

The New England Journal of Medicine

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VOLUME 343

AUGUST 24, 2000

NUMBER 8



EFFECTS OF ESTROGEN REPLACEMENT ON THE PROGRESSION OF CORONARY-ARTERY ATHEROSCLEROSIS

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ABSTRACT

Background Heart disease is a major cause of illness and death in women. To understand better the role of estrogen in the treatment and prevention of heart disease, more information is needed about its effects on coronary atherosclerosis and the extent to which concomitant progestin therapy may modify these effects.

Methods We randomly assigned a total of 309 women with angiographically verified coronary disease to receive 0.625 mg of conjugated estrogen per day, 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate per day, or placebo. The women were followed for a mean (\pm SD) of 3.2 ± 0.6 years. Base-line and follow-up coronary angiograms were analyzed by quantitative methods.

Results Estrogen and estrogen plus medroxyprogesterone acetate produced significant reductions in low-density lipoprotein cholesterol levels (9.4 percent and 16.5 percent, respectively) and significant increases in high-density lipoprotein cholesterol levels (18.8 percent and 14.2 percent, respectively); however, neither treatment altered the progression of coronary atherosclerosis. After adjustment for measurements at base line, the mean (\pm SE) minimal coronary-artery diameters at follow-up were 1.87 ± 0.02 mm, 1.84 ± 0.02 mm, and 1.87 ± 0.02 mm in women assigned to estrogen, estrogen plus medroxyprogesterone acetate, and placebo, respectively. The differences between the values for the two active-treatment groups and the value for the placebo group were not significant. Analyses of several secondary angiographic outcomes and subgroups of women produced similar results. The rates of clinical cardiovascular events were also similar among the treatment groups.

Conclusions Neither estrogen alone nor estrogen plus medroxyprogesterone acetate affected the progression of coronary atherosclerosis in women with established disease. These results suggest that such women should not use estrogen replacement with an expectation of cardiovascular benefit. (N Engl J Med 2000;343:522-9.)

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POSTMENOPAUSAL estrogen replacement has been recommended for the secondary prevention of heart disease in women¹⁻³ on the basis of abundant observational data showing that women who received postmenopausal hormone-replacement therapy had fewer cardiovascular events than those who did not^{4,5} and numerous clinical and laboratory studies demonstrating favorable effects of estrogen on cardiovascular risk factors and experimental atherosclerosis.^{6,7} Thus, it was a surprise when the Heart and Estrogen/Progestin Replacement Study found no overall effect of 4.1 years of treatment with conjugated estrogen plus medroxyprogesterone acetate on the risk of nonfatal myocardial infarction and death from coronary heart disease among women with established coronary atherosclerosis.⁸ These results were complicated by an early increase and a late reduction in risk within the overall null effect.

Several hypotheses have been proposed to explain these results. Some have argued that a single, relatively short clinical trial may not reliably predict long-term benefit, especially when so much a priori evidence suggests that estrogen should be beneficial.^{9,10} Others have wondered whether the favorable effects of estrogen are attenuated by medroxyprogesterone acetate.¹¹ Finally, real benefits of estrogen may have been offset by previously unrecognized or underem-

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phasized prothrombotic or proinflammatory effects — possibly limited to a subgroup of women.¹² Such questions have made it difficult for women and their physicians to know how to respond to these results. To clarify the role of estrogen in the secondary prevention of heart disease, more information is needed about its effects on the underlying disease process — coronary atherosclerosis — and the extent to which medroxyprogesterone acetate may modify the effects of estrogen.

The Estrogen Replacement and Atherosclerosis trial is a randomized, double-blind, placebo-controlled clinical trial that has examined the effects of hormone-replacement therapy on the progression of coronary atherosclerosis in women. A total of 309 postmenopausal women who had angiographically verified coronary artery disease at base line were randomly assigned to receive unopposed estrogen, estrogen plus medroxyprogesterone acetate, or placebo and were scheduled for coronary angiography about three years after randomization. In this report we describe the effects of treatment on the progression of coronary atherosclerosis as measured by quantitative coronary angiography.

METHODS

Subjects

The study design was approved by institutional review boards at the participating sites and has been described in detail elsewhere.¹³ Between January 1995 and December 1996, women were recruited at one of six clinical sites (see the Appendix). Women were eligible if they were postmenopausal, were not currently receiving estrogen-replacement treatment, and had one or more epicardial coronary stenoses of at least 30 percent of the luminal diameter, as measured by quantitative coronary angiography. Postmenopausal status was defined as the presence of one of the following conditions: an age of at least 55 years without natural menses for at least five years; no natural menses for at least one year and a serum follicle-stimulating hormone level of more than 40 IU per liter; documented bilateral oophorectomy; or self-reported bilateral oophorectomy, a follicle-stimulating hormone level of more than 40 IU per liter, and a serum estradiol level of less than 25 pg per milliliter (91.8 pmol per liter). The 28 women who were taking replacement estrogen at the screening visit were asked to stop for three months before being assigned to treatment.

Women were excluded if they had known or suspected breast or endometrial carcinoma, previous or planned coronary-artery bypass surgery, a history of deep-vein thrombosis or pulmonary embolism, symptomatic gallstones, a serum aspartate aminotransferase level more than 1.5 times the normal value, a triglyceride level of more than 400 mg per deciliter (4.52 mmol per liter) while fasting, a serum creatinine level of more than 2.0 mg per deciliter (176.8 μ mol per liter), more than 70 percent stenosis of the left main coronary artery, uncontrolled hypertension, or uncontrolled diabetes. Of the 815 women screened, 309 (38 percent) were subsequently enrolled. In 150 of the 309 women (49 percent), the base-line angiogram was obtained for clinical evaluation of ischemic heart disease. In the others, base-line research angiography was performed to establish eligibility.

Treatment

After their informed consent had been obtained, the 309 eligible women were randomly assigned to three groups by a per-

mutated-block randomization procedure after stratification according to their use of lipid-lowering therapy and the clinical site. Each woman received two tablets daily. The women in the estrogen group received one tablet containing 0.625 mg of conjugated equine estrogen (Premarin, Wyeth–Ayerst Research, Radnor, Pa.) and a placebo tablet. Those in the estrogen-plus-medroxyprogesterone group received a tablet containing 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth–Ayerst) and a placebo tablet. Those in the placebo group received two placebo tablets.

Follow-up

The participants were followed up in the clinic every six months and were contacted by telephone at three-month intervals between clinic visits. During each visit, compliance with study medication was assessed by pill count, and an interval medical history was taken. For any suspected cardiovascular event, the admission and discharge notes, electrocardiograms, cardiac-enzyme values, and data from cardiovascular testing and procedures were abstracted and sent to an independent end-point adjudicator who was unaware of the women's treatment assignments. The classification strategy was based on that used in the Heart and Estrogen/Progestin Replacement Study.^{13,14}

At base line and annually thereafter, all the women underwent screening mammography and gynecologic examinations, including Papanicolaou smears and endometrial aspiration or vaginal ultrasound examination to detect subclinical hyperplasia. All gynecologic examinations, data collection, and management of gynecologic adverse events were performed by staff and physicians other than those responsible for the collection of data on cardiovascular end points.

Angiographic data obtained at base line and a mean (\pm SD) of 3.2 ± 0.6 years later were available for 248 of the 309 subjects (80 percent). Twelve women (4 percent) died before undergoing follow-up angiography, and 44 (14 percent) dropped out or refused follow-up angiography; the base-line or follow-up films of 5 women (2 percent) were lost. Among the women for whom angiographic follow-up data were available, those assigned to unopposed estrogen took 74 percent of their prescribed study medication, as compared with 84 percent in the women assigned to estrogen plus medroxyprogesterone acetate and 86 percent in those assigned to placebo ($P=0.03$). Five women assigned to placebo stopped taking the study drug and began taking open-label estrogen during the trial.

Angiographic Evaluation

Base-line and follow-up coronary angiography was performed in identical standardized fashion after the administration of 0.4 mg of sublingual nitroglycerin (unless contraindicated by hypotension). A minimum of three sets of orthogonal views of the left coronary artery and one of the right coronary artery were obtained at base line and repeated exactly at follow-up. Clinically indicated coronary angiograms obtained within six months of the final angiogram required by the study protocol were treated as final angiograms to avoid the need to ask these women to undergo further angiography. For women who underwent percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting during follow-up (59 women [19 percent]), the angiogram obtained before the intervention was also analyzed. In 11 women (4 percent of the 309 women enrolled in the study), a clinically indicated interim angiogram without a subsequent invasive procedure was the only angiographic follow-up available.

Review and analysis of the paired films were performed with a previously validated system of cine projectors (SME-3500, Sony, Park Ridge, N.J.) and software (QCAPlus, Sanders Data Systems, Palo Alto, Calif.).^{15,16} With this system, the mean intraoperator difference between blinded duplicate measurements of minimal diameter for vessels with lesions is 0.02 mm.¹⁶ The reference, minimal, and average luminal diameters, as well as the degree of stenosis as a percentage of the reference diameter, were obtained

for 10 proximal and up to 11 optional epicardial coronary segments, as explained in detail previously.¹³ If a lesion was evident on either film, the analysis was directed to that portion of the segment. In segments with no obvious lesions, as much as possible of the proximal portion of the segment in question was analyzed. In 84 subjects, one or more segments could not be analyzed at base line or follow-up because of total occlusion or intervening coronary-artery bypass graft surgery. The analyses were performed by operators who were unaware of the women's treatment assignments and the temporal sequence of the films.

Statistical Analysis

The primary outcome was prespecified as the mean minimal coronary-artery diameter within each subject at follow-up, analyzed on an intention-to-treat basis.¹³ A mixed-model analysis of covariance was fitted, with adjustment for angiographic measurement at base line, location of the segment in the coronary tree, length of follow-up, the specific clinic, use of lipid-lowering therapy at base line, and a random subject effect. The analysis did not assume that variation in disease progression was the same across all locations in the coronary tree and allowed for correlation in responses of the segment within a given subject. Although the individual coronary segment was the unit of measurement, group comparisons were based on effects in the subjects, since the subject was the unit of randomization. Sensitivity analyses were performed to assess the effect of including subjects with clinically indicated follow-up angiography, segments measured before coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty, and segments that were unavailable for analysis because of new total occlusions that occurred during follow-up.

Other angiographic outcomes included stenosis as a percentage of the reference diameter and the development of new lesions in a patient, defined as the presence of one or more segments with less than 15 percent stenosis at base line and an increase of 15 percentage points or more at follow-up. Models focusing on change in diameter were also examined. The study was designed to have 80 percent power to detect a difference of 0.054 mm in the degree of change in minimal luminal diameter from base line to follow-up between the active-treatment groups and the placebo group. All tests of hypotheses and reported P values are two-sided.

RESULTS

Base-Line Characteristics

The base-line characteristics of the study population are summarized in Table 1. The mean age was 65.8 years (range, 41.8 to 79.9). More women in the group receiving unopposed estrogen reported using nitrates at base line ($P=0.01$); however, this difference was not statistically significant among the 248 women included in the angiographic analysis. There were no other significant differences among the three treatment groups, with or without the inclusion of women for whom angiographic data were not available.

Effects on Lipids

Among the 248 women for whom angiographic follow-up data were available, those assigned to unopposed estrogen and those assigned to estrogen plus medroxyprogesterone acetate had reductions in plasma levels of low-density lipoprotein cholesterol of 9.4 ± 20.9 percent and 16.5 ± 21.8 percent, respectively, as compared with 1.3 ± 21.5 percent in the placebo group ($P=0.02$ for the comparison of estrogen with placebo, and $P<0.001$ for the comparison of estrogen plus

medroxyprogesterone acetate with placebo). Similarly, women in both treatment groups had significantly greater increases in plasma levels of high-density lipoprotein cholesterol (18.8 ± 20.8 percent and 14.2 ± 17.1 percent, respectively) than women taking placebo (6.8 ± 15.6 percent; $P<0.01$ for both comparisons). Women in both treatment groups also had increased triglyceride levels (by 6.1 ± 34.1 percent and 10.1 ± 36.0 percent, respectively); however, these increases were not significantly different from that in the placebo group (2.2 ± 39.0 percent, $P>0.10$ for both comparisons).

Effects on Angiographic Outcomes

The primary analysis included data on 2317 proximal coronary segments in the 248 women with angiographic follow-up (a mean of 9.3 segments per subject). After adjustment for base-line minimal diameter and other prespecified covariates, the within-subject mean minimal coronary-artery diameters at follow-up were not significantly different between the active-treatment groups and the placebo group (Table 2). Among women who took at least 80 percent of their study medication, the results were the same. Parallel analyses with the percentage of stenosis as the outcome of interest also yielded similar results. Expressing the data in terms of the change in mean minimal diameter from base line to follow-up (after adjustment for the covariates in the primary analysis) also revealed no significant differences among groups. One or more new lesions developed in 30 percent of the patients taking estrogen and 20 percent of those receiving combined therapy during follow-up, as compared with 33 percent of those in the placebo group ($P=0.62$ for the comparison of estrogen with placebo, and $P=0.06$ for the comparison of estrogen plus medroxyprogesterone acetate with placebo). When data from all 3112 measurable coronary segments were analyzed, the results were similar (data not shown).

Because the effects of estrogen may differ in segments with minimal disease and in those with more extensive disease, analyses were performed after stratification according to the severity of disease at base line. Among the 1067 segments with 0 to 24 percent stenosis at base line, there were no significant differences among the groups in unadjusted or adjusted follow-up values; results were similar when analyses were limited to the 999 segments with 25 to 49 percent stenosis or the 251 segments with at least 50 percent stenosis at base line.

To determine whether either of the active treatments might be more efficacious in certain subgroups, the change in mean minimal diameter was compared among treatment groups after stratification according to age and various clinical characteristics (Table 3). No favorable effects of treatment were found in any of the subgroups.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 309 SUBJECTS ACCORDING TO TREATMENT GROUP.*

VARIABLE	ESTROGEN (N=100)	ESTROGEN PLUS MPA (N=104)	PLACEBO (N=105)
Age — yr	66.3±7.6	65.5±6.5	65.6±7.3
Race — no. (%)			
White	81 (81)	87 (84)	85 (81)
Black	14 (14)	15 (14)	14 (13)
Other	5 (5)	2 (2)	6 (6)
No. of coronary arteries with ≥50% stenosis — no. of subjects (%)			
0	30 (30)	30 (29)	34 (32)
1	33 (33)	30 (29)	36 (34)
2	27 (27)	27 (26)	23 (22)
3	10 (10)	17 (16)	12 (11)
Cardiac history — no. (%)			
MI	48 (48)	43 (41)	58 (55)
PTCA	51 (51)	51 (49)	44 (42)
Risk factors for coronary heart disease			
Diabetes — no. (%)†	25 (25)	30 (29)	31 (30)
Hypertension — no. (%)‡	60 (60)	75 (73)	72 (69)
Systolic BP — mm Hg	131.0 (17)	136.2 (18)	134.4 (17)
Diastolic BP — mm Hg	73.4 (9)	74.1 (9)	74.4 (9)
Current smoking — no. (%)	18 (18)	17 (16)	22 (21)
BMI >27.5 — no. (%)	64 (64)	57 (56)	56 (53)
Physical activity — no. (%)§	63 (63)	53 (52)	52 (50)
Gynecologic history			
Years since menopause	23.2±8.4	22.2±9.4	24.0±10.4
Hysterectomy — no. (%)	56 (56)	64 (62)	69 (66)
Oophorectomy — no. (%)	25 (25)	31 (30)	38 (36)
Taking estrogen — no. (%)¶	9 (9)	8 (8)	11 (10)
Laboratory measurements			
Total cholesterol — mg/dl	212±46	220±41	217±42
LDL cholesterol — mg/dl	131±39	138±37	136±38
HDL cholesterol — mg/dl	43±10	46±13	47±12
Triglycerides — mg/dl**	197±111	176±88	206±121
Non-HDL cholesterol — mg/dl	169±46	174±42	173±41
Fibrinogen — mg/dl	367±64	373±75	379±85
Fasting glucose — mg/dl**	108±28	102±2	108±37
Estradiol — pg/ml**	12±6	14±9	12±7
Concomitant medications — no. (%)			
Aspirin or ticlopidine	67 (67)	75 (73)	73 (70)
Calcium-channel blockers	61 (61)	53 (52)	57 (54)
Beta-blockers	39 (39)	48 (47)	49 (47)
Nitrates††	50 (50)	39 (38)	31 (30)
Lipid-lowering agents	34 (34)	39 (38)	39 (37)
Diuretics	32 (32)	32 (31)	33 (31)
ACE inhibitors	24 (24)	27 (26)	17 (16)
Oral hypoglycemics	16 (16)	14 (14)	19 (18)
Insulin	13 (13)	12 (12)	11 (10)

*Plus-minus values are means ±SD. Differences among groups were analyzed by Fisher's exact test for categorical variables and analysis of variance for continuous variables. MPA denotes medroxyprogesterone acetate, MI myocardial infarction, PTCA percutaneous transluminal coronary angioplasty, BP blood pressure, BMI body-mass index (the weight in kilograms divided by the square of the height in meters), LDL low-density lipoprotein, HDL high-density lipoprotein, and ACE angiotensin-converting enzyme. Data on hypertension, body-mass index, physical activity, and concomitant medications were missing for one subject in the group assigned to estrogen plus medroxyprogesterone acetate.

†Classification was based on response to the question, "Have you ever been told by a physician that you have diabetes, sugar diabetes, or high blood sugar?"

‡Classification was based on response to the question, "Have you ever been told by a physician that you have hypertension or high blood pressure?"

§Classification was based on whether participants walked "some or often," as opposed to "seldom or none."

¶These women underwent a three-month washout period before entering the trial.

||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; to convert values for glucose to millimoles per liter, multiply by 0.05551; and to convert values for estradiol to picomoles per liter, multiply by 3.671.

**Testing was performed with log transformation to better approximate a normal distribution.

††P=0.01 for differences among all three groups by Fisher's exact test.

TABLE 2. MEAN (\pm SE) BASE-LINE AND FOLLOW-UP ANGIOGRAPHIC RESULTS ACCORDING TO TREATMENT GROUP.*

SUBJECTS AND VARIABLE	ESTROGEN (N=79)	ESTROGEN PLUS MPA (N=85)	PLACEBO (N=84)	P VALUE	
				ESTROGEN VS. PLACEBO	ESTROGEN PLUS MPA VS. PLACEBO
All subjects					
Minimal coronary-artery diameter (mm)					
Base line	1.98 \pm 0.03	1.91 \pm 0.04	1.98 \pm 0.04	0.93	0.17
Follow-up	1.91 \pm 0.04	1.80 \pm 0.05	1.88 \pm 0.04	0.64	0.22
Adjusted follow-up†	1.87 \pm 0.02	1.84 \pm 0.02	1.87 \pm 0.02	0.81	0.23
Adjusted change‡	-0.09 \pm 0.02	-0.12 \pm 0.02	-0.09 \pm 0.02	0.97	0.38
Stenosis (%)					
Base line	28.53 \pm 0.84	29.65 \pm 0.90	27.80 \pm 0.84	0.56	0.13
Follow-up	31.77 \pm 0.97	33.86 \pm 1.55	31.48 \pm 1.23	0.88	0.19
Adjusted follow-up†	32.72 \pm 0.93	33.68 \pm 0.93	32.44 \pm 0.94	0.81	0.27
Adjusted change‡	4.01 \pm 0.92	4.75 \pm 0.92	4.11 \pm 0.93	0.93	0.56
Subjects who complied with treatment§					
Minimal coronary-artery diameter (mm)					
Base line	1.99 \pm 0.04	1.87 \pm 0.05	1.98 \pm 0.04	0.88	0.07
Follow-up	1.91 \pm 0.04	1.77 \pm 0.06	1.88 \pm 0.04	0.72	0.12
Adjusted follow-up†	1.85 \pm 0.03	1.84 \pm 0.03	1.85 \pm 0.03	0.99	0.63
Adjusted change‡	-0.11 \pm 0.03	-0.11 \pm 0.03	-0.10 \pm 0.02	0.95	0.86
Stenosis (%)					
Base line	28.60 \pm 0.84	30.49 \pm 1.06	27.63 \pm 0.92	0.49	0.03
Follow-up†	31.83 \pm 1.06	33.96 \pm 1.81	31.02 \pm 1.23	0.70	0.14
Adjusted follow-up†	33.19 \pm 1.03	33.10 \pm 0.95	32.63 \pm 0.92	0.65	0.68
Adjusted change‡	4.38 \pm 1.03	4.02 \pm 0.95	4.23 \pm 0.92	0.90	0.85

*MPA denotes medroxyprogesterone acetate.

†Values have been adjusted for base-line measurements and other prespecified covariates. See the Methods section for details.

‡Values have been adjusted for the length of follow-up, location of segment, clinic, and use or nonuse of lipid-lowering therapy at base line.

§Compliance was defined as taking at least 80 percent of the prescribed study medications.

Cardiovascular and Other Clinical Events

Nine women died of coronary disease and 19 had nonfatal myocardial infarctions during follow-up. There were no significant differences among the treatment groups in the rates of these events either during the whole follow-up period or during the first year (Table 4). The rates of coronary revascularization, hospitalization for unstable angina, any coronary disease event, stroke or transient attack, and death from all causes were also similar among the groups. Five women assigned to unopposed estrogen had venous thromboembolic events, as compared with two assigned to combined therapy and one assigned to placebo ($P=0.11$ for the comparison of unopposed estrogen with placebo).

During follow-up, no women had evidence of endometrial carcinoma (Table 5). However, more women in the group assigned to unopposed estrogen had simple or complex hyperplasia ($P<0.001$) during follow-up. In addition, heavy or persistent vaginal bleeding occurred in slightly more than half of the women taking unopposed estrogen who had a uterus; eight of these women (19 percent) ultimately required di-

lation and curettage. The rates of cholecystectomy and breast or other cancers were not significantly different among groups, although the incidence of these events was very low. Fractures (at all sites) were more than twice as common in the placebo group as in the active-treatment groups, but this difference did not reach statistical significance ($P=0.09$).

DISCUSSION

Coronary atherosclerosis is the underlying cause of most death and disability among women in the developed world. Effective measures to slow its progression in both women and men are still urgently needed. Several lines of evidence suggest that estrogen replacement should be beneficial in postmenopausal women. However, our results indicate that a mean of 3.2 years of estrogen replacement did not slow the progression of coronary atherosclerotic lesions in women. These data are consistent with the results of the Heart and Estrogen/Progestin Replacement Study⁸ that showed no overall effect of estrogen plus medroxyprogesterone acetate on the risk of clinical cardiovascular events in women with es-

TABLE 3. MEAN (\pm SE) CHANGES IN MINIMAL DIAMETER, ACCORDING TO TREATMENT GROUP, IN SELECTED SUBGROUPS.*

VARIABLE	No. OF SUBJECTS	ESTROGEN (N=79)	ESTROGEN PLUS MPA (N=85)	PLACEBO (N=84)	P VALUE	
					ESTROGEN VS. PLACEBO	ESTROGEN PLUS MPA VS. PLACEBO
millimeters						
Age						
\leq 66 yr	123	-0.08 \pm 0.03	-0.10 \pm 0.03	-0.09 \pm 0.03	0.75	0.73
>66 yr	125	-0.10 \pm 0.03	-0.14 \pm 0.04	-0.10 \pm 0.04	0.92	0.35
Diabetes						
Yes	69	-0.07 \pm 0.05	-0.20 \pm 0.04	-0.15 \pm 0.04	0.19	0.33
No	179	-0.11 \pm 0.03	-0.09 \pm 0.03	-0.08 \pm 0.03	0.26	0.67
Hypertension†						
Yes	168	-0.08 \pm 0.03	-0.12 \pm 0.02	-0.07 \pm 0.03	0.73	0.10
No	79	-0.09 \pm 0.04	-0.09 \pm 0.05	-0.14 \pm 0.04	0.40	0.43
Current smoking						
Yes	44	-0.03 \pm 0.04	-0.03 \pm 0.04	-0.00 \pm 0.04	0.55	0.55
No	204	-0.09 \pm 0.03	-0.12 \pm 0.02	-0.10 \pm 0.03	0.75	0.46
Prior MI						
Yes	115	-0.07 \pm 0.04	-0.16 \pm 0.04	-0.05 \pm 0.04	0.67	0.01
No	133	-0.10 \pm 0.03	-0.07 \pm 0.03	-0.11 \pm 0.03	0.85	0.32
Current statin use						
Yes	88	-0.08 \pm 0.04	-0.08 \pm 0.04	-0.13 \pm 0.04	0.29	0.23
No	160	-0.11 \pm 0.03	-0.14 \pm 0.03	-0.08 \pm 0.03	0.34	0.07
Current aspirin use						
Yes	183	-0.10 \pm 0.03	-0.13 \pm 0.03	-0.12 \pm 0.03	0.59	0.80
No	65	-0.02 \pm 0.03	-0.08 \pm 0.03	0.01 \pm 0.03	0.49	0.04

*MPA denotes medroxyprogesterone acetate, and MI myocardial infarction.

†Data were missing for one subject in the group assigned to estrogen plus medroxyprogesterone acetate.

established heart disease. These data go beyond previous work by demonstrating that unopposed estrogen was no more effective than estrogen plus medroxyprogesterone acetate in slowing disease progression.

The clinical relevance of these angiographic findings is underscored by the remarkable agreement between angiographic and clinical results in trials of lipid-lowering therapy¹⁷ and by the fact that subjects in other studies who were followed over time showed dramatic reductions in clinical events if they had slowing of angiographically evident disease.¹⁸⁻²² Nonetheless, the progression of anatomically defined disease measures only one of several processes that combine to produce acute ischemic events. Other studies are needed to elucidate the effects of estrogen on ulceration and thrombosis of existing lesions.

How can the lack of a treatment effect in our study be explained, given the established effects of estrogen on lipid metabolism, endothelial function, and other factors involved in the pathogenesis and progression of atherosclerosis?^{6,7,23} One possibility is that estrogen has proinflammatory effects that offset its beneficial effects. Two recent epidemiologic studies^{24,25} and two clinical trials^{26,27} reported significantly higher levels of C-reactive protein in women using unopposed estrogen or estrogen with various progestins. Elevated levels of this protein, and the underlying inflammation that it presumably reflects, are clearly associated with the risk of clinical cardiovascular events

TABLE 4. CLINICAL CARDIOVASCULAR EVENTS AND DEATH DURING 3.2 YEARS OF FOLLOW-UP, ACCORDING TO TREATMENT GROUP.*

EVENT	ESTROGEN (N=100)	ESTROGEN PLUS MPA (N=104)	PLACEBO (N=105)	P VALUE†
CHD events				
Death due to CHD	4 (4)	2 (2)	3 (3)	0.65
Fatal MI	1 (1)	1 (1)	1 (1)	1.00
Other deaths	3 (3)	1 (1)	2 (2)	0.53
Nonfatal MI	6 (6)	6 (6)	7 (7)	1.00
Revascularization‡	18 (18)	20 (19)	24 (23)	0.68
Hospitalization for unstable angina	18 (18)	15 (14)	22 (21)	0.47
Any CHD event	29 (29)	28 (27)	34 (32)	0.69
MI or death from coronary disease in year 1	2 (2)	5 (5)	3 (3)	0.57
Other vascular events				
Stroke or TIA	5 (5)	6 (6)	6 (6)	1.00
Venous thromboembolic events§	5 (5)	2 (2)	1 (1)	0.16
Death from any cause	8 (8)	3 (3)	6 (6)	0.28

*Some subjects had more than one cardiovascular event. MPA denotes medroxyprogesterone acetate, MI myocardial infarction, CHD coronary heart disease, and TIA transient ischemic attack.

†P values are for the comparison among the three treatment groups by Fisher's exact test.

‡Revascularization consisted of coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty.

§Venous thromboembolic events consisted of clinically verified deep-vein thrombosis or pulmonary embolism. For the comparison of placebo with estrogen, P=0.11 by Fisher's exact test.

TABLE 5. GYNECOLOGIC AND OTHER CLINICAL EVENTS DURING 3.2 YEARS OF FOLLOW-UP, ACCORDING TO TREATMENT GROUP.

VARIABLE	ESTROGEN (N=100)	ESTROGEN PLUS MPA (N=104)*		PLACEBO (N=105)	P VALUE†
		number (percent)			
Gynecologic events‡					
Endometrial evaluation					
Simple hyperplasia	8 (19)	0 (0)	0 (0)	0 (0)	<0.001
Complex hyperplasia	11 (26)	2 (5)	0 (0)	0 (0)	<0.001
Carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	1.00
Heavy or persistent bleeding§	23 (53)	12 (30)	1 (3)	1 (3)	<0.001
Dilation and curettage	8 (19)	5 (12)	0 (0)	0 (0)	0.02
Hysterectomy	2 (5)	0 (0)	2 (6)	2 (6)	0.46
Other events					
Breast cancer	1 (1)	0 (0)	0 (0)	0 (0)	0.35
Other cancer	0 (0)	3 (3)	3 (3)	3 (3)	0.25
Fractures	6 (6)	7 (7)	15 (14)	15 (14)	0.09
Cholecystectomy	2 (2)	4 (4)	2 (2)	2 (2)	0.67

*MPA denotes medroxyprogesterone acetate.

†P values are for the comparison among the three treatment groups by Fisher's exact test.

‡For gynecologic events, the most severe diagnosis in each subject is given. Percentages are given for the women who had a uterus at base line: 43 in the estrogen group, 40 in the estrogen plus medroxyprogesterone acetate group, and 35 in the placebo group.

§Heavy bleeding was defined as that which saturates more than one light-absorbency pad in 12 hours; persistent bleeding was defined as any bleeding lasting for 14 days.

in women.²⁸ However, it is not known whether treatments that increase the levels of C-reactive protein promote the progression of coronary disease.

Another possible explanation for our results is that estrogen is more effective in preventing the development of atherosclerosis than in slowing the progression of disease once it is established. In ovariectomized monkeys and rabbits in which atherosclerosis has not yet developed, estrogen inhibits the development of disease,^{29,30} yet similar studies in animals with established disease have shown no effect on progression.^{15,31} In animals, the ability of estrogen to prevent the accumulation of cholesterol in the vessel wall appears to require a healthy endothelium.³² Since atherosclerosis and aging are associated with impaired endothelial function,³³ older women or women with established disease may be less likely to realize a cardiovascular benefit from estrogen. The Women's Health Initiative, a large clinical trial in predominantly healthy women, will provide important data about estrogen use for the primary prevention of heart disease.³⁴

As in any clinical trial of the prevention of chronic disease, the conclusions of this study would be stronger with more subjects and longer follow-up. However, the nearly identical rates of disease progression among the three groups after a mean of 3.2 years offer little reason to suspect that a significant difference would

emerge with longer follow-up. Furthermore, the 95 percent confidence limits for the differences between the active-treatment and placebo groups in measures of minimal diameter at follow-up exclude benefits greater than 0.021 mm for estrogen plus medroxyprogesterone acetate and 0.049 mm for unopposed estrogen.

Side effects, such as vaginal bleeding, especially in the group receiving unopposed estrogen, produced differential rates of compliance and opportunities for unblinding. However, the results of analyses of the subjects who complied with treatment were virtually identical to intention-to-treat analyses, and assessments of angiograms and clinical cardiovascular events were performed by persons who had no contact with the women or knowledge of the treatment assignments. Despite random assignment to treatment, there was a nonsignificant trend toward more severe disease at base line among women assigned to combined therapy. Therefore, follow-up angiographic measures were compared after adjustment for base-line measurements.

Our trial did not have enough subjects to allow us to draw conclusions with confidence about the effects of treatment on clinical events. In particular, there were not enough subjects for us to confirm or refute the pattern of excess risk of cardiovascular events that was found during year 1 in the Heart and Estrogen/Progestin Replacement Study and suggested in preliminary data from the Women's Health Initiative (Rossouw J; personal communication). The nonsignificant trends toward more venous thromboembolic events and fewer fractures in the active-treatment groups are consistent with previously established effects of hormone therapy.

In summary, an average of 3.2 years of treatment with either unopposed conjugated estrogen (0.625 mg per day) or estrogen plus medroxyprogesterone acetate (2.5 mg per day) did not slow the progression of coronary atherosclerosis in women with established disease. These data are consistent with the overall null effect of estrogen plus medroxyprogesterone acetate on clinical events in the Heart and Estrogen/Progestin Replacement Study. On the basis of these results, women with heart disease should not use conjugated estrogen, alone or in combination with medroxyprogesterone acetate, with an expectation of cardiovascular benefit. Unless or until other data to the contrary emerge, it seems reasonable to extend this recommendation to other formulations of estrogen and progestin as well. Estrogen therapy may still be effective for the primary prevention of coronary heart disease, but this has not yet been verified. In the meantime, women and their physicians should redouble efforts to use forms of treatment and prevention already proved to slow the progression of coronary disease and prevent cardiovascular events, including lipid-lowering therapy when indicated.

Supported by a grant from the National Heart, Lung, and Blood Institute (U01 HL-45488) and by a National Center for Research Resources General Clinical Research Center grant (M01 RR07122). Study medications were provided by Wyeth-Ayerst Research.

We are indebted to Karen Potvin Klein, M.A., E.L.S., for her editorial contributions.

APPENDIX

The following were committee members, investigators, and staff of the Estrogen Replacement and Atherosclerosis Trial: Data Safety and Monitoring Board: T. Bush, C. Davis, C. Furberg (ex officio), D. Gordon (ex officio), A. Guerci (chair), A. Jacobs, C. Timmons, and R. Tong; Quantitative Coronary Angiography Consultants: G. Brown and W. Saunders; Internal Advisory Committee: G. Burke, T. Clarkson, W. Hazzard, and W. Little; Cardiovascular Endpoint Committee: B. Psaty; Steering Committee: B. Brosnihan, S. Folmar, C. Furberg (cochair), K. Geisinger, D. Herrington (cochair, principal investigator), D. Reboussin, P. Sharp, S. Shumaker, and T. Snyder; University of Alabama at Birmingham: W. Rogers, V. Bittner, R. Varner, A. Murphy, S. Rolli, and B. Vaughn; Carolinas Medical Center, Charlotte, N.C.: G. Kowalchuk, E. Harrison, J. Allan, and J. Smith; Forsyth Memorial Hospital, Winston-Salem, N.C.: D. Givens and T. Gerald; Moses Cone Health System, Greensboro, N.C.: T. Stuckey, J. Schaal, H. Smith III, M. Boozer, V. Bradsher, K. Cheshire, J. Khemlani, and S. Milks; Hartford Hospital, Hartford, Conn.: D. Waters, L. Chaffkin, S. Giri, A. Olivar, J. DeDominicis, J. Macer, J. Pazdar, and M. Siwy; Wake Forest University School of Medicine, Winston-Salem, N.C.: D. Herrington, K. Geisinger, F. Kahl, P. Sharp, S. Shumaker, T. Snyder, K. Blinson, D. Combs, M. Davis, L. Doomy, M. Drum, L. Fan, S. Gorham, J. Griffin, J. Iannuzzi, P. Kelley, K. Klein, J. Lundy, B. Pusser, and V. Wilson; Data Coordinating Center: D. Reboussin, A. Florance, R. Fussell, M. James, C. Kancler, C. Kay, K. Lane, S. Reece, S. Stone, and T. Terrell.

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