

ORIGINAL ARTICLE

Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women

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ABSTRACT

BACKGROUND

In postmenopausal women with coronary artery disease, conjugated equine estrogen with or without continuous administration of medroxyprogesterone acetate has failed to slow the progression of atherosclerosis. Whether 17β -estradiol (the endogenous estrogen molecule) alone or administered sequentially with medroxyprogesterone acetate can slow the progression of atherosclerosis is unknown.

METHODS

We conducted a double-blind, placebo-controlled trial in 226 postmenopausal women (mean age, 63.5 years) who had at least one coronary-artery lesion. Participants were randomly assigned to usual care (control group), estrogen therapy with micronized 17β -estradiol alone (estrogen group), or 17β -estradiol plus sequentially administered medroxyprogesterone acetate (estrogen-progestin group). In all patients the low-density lipoprotein (LDL) cholesterol level was reduced to a target of less than 130 mg per deciliter. The primary outcome was the average per-participant change between baseline and follow-up coronary angiograms in the percent stenosis measured by quantitative coronary angiography.

RESULTS

After a median of 3.3 years of follow-up, the mean (\pm SE) change in the percent stenosis in the 169 participants who had a pair of matched angiograms was 1.89 ± 0.78 percentage points in the control group, 2.18 ± 0.76 in the estrogen group, and 1.24 ± 0.80 in the estrogen-progestin group ($P=0.66$ for the comparison among the three groups). The mean difference in the percent stenosis between the estrogen group and the control group was 0.29 percentage point (95 percent confidence interval, -1.88 to 2.46), and the mean difference between the estrogen-progestin group and the control group was -0.65 (95 percent confidence interval, -2.87 to 1.57).

CONCLUSIONS

In older postmenopausal women with established coronary-artery atherosclerosis, 17β -estradiol either alone or with sequentially administered medroxyprogesterone acetate had no significant effect on the progression of atherosclerosis.

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A LARGE BODY OF DATA FROM OBSERVATIONAL and mechanistic studies suggests that therapy with estrogen alone and estrogen plus sequential progestin therapy are cardioprotective.^{1,2} Only recently has the effectiveness of hormone therapy in slowing the progression of atherosclerosis begun to be studied in randomized, controlled trials.³⁻⁷ Most of these trials have used continuous, daily administration of a combination of conjugated equine estrogen and medroxyprogesterone acetate, a hormone regimen that has failed to show cardioprotection, and that may, in fact, cause an early increase in the risk of myocardial infarction.⁷⁻⁹ Such combination therapy and therapy with conjugated equine estrogen alone have also failed to slow the progression of coronary-artery atherosclerosis in postmenopausal women with established coronary artery disease.^{4,7} Many questions remain regarding the effectiveness of other estrogenic compounds, doses, regimens, and routes of administration, and it is uncertain whether 17β -estradiol (the endogenous estrogen molecule) would have effects on the progression of atherosclerosis different from those of other formulations of estrogen that have been studied.¹⁰

We present the primary results of the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), a randomized, double-blind, placebo-controlled trial that was designed to test the effects of oral micronized 17β -estradiol with or without sequentially administered medroxyprogesterone acetate on the progression of atherosclerosis in postmenopausal women with angiographically documented coronary artery disease.

METHODS

STUDY PARTICIPANTS

Women who either had or did not have a uterus were eligible for the study if they were postmenopausal (as indicated by a serum estradiol level below 20 pg per milliliter), were 75 years of age or younger, had a low-density lipoprotein (LDL) cholesterol level of 100 to 250 mg per deciliter (2.59 to 6.46 mmol per liter) and a total triglyceride level of less than 400 mg per deciliter (4.52 mmol per liter), and had at least one coronary-artery lesion occluding 30 percent or more of the luminal diameter. Women who had undergone percutaneous transluminal coronary angioplasty were eligible if they had at least 20 percent

stenosis in a segment of a coronary artery that was not crossed by the guidewire used for angioplasty. Women who had undergone coronary-artery bypass grafting were eligible if they had at least 20 percent stenosis in a segment of a coronary artery that was not proximal to a patent graft. Women were excluded if they smoked more than 15 cigarettes per day, had received a diagnosis of breast cancer or gynecologic cancer within the five years before screening, had a life-threatening disease and a projected survival of less than five years, had a diastolic blood pressure of more than 110 mm Hg, had a fasting serum glucose concentration of more than 200 mg per deciliter, had thyroid disease, had a serum creatinine level of more than 2.5 mg per deciliter (220 μ mol per liter), had congestive heart failure (Killip class III or IV and an ejection fraction below 30 percent), had more than five hot flashes per day that interfered with their daily activities, had plans to undergo a coronary-artery revascularization procedure within six months after the first screening visit, had a baseline coronary angiogram that had been obtained before or less than six months after a revascularization procedure, or had had a myocardial infarction less than six weeks before the first screening visit. All participants gave written informed consent, and the study was approved by the institutional review board at the University of Southern California.

SCREENING, RANDOMIZATION, AND TREATMENT

The study was conducted from June 1995 to October 2000. Participants were recruited from five sites. Eligible participants were randomly assigned to one of the three treatment groups, with stratification according to the presence or absence of diabetes mellitus. The data coordinating center performed the randomization with the use of a computerized random-number generator. Treatment-group assignment was carefully monitored, and adaptive randomization¹¹ was used to adjust for imbalances among the treatment groups in the total cholesterol level. The participants, gynecologists, clinical staff, and image analysts were unaware of the treatment-group assignment.

Participants randomly assigned to the estrogen group received 1 mg of oral micronized 17β -estradiol (Estrace, Mead Johnson) daily, plus a placebo tablet matching medroxyprogesterone acetate for 12 consecutive days of every month. Participants randomly assigned to the estrogen-progestin group received 1 mg of oral micronized 17β -estradiol dai-

ly, plus 5 mg of medroxyprogesterone acetate (Provera, Upjohn) daily for 12 consecutive days of every month. Participants randomly assigned to the control group received two placebo tablets, one matching the 17 β -estradiol and taken daily and the other matching the medroxyprogesterone acetate and taken for 12 consecutive days of every month. The LDL cholesterol level was reduced to a target of less than 130 mg per deciliter (3.36 mmol per liter) by means of dietary intervention (25 percent of calories from fat and 7 percent from saturated fats; less than 200 mg of dietary cholesterol per day) and lipid-lowering therapy (primarily with a hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitor).

FOLLOW-UP

Participants had follow-up visits every month for the first 6 months and every other month for the remainder of the trial (36 months). Dietary intake was monitored with the use of a three-day dietary diary (Nutrition Scientific); compliance with study medication was assessed with the use of pill counts and measurement of serum estradiol; and the use of nonstudy medications and dietary supplements was ascertained. Vital signs and clinical events were recorded at each visit. Blood samples were drawn after an eight-hour fast every six months. Electrocardiography, mammography, a Papanicolaou smear, and a pelvic examination with transvaginal ultrasonography were performed yearly. Uterine biopsy was performed if the endometrial thickness was greater than 5 mm.

ACQUISITION AND EVALUATION OF CORONARY ANGIOGRAMS

Coronary angiography was performed with the percutaneous femoral technique, and right and left anterior oblique views were obtained in order to show all lesions.¹²⁻¹⁵ Follow-up angiography was scheduled three years after the base-line angiogram was obtained and was performed according to the same protocol followed at base line. A clinically indicated coronary angiogram obtained within six months before the scheduled final angiography or before a revascularization procedure followed the same protocol used at base line and was used as the final angiogram if one was not available.

With the treatment-group assignment masked, all readable pairs of angiograms showing identical views of the coronary arteries were evaluated by an expert panel of two angiographers and a modera-

tor.¹²⁻¹⁶ The panel reached a consensus on a global change score (indicating regression, no change, or progression) that integrated the visual changes that they observed. All lesions in native arteries (excluding those proximal to grafts) and all lesions in grafts were assessed.

Quantitative coronary angiographic analyses were performed according to validated methods by a single technician who was unaware of the treatment-group assignment.^{12,13,15,17,18} Arterial segments were defined as extending from branch to branch. All lesions in native arteries (excluding those proximal to grafts) and all lesions in grafts were analyzed. The percent stenosis and the minimal luminal diameter were measured at the site of lesions identified by the panel, by the imaging analyst, or both.

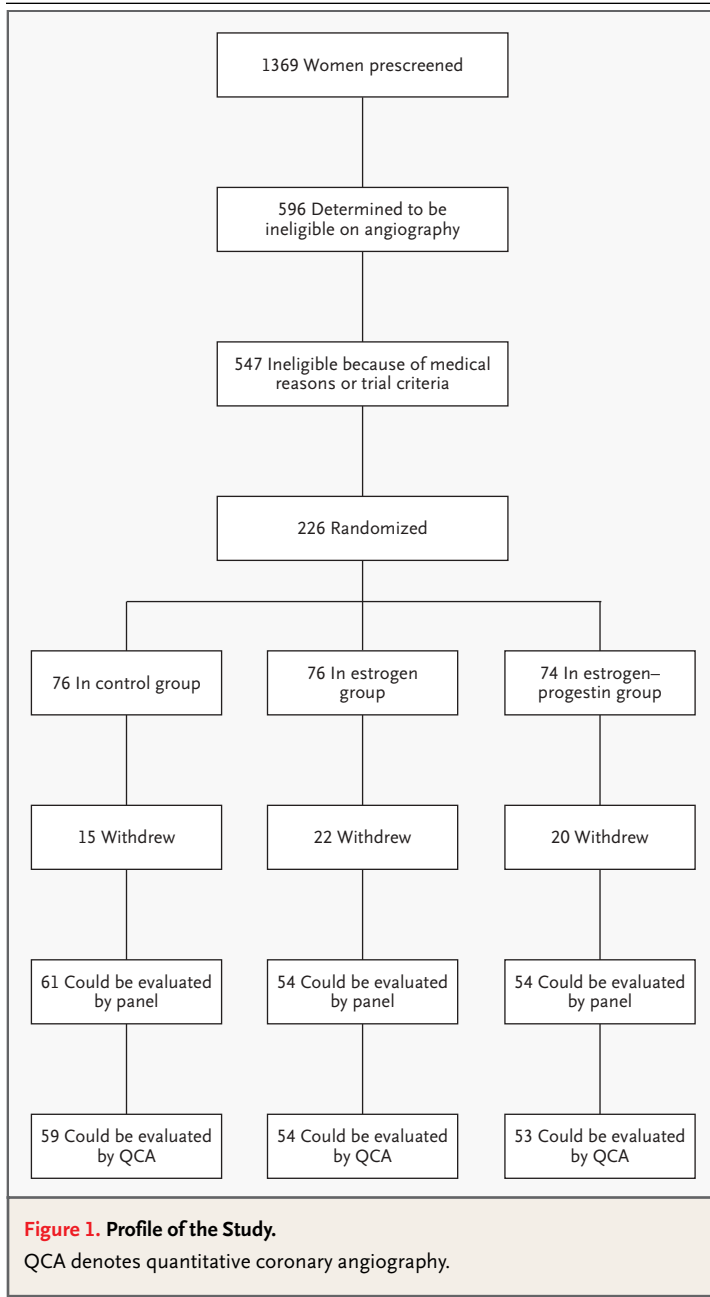
BIOCHEMICAL VARIABLES

Lipoproteins and estradiol were measured with the use of standardized enzymatic¹⁹ and radioimmunoassay³ methods, respectively.

STATISTICAL ANALYSIS

The primary end point was the average (per-participant) change from base line in the percent stenosis in all lesions evaluated by quantitative coronary angiography. According to the power calculations, a sample of 61 participants in each treatment group was required in order to detect a treatment-effect size (the mean difference between the estrogen group and the control group or between the estrogen-progestin group and the control group in the percent stenosis divided by the standard deviation of the difference) of 0.51 or greater with 80 percent power at the 0.05 level of significance (two-sided). Two secondary end points were the average (per-participant) change in minimal luminal diameter (on quantitative coronary angiography) and the global change score. Analyses of the changes in the percent stenosis and the minimal luminal diameter were specified a priori for subgroups defined according to the presence or absence of diabetes and subgroups defined according to the percent stenosis at base line (<50 percent or \geq 50 percent).

Analyses included participants with a scheduled follow-up angiogram or an early clinically indicated follow-up angiogram; participants without a follow-up angiogram were excluded. Analysis of variance and the chi-square test were used to compare the treatment groups at base line and during the study



in terms of changes in lipoprotein and estradiol levels and the incidence of adverse events. Analysis of covariance (with covariates for the presence or absence of diabetes and for variables that were unevenly distributed among the groups at base line) was used to compare the differences among the treatment groups in the percent stenosis and the minimal luminal diameter. The treatment groups

were compared in terms of the global change scores with the use of chi-square methods, with and without adjustment for diabetes status. Statistical analyses were conducted with the use of SAS software (SAS Institute), and a P value of 0.05 was considered to indicate statistical significance. No interim analyses were performed.

RESULTS

BASE-LINE CHARACTERISTICS

Of the 1369 women who were prescreened, 773 had qualifying base-line angiograms and were invited for screening (Fig. 1). Of these women, 68 (9 percent) were excluded for medical reasons, and 479 (62 percent) were excluded on the basis of other trial criteria; the remaining 226 women (29 percent, 115 [51 percent] of whom had diabetes and 111 [49 percent] of whom did not have diabetes) underwent randomization.

The mean (\pm SD) age was 63.5 ± 6.5 years (range, 48 to 75); the mean time from menopause to randomization was 18.2 years (range, 0.1 to 48.6); and approximately 70 percent of the participants were members of racial or ethnic minority groups (Table 1). Because of the imbalance among the groups in age and race or ethnic background, these variables were included as covariates in subsequent analyses.

A total of 169 participants had a follow-up angiogram that could be evaluated; of the 57 participants without a follow-up angiogram, 15 were in the control group, 22 in the estrogen group, and 20 in the estrogen-progestin group ($P=0.39$ for the comparison among the three groups). All participants with follow-up angiograms could be evaluated by the panel, but three participants (two in the control group and one in the estrogen-progestin group) could not be evaluated by quantitative coronary angiography for technical reasons. Of the 57 participants who did not have a follow-up angiogram, 13 completed the study; 8 of these participants declined a final angiogram, and 5 had a final angiogram that could not be evaluated because they had undergone coronary-artery revascularization. The remaining 44 participants (11 in the control group, 17 in the estrogen group, and 16 in the estrogen-progestin group; $P=0.38$ for the comparison among the three groups) did not complete the study and did not have a final angiogram. Reasons for noncompletion included death (in 5 participants), medical problems

(in 7), open-label use of estrogen therapy (in 4), loss to follow-up (in 5), and personal reasons (in 23). As compared with the participants with a final angiogram, the participants without a final angiogram were more likely not to be married ($P=0.05$) and tended to have a greater ratio of waist circumference to hip circumference ($P=0.03$). The two groups did not differ in terms of laboratory variables. The effect of the reduced sample size on the statistical power was nominal, decreasing the power from 80 percent to 76 percent and increasing the detectable effect size from 0.51 to 0.53 when 80 percent power was maintained.

COMPLIANCE

The mean level of compliance with study treatment was 93.6 percent with the estrogen-matching placebo and 98.4 percent with the progestin-matching placebo in the control group, 92.6 percent with estrogen and 99.9 percent with the progestin-matching placebo in the estrogen group, and 94.1 percent with estrogen and 96.1 percent with progestin in the estrogen-progestin group ($P=0.61$ for the comparison among the three groups with respect to the use of estrogen or estrogen-matching placebo; $P=0.28$ for the comparison among the three groups with respect to the use of progestin or progestin-matching placebo). At base line, there were no significant differences among the treatment groups in the serum estradiol level ($P=0.74$ for the comparison among the three groups). During follow-up, the serum estradiol levels and the changes in these levels were significantly different among the treatment groups ($P<0.001$ for the comparison among the three groups), with a significant increase from base line to follow-up in the mean serum estradiol level in the estrogen group (from 13.7 pg per milliliter to 39.5 pg per milliliter [50.3 pmol per liter to 145.0 pmol per liter], $P<0.001$) and the estrogen-progestin group (from 12.8 pg per milliliter to 43.4 pg per milliliter [47.0 pmol per liter to 159.3 pmol per liter], $P<0.001$). There was no significant change in the control group (from 13.2 pg per milliliter to 13.0 pg per milliliter [48.5 pmol per liter to 47.7 pmol per liter], $P=0.84$).

CORONARY ANGIOGRAPHIC OUTCOMES

The median duration of angiographic follow-up was 3.3 years (interquartile range, 3.1 to 3.5) and did not differ significantly among treatment groups ($P=0.91$). Table 2 presents the results of quantita-

Table 1. Base-Line Demographic and Clinical Characteristics of the 226 Participants.*

Variable	Control Group (N=76)	Estrogen Group (N=76)	Estrogen-Progestin Group (N=74)	P Value
Age — yr	64.2±6.2	61.8±6.7	64.4±6.4	0.02
Race or ethnic group — no. (%)				0.02
Non-Hispanic white	21 (28)	16 (21)	32 (43)	
Non-Hispanic black	11 (14)	17 (22)	10 (14)	
Hispanic	40 (53)	32 (42)	28 (38)	
Asian	4 (5)	11 (14)	4 (5)	
Marital status — no. (%)				0.39
Never married	5 (7)	3 (4)	7 (9)	
Married	30 (39)	40 (53)	33 (45)	
Separated, divorced, or widowed	41 (54)	33 (43)	34 (46)	
Educational level — no. (%)				0.34
≤High school	50 (66)	44 (58)	41 (55)	
>High school	26 (34)	32 (42)	33 (45)	
Smoking status — no. (%)				0.55
Current smoker	7 (9)	11 (14)	8 (11)	
Former smoker	28 (37)	27 (36)	34 (46)	
Never smoked	41 (54)	38 (50)	32 (43)	
Diabetes — no. (%)	40 (53)	38 (50)	37 (50)	0.93
Hysterectomy — no. (%)	28 (37)	39 (51)	33 (45)	0.20
Oophorectomy†	17 (61)	22 (56)	21 (64)	0.97
Time since menopause — yr	18.3±10.5	16.7±10.3	19.7±10.5	0.23
Pulse — beats/min	62.8±7.4	62.8±6.2	64.2±6.9	0.37
Blood pressure — mm Hg				
Systolic	141.6±22.4	138.1±21.7	142.3±24.6	0.49
Diastolic	75.9±10.5	76.5±11.1	75.3±12.5	0.82
Weight — lb	159.2±31.7	164.5±33.9	162.7±34.4	0.61
Waist-to-hip ratio	0.90±0.08	0.89±0.09	0.90±0.08	0.59
Body-mass index	30.0±5.4	30.6±5.6	30.2±5.6	0.83

* Plus-minus values are means ±SD. P values were derived by the chi-square test for categorical variables and by analysis of variance for continuous variables. To convert values for weight to kilograms, multiply by 0.45. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Percentages given are the percentages of the women who had had a hysterectomy.

tive coronary angiography adjusted for diabetes status, race or ethnic group, and age. The percent stenosis and the minimal luminal diameter at base line did not differ significantly among the treatment groups. The mean change in these end points among all lesions (or among lesions stratified according to severity) did not differ significantly

Table 2. Results of Quantitative Coronary Angiography in All Lesions.*

Variable	Control Group	Estrogen Group	Estrogen-Progestin Group	P Value	Mean Difference	
					Estrogen Group minus Control Group	Estrogen-Progestin Group minus Control Group
All participants						
No. of participants	59	54	53			
All lesions						
Percent stenosis						
At base line	36.62±1.15	37.66±1.11	37.10±1.18	0.79		
Change	1.89±0.78	2.18±0.76	1.24±0.80	0.66	0.29	-0.65
95% CI	0.33 to 3.45	0.66 to 3.70	-0.37 to 2.85		-1.88 to 2.46	-2.87 to 1.57
Minimal luminal diameter (mm)						
At base line	1.88±0.07	1.81±0.07	1.82±0.07	0.71		
Change	-0.13±0.04	-0.15±0.04	-0.11±0.04	0.79	-0.02	0.02
95% CI	-0.21 to -0.05	-0.23 to -0.07	-0.19 to -0.03		-0.13 to 0.09	-0.09 to 0.13
Mild-to-moderate lesions (<50% stenosis at base line)						
Percent stenosis						
At base line	31.34±0.82	32.59±0.78	32.34±0.83	0.47		
Change	3.46±0.89	3.44±0.86	2.99±0.91	0.91	-0.02	-0.47
95% CI	1.68 to 5.24	1.71 to 5.17	1.16 to 4.82		-2.48 to 2.44	-3.00 to 2.06
Minimal luminal diameter (mm)						
At base line	2.02±0.07	1.97±0.06	1.95±0.07	0.66		
Change	-0.18±0.04	-0.18±0.04	-0.16±0.04	0.93	0.00	0.02
95% CI	-0.26 to -0.10	-0.26 to -0.10	-0.24 to -0.08		-0.11 to 0.11	-0.09 to 0.13
Severe lesions (≥50% stenosis at base line)						
Percent stenosis						
At base line	59.21±1.21	59.60±1.18	60.36±1.24	0.76		
Change	-3.18±1.17	-2.34±1.13	-4.98±1.19	0.25	0.84	-1.80
95% CI	-5.52 to -0.84	-4.61 to -0.07	-7.37 to -2.59		-2.40 to 4.08	-5.11 to 1.51
Minimal luminal diameter (mm)						
At base line	1.16±0.07	1.08±0.07	1.08±0.07	0.59		
Change	0.07±0.03	0.02±0.03	0.08±0.03	0.40	-0.05	0.01
95% CI	0.01 to 0.13	-0.04 to 0.08	0.02 to 0.14		-0.14 to 0.04	-0.07 to 0.09

among the groups. The mean progression of stenosis in participants with diabetes was approximately twice as rapid as that in participants without diabetes. The angiographic end points did not differ significantly among the treatment groups, either among participants with diabetes or among those without diabetes.

Table 3 presents the results of the panel's evaluations. Most participants were categorized as having progression of coronary-artery atherosclerosis (99 of 169 participants [58.6 percent]). More partici-

pants with diabetes than participants without diabetes had progression (54 of 80 [67.5 percent] vs. 45 of 89 [50.6 percent], $P=0.03$). There were no significant differences among the treatment groups in the global change score, either overall or within subgroups stratified according to diabetes status.

LABORATORY VARIABLES

There were no significant differences among the treatment groups in the lipoprotein levels at base line (Table 4). As compared with participants in the

Table 2. (Continued.)

Variable	Control Group	Estrogen Group	Estrogen-Progestin Group	P Value	Mean Difference	
					Estrogen Group minus Control Group	Estrogen-Progestin Group minus Control Group
Participants with diabetes						
No. of participants	31	23	25			
Percent stenosis						
At base line	35.62±1.47	37.86±1.69	39.09±1.54	0.21		
Change	2.60±0.95	2.49±1.09	1.28±1.00	0.54	-0.11	-1.32
95% CI	0.66 to 4.54	0.23 to 4.75	-0.78 to 3.34		-3.02 to 2.80	-4.10 to 1.46
Minimal luminal diameter (mm)						
At base line	1.89±0.04	1.80±0.11	1.78±0.10	0.65		
Change	-0.15±0.05	-0.18±0.05	-0.14±0.05	0.85	-0.03	0.01
95% CI	-0.25 to -0.05	-0.28 to -0.08	-0.24 to -0.04		-0.18 to 0.12	-0.13 to 0.15
Participants without diabetes						
No. of participants	28	31	28			
Percent stenosis						
At base line	37.29±1.74	37.39±1.45	35.11±1.81	0.54		
Change	1.36±1.28	1.39±1.06	0.58±1.33	0.86	0.03	-0.78
95% CI	-1.27 to 3.99	-0.77 to 3.55	-2.15 to 3.31		-3.27 to 3.33	-4.48 to 2.92
Minimal luminal diameter (mm)						
At base line	1.86±0.10	1.85±0.08	1.88±0.10	0.97		
Change	-0.13±0.06	-0.09±0.05	-0.07±0.06	0.75	0.04	0.06
95% CI	-0.25 to -0.01	-0.19 to 0.01	-0.19 to 0.05		-0.12 to 0.20	-0.11 to 0.23

* Three participants could not be evaluated by quantitative coronary angiography. Plus-minus values are means ±SE. P values were derived by analysis of covariance, with diabetes status, race or ethnic group, and age as covariates. P values for the interaction between treatment group and diabetes status were as follows: P=0.15 for the comparison of percent stenosis at base line; P=0.80 for the comparison of the change in the percent stenosis; P=0.85 for the comparison of the minimal luminal diameter at base line; and P=0.68 for the comparison of the change in minimal luminal diameter. CI denotes confidence interval.

control group, participants in the estrogen and estrogen-progestin groups had significantly greater percentage increases in the high-density lipoprotein (HDL) cholesterol level and significantly greater percentage decreases in the LDL cholesterol level.

ADVERSE CLINICAL AND GYNECOLOGIC EVENTS

In total, there were nine deaths (four in the control group, two in the estrogen group, and three in the estrogen-progestin group). The causes of death included cardiovascular causes (in five participants), lung cancer (in one), sepsis (in one), cryptogenic cirrhosis (in one), and respiratory failure (in one). At least one "hard" cardiovascular event (death from

cardiovascular causes, nonfatal myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, reversible ischemic neurologic deficit, deep venous thrombosis, or pulmonary embolism) occurred in 50 of the 226 participants (16 in the control group, 16 in the estrogen group, and 18 in the estrogen-progestin group; P=0.86 for the comparison among the three groups); when revascularization was included as a cardiovascular event (a "soft" cardiovascular event), the total was 67 participants with at least one event (23 in the control group, 19 in the estrogen group, and 25 in the estrogen-progestin group; P=0.50). There was no significant difference among the groups in

Table 3. Global Change Scores.*

Global Score	Control Group	Estrogen Group	Estrogen-Progestin Group	P Value
	no./total no. (%)			
All participants				0.33†
Regression	3/61 (5)	5/54 (9)	1/54 (2)	
No change	24/61 (39)	15/54 (28)	22/54 (41)	
Progression	34/61 (56)	34/54 (63)	31/54 (57)	
Participants with diabetes				0.67
Regression	3/32 (9)	3/23 (13)	1/25 (4)	
No change	7/32 (22)	4/23 (17)	8/25 (32)	
Progression	22/32 (69)	16/23 (70)	16/25 (64)	
Participants without diabetes				0.18
Regression	0/29	2/31 (6)	0/29	
No change	17/29 (59)	11/31 (35)	14/29 (48)	
Progression	12/29 (41)	18/31 (58)	15/29 (52)	

* P values were derived by the chi-square test.

† P=0.21 with adjustment for diabetes status.

the number of cardiovascular events occurring during the first year of study treatment.

Among the 126 participants who had a uterus, the endometrial thickness was measured as 5 mm or more in a total of 28 instances in 20 participants in the control group, in 43 instances in 21 participants in the estrogen group, and in 57 instances in 27 participants in the estrogen-progestin group. Simple hyperplasia without atypia occurred in two participants in the estrogen group. Two participants in the estrogen group underwent hysterectomy during the study, one because of complex hyperplasia with atypia and one because of preexisting uterine prolapse. Breast cancer was diagnosed in one participant in the control group; uterine cancer was not diagnosed in any of the participants.

DISCUSSION

As an addition to lipid-lowering therapy, oral 17 β -estradiol alone and 17 β -estradiol with sequentially administered medroxyprogesterone acetate had no significant effect on the progression of coronary-artery atherosclerosis in older women with preexisting coronary artery disease who were studied an average of 18 years after menopause. The results of

our study are consistent with those of other trials of hormonal interventions for atherosclerosis in women with preexisting cardiovascular disease,⁴⁻⁷ as well as with those of studies examining cardiovascular events,^{8,9,20-22} of which the imaging end point that we used is highly predictive.²³ However, the results of WELL-HART are strikingly different from those of the Estrogen in the Prevention of Atherosclerosis Trial (EPAT),³ a sister study to WELL-HART that we also conducted. EPAT was a randomized, controlled trial that used protocols that were similar to those used in the current trial and that was conducted by the same personnel but that found that, relative to placebo, oral 17 β -estradiol alone slowed the progression of carotid intima-media thickness.³ Together, the two studies were designed to determine the effects of hormone therapy on the progression of atherosclerosis in postmenopausal women with preexisting cardiovascular disease (WELL-HART) and in postmenopausal women without such disease (EPAT). The divergent outcomes of the two studies may be related to the timing of the intervention relative to the stage of atherosclerosis, as reflected by the different imaging methods used. Carotid-wall thickness is a measure of early, subclinical, asymptomatic atherosclerosis, whereas coronary angiography is used to evaluate late-stage, symptomatic atherosclerosis.

Accumulating data indicate that estrogen has little effect in reversing atherosclerosis once it is established, whereas it significantly reduces the extent of atherosclerosis if therapy is initiated at an early stage.²⁴ In nonhuman primates, when the initiation of estrogen therapy is delayed for two years (equivalent to six years in humans) after oophorectomy, there is no effect on the extent of atherosclerosis.²⁵ However, when estrogen is administered immediately after oophorectomy in primates that are fed an atherogenic diet, the development of atherosclerosis is significantly reduced.²⁶⁻²⁸ Our results are consistent with those of the first set of studies in primates, in which hormone therapy was initiated many years after atherosclerosis had developed. The results of EPAT are consistent with the latter set of studies in primates, in which estradiol therapy was initiated earlier in the atherosclerotic process. The time from menopause to randomization was approximately five years shorter in EPAT than in WELL-HART.

Since the progression of atherosclerosis is silent, women may have advanced but asymptomatic vascular disease many years after menopause. Given this fact, the timing of treatment relative to meno-

pause or perimenopause may be important in slowing the progression of atherosclerosis. In humans, nondiseased coronary-artery vessels dilate in response to the administration of estrogen, whereas diseased vessels do not respond.²⁹ The lack of estrogen-receptor expression in the presence of atherosclerosis could result in a decreased ability of vascular tissue to respond to estrogen.³⁰ This lack of estrogen-receptor expression may result from methylation of the promoter region of the gene for estrogen receptor α , which occurs in aging and diseased vessels.³¹

Comparison of the current results with those of EPAT indicates that other factors such as concomitant lipid-lowering therapy may overshadow the potential beneficial effects of estrogen on the progression of atherosclerosis. Although all participants in the WELL-HART study received lipid-lowering therapy, 40 percent of the participants in EPAT did not. Subgroup analyses in EPAT indicated that 17 β -estradiol therapy alone significantly slowed the progression of atherosclerosis relative to that in the women in the placebo group who did not receive lipid-lowering therapy but had no demonstrable effect relative to that in the women in the placebo group who did receive such therapy.³ Unopposed 17 β -estradiol alone and lipid-lowering therapy alone had similar effects on the progression of atherosclerosis.³ Similar results were observed in the Asymptomatic Carotid Artery Progression Study.³² These data indicate that estrogen slows the progression of atherosclerosis but that this effect is overshadowed by the effects of lipid-lowering therapy.

The trials that have been completed to date have not adequately tested the hypothesis that estrogen is cardioprotective. Observational studies indicate that there is cardiovascular benefit in women in whom hormone therapy is initiated early after the onset of menopause for the amelioration of hot flashes.¹ EPAT has been the closest test of this pattern of hormone use, but it was not a complete test. Hot flashes are a result of vasomotor instability and may occur during a time when the vascular wall is still responsive to hormone therapy.

In contrast to previous trials using continuous, daily administration of a combination of conjugated equine estrogen and medroxyprogesterone acetate,⁷⁻⁹ our study found no increase in the rate of coronary events during the first year of hormone therapy. These results suggest that continuous, daily therapy with medroxyprogesterone acetate may

Table 4. Lipoprotein Levels at Base Line and Changes in Lipoprotein Levels.*

Variable	Control Group (N=76)	Estrogen Group (N=76)	Estrogen-Progestin Group (N=74)	P Value
Total cholesterol				
Base-line level (mg/dl)	233.0 \pm 38.9	232.9 \pm 43.6	234.1 \pm 49.8	0.98
Percent change	-10.9 \pm 12.2	-12.7 \pm 10.3	-13.2 \pm 11.3	0.44
HDL cholesterol				
Base-line level (mg/dl)	50.1 \pm 8.3	49.5 \pm 10.3	47.9 \pm 8.4	0.31
Percent change	5.7 \pm 8.5	12.0 \pm 11.3	9.4 \pm 11.6	0.002
LDL cholesterol				
Base-line level (mg/dl)	145.9 \pm 35.5	146.4 \pm 40.3	145.4 \pm 40.9	0.99
Percent change	-14.9 \pm 19.8	-22.2 \pm 14.0	-20.4 \pm 14.0	0.02
Triglycerides				
Base-line level (mg/dl)	186.7 \pm 95.3	195.4 \pm 109.1	225.0 \pm 157.6	0.14
Percent change	-6.8 \pm 26.3	-4.8 \pm 24.4	-6.7 \pm 30.4	0.89

* Plus-minus values are means \pm SD. P values are for the comparisons among the three groups and were derived by analysis of variance. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

initially have negative cardiovascular consequences. Although the statistical power to detect an early increase in the risk of cardiovascular events in our study was limited, other trials testing estradiol therapy have also not shown a significantly increased risk of coronary events during the first year of therapy.^{3,5,20-22} Participants in our study received an HMG-CoA-reductase inhibitor along with hormone therapy, and this may also account for the absence of early cardiovascular events. In subgroup analyses in the Heart and Estrogen/Progestin Replacement Study (HERS), the rate of coronary events during the first year of intervention was equivalent in the placebo and hormone-therapy groups among participants taking HMG-CoA-reductase inhibitors.³³ Estrogen therapy increases the production and activity of matrix metalloproteinases, degradative enzymes that are important in the destabilization and rupture of plaque.^{34,35} The administration of an HMG-CoA-reductase inhibitor along with estrogen may reduce the instability of plaque and the risk of plaque rupture.^{36,37}

In summary, our results are in agreement with those of previous randomized, controlled trials in elderly women with coronary artery disease studied an average of two decades after menopause. Our study also provides additional information regarding a particular estrogen compound and a particular

hormone regimen. Our results extend the previous null findings to a population predominantly composed of members of minority groups and to a population of patients with diabetes mellitus. However, comparison with EPAT indicates that estrogen therapy may be effective in slowing the progression of atherosclerosis when it is initiated early in menopause, while the vascular wall remains responsive to estrogen. The difference in outcomes between WELL-HART and EPAT warrants further investigation.

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APPENDIX

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REFERENCES

- Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis* 1995;38:199-210.
- The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208. [Erratum, *JAMA* 1995;274:1676.]
- Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-53.
- Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9.
- Angerer P, Stork S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. *Arterioscler Thromb Vasc Biol* 2001;21:262-8.
- Byington RP, Furberg CD, Herrington DM, et al. Effect of estrogen plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: HERS B-mode substudy. *Arterioscler Thromb Vasc Biol* 2002;22:1692-7.
- Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-40.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-13.
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
- Hodis HN, Mack WJ, Lobo RA. What is the cardioprotective role of hormone replacement therapy? *Curr Atheroscler Rep* 2003;5:56-66.
- Wei L-J. A class of designs for sequential clinical trials. *J Am Stat Assoc* 1977;72:382-6.
- Blankenhorn DH, Johnson RL, Nessim SA, Azen SP, Sanmarco ME, Selzer RH. The Cholesterol Lowering Atherosclerosis Study (CLAS): design, methods, and baseline results. *Control Clin Trials* 1987;8:356-87.
- Cashin-Hemphill L, Krams DM, Azen SP, et al. The Monitored Atherosclerosis Regression Study (MARS): design, methods and base-line results. *Online J Curr Clin Trials* 1992 Oct. 23;Doc. No. 26. [Erratum, *Online J Curr Clin Trials* 1992 Nov. 14;Doc. No. 29.]
- Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233-40. [Erratum, *JAMA* 1988;259:2698.]
- Blankenhorn DH, Azen SP, Krams DM, et al. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 1993;119:969-76.
- Azen SP, Cashin-Hemphill L, Pogoda J, et al. Evaluation of human panelists in assessing coronary atherosclerosis. *Arterioscler Thromb* 1991;11:385-94.
- Blankenhorn DH, Selzer RH, Mack WJ, et al. Evaluation of colestipol/niacin therapy with computer-derived coronary end point measures: a comparison of different measures of treatment effect. *Circulation* 1992;86:1701-9.
- Selzer RH, Hagerty C, Azen SP, et al. Precision and reproducibility of quantitative coronary angiography with applications to controlled clinical trials: a sampling study. *J Clin Invest* 1989;83:520-6.
- The Lipid Research Clinics Program. Manual of laboratory operations. Vol. 1. Lipid and lipoprotein analysis. Bethesda, Md.: National Heart and Lung Institute, May 1974. (DHEW publication no. (NIH) 75-628.)
- Viscoli CM, Brass LM, Kernan WN, Sarel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9.
- Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone

- replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *BJOG* 2002;109:1056-62.
22. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for the prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002;360:2001-8.
23. Azen SP, Mack WJ, Cashin-Hemphill L, et al. Progression of coronary artery disease predicts clinical coronary events: long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. *Circulation* 1996;93:34-41.
24. Rosenfeld ME, Kauser K, Martin-McNulty B, Polinsky P, Schwartz SM, Rubanyi GM. Estrogen inhibits the initiation of fatty streaks throughout the vasculature but does not inhibit intra-plaque hemorrhage and the progression of established lesions in apolipoprotein E deficient mice. *Atherosclerosis* 2002;164:251-9.
25. Williams JK, Anthony MS, Honore EK, et al. Regression of atherosclerosis in female monkeys. *Arterioscler Thromb Vasc Biol* 1995;15:827-36.
26. Clarkson TB, Anthony MS, Jerome CP. Lack of effect of raloxifene on coronary artery atherosclerosis of postmenopausal monkeys. *J Clin Endocrinol Metab* 1998;83:721-6.
27. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol* 1997;17:217-21.
28. Clarkson TB, Anthony MS, Morgan TM. Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogen and soy phytoestrogens. *J Clin Endocrinol Metab* 2001;86:41-7.
29. Campisi R, Nathan L, Pampaloni MH, et al. Noninvasive assessment of coronary microcirculatory function in postmenopausal women and effects of short-term and long-term estrogen administration. *Circulation* 2002;105:425-30.
30. Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. *Circulation* 1994;89:1501-10.
31. Post WS, Goldschmidt-Clermont PJ, Wilhide CC, et al. Methylation of the estrogen receptor gene is associated with aging and atherosclerosis in the cardiovascular system. *Cardiovasc Res* 1999;43:985-91.
32. Espeland MA, Applegate WB, Furberg CD, Lefkowitz DS, Rice L, Hunninghake D. Estrogen replacement therapy and progression of intimal-medial thickness in the carotid arteries of postmenopausal women. *Am J Epidemiol* 1995;142:1011-9.
33. Herrington DM, Vittinghoff E, Lin F, et al. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 2002;105:2962-7.
34. Zanger D, Yang BK, Ardans J, et al. Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. *J Am Coll Cardiol* 2000;36:1797-802.
35. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circ Res* 2002;90:251-62.
36. Luan Z, Chase AJ, Newby AC. Statins inhibit secretion of metalloproteinases-1, -2, -3, and -9 from vascular smooth muscle cells and macrophages. *Arterioscler Thromb Vasc Biol* 2003;23:769-75.
37. Son JW, Koh KK, Ahn JY, et al. Effects of statin on plaque stability and thrombogenicity in hypercholesterolemic patients with coronary artery disease. *Int J Cardiol* 2003;88:77-82.

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