and the effects of all four treatments are summarized in Table 2.

All three active treatments—simvastatin, HRT, and their combination—significantly reduced total cholesterol levels compared to placebo values by 35%, 13% and 33%, respectively ($p < 0.001$). However, simvastatin and its combination with HRT was more effective than HRT alone ($p < 0.001$), whereas the combination was not better than simvastatin alone. Similarly, LDL cholesterol was significantly reduced by

45%, 20% and 46%, respectively, compared to placebo ($p < 0.001$), and again simvastatin alone and in combination, proved superior to HRT ($p < 0.001$), with the combination therapy not different from simvastatin (Fig. 1). Apolipoprotein B, however, was significantly reduced by simvastatin both alone and in combination by 39% and 35%, respectively, compared to placebo ($p < 0.001$), whereas HRT alone had no significant effect; there was no difference between simvastatin and the combination regimen in apolipoprotein B levels (Fig. 2). When the overall effect of each drug, simvastatin and HRT, alone and in combination, was examined, both were found to have significant effect on total and LDL cholesterol ($p < 0.001$ and $p = 0.015$ for total cholesterol and $p < 0.001$ and $p = 0.002$ for LDL cholesterol, respectively) and the interaction term between the two drugs was also significant ($p < 0.001$ for both total and LDL cholesterol). Likewise, the interaction term between simvastatin and HRT for apolipoprotein B was significant ($p = 0.014$), but only the overall effect of simvastatin on this parameter was of statistical significance ($p < 0.001$).

None of the active treatments had any significant effect on HDL cholesterol levels compared to placebo (Fig. 1), the overall effect of each drug and their interaction term being also nonsignificant. However, apolipoprotein A-I was significantly increased by HRT alone and in combination with simvastatin by 11% and 12%, respectively, compared to placebo ($p = 0.038$ and $p = 0.028$); the combination was not superior to HRT alone (Fig. 2). The overall effect of HRT, alone and combined with apolipoprotein A-I, was significant ($p = 0.003$), whereas the simvastatin effect and their interaction term were not.

Triglyceride levels were decreased by 33% by simvastatin compared to placebo ($p = 0.009$) (Fig. 1) and the overall effect of simvastatin, alone and in combination, on triglycerides was significant ($p = 0.001$), but the HRT effect and their interaction term were not.

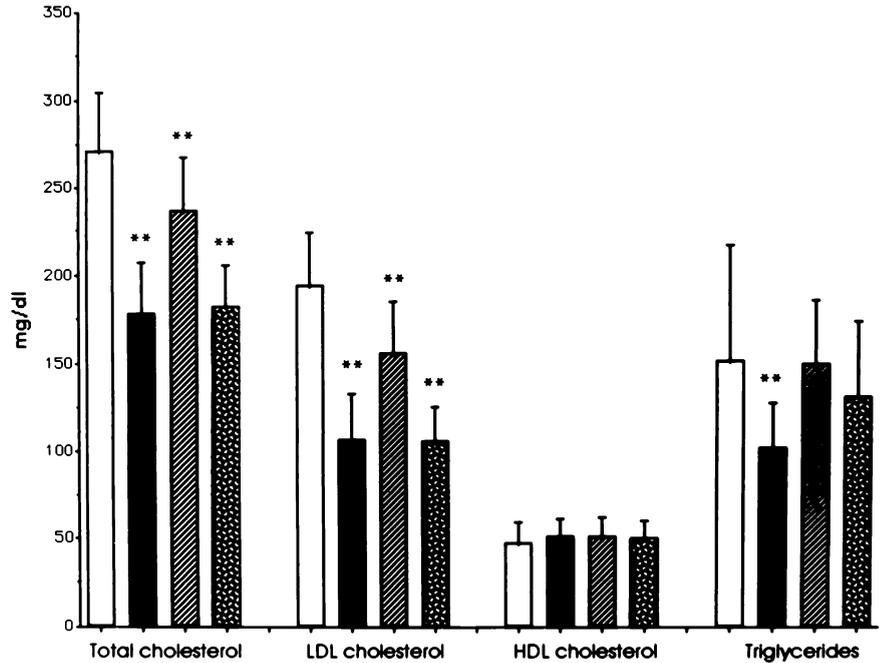
Only HRT, alone and combined with simvastatin, significantly reduced Lp(a) levels by 23% and 33% compared to placebo ($p = 0.019$ and $p = 0.001$, respectively), with simvastatin having no effect. The combination of HRT and simvastatin were not more effective in Lp(a) reduction than HRT alone (Fig. 2). The overall effect of HRT, alone and combined,

Table 2. Effects of Placebo, Simvastatin, HRT and the Combination of Simvastatin and HRT on Serum Lipids and Lipoprotein Levels of 16 Postmenopausal, Hypercholesterolemic Women With Coronary Artery Disease

	Total Cholesterol	LDL	HDL	Triglycerides	Apo B	Apo A-I	Lp(a)
Placebo	272 ± 33 (214–321)	194 ± 30 (146–240)	48 ± 11 (32–77)	151 ± 64 (72–277)	172 ± 23 (135–229)	170 ± 25 (126–210)	30 ± 21 [24] (8–24)
Simvastatin	178 ± 29** (120–242)	106 ± 26** (61–168)	51 ± 10 (36–72)	101 ± 25** (70–150)	105 ± 21** (70–151)	177 ± 21 (143–224)	31 ± 22 [23] (8–96)
HRT	237 ± 31** (185–286)	155 ± 29** (107–209)	52 ± 11 (34–73)	149 ± 36 (108–253)	160 ± 26 (114–200)	189 ± 21* (161–233)	23 ± 16* [16] (8–66)
Simvastatin/HRT	182 ± 24** (146–226)	105 ± 20** (73–149)	50 ± 10 (36–73)	130 ± 42 (62–206)	112 ± 22** (76–15)	190 ± 26* (156–258)	20 ± 16** [16] (48–74)

Values are expressed as mean ± SD (range). For Lp(a), median values are also presented in brackets. Results are expressed in milligrams per deciliter. * $p < 0.05$; ** $p < 0.01$. HRT = hormone replacement therapy; other abbreviations as in Table 1.

Figure 1. Total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels (mean \pm SD) with placebo, simvastatin, HRT and the combination of simvastatin and HRT. **p < 0.01 compared to placebo.



on Lp(a) was very significant ($p < 0.001$); however, the simvastatin effect and their interaction term were not.

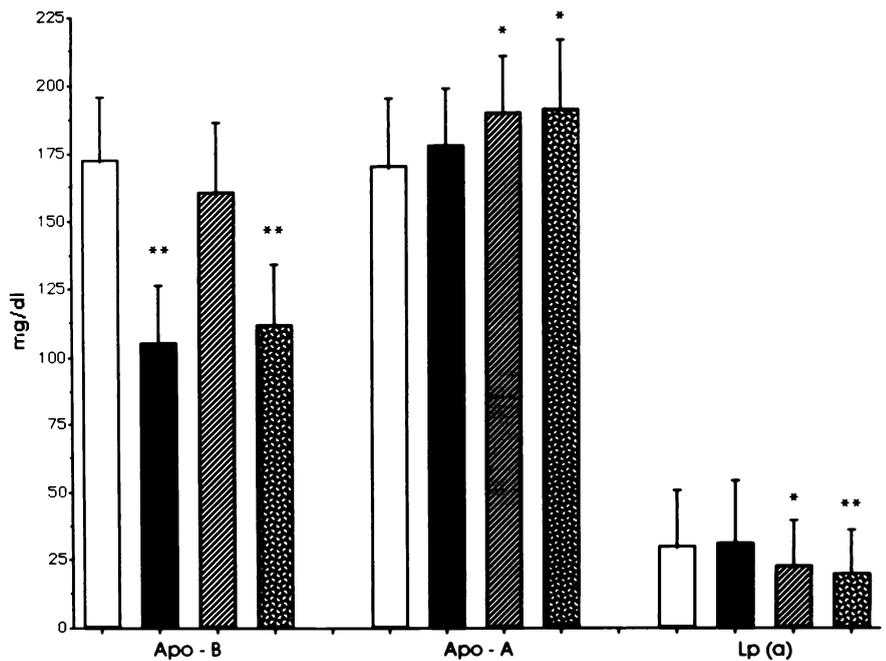
Two thirds of the patients had total cholesterol <180 mg/dl and LDL <100 mg/dl on both simvastatin and the combined therapy whereas none achieved these targets on HRT alone. All patients had triglycerides <200 mg/dl and HDL >35 mg/dl on simvastatin and the combination therapy, and all but one on HRT alone. Lipoprotein (a) <30 mg/dl was reached in 11, 12

and 15 patients with simvastatin, HRT and the combined therapy, respectively.

Discussion

This study compared the effects of HRT (conjugated estrogen plus medroxyprogesterone acetate), simvastatin and their

Figure 2. Apolipoprotein B, apolipoprotein A-I and Lp(a) levels (mean \pm SD) with placebo, simvastatin, HRT and the combination of simvastatin and HRT. *p < 0.05 and **p < 0.01 compared to placebo.



combination with placebo in postmenopausal women with hypercholesterolemia and CAD. We found that all three treatments significantly reduced total and LDL cholesterol compared to placebo. Simvastatin, however, both alone and in combination with HRT, was more effective than HRT alone. In addition, simvastatin, alone and combined, significantly decreased apolipoprotein B levels, whereas HRT failed to do so. Conversely, HRT, alone and combined with simvastatin, significantly increased apolipoprotein A-I and decreased Lp(a) levels compared to placebo, whereas simvastatin had no significant effect on either of these parameters. The HDL cholesterol level did not change significantly with any of the treatments, and triglycerides were lower in the simvastatin group compared to placebo.

Effects on lipid levels. Estrogen lowers LDL cholesterol by upregulating LDL receptors in the liver and enhancing LDL catabolism (18). We indeed found a significant decrease in total and LDL cholesterol levels with HRT, but simvastatin proved to be more powerful in total and LDL cholesterol reduction; the combination of the two treatments was not superior than simvastatin alone. None of our women had a total cholesterol <180 mg/dl and an LDL cholesterol <100 mg/dl on HRT alone. Our results are similar to previous studies (29,30). In the study by Darling et al. (29), even a lower dose of simvastatin (10 mg) was more effective than HRT in total and LDL cholesterol reduction. Likewise in the study by Davidson et al. (30), pravastatin was better than conjugated estrogen in total and LDL cholesterol reduction, and the combination of conjugated estrogen with pravastatin was shown to further decrease only the LDL/HDL ratio compared to pravastatin alone. The LDL subfractions were not measured.

Simvastatin and HRT increased HDL by 6% and 8%, respectively, but this did not reach statistical significance compared to placebo; the HDL subfractions were not evaluated. In the study by Darling et al. (29), both simvastatin and HRT increased HDL by 7%, but the significance of this is not reported. Our results are also comparable with Denke (31), who used the same HRT regimen and found a 6% increase in HDL levels after 3 months of treatment. Estrogen use is associated with elevations in HDL by up to 25% (9,18,19,30), and HDL seems to be the best predictor of coronary heart disease risk in women (32,33). Estrogen's induced rise in HDL, however, is blunted by the addition of progestins (21-23,34). In addition, there are reports of combined estrogen and progestin administration where HDL levels are unchanged (14,35,36) or have even decreased (37,38).

Hormone replacement therapy, alone and combined with simvastatin, did not increase triglycerides levels. Unopposed estrogen usually but not invariably (39,40) increases triglycerides levels, possibly in a dose-dependent manner (18), and progestins seem to attenuate this effect (22). The Framingham Offspring Study (34), however, showed no change in triglyceride levels with the combination therapy and neither did other studies assessing oral continuous combined therapy (35,38).

Effects on lipoprotein levels. We found a significant decrease in Lp(a) with HRT, both alone and combined with simvastatin. This is in agreement with previous studies (9,20,29,35,36,41). Lipoprotein(a) is a lipoprotein with structural features of LDL and plasminogen and therefore is believed to be both proatherogenic and antithrombotic. Additionally, Lp(a) concentrations appear to be relatively resistant to environmental changes, and at present there is no effective therapy available to lower high Lp(a) levels. Epidemiologic studies have demonstrated a significant correlation between increased levels of Lp(a) and the incidence of coronary disease (42). Whether Lp(a) is an independent risk factor, however, remains controversial (43), and its importance seems to decline with age, particularly in women (44).

Hormone replacement therapy, alone and in combination with simvastatin, significantly increased apolipoprotein A-I levels; similarly, previous studies (14,18,19,34) have reported that estrogen use is associated with elevations in apolipoprotein A-I by 13% to 22%, due to increased synthesis, and this effect is not abolished or attenuated by the addition of progesterone (19,34) in contrast to HDL levels that are significantly affected by progestins (34). The elevation of apolipoprotein A-I in response to HRT would be expected to favorably affect the atherogenic risk.

Apolipoprotein B was significantly reduced by simvastatin, alone and in combination, whereas HRT caused only a mild reduction in apolipoprotein B levels. Likewise, the Framingham Offspring study (34) reported a nonsignificant decrease in apolipoprotein B values in users of combined HRT versus nonusers; other studies, however, found a more pronounced decrease in apolipoprotein B levels with HRT (35,41).

Secondary prevention with statins and HRT. Lipid-lowering therapy appears to be beneficial in women with known CAD. Although data are limited, there is substantial evidence that there is a >50% reduction in CAD mortality among treated women (45). In both the 4 S (27) and the CARE (28) studies, HMG-CoA reductase inhibitor therapy was associated with equivalent or even greater risk reduction in major coronary events in women compared to men. Although the NCEP currently recommends an LDL <100 mg/dl for both men and women with CAD (46), a recent report claims that more than 90% of women in the United States are undertreated (47).

There is increasing epidemiologic evidence that postmenopausal HRT reduces total and cardiovascular morbidity (1,2) and mortality (3,4) with multiple mechanisms (48,49). A very recent analysis, using a Markov model, suggests that HRT may increase life expectancy for almost all postmenopausal women by 3 years (50). However, there is an increased relative risk of breast cancer in long-term users of HRT (51) and possibly of deep vein thrombosis and pulmonary embolism (52-54). Recently, selective estrogen-specific modulators have been shown to decrease total and LDL cholesterol and increase bone mineral density without inducing endometrial hyperplasia (55).

Limitations. The sample size is small and although our results are significant, larger cohorts need to be studied. The

length of treatment may have been inadequate, at least for HRT; this may explain our negative HDL results as well as the discordance between HDL and apo A-I effects.

Conclusions. We have shown that conjugated estrogen combined continuously with medroxyprogesterone acetate in conventional doses, although significantly decreases total and LDL cholesterol compared to placebo, fails to achieve the levels currently recommended for secondary prevention. It seems, therefore, that only a few women with mild hypercholesterolemia may adequately be treated with HRT as a single lipid-lowering therapy, an option that should not be omitted because it is cost effective and has other noncardiovascular benefits (56–58). Hormone replacement therapy significantly increases apolipoprotein A-I levels and decreases Lp(a) compared to placebo, and this is a unique effect that an HMG-CoA reductase inhibitor does not exert. The combination of HRT and simvastatin is well tolerated, is without any serious adverse reactions, at least during short-term administration, and is extremely effective in lowering LDL and Lp(a) and raising apolipoprotein A-I levels. We therefore conclude that postmenopausal women with hypercholesterolemia and CAD should, in a stepwise fashion, be treated with diet, followed by HRT, if not contraindicated, and if inadequate as monotherapy, followed by a statin alone or in combination with HRT.

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