

A CLINICAL TRIAL OF ESTROGEN-REPLACEMENT THERAPY AFTER ISCHEMIC STROKE

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ABSTRACT

Background Observational studies have suggested that estrogen-replacement therapy may reduce a woman's risk of stroke and death.

Methods We conducted a randomized, double-blind, placebo-controlled trial of estrogen therapy (1 mg of estradiol-17 β per day) in 664 postmenopausal women (mean age, 71 years) who had recently had an ischemic stroke or transient ischemic attack. Women were recruited from 21 hospitals in the United States and were followed for the occurrence of stroke or death.

Results During a mean follow-up period of 2.8 years, there were 99 strokes or deaths among the women in the estradiol group, and 93 among those in the placebo group (relative risk in the estradiol group, 1.1; 95 percent confidence interval, 0.8 to 1.4). Estrogen therapy did not reduce the risk of death alone (relative risk, 1.2; 95 percent confidence interval, 0.8 to 1.8) or the risk of nonfatal stroke (relative risk, 1.0; 95 percent confidence interval, 0.7 to 1.4). The women who were randomly assigned to receive estrogen therapy had a higher risk of fatal stroke (relative risk, 2.9; 95 percent confidence interval, 0.9 to 9.0), and their nonfatal strokes were associated with slightly worse neurologic and functional deficits.

Conclusions Estradiol does not reduce mortality or the recurrence of stroke in postmenopausal women with cerebrovascular disease. This therapy should not be prescribed for the secondary prevention of cerebrovascular disease. (N Engl J Med 2001;345:1243-9.)

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ALTHOUGH many observational studies have linked postmenopausal estrogen therapy with a reduced risk of vascular disease, especially morbidity and mortality from cardiovascular causes,¹ concern has persisted that these findings may be attributable not to estrogen therapy but to other differences between users and nonusers of such therapy.² Although estrogen therapy may have favorable effects on lipid metabolism,³ coagulation,^{4,5} and vascular tone,^{6,7} it may also have adverse prothrombotic and proinflammatory effects.^{8,9}

In 1998, the findings of the first placebo-controlled, randomized clinical trial of hormone-replacement therapy for the secondary prevention of cardiac disease in postmenopausal women, the Heart and Estrogen/Progestin Replacement Study (HERS), were reported. Surprisingly, daily therapy with conjugated estrogen

and progestin did not reduce the incidence of coronary events or death from any cause during four years of follow-up.¹⁰

When that study began, epidemiologic research also suggested that estrogen might protect against stroke,¹¹⁻¹⁴ although this evidence was less consistent than that for protection against coronary heart disease. Some studies reported no effect of estrogen use on the risk of stroke,¹⁵⁻²² and two large cohort studies reported an increased risk.^{23,24} Our study, the Women's Estrogen for Stroke Trial, was designed in 1993 as a randomized, placebo-controlled trial of estrogen replacement for the secondary prevention of cerebrovascular disease. The primary end point was death from any cause or nonfatal stroke; secondary outcomes were transient ischemic attack and nonfatal myocardial infarction. Other prespecified analyses included the effect of estrogen on the rate of death alone, the incidence of stroke alone, the severity of recurrent strokes, and the incidence of cardiac events.

METHODS

Study Participants

A description of the design and methods of our study has been reported previously.²⁵ We enrolled postmenopausal women older than 44 years of age within 90 days after a qualifying ischemic stroke or transient ischemic attack. Women were recruited between December 1993 and May 1998. Women were excluded if their index event was disabling (had a severity score greater than 5 on the scale used in the North American Symptomatic Carotid Endarterectomy Trial²⁶) or if it occurred while the woman was taking estrogen. Women were considered postmenopausal if they had had amenorrhea for at least 12 months or if they had undergone hysterectomy and were older than 55 years of age.

Women were not eligible if they had a history of breast or endometrial cancer, had had a venous thromboembolic event while receiving estrogen-replacement therapy, had a neurologic or psychiatric disease that could complicate the evaluation of end points, or had a coexisting condition that limited their life expectancy. Screening tests to confirm eligibility were required before entry; these included computed tomography to rule out nonischemic causes of the stroke syndrome, clinical breast examination, mammography, and (in women who had not undergone hysterectomy) a Papanicolaou smear. All women provided written informed consent for their participation and were specifically informed about

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the potential risk of uterine cancer associated with estrogen therapy. Approval was obtained from the institutional review board at each participating hospital.

Neurologic deficits were assessed by a nurse during an initial home visit with the use of the National Institutes of Health Stroke Scale (NIHSS),²⁷ a measure of 11 categories of neurologic signs. Index events were verified by a neurologist associated with the study who reviewed the nurse's assessment and pertinent medical records. When women entered the study, their self-reported functional ability in activities of daily living was recorded with the use of the Barthel index.²⁸

Randomization

At the start of the trial, a master list of computer-generated random treatment assignments was stored at the investigational pharmacy at Yale–New Haven Hospital. Randomization was stratified according to clinical center (21 hospitals) and base-line risk group as defined according to a previously validated clinical index (three groups)²⁹ and was performed so as to equalize treatment assignments in blocks of four subjects. Participants were randomly assigned to receive either estradiol-17 β (Estrace, Mead Johnson, Evansville, Ind.) at the standard replacement dose of 1 mg daily or matching placebo. The use of a regimen of estrogen alone was chosen to avoid any possible antagonizing effects of progestins on the hemodynamic benefits of estrogen.⁶

The women and the investigators were unaware of the treatment assignment. The study internist could be unblinded when there was an overriding concern about a woman's clinical care; this occurred in the case of six women in the estradiol group and seven women in the placebo group. The investigators who were involved in the assessment of outcomes were not informed of the occurrence of vaginal bleeding or other effects of active therapy.

Follow-up Procedures

Every three months after entry, a nurse contacted each woman by telephone to promote compliance with the study-drug regimen, assess side effects, and screen for outcomes with the use of a standardized questionnaire.³⁰ The women were also asked whether any of the following events had occurred: stroke, transient ischemic attack, myocardial infarction, blood clot in the leg or lung, hospital admission or emergency room visit, and vaginal bleeding. We reviewed the medical records for all reported events.

To screen for endometrial hyperplasia, women with a uterus underwent transvaginal ultrasonography annually or received an annual 12-day course of medroxyprogesterone acetate (5 mg daily). Women with abnormal findings on ultrasonography (an endometrial thickness of more than 5 mm or evidence of an irregular endometrial surface) or who had vaginal bleeding before day 11 of the course of progestin were referred for endometrial biopsy.³¹ Adherence to the study regimen was monitored by means of pill counts.

Monitoring for Adverse Events

We monitored the women for the occurrence of endometrial hyperplasia or cancer by referring them for endometrial biopsy or transvaginal ultrasonography whenever unexpected vaginal bleeding occurred and at the end of their participation in the study. Mammography was performed annually to monitor for breast cancer. We also monitored the women for venous thromboembolic events; a diagnosis of deep venous thrombosis required a positive duplex ultrasonogram or venogram, and a diagnosis of pulmonary embolus required a ventilation–perfusion scan indicating a high probability of pulmonary embolus, a positive pulmonary angiogram, or a diagnostic computed tomographic scan of the chest. When a diagnosis of endometrial cancer, breast cancer, or venous thrombosis was confirmed, the study drug was discontinued, but follow-up for the occurrence of the trial outcomes continued.

Ascertainment of Outcomes

Stroke was defined as an acute neurologic event of at least 24 hours' duration, with focal signs and symptoms and without evi-

idence supporting any alternative explanation; strokes were classified as ischemic or hemorrhagic on the basis of brain imaging.²⁶ Transient ischemic attack, a secondary outcome, was defined by the presence of focal neurologic or retinal symptoms lasting more than 30 seconds and resolving in less than 24 hours. Each suspected neurologic event was initially evaluated by the principal neurologist through the review of records and in consultation with the treating physician, the woman, or both. When a nonfatal stroke occurred, the study drug was stopped and follow-up ended. The severity of strokes was quantified with the use of the NIHSS and the Barthel index during a final visit that was conducted, whenever possible, one month after the stroke occurred. All suspected neurologic events were adjudicated at the conclusion of the trial by the principal neurologist and two independent neurologists specializing in stroke.

Hospital records, nurses' notes, and death certificates were obtained for all deaths. Any confirmed stroke that was followed by death within 30 days was classified as a fatal stroke. Deaths from cardiovascular causes included deaths that followed definite or possible acute myocardial infarction as well as deaths from coronary events as defined according to the criteria of the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease project.³² Suspected nonfatal myocardial infarctions were evaluated by a clinical investigator according to prespecified criteria based on the measurement of cardiac enzymes and electrocardiographic tracings.³³

Statistical Analysis

Under the assumptions that the 3-year rate of the primary outcome (death or nonfatal stroke) would be reduced from 25 percent (in the placebo group) to 15 percent (in the estradiol group), that the average duration of follow-up would be 3.5 years, and that the dropout rate would be 10 percent (including women in whom treatment was discontinued and those who were lost to follow-up), we required a sample of 652 women to achieve 80 percent power at a two-tailed alpha level of 0.05.³⁴ The P values for stopping the trial after the five prespecified interim analyses were set at 0.001, 0.001, 0.004, 0.012, and 0.024 with the use of the O'Brien–Fleming guidelines for early termination.³⁵ An independent external performance and safety monitoring board reviewed the study protocol and monitored adverse events and interim results during the trial.

All analyses were conducted according to the intention-to-treat principle. Time-to-event curves for each treatment group were calculated by the Kaplan–Meier method³⁶ and compared by means of the log-rank test.³⁷ The estimates of relative risk, with 95 percent confidence intervals, were derived from Cox proportional-hazards models.³⁸ We used another Cox proportional-hazards model to estimate relative risks for the women in both treatment groups whose average compliance with the study regimen was at least 80 percent (as-treated analysis).

RESULTS

Of the 5296 women who were identified as having had cerebrovascular events that met the criteria for eligibility, 2772 were found to be ineligible for enrollment (652 were not capable of providing informed consent, 632 had severe coexisting conditions, 512 were already taking estrogen, 326 had a history of breast cancer, 191 did not speak English, 171 lived out of state, 133 were premenopausal, 108 had a history of endometrial cancer, 38 had other contraindications to estrogen therapy, and 9 were enrolled in another trial). Among the 2524 eligible women, 1843 declined to participate and 17 could not be randomly assigned to a treatment group within 90 days after their qualifying event. The final cohort comprised 664 women (26 percent of the eligible women); 337 were

assigned to the estradiol group and 327 to the placebo group.

The mean age of the enrolled women was 71 years (range, 46 to 91). Eighty-four percent reported their race as non-Hispanic white, 40 percent were currently married, and the median level of education was completion of the 12th grade. The qualifying event was stroke for 75 percent of the women. There were no significant differences in demographic or clinical characteristics according to treatment group (Table 1).

All women who were alive and had not had a stroke during the study period were withdrawn from the study during the close-out period (May 1999 through November 1999). The mean (\pm SD) duration of follow-up was 33 ± 17 months. At the end of the study, the women who had not reached an end point had been followed for at least 12 months (mean, 38 ± 15). Vital status was confirmed for all women at the conclusion of the trial. Nine women (six in the estradiol group and three in the placebo group) declined an exit visit. During the trial, the study drug was discontinued in 116 women in the estradiol group (34 percent) and 79 women in the placebo group (24 percent). Among the women who discontinued the study drug, four in the estradiol group (1 percent) and seven in the placebo group (2 percent) reported using open-label estrogen. Overall, the mean compliance with study medication (including compliance by the women who discontinued treatment) was 70 percent (66 percent in the estradiol group and 74 percent in the placebo group); compliance among women who did not discontinue the study drug was 90 percent in both treatment groups.

Trial Outcomes

Primary Outcomes

A total of 89 deaths and 103 nonfatal strokes occurred during the trial (Table 2). Primary outcomes were confirmed for 99 women in the estradiol group and 93 women in the placebo group. As shown in Figure 1, there was no significant difference between the treatment groups in the incidence of death or nonfatal stroke. Slightly more women in the estradiol group than in the placebo group died during follow-up (48 vs. 41), but the difference was not significant (Table 2). However, death due to stroke was more common in the estradiol group (Fig. 2) (relative risk, 2.9; 95 percent confidence interval, 0.9 to 9.0). This increase primarily reflected a difference in the incidence of ischemic stroke (Table 2). The rates of death from cardiovascular causes and death from other causes were similar in the two treatment groups (Table 2).

The incidence of nonfatal stroke and nonfatal ischemic stroke was similar in the two treatment groups (Table 2). When nonfatal events were included in the analysis, the risk of stroke was not significantly different between the two treatment groups (Fig. 2). Ad-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE WOMEN.*

CHARACTERISTIC	ESTRADIOL GROUP (N=337)	PLACEBO GROUP (N=327)	P VALUE†
Sociodemographic characteristics			
Age (yr)	72 \pm 10	71 \pm 10	0.44
Race (%)			0.95
White	84	83	
Black	13	13	
Other	3	4	
Married (%)	39	43	0.27
Education (yr)	12 \pm 3	12 \pm 3	0.42
Clinical characteristics			
Myocardial infarction (%)‡	25	23	0.49
Congestive heart failure (%)	13	16	0.23
Atrial fibrillation (%)	7	7	0.85
Hypertension (%)	75	72	0.43
Diabetes (%)§	25	31	0.07
Current cigarette smoking (%)	11	14	0.21
Body-mass index¶	28 \pm 7	28 \pm 5	0.34
Previous estrogen-replacement therapy (%)	28	31	0.49
Hysterectomy (%)	44	45	0.73
Not receiving antithrombotic therapy (%)	8	11	0.19
Neurologic characteristics			
History of stroke before index event (%)	19	18	0.87
Stroke as index event (%)	75	75	0.82
NIHSS score (%)**			0.28
0-1	47	48	
2-8	52	50	
\geq 9	1	2	
Median	2	2	
Barthel index (%)††			0.14
95-100	84	89	
55-90	15	10	
0-50	<1	1	
Median	100	100	
Summary risk stratum (%)‡‡			
Low	13	12	0.89
Medium	66	68	
High	21	20	

*Plus-minus values are means \pm SD. Data on congestive heart failure were missing for three women in the estradiol group and five in the placebo group; data on hypertension were missing for one woman in the estradiol group and two in the placebo group; data on smoking status were missing for two women in the placebo group; data on previous estrogen therapy were missing for six women in the estradiol group and three in the placebo group; data on previous stroke were missing for three women in the placebo group; scores on the National Institutes of Health Stroke Scale (NIHSS) were missing for one woman in the estradiol group and one in the placebo group; and scores on the Barthel index were missing for one woman in the estradiol group and two in the placebo group.

†P values are based on the chi-square test for the comparison of proportions or the t-test for the comparison of means.

‡Values include women who were hospitalized for myocardial infarction or who had evidence of a myocardial infarction on electrocardiography.

§Values include women who were taking insulin or receiving oral treatment for diabetes.

¶The body-mass index is the weight in kilograms divided by the square of the height in meters.

||Antithrombotic therapy included aspirin, ticlopidine, dipyridamole, and warfarin.

**NIHSS scores range from 0 to 42, with 0 indicating no deficits and 42 indicating most severe deficit.

††Scores on the Barthel index range from 0 to 100, with 100 indicating no deficits and 0 indicating complete dependence.

‡‡Risk strata were defined on the basis of a validated instrument that included five clinical features (age, blood pressure, diabetes, cardiac disease, and index event [stroke vs. transient ischemic attack]).

TABLE 2. OUTCOMES ACCORDING TO TREATMENT ASSIGNMENT.

OUTCOME	ESTRADIOL GROUP (N=337)	PLACEBO GROUP (N=327)	RELATIVE RISK (95% CI)*
	no.		
Primary outcomes			
Death or nonfatal stroke	99	93	1.1 (0.8–1.4)
Death	48	41	1.2 (0.8–1.8)
Fatal stroke	12	4	2.9 (0.9–9.0)
Ischemic	9	2	4.4 (0.9–20.2)
Hemorrhagic	3	2	1.4 (0.2–8.7)
Cardiovascular causes	11	13	0.8 (0.4–1.9)
Myocardial infarction	1	5	0.2 (0.0–1.7)
Other coronary cause	10	8	1.2 (0.5–3.2)
Other cause†	25	24	1.0 (0.6–1.8)
Nonfatal stroke	51	52	1.0 (0.7–1.4)
Ischemic	47	49	1.0 (0.6–1.4)
Hemorrhagic	4	3	1.3 (0.3–6.0)
Any stroke	63	56	1.1 (0.8–1.6)
Secondary outcomes‡			
Nonfatal myocardial infarction	14	12	1.2 (0.5–2.5)
Transient ischemic attack	30	25	1.2 (0.7–2.0)

*The relative risks (and 95 percent confidence intervals [CIs]) for the primary outcomes were derived from a proportional-hazards model including data for the entire duration of follow-up. The secondary outcomes could occur more than once during follow-up; the relative risks of these outcomes were derived from the analysis of the time to the first event.

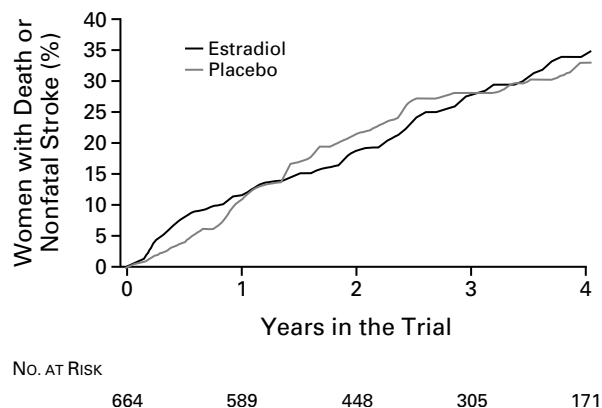
†Other causes of death included cancer (in 10 women — non-Hodgkin's lymphoma in 2, breast cancer in 2, cancer of the colon, liver, lung, pancreas, and pelvis in 1 each, and metastatic cancer with an unknown primary site in 1), infection in 8 women, renal failure in 5 women, congestive heart failure in 2 women, pulmonary embolus in 2 women, gastrointestinal bleeding in 2 women, ischemic bowel in 2 women, chronic obstructive pulmonary disease in 2 women, and miscellaneous causes in 3 women (abdominal aortic aneurysm, peripheral arterial disease, and small bowel obstruction). For six women in the estradiol group and seven in the placebo group, the cause of death was not determined; in these cases, there was no autopsy and no history of described symptoms consistent with ischemic heart disease, or other diagnosis.

‡Some women had more than one event — in the estradiol group, two women had two myocardial infarctions, two had two transient ischemic attacks, and one had three transient ischemic attacks; in the placebo group, one woman had two myocardial infarctions, one had three myocardial infarctions, four had two transient ischemic attacks, one had three transient ischemic attacks, and one had four transient ischemic attacks.

justment for base-line risk factors (older age, history or electrocardiographic evidence of myocardial infarction, congestive heart failure, hypertension, diabetes, and current smoking) did not materially affect these results.

Because an increase in vascular events with hormone-replacement therapy was observed in the first year of follow-up in HERS,¹⁰ we conducted a post hoc analysis of early cerebrovascular events. During the first six months, 3 fatal strokes and 18 nonfatal strokes occurred in women in the estradiol group, as compared with 1 fatal stroke and 8 nonfatal strokes in women in the placebo group ($P=0.03$ by the log-rank test; relative risk of any stroke at six months, 2.3; 95 percent confidence interval, 1.1 to 5.0).

We also compared the two treatment groups in terms of the severity of nonfatal strokes (Table 3).

**Figure 1.** Kaplan–Meier Curves for the Time to the Primary Outcome (Death or Nonfatal Stroke).

$P=0.69$ by the log-rank test for the comparison between groups.

The median interval between a nonfatal stroke and the evaluation of its severity was 35 days for women in the estradiol group and 39 days for women in the placebo group. Women assigned to the estradiol group were less likely than women in the placebo group to have no neurologic deficits or only mild impairment of neurologic function (a NIHSS score of 0 or 1) after stroke and less likely to have functional independence (a Barthel index of 90 or higher), although neither of these differences was statistically significant. When fatal strokes were included in the analysis, the differences in severity were more extreme.

Secondary Outcomes

No significant difference was observed between the treatment groups in the incidence of transient ischemic attack or nonfatal myocardial infarction (Table 2). The risk of any cardiac event (fatal or nonfatal) did not differ significantly between the two groups (relative risk in the estradiol group, 1.1; 95 percent confidence interval, 0.6 to 1.9).

Outcomes According to Treatment Received

When the analysis was restricted to the 397 women who took at least 80 percent of the assigned study medication, the adjusted relative risk for women in the estradiol group as compared with those in the placebo group was nonsignificantly elevated for death or nonfatal stroke (relative risk, 1.2; 95 percent confidence interval, 0.8 to 1.8), for any stroke (relative risk, 1.3; 95 percent confidence interval, 0.8 to 2.1), and for death from any cause (relative risk, 1.2; 95 percent confidence interval, 0.7 to 2.3).

Vital Status at the End of the Trial

An additional 28 deaths occurred in women who had a nonfatal stroke as their study end point (15 in

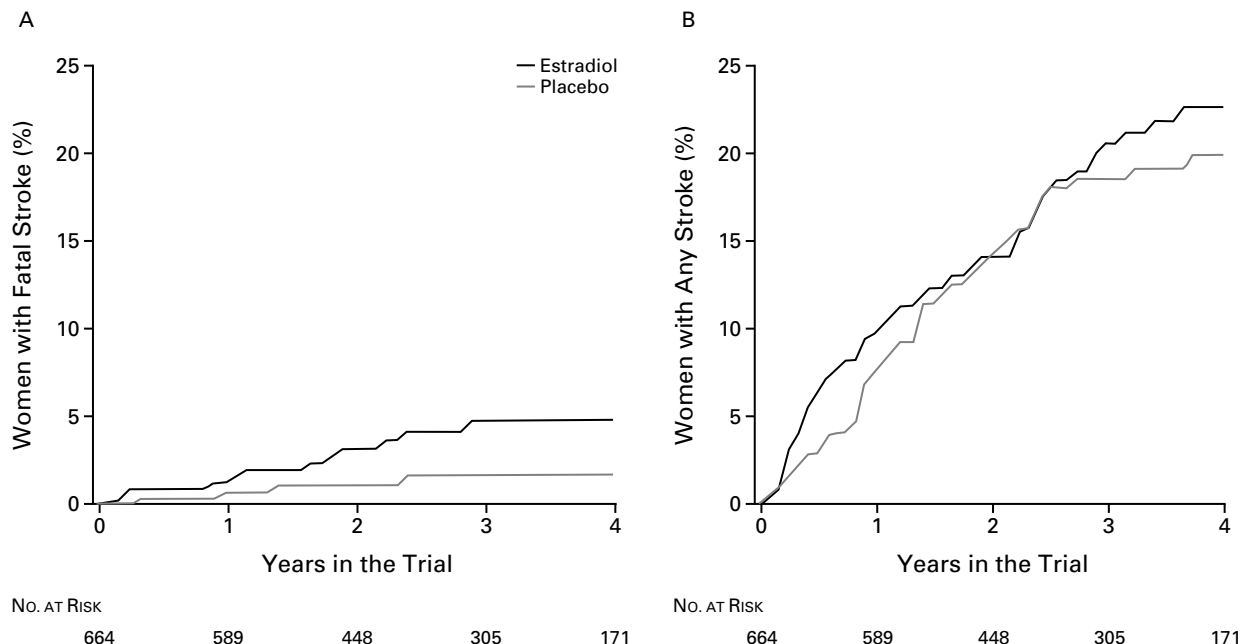


Figure 2. Kaplan–Meier Curves for the Time to Fatal Stroke (Panel A) and the Time to Any Stroke (Nonfatal or Fatal) (Panel B). P=0.05 by the log-rank test for the analysis of time to fatal stroke; P=0.57 by the log-rank test for the analysis of time to any stroke.

the estradiol group and 13 in the placebo group). Including these deaths, overall mortality was 18.4 percent in the estradiol group and 16.3 percent in the placebo group.

Other Events during Follow-up

The women in the estradiol group did not have higher rates of venous thromboembolic events, breast cancer, or hospitalization for fractures than those in the placebo group. However, women in the estradiol group were more likely to have vaginal bleeding, to have endometrial hyperplasia, and to require a hysterectomy (Table 4). Two women in the estradiol group were found to have endometrial adenocarcinoma after having vaginal bleeding (one three months after randomization and the other six months after randomization).

DISCUSSION

In this high-risk population of postmenopausal women with a recent cerebrovascular event, treatment with estradiol-17β for three years was ineffective in reducing the overall risk of stroke or death or the incidence of the individual end points of death, fatal or nonfatal stroke, transient ischemic attack, or cardiac events during follow-up. Moreover, this therapy was associated with adverse effects on the endometrium, including elevated rates of vaginal bleeding and endometrial hyperplasia and a more frequent need for hysterectomy.

TABLE 3. SEVERITY OF NONFATAL STROKES.*

SEVERITY	ESTRADIOL GROUP (N=51)	PLACEBO GROUP (N=52)	P VALUE
	no. (%)		
NIHSS			0.12
0–1	9 (19)	16 (33)	
≥2	39 (81)	33 (67)	
Barthel index			0.16
95–100	21 (44)	29 (58)	
<95	27 (56)	21 (42)	

*Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with 0 indicating no deficits and 42 indicating the most severe deficit. Scores on the Barthel index range from 0 to 100, with 100 indicating no deficits and 0 indicating complete dependence. Scores on the NIHSS were missing for three women in the estradiol group and three in the placebo group; scores on the Barthel index were missing for three women in the estradiol group and two in the placebo group.

Although we cannot rule out the possibility that estrogen therapy has minimal cerebrovascular benefits, our study had sufficient power to rule out reductions in the risk of death or stroke of more than 20 percent. The challenges involved in getting women to continue taking estrogen are well documented,³⁹ and non-compliance may have limited our ability to detect an effect of treatment. However, the compliance rates achieved in this trial (mean, 66 percent over a three-

TABLE 4. OTHER EVENTS DURING FOLLOW-UP, ACCORDING TO TREATMENT GROUP.*

EVENT	ESTRADIOL GROUP (N=337)	PLACEBO GROUP (N=327)	RELATIVE RISK (95% CI)
	no.		
Venous thromboembolic event†	3	4	0.8 (0.2–3.4)
Deep venous thrombosis	1	2	0.5 (0.0–5.8)
Pulmonary embolism	2	2	1.0 (0.1–7.1)
Breast cancer‡	5	5	1.0 (0.3–3.5)
Bone fracture§	30	33	0.9 (0.5–1.5)
Hip	9	14	0.6 (0.3–1.4)
Other	24	19	1.3 (0.7–2.3)
Endometrial abnormality¶			
Vaginal bleeding	115	33	4.8 (3.2–7.0)
Hyperplasia**			
Simple	24	1	24.5 (3.3–180.9)
Complex	10	2	5.0 (1.1–22.7)
Endometrial cancer††	2	0	—
Hysterectomy	6	1	5.9 (0.7–48.9)

*CI denotes confidence interval.

†One woman in the estradiol group had both deep venous thrombosis and pulmonary embolism.

‡One woman in the placebo group was given a diagnosis of breast cancer two months after randomization.

§Values are the numbers of women discharged from the hospital with a diagnosis of fracture; three women in the estradiol group had fractures in both the hip and another site (lumbar spine, hand, and femur).

¶Data are for the 189 women in the estradiol group and the 180 women in the placebo group who had not undergone hysterectomy before study entry.

||Values are the numbers of women who reported any episode of unexpected vaginal bleeding during the trial. The estimates of relative risk are for the time to the first episode of bleeding. A total of 226 episodes of unexpected bleeding were reported in the estradiol group, and 46 in the placebo group.

**Values are the numbers of women with a diagnosis of endometrial hyperplasia; women with more than one type of hyperplasia are included under the more advanced category. The estimates of relative risk are for the time to the first diagnosis. The diagnoses were made within six months after randomization for 14 women in the estradiol group with simple hyperplasia and 3 women in the estradiol group with complex hyperplasia.

††Bleeding began 180 days after randomization in one of the women in whom endometrial adenocarcinoma was diagnosed and 88 days after randomization in the other; the diagnosis was confirmed by biopsy on day 259 and day 222, respectively.

year period) are considerably higher than those found among estrogen users in the community.⁴⁰ Furthermore, the point estimates for increased risk among women who adhered well to the study regimen indicate that it is unlikely that we missed a benefit of treatment because of noncompliance.

The incidence of venous thromboembolic events in the estradiol group in our study was low, and it did not differ significantly from that in the placebo group. As in other studies, the incidence of breast cancer was not affected by estrogen therapy during the relatively short period of follow-up. The risk of bone fracture was also not significantly altered by treatment with estrogen.

Although our findings differ from those of obser-

vational studies that have reported a reduction in the risk of stroke associated with estrogen use,^{11–14} they are consistent with other large population studies that have reported increases in the risk of stroke among generally healthy, relatively young postmenopausal women who were receiving estrogen therapy.^{23,41} HERS, another randomized trial of estrogen for the secondary prevention of vascular disease in women, tested a different regimen from the one we used (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate per day) and enrolled slightly younger women (mean age, 67 years) with established coronary disease. That trial found no overall reduction in the risk of cardiovascular events and, in a recent secondary analysis, no reduction in the risk of stroke in the study population (relative hazard, 1.23; 95 percent confidence interval, 0.89 to 1.70).⁴² Although fatal stroke occurred more commonly in the participants in HERS who were assigned to estrogen–progestin therapy, the increase in risk was not statistically significant.

Estrogen therapy may worsen the injury caused by recurrent cerebral ischemia. In our study, women in the estradiol group were more likely than those in the placebo group to die from a stroke, and nonfatal events in the estradiol group were associated with greater neurologic and functional deficits, although these findings were not statistically significant. These data also suggest the possibility of an increase in the risk of stroke early after the initiation of therapy among women randomly assigned to receive estrogen. The mechanism by which exogenous estrogen may exacerbate the injury caused by stroke or may precipitate stroke is unclear. Although estrogen has been shown to reduce some vascular risk factors, it is also associated with potentially deleterious effects. Estrogen has direct effects on neurons and might increase sensitivity to ischemia, either by modulating the excitatory effects of glutamate or by modifying the inhibitory effects of γ -aminobutyric acid.⁴³ Another possible mechanism for an adverse effect of treatment may involve proinflammatory effects of estrogen.^{9,44}

The ongoing Women's Health Initiative, a randomized trial, should help clarify the role of estrogen in the primary prevention of cardiovascular disease, including stroke. Our results indicate that estrogen therapy should not be initiated for the purpose of secondary prevention of cerebrovascular disease and add to the evolving body of evidence from clinical trials that do not show a benefit of estrogen for women with established vascular disease.

Supported by a grant (1-RO1-N531251) from the National Institute of Neurological Disorders and Stroke and by Mead Johnson Laboratories, which also provided the study drug. Dr. Suissa was supported by a Senior Scientist Award from the Medical Research Council of Canada.

Drs. Viscoli, Brass, Kernan, Suissa, and Horwitz have received research support from Novartis. Dr. Suissa has also received research funding from Schering and Organon.

APPENDIX

The members of the Women's Estrogen for Stroke Trial performance and safety monitoring board were as follows: Barbara C. Tilley, Ph.D. (chair), Department of Biometry and Epidemiology, Medical University of South Carolina; Joseph P. Broderick, M.D., Department of Neurology, University of Cincinnati Medical Center; Patricia H. Davis, M.D., Department of Neurology, University of Iowa, Iowa City; Patrick D. Lyden, M.D., Neuroscience Department, University of California, San Diego; Veronica A. Ravnikar, M.D., Department of Obstetrics and Gynecology, University of Massachusetts School of Medicine, Worcester; and John R. Marler, M.D., Division of Stroke, Trauma, and Neurodegenerative Disorders, National Institute of Neurological Disorders and Stroke, Bethesda, Md.

REFERENCES

- Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
- Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med* 1991;115:455-6.
- 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.]
- Gebara OCE, Mittelman MA, Sutherland P, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation* 1995;91:1952-8.
- Koh KK, Mincemoyer R, Bui MN, et al. Effects of hormone-replacement therapy on fibrinolysis in postmenopausal women. *N Engl J Med* 1997;336:683-90.
- Sarrel P. Ovarian hormones and the circulation. *Maturitas* 1990;12:287-98.
- Lieberman EH, Gerhard MD, Uchata A, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994;121:936-41.
- Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-80.
- Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999;100:717-22.
- 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.
- Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal estrogen treatment and stroke: a prospective study. *BMJ* 1988;297:519-22.
- Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynecol* 1990;97:1080-6.
- Finucane FF, Madans JH, Bush TL, Wolf PH, Kleinman JC. Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993;153:73-9.
- Falkeborn M, Persson I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of stroke: follow-up of a population-based cohort in Sweden. *Arch Intern Med* 1993;153:1201-9.
- Pfeffer RI, Van Den Noort S. Estrogen use and stroke risk in postmenopausal women. *Am J Epidemiol* 1976;103:445-56.
- Pfeffer RI. Estrogen use, hypertension and stroke in postmenopausal women. *J Chronic Dis* 1978;31:389-98.
- Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Risk of vascular disease in women: smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *JAMA* 1979;242:1150-4.
- Rosenberg SH, Fausone V, Clark R. The role of estrogens as a risk factor for stroke in postmenopausal women. *West J Med* 1980;133:292-6.
- Boysen G, Nyboe J, Appleyard M, et al. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. *Stroke* 1988;19:1345-53.
- Thompson SG, Meade TW, Greenberg G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Community Health* 1989;43:173-8.
- Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997;350:1277-83.
- Petitti DB, Sidney S, Quesenberry CP Jr, Bernstein A. Ischemic stroke and use of estrogen and estrogen/progestogen as hormone replacement therapy. *Stroke* 1998;29:23-8.
- Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham Study. *N Engl J Med* 1985;313:1038-43.
- Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991;325:756-62.
- Kernan WN, Brass LM, Viscoli CM, Sarrel PM, Makuch R, Horwitz RI. Estrogen after ischemic stroke: clinical basis and design of the Women's Estrogen for Stroke Trial. *J Stroke Cerebrovasc Dis* 1998;7:85-95.
- Special report from the National Institute of Neurological Disorders and Stroke: classification of cerebrovascular diseases III. *Stroke* 1990;21:637-76.
- Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20:864-70.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *MD State Med J* 1965:61-5.
- Kernan WN, Horwitz RI, Brass LM, Viscoli CM, Taylor KJW. A prognostic system for transient ischemia or minor stroke. *Ann Intern Med* 1991;114:552-7.
- Karanjia PN, Nelson JJ, Lefkowitz DS, et al. Validation of the ACAS TIA/stroke algorithm. *Neurology* 1997;48:346-51.
- Padwick ML, Pryse-Davies J, Whitehead MI. A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. *N Engl J Med* 1986;315:930-4.
- Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas A-M, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90:583-612.
- TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI II A results. *JAMA* 1988;260:2849-58.
- Casagrande JT, Pike MC. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics* 1978;34:483-6.
- O'Brien PC, Fleming FR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Ravnikar V. Compliance with hormone therapy. *Am J Obstet Gynecol* 1987;156:1332-4.
- Berman R, Epstein R, Lydick E. Compliance of women in taking estrogen replacement therapy. *J Womens Health* 1996;5:213-20.
- Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61.
- Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638-42.
- Murphy DD, Cole NB, Greenberger V, Segal M. Estradiol increases dendritic density by reducing GABA neurotransmission in hippocampal neurons. *J Neurosci* 1998;18:2550-9.
- van Baal WM, Kenemans P, van der Mooren MJ, Kessel H, Emeis JJ, Stehouwer CD. Increased C-reactive protein levels during short-term hormone replacement therapy in healthy postmenopausal women. *Thromb Haemost* 1999;81:925-8.

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