Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative

Susan L. Hendrix, DO; Sylvia Wassertheil-Smoller, PhD; Karen C. Johnson, MD, MPH; Barbara V. Howard, PhD; Charles Kooperberg, PhD; Jacques E. Rossouw, MD; Maurizio Trevisan, MD, PhD; Aaron Aragaki, MS; Alison E. Baird, MD, PhD; Paul F. Bray, MD; Julie E. Buring, ScD; Michael H. Criqui, MD, MPH; David Herrington, MD; John K. Lynch, DO, MPH; Stephen R. Rapp, PhD; James Torner, PhD; for the WHI Investigators*

Background—The Women's Health Initiative (WHI) Estrogen Alone trial assessed the balance of benefits and risks of hormone use in healthy postmenopausal women. The trial was stopped prematurely because there was no benefit for coronary heart disease and an increased risk of stroke. This report provides a thorough analysis of the stroke finding using the final results from the completed trial database.

Methods and Results—The WHI Estrogen Alone hormone trial is a multicenter, double-blind, placebo-controlled, randomized clinical trial in 10 739 women aged 50 to 79 years who were given daily conjugated equine estrogen (CEE; 0.625 mg; n=5310) or placebo (n=5429). During an average follow-up of 7.1 years, there were 168 strokes in the CEE group and 127 in the placebo group; 80.3% of strokes were ischemic. For all stroke the intention-to-treat hazard ratio [HR] (95% CI) for CEE versus placebo was 1.37 (1.09 to 1.73). The HR (95% CI) was 1.55 (1.19 to 2.01) for ischemic stroke and 0.64 (0.35, 1.18) for hemorrhagic stroke. The HRs indicate excess risk of ischemic stroke was apparent in all categories of baseline stroke risk, including younger and more recently menopausal women and in women with prior or current use of statins or aspirin.

Conclusions—CEE increases the risk of ischemic stroke in generally healthy postmenopausal women. The excess risk appeared to be present in all subgroups of women examined, including younger and more recently menopausal women. There was no convincing evidence to suggest that CEE had an effect on the risk of hemorrhagic stroke. **(*Circulation*. 2006;113:2425-2434.)**

Key Words: women ■ stroke ■ hormones ■ estrogen

Stroke is a major health problem for women as they age.[1] Ischemic stroke is uncommon in women before menopause, which led to the premise that reproductive hormones protect women from stroke before menopause.[2,3] In addition, laboratory data and animal models have long suggested a beneficial effect of estrogen on the brain.[4–6] Recent clinical trial data, however, have challenged the assumption that hormone therapy might protect against cerebrovascular disease.[7,8] Although the observational data suggested that hormone use was protective for coronary heart disease,[9–13] the effect on stroke was less consistent.[14–17] The Framingham Study reported a 2-fold increased risk of stroke in estrogen users,[14] whereas the Nurse's Health Study reported no increase in the risk of stroke in hormone users.[18] Two subsequent observational studies reported a risk reduction in stroke with hormone use,[15,16] and 1 showed a transient increase in stroke.[17] The Women's Estrogen for Stroke Trial (WEST) of estradiol alone in women who had a prior stroke indicated higher event rates in the

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From the Department of Obstetrics and Gynecology (S.L.H.), Wayne State University School of Medicine/Hutzel Women's Hospital, Detroit, Mich; The Albert Einstein College of Medicine (S.W.-S.), Bronx, NY; Department of Preventive Medicine (K.C.J.), University of Tennessee Health Science Center, Memphis, Tenn; MedStar Research Institute (B.V.H.), Washington, DC; Fred Hutchinson Cancer Research Center (C.K., A.A.), Seattle, Wash; National Heart, Lung, and Blood Institute (J.E.R.), Bethesda, Md; State University of New York (M.T.), Buffalo, NY; National Institute of Neurological Disorders and Stroke, Stroke Neuroscience Unit (A.E.B.) and Neuroepidemiology Branch (J.K.L.), Bethesda, Md; Baylor College of Medicine (P.F.B.), Houston, Tex; Harvard Medical School (J.E.B.), Boston, Mass; University of California at San Diego (M.H.C.), La Jolla, Calif; Wake Forest University Health Sciences (D.H., S.R.R.), Winston-Salem, NC; and Department of Epidemiology (J.T.), University of Iowa College of Public Health, Iowa City, Iowa.

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***The online-only Data Supplement, which lists the Women's Health Initiative Investigators, can be found at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.594077/DC1.**

Correspondence to Susan L. Hendrix, DO, Department of Obstetrics and Gynecology, Wayne State University/Hutzel Women's Hospital, 3990 John R, 7 Brush North, Detroit, MI 48201. E-mail shendrix@med.wayne.edu

estrogen group relative to placebo during the first 6 months and an overall null result.[19]

The Women's Health Initiative[1] (WHI) conducted 2 separate randomized, double-blind, clinical trials of the effects of long-term use of hormones: estrogen plus progestin (E+P) versus placebo among women with an intact uterus and estrogen alone versus placebo among women who had had a hysterectomy. In 2002, the clinical trial of E+P was terminated 3 years before its planned completion date because of an increase in breast cancer risk and cardiovascular disease (CVD), including stroke, and no overall benefit.[20] After an average 5.6 years of follow-up, there was a 31% increase in overall stroke risk and a 44% increase in ischemic stroke risk in the E+P group compared with placebo.[21]

At the time the E+P trial was stopped, it was not known whether estrogen alone would have similar or different effects. In February 2004, the E-alone trial was stopped after an average of 7.1 years of follow-up, before its planned completion in September 2005, because interim data indicated an excess stroke risk with estrogen alone and no indication for coronary heart disease or overall benefit.[22] The present report differs from the initial report because it includes 19 additional adjudicated stroke cases that occurred before trial termination and additional detail on stroke subtypes and severity. Furthermore, the present report examines stroke risk in subgroups of women and compares the effects of estrogen alone with E+P using data from the 2 WHI trials of hormones.

Methods

Study Population

Details of the study design and baseline characteristics have been published elsewhere.[23,24] Women aged 50 to 79 years were eligible for the WHI Estrogen Alone trial if they had a hysterectomy, with or without an oophorectomy, had no history of breast cancer ever or of other cancers within the past 10 years (except nonmelanoma skin cancer), had not had a heart attack or stroke within the past 6 months, had a predicted survival of 3 or more years, and planned to remain in the area for at least 3 years.[25] Women with systolic blood pressure (SBP) >200 mm Hg or diastolic blood pressure (DBP) >105 mm Hg were told to see their physician within a predefined period of time depending on level of blood pressure and were not eligible to participate in the study until their blood pressure was under control. Those women who were currently taking hormones were required to have a 3-month washout period before their baseline visit. The study was approved by the institutional review committee at each site.

Study Medication

After giving written informed consent, women were randomized to conjugated equine estrogen (CEE) 0.625 mg/d (Premarin) or a matching placebo provided by Wyeth-Ayerst (St. Davids, Pa). Study medication was discontinued permanently by protocol for women who developed breast cancer, deep vein thrombosis, pulmonary embolism, malignant melanoma, meningioma, or a triglyceride level >1000 mg/dL (11.3 mmol/L) or who received a prescription for estrogen, testosterone, or selective estrogen-receptor modulators from their personal physician. Participants who had acute myocardial infarction, stroke, fracture, or major injury involving hospitalization; surgery involving use of anesthesia; or any illness resulting in immobilization for >1 week were temporarily discontinued from study medications, but the medications could be restarted if medically appropriate.

Follow-Up and End-Point Determination

Data were collected semiannually on potential outcome events from participants. When such an event was identified from self-report questionnaires, medical records information and death certificates were obtained, and the potential outcome was adjudicated by a trained local physician.[26] Subsequently, all locally adjudicated stroke cases, as well as all self-reported strokes not deemed to have been strokes by the local adjudicators, were forwarded to study neurologists for central adjudication. This report presents stroke data centrally confirmed by neurologists. Local and central adjudicators were blinded to treatment assignment.

The stroke diagnosis requiring and/or occurring during hospitalization was based on the rapid onset of a neurological deficit attributable to an obstruction or rupture of the arterial system that was not known to be secondary to brain trauma, tumor, infection, or other cause. The neurological deficit lasted >24 hours unless death supervened or there was a demonstrable lesion on computed tomography or MRI compatible with an acute stroke. Strokes were classified as ischemic or hemorrhagic on review of reports of brain imaging studies. A stroke was defined as procedure-related if it occurred within 24 hours after any procedure or within 30 days after cardioversion or an invasive cardiovascular procedure. Six categories of stroke were combined into 3 final categories that included hemorrhagic, ischemic, and other stroke; additional details are provided elsewhere.[21] Subarachnoid hemorrhage not resulting from a procedure was included as 1 of the stroke categories above.

Ischemic strokes were further classified by the central neurologist adjudicators according to the Oxfordshire[27] and TOAST[28] (the Trial of Org 10172 Acute Stroke Treatment) criteria to look at stroke subtypes. The Oxfordshire classification is based on clinical assessment of the patient in whom a computed tomographic brain scan has excluded cerebral hemorrhage and describes the location of the stroke. The TOAST classification focuses on the presumed underlying stroke mechanism, and its use requires extensive clinical diagnosis and workup. The Glasgow Outcome Scale score was ascertained on the basis of clinical information available at the time of hospital discharge to provide an assessment of severity of stroke outcome.[29]

Definition of Variables

Hypertension was defined as either a self-report of taking medications for hypertension or an elevation of blood pressure (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) measured at the first clinic visit by certified staff using standardized procedures and instruments, with a conventional mercury sphygmomanometer. The participant was seated and resting for 5 minutes before blood pressure measurement, and the average of 2 seated readings, obtained at least 30 seconds apart, was used for analyses.

Vasomotor symptoms were assessed from responses to questions on the presence of hot flashes or night sweats (none, mild, moderate, or severe) from the entire cohort at baseline and 1 year. A 12-lead ECG was performed at baseline and every 3 years. Framingham stroke risk scores were calculated, providing estimates of the probability of stroke within 10 years for women aged 55 to 84 years, on the basis of use of antihypertensive medications and SBP, age, diabetes mellitus, cigarette smoking, prior CVD, atrial fibrillation, and left ventricular hypertrophy by ECG.[30]

Statistical Analyses

Baseline characteristics were compared between placebo and CEE groups by t tests and χ^2 tests of association. The Fisher exact test was used for comparisons between randomization assignment and stroke-severity classification. The Cochran-Armitage test was used to determine whether treatment assignment was associated with a linear trend in stroke severity.

Cox proportional hazards analyses and Kaplan-Meier curves were used to compare outcome event rates. Additional analyses examined effects of CEE in 14 subgroups of special clinical interest: by age group, race/ethnicity, years since menopause, years since bilateral oophorectomy, prior history of CVD (angina, myocardial infarction, stroke, congestive heart failure, CABG, or PTCA), hypertensive status, treatment for diabetes mellitus, body mass index, smoking, duration of prior hormone use, statin use, aspirin use, vasomotor symptoms at baseline, and tertiles of Framingham stroke risk score at baseline.

All primary analyses of time-to-first stroke were based on the intention-to-treat principle. The effect modification of stroke risk with CEE by subgroups was assessed one at a time by testing

whether the interaction of time and CEE was significant. All Cox models were stratified on the basis of age, prior stroke, and randomization assignment in the dietary modification trial. The proportional hazards assumption was verified by visual inspection and by formally testing the interaction of time and CEE and was not statistically significant. Secondary analyses were performed to adjust for pill-taking adherence to determine whether any risk conferred by CEE could be explained by increases in SBP during follow-up, to account for differential aspirin or statin use during follow-up, and whether risk differed by stroke type. These analyses were planned a priori by the writing group before data analysis. In the adherence-adjusted analyses, participants' event histories were censored 6 months after they became nonadherent (defined as taking fewer than 80% of study pills). A Cox model that included follow-up SBP as a time-dependent covariate was used to estimate the risk of estrogen unrelated to any effect on SBP. Differential use of aspirin and statin during follow-up was also adjusted for by fitting these variables as time-dependent covariates. Differences in risk between ischemic and hemorrhagic strokes were assessed by competing-risks analysis using Cox models. Significance was based on a Wald χ^2 test of scaled coefficient differences. Analyses were performed by SAS statistical software version 9.0 (SAS Inc, Cary, NC).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

In the estrogen-alone trial, there were 10 739 women eligible and randomized to CEE (n=5310) or placebo (n=5429). Vital status was known for 10 176 participants (94.8%; see flow diagram in original report[22]). During follow-up, 5.2% of women withdrew, were considered lost to follow-up, or had stopped providing outcomes information for >18 months. By March 1, 2004, at study termination, 54.0% of CEE participants and 53.5% of placebo participants had discontinued their study medication.

Baseline Characteristics

Baseline characteristics of the CEE and placebo groups are shown in Table 1. There were no significant differences between the 2 groups. The average age was 63.6 years, and 30.8% were in the 50-to-59-year-old age group. More than 50% had never used hormones before enrollment. Thirteen percent of participants in both groups were current hormone users at baseline and were required to have a 3-month washout before randomization. Prior stroke was reported by 1.6%, transient ischemic attack by 2.4%, hypertension by 48%, and treated diabetes mellitus by 7.7%, and 10.5% were current smokers.

Stroke and Stroke Subtype Events

During an average (SD) follow-up of 7.1 (1.6) years, there were 168 strokes in the CEE group and 127 in the placebo group (Table 2). The intention-to-treat hazard ratio [HR] (95% CI) for all stroke subtypes combined for estrogen alone versus placebo was 1.37 (1.09 to 1.73) and included ischemic strokes, hemorrhagic strokes, and other types of strokes. Other strokes that could not be classified as either ischemic or hemorrhagic made up <5% of all stroke subtypes combined and are presented in Table 3. The HR (95% CI) was 1.55 (1.19 to 2.01) for ischemic stroke and 0.64 (0.35 to 1.18) for hemorrhagic stroke. Ischemic strokes accounted for 80.3% of all strokes (84.5% in the CEE group and 74.8% in the placebo group), and hemorrhagic strokes accounted for 14.9% (10.1% for CEE and 21.3% for placebo). Sensitivity analyses were conducted to evaluate the effect of lack of adherence to assigned study medication. With adherence adjustment, the HR (95% CI) was 1.93 (1.34 to 2.78) for ischemic stroke and 1.16 (0.48 to 2.82) for hemorrhagic stroke (Table 2). A competing-risks analysis suggested that the HRs for ischemic and hemorrhagic stroke were different (P=0.009). There were no significant differences in distribution of stroke subtypes or severity by the Glasgow Outcome Scale, including fatal strokes, in the CEE or placebo groups (Table 3).

Subgroup Analyses for Ischemic Strokes

To determine whether subgroups of women were at lower or higher risk for ischemic stroke events with CEE, we evaluated several demographic and clinical characteristics. Analyses of the more biologically plausible clinical variables are shown in Table 4.

HRs for ischemic strokes did not differ significantly in the different subgroups based on age, race or ethnicity, years since menopause or bilateral oophorectomy, prior CVD, hypertension status or diabetes mellitus, body mass index, smoking, prior hormone use, Framingham risk score, vasomotor symptoms at baseline, or statin or aspirin use at baseline. Because these subgroups may be of particular interest to some readers, point estimates and CIs are shown even if a null finding was found.

Cumulative hazard rates for ischemic stroke are shown by age decade in Table 4. For participants aged 50 to 59, 60 to 69, and 70 to 79 years at baseline, HRs with 95% CIs were 1.09 (0.54 to 2.21), 1.72 (1.17 to 2.54), and 1.52 (1.02 to 2.29), respectively (P for interaction=0.95). However, the HR was 2.62 (1.01 to 6.81) for women <10 years since menopause and 2.48 (0.64 to 9.63) for women whose bilateral oophorectomy had been performed within the past 10 years. Those with no prior history of CVD had an HR of 1.73 for CEE compared with placebo (95% CI 1.28 to 2.33), whereas those with a history of CVD had an HR of 1.01, (95% CI 0.58 to 1.75, P=0.09).

The HR for ischemic stroke was similar among white, black, and Hispanic women (Table 4; Figure 1). Because the number of events in women of other races was small, and some racial subgroups did not have any stroke events, we were unable to estimate the HR in some categories (Table 4). In analyses adjusted for adherence, the HRs (95% CIs) increased for blacks to 3.48 (1.12 to 10.80) and for Hispanics to 4.03 (0.45 to 36.11) and remained relatively unchanged for whites at 1.67 (1.12 to 2.50).

Blood Pressure Effects

As reported previously,[22] SBP at year 1 was higher by a mean (SE) of 1.1 (0.4) mm Hg in women taking CEE than in women taking placebo (P=0.003) and remained similarly elevated throughout follow-up. Because SBP is a strong risk factor for stroke, we explored the relationship of stroke risk to blood pressure more extensively by adjusting for SBP as a time-dependent covariable and estimating the HRs for comparisons of CEE with placebo on the risk of both ischemic and hemorrhagic stroke (Table 2). The addition of SBP as a time-dependent covariable did not appreciably change the risk associated with CEE use. The HR for ischemic stroke changed from 1.55 to

TABLE 1. Baseline Characteristics of the WHI Estrogen-Alone Trial Participants With Prior Hysterectomy (n=10 739) by Randomization Assignment*

Characteristics	CEE (n=5310)	Placebo (n=5429)	P*
Age group at screening, y			0.85
50–59	1637 (30.8)	1673 (30.8)	
60–69	2387 (45.0)	2465 (45.4)	
70–79	1286 (24.2)	1291 (23.8)	
Race/ethnicity			0.81
White	4007 (75.5)	4075 (75.1)	
Black	782 (14.7)	835 (15.4)	
Hispanic	322 (6.1)	333 (6.1)	
American Indian	41 (0.8)	34 (0.6)	
Asian/Pacific Islander	86 (1.6)	78 (1.4)	
Unknown	72 (1.4)	74 (1.4)	
Smoking			0.33
Never	2723 (51.9)	2705 (50.4)	
Past	1986 (37.8)	2089 (38.9)	
Current	542 (10.3)	571 (10.6)	
Hormone use			0.50
Never	2769 (52.2)	2770 (51.1)	
Past	1871 (35.2)	1948 (35.9)	
Current	669 (12.6)	708 (13.0)	
Duration of prior hormone use, y			0.65
<5	1352 (53.2)	1412 (53.1)	
5–10	469 (18.5)	515 (19.4)	
≥10	720 (28.3)	732 (27.5)	
Statin use at baseline†	394 (7.4)	427 (7.9)	0.39
Aspirin use (≥80 mg/d) at baseline	1030 (19.4)	1069 (19.7)	0.70
Hypertension‡	2386 (48.0)	2387 (47.4)	0.56
History of CVD§	477 (9.1)	469 (8.7)	0.53
History of MI	165 (3.1)	172 (3.2)	0.86
History of stroke	76 (1.4)	92 (1.7)	0.27
History of TIA	136 (2.6)	125 (2.3)	0.38
ECG rhythm (atrial fibrillation)	5 (0.1)	10 (0.2)	0.21
LVH (Minnesota code)	361 (6.9)	371 (7.0)	0.97
Treated for diabetes (pills or shots)	410 (7.7)	411 (7.6)	0.78
History of carotid endarterectomy/angioplasty	20 (0.4)	18 (0.3)	0.69
Framingham risk			0.46
Lower tertile (0–5)	1544 (29.1)	1557 (28.7)	
Middle tertile (6–9)	1874 (35.3)	1978 (36.4)	
Upper tertile (10–25)	1892 (35.6)	1894 (34.9)	
Dietary modification trial			0.45
Control	1039 (19.6)	1068 (19.7)	
Intervention	615 (11.6)	670 (12.3)	
Not randomized	3656 (68.9)	3691 (68.0)	
Body mass index, mean (SD), kg/m^2	30.1 (6.1)	30.1 (6.2)	0.88
Blood pressure, mean (SD), mm Hg			
Systolic	130.4 (17.5)	130.2 (17.6)	0.70
Diastolic	76.6 (9.2)	76.5 (9.4)	0.79
Pulse pressure	53.8 (15.3)	53.7 (15.0)	0.78

MI indicates myocardial infarction; TIA, transient ischemic attack; and LVH, left ventricular hypertrophy.

Values are n (%) unless otherwise indicated. Percentages may not sum to 100 due to rounding. Some of the categories do not sum to the totals due to missing data.

*Categorical variables are based on χ^2 tests, and continuous variables are based on t tests.

†Statins are 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

‡Hypertension was defined as taking medication or having high SBP (≥140 mm Hg) or DBP (≥90 mm Hg).

§Includes self-reported history of MI, angina, stroke, congestive heart failure, CABG, and PTCA.

TABLE 2. Counts of Stroke Events, Annualized Percentages, and HRs of the WHI Estrogen-Alone Trial Participants by Randomization Assignment and in Selected Subgroups

Outcomes	No. (Annualized %) CEE (n=5310)	Placebo (n=5429)	HR (95% CI)*	P
Follow-up time, mean (SD), mo	85.0 (19.5)	85.4 (19.8)		
All stroke	168 (0.45)	127 (0.33)	1.37 (1.09–1.73)	0.008
Ischemic stroke	142 (0.38)	95 (0.25)	1.55 (1.19–2.01)	0.001
Adjusted for adherence			1.93 (1.34–2.78)	<0.001
Adjusted for SBP (time dependent)			1.51 (1.16–1.96)	0.002
Adjusted for statin use (time dependent)			1.53 (1.18–1.99)	0.001
Adjusted for aspirin use (time dependent)			1.55 (1.19–2.01)	0.001
Hemorrhagic stroke	17 (0.05)	27 (0.07)	0.64 (0.35–1.18)	0.15
Adjusted for adherence			1.16 (0.48–2.82)	0.74
Adjusted for SBP (time dependent)			0.63 (0.34–1.16)	0.14
Adjusted for statin use (time dependent)			0.64 (0.35–1.18)	0.15
Adjusted for aspirin use (time dependent)			0.64 (0.35–1.18)	0.16

*From Cox regression model stratified by age, previous stroke, and dietary modification randomization assignment.

1.51, and the HR for hemorrhagic stroke changed from 0.64 to 0.63. Thus, the effect of CEE on SBP did not explain the excess risk for ischemic stroke observed in the intention-to-treat analysis. DBP did not differ significantly between treatment assignments during follow-up and thus was not used in the Cox proportional hazards models in Table 2.

Statin and Aspirin Use

There was differential use of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) over time between the CEE and placebo groups. For the CEE participants, statin use was 7.4% at baseline, 9.0% at year 1, and 19.8% at year 6, and in the placebo group, it was 7.9% ($P=0.39$ versus CEE), 10.7% ($P=0.004$ versus CEE), and 27.3% ($P<0.001$ versus CEE), respectively. There was no appreciable change in the HR for stroke for CEE versus placebo when statin use was treated as a time-dependent covariable in the model (HR for ischemic stroke changed from 1.55 to 1.53; hemorrhagic stroke remained at 0.64; Table 2). Thus, differential statin use over time did not explain the increased risk of ischemic stroke observed in the CEE group.

There was no detectable difference in aspirin use during follow-up between the CEE and placebo groups (eg, 19.1% and 19.2% of participants given placebo and CEE were using aspirin at year 1, ≥80 mg/d for longer than a month, respectively; $P=0.88$). When aspirin use as a time-dependent covariable was added to the model, the risk of stroke in the CEE group compared with the placebo group was basically unchanged, with an HR (95% CI) of 1.55 (1.19 to 2.01) for ischemic stroke and 0.64 (0.35 to 1.18) for hemorrhagic stroke (Table 2).

Comparison of Effects of CEE and E+P

The overall effects of estrogen alone or E+P on ischemic stroke are similar, although they may differ in magnitude and timing (Figure 2). The event rates in the estrogen-alone trial were slightly higher than in the E+P trial. The annualized event rate for estrogen alone was 38 per 10 000 women; for E+P, it was 26 per 10 000 women; and for the placebo groups in estrogen alone and E+P, they were 25 and 18 per 10 000 women, respectively.[20,22] Figure 2 shows the cumulative hazards of ischemic stroke for women in the estrogen-alone and E+P trials. In the E+P trial, the actively treated group began to show an increased risk of stroke by year 2 of follow-up, whereas in the estrogen0alone trial, the increased risk in the actively treated group did not appear until after 4 years of follow-up.

Because there were small numbers of hemorrhagic strokes in each of the 2 trials, and because the effects of estrogen alone (HR 0.64, 95% CI 0.35 to 1.18) or E+P (HR 0.82, 95% CI 0.43 to 1.56) were in a similar direction, we combined women in the 2 trials to examine the effects of hormone therapy on hemorrhagic stroke. The resulting HR (95% CI) of 0.72 (0.47 to 1.12) for the 2 trials combined shows no significant effect of hormone therapy on hemorrhagic stroke. In the estrogen-alone trial we could not detect a statistically significant interaction between aspirin use at baseline and randomization assignment and risk of hemorrhagic stroke ($P=0.10$), although the point estimate was lower for participants not using aspirin, at 0.46 (95% CI 0.22 to 0.97), than for those using aspirin at baseline (1.47; 95% CI 0.46 to 4.67). Among participants who experienced a hemorrhagic stroke, 7 taking CEE and 5 taking placebo were taking aspirin at baseline (10 and 22 patients in the CEE and placebo groups, respectively, were not taking aspirin). Even after the 2 trials were combined, there was no compelling evidence of an interaction with aspirin, with an HR (95% CI) of 0.60 (0.36 to 1.01) for nonusers at baseline and 1.19 (0.51 to 2.77) for aspirin users at baseline.

Discussion

CEE increases the risk of ischemic stroke in generally healthy postmenopausal women, and this excess risk was present in all subgroups of women examined. This trial was unable to detect an effect of CEE on the risk of hemorrhagic stroke, in part because of the low number of hemorrhagic strokes. The

TABLE 3. Diagnosis, Classification, and Severity of Centrally Adjudicated Stroke in the WHI Estrogen-Alone Trial Participants With Prior Hysterectomy (n=10 739) by Randomization Assignment*

Variables	No. (%) CEE (n=5310)	Placebo (n=5429)	P†
Stroke diagnosis			
Ischemic stroke‡	142 (84.5)	95 (74.8)	0.01‖
Hemorrhagic stroke§	17 (10.1)	27 (21.3)	
Subarachnoid	6 (3.6)	8 (6.3)	
Intraparenchymal	10 (6.0)	18 (14.2)	
Other or unspecified intracranial	1 (0.6)	1 (0.8)	
Other stroke¶	1 (0.6)	1 (0.8)	
Report of cerebrovascular death only#	7 (4.2)	4 (3.2)	
Not yet categorized**	1 (0.6)	0 (0)	
Total	168 (100)	127 (100)	
TOAST classification of ischemic stroke			
Large-artery atherosclerosis	8 (5.6)	7 (7.4)	0.43
Cardioembolism	26 (18.3)	13 (13.7)	
Small-vessel occlusion	33 (23.2)	23 (24.2)	
Stroke of other determined origin	9 (6.3)	12 (12.6)	
Stroke of undetermined origin	66 (46.5)	40 (42.1)	
≥2 Causes identified	5 (3.5)	3 (3.2)	
Negative evaluation	28 (19.7)	19 (20.0)	
Incomplete evaluation	33 (23.2)	18 (18.9)	
Total	142 (100)	95 (100)	
Oxfordshire classification of ischemic stroke			
Total anterior circulation infarct	6 (4.2)	7 (7.4)	0.46
Partial anterior circulation infarct	64 (45.1)	46 (48.4)	
Lacunar infarct	43 (30.3)	29 (30.5)	
Posterior circulation infarct	29 (20.4)	13 (13.7)	
Total	142 (100)	95 (100)	
Glasgow Outcome Scale††			
Good recovery	47 (28.0)	39 (30.7)	0.71
Moderately disabled	44 (26.2)	30 (23.6)	
Severely disabled	44 (26.2)	28 (22.1)	
Vegetative survival	0 (0.0)	1 (0.8)	
Death#	17 (10.1)	15 (11.8)	
Unable to categorize outcome	15 (8.9)	14 (11.0)	
Not yet categorized**	1 (0.6)	0 (0)	
Total	168 (100)	127 (100)	

*Percentages may not sum to 100 due to rounding. Some of the categories do not sum to the totals due to missing data.

†*P* value based on Fisher exact test. Unless noted otherwise, test of association is between randomization assignment and main stroke classifications indicated by braces.

‡Occlusion of cerebral arteries with infarction.

§Subarachnoid, intracerebral, or other or unspecified intracranial hemorrhage (nontraumatic subdural or extradural hematomas).

‖Only ischemic and hemorrhagic classifications considered.

¶Acute but ill-defined cerebrovascular disease or procedure-related stroke.

#Includes 1 death that was locally confirmed and not yet centrally confirmed.

**Only locally confirmed and not yet centrally confirmed.

††*P* value for 1-sided Cochran-Armitage test for trend was 0.49.

similarity in the results in the 2 independent trials (with slightly different baseline risk levels) substantially strengthens the overall findings and implicates estrogen (as opposed to progestin) as the more likely cause of stroke. This finding is consistent with previous research reporting that progestin-only oral contraceptives did not increase the risk of stroke.[31]

In the estrogen-alone trial, similar to the E+P trial, 80% of all strokes were ischemic, whereas 15% were hemorrhagic. The increased risk of stroke appears to be primarily related to ischemic stroke. In an attempt to better understand the effect of hormone therapy on hemorrhagic stroke, we combined the estrogen-alone and E+P hemorrhagic stroke outcomes to increase power. Although the result was not statistically significant, the point estimate of the risk ratio was below unity in both studies, which suggests that estrogen with or without progestin therapy is unlikely to increase the risk of hemorrhagic stroke.

The theoretical "neuroprotective" effect of estrogen causing less severe strokes and better stroke outcome[32] was not confirmed in the present study, similar to the E+P trial. There were no differences in stroke severity as categorized by the Glasgow Outcome Scale. There was no different pattern of distribution of stroke classification (TOAST and Oxfordshire) when we compared CEE with placebo. The numbers of deaths were balanced between the CEE and placebo groups.

The stroke risk did not vary significantly with the severity of vasomotor symptoms, statin or aspirin use, or previous hormone use. Although the HRs of blacks and Hispanics were similar to those of whites, when adjusted for adherence (on average, blacks/Hispanics had lower adherence than whites), the HRs had a more marked increase than in whites. Thus, the absolute risk for blacks may be higher overall because of a higher background risk. These findings are similar to those of other studies and remain unexplained.[33,34]

Because use of statins or aspirin had no effect modification on the HR estimate for stroke outcome in the present trial, clinical use of statins or aspirin is unlikely to prevent stroke in women taking CEEs. Consideration of factors such as high blood pressure, diabetes mellitus, or a high Framingham risk score is relevant to clinical decision making when hormone therapy is prescribed, because estrogen use may further increase the risk of stroke in these women who have a high underlying risk of stroke.

Women without a history of CVD who were assigned CEE had an elevated relative risk of stroke compared with similar women given placebo (HR 1.73). In contrast, in women with a prior history of CVD, there was no difference in stroke rates between the 2 treatment groups (HR 1.01). Similarly, increased stroke risk associated with CEE appeared to be lower in the 50-to-59-year-old group (HR 1.09) than in the 60-to-69-year-old group (HR 1.72) or the 70-to-79-year-old group (HR 1.52), but when tested statistically, the interaction with age was not significant. Furthermore, there was no evidence of a differential effect of CEE by years since menopause or years since bilateral oophorectomy. In the E+P trial, the highest HR was observed for women aged 50 to 59 years, and years since menopause did not play a role.[21] Although the small numbers in these subgroups prevent us from drawing definitive conclusions, overall, the WHI findings do not

TABLE 4. Counts of Ischemic Stroke Events, Annualized Percentages, and HRs of the WHI Estrogen-Alone Trial Participants by Randomization Assignment and in Selected Subgroups*

Outcomes	No. (Annualized %) CEE (n=5310)	Placebo (n=5429)	HR (95% CI)†	P
Age, y‡				0.95§
50–59	16 (0.13)	15 (0.12)	1.09(0.54–2.21)	
60–69	68 (0.41)	41 (0.24)	1.72(1.17–2.54)	
70–79	58 (0.66)	39 (0.44)	1.52(1.02–2.29)	
Race or ethnicity				0.93
White	106 (0.37)	70 (0.24)	1.55(1.15–2.10)	
Black	28 (0.51)	19 (0.32)	1.61(0.90–2.90)	
Hispanic	6 (0.26)	3 (0.13)	2.02(0.50–8.09)	
American Indian	1 (0.36)	1 (0.42)	N/A	
Asian/Pacific Islander	0 (0.00)	2 (0.37)	N/A	
Unknown	1 (0.20)	0 (0.00)	N/A	
Years since menopause				0.16§
<10	15 (0.25)	6 (0.10)	2.62(1.01–6.81)	
10 to 20	35 (0.34)	22 (0.21)	1.66(0.97–2.82)	
≥20	72 (0.47)	57 (0.35)	1.32(0.93–1.87)	
Years since bilateral oophorectomy				0.64
Never had bilateral oophorectomy	76 (0.36)	54 (0.26)	1.42(1.00–2.01)	
<10 y	7 (0.37)	3 (0.15)	2.48(0.64–9.63)	
10–20 y	18 (0.37)	8 (0.15)	2.34(1.01–5.38)	
≥20 y	30 (0.45)	23 (0.31)	1.46(0.85–2.51)	
Prior history of CVD‖				0.09
No	113 (0.34)	68 (0.20)	1.73(1.28–2.33)	
Yes	26 (0.68)	26 (0.69)	1.01(0.58–1.75)	
Hypertension status				0.77
No	35 (0.19)	21 (0.11)	1.73(1.00–2.97)	
Yes	100 (0.61)	65 (0.39)	1.57(1.15–2.15)	
Treated for diabetes (pills or shots)				0.23
No	119 (0.34)	84 (0.23)	1.46(1.10–1.93)	
Yes	23 (0.84)	11 (0.39)	2.34(1.14–4.81)	
Body mass index, kg/m^2				0.70§
<25	30 (0.38)	18 (0.23)	1.67(0.93–3.00)	
25–29	42 (0.33)	28 (0.21)	1.59(0.98–2.56)	
≥30	69 (0.41)	48 (0.28)	1.47(1.01–2.13)	
Smoking				0.89
Never	68 (0.35)	47 (0.24)	1.46(1.00–2.12)	
Past	56 (0.40)	36 (0.24)	1.66(1.09–2.53)	
Current	15 (0.40)	11 (0.28)	1.44(0.66–3.13)	
Duration of prior hormone use, y				0.29
None	78 (0.40)	40 (0.20)	2.00(1.37–2.94)	
<5	35 (0.36)	28 (0.28)	1.32(0.80–2.18)	
5 to 10	11 (0.33)	10 (0.27)	1.14(0.49–2.70)	
≥10	18 (0.36)	17 (0.33)	1.08(0.56–2.11)	
Statin use				0.36
No	131 (0.37)	90 (0.25)	1.49(1.14–1.95)	
Yes	11 (0.41)	5 (0.17)	2.48(0.86–7.15)	

TABLE 4. Continued

Outcomes	No. (Annualized %) CEE (n=5310)	Placebo (n=5429)	HR (95% CI)†	*P*
Aspirin use				0.88
No	106 (0.35)	69 (0.22)	1.57(1.16–2.12)	
Yes	36 (0.50)	26 (0.35)	1.50(0.90–2.48)	
Moderate or severe vasomotor symptoms¶				0.45
No	118 (0.38)	75 (0.24)	1.63(1.22–2.17)	
Yes	22 (0.34)	18 (0.27)	1.25(0.67–2.33)	
Framingham stroke risk				0.23
Low risk, first tertile	7 (0.06)	7 (0.06)	0.89(0.34–2.31)	
Medium risk, second tertile	45 (0.33)	20 (0.14)	1.87(1.19–2.92)	
High risk, third tertile	90 (0.70)	68 (0.52)	1.26(0.95–1.67)	

*Some of the categories may not sum to the total number of strokes per treatment group because of missing data.
†From Cox regression model stratified by age, previous stroke, and dietary modification randomization assignment.
‡From Cox regression model stratified by previous stroke and dietary modification randomization assignment.
§Continuous values were used in the tests for interaction with treatment assignment.
‖From Cox regression model stratified by age and dietary modification randomization assignment.
¶Symptoms were night sweats, hot flashes, or both.

support a suggestion of lower risk of stroke in younger women or more recently menopausal women randomized to menopausal hormone therapy. This issue will be examined in more detail in combined analyses of the 2 trials.

Limitations to the present study include its restriction to postmenopausal women taking 1 formulation of estrogen, CEE, at a single dose of 0.625 mg. Because we only studied 1 formulation of estrogen, the impact of other estrogen preparations on stroke risk remains uncertain.

In summary, these results from a large, randomized, double-blind, clinical trial conducted across the United States in healthy menopausal women indicate that CEE use causes a significant increase in the risk of ischemic stroke. There was no indication that the risk of estrogen use was different in any subgroup

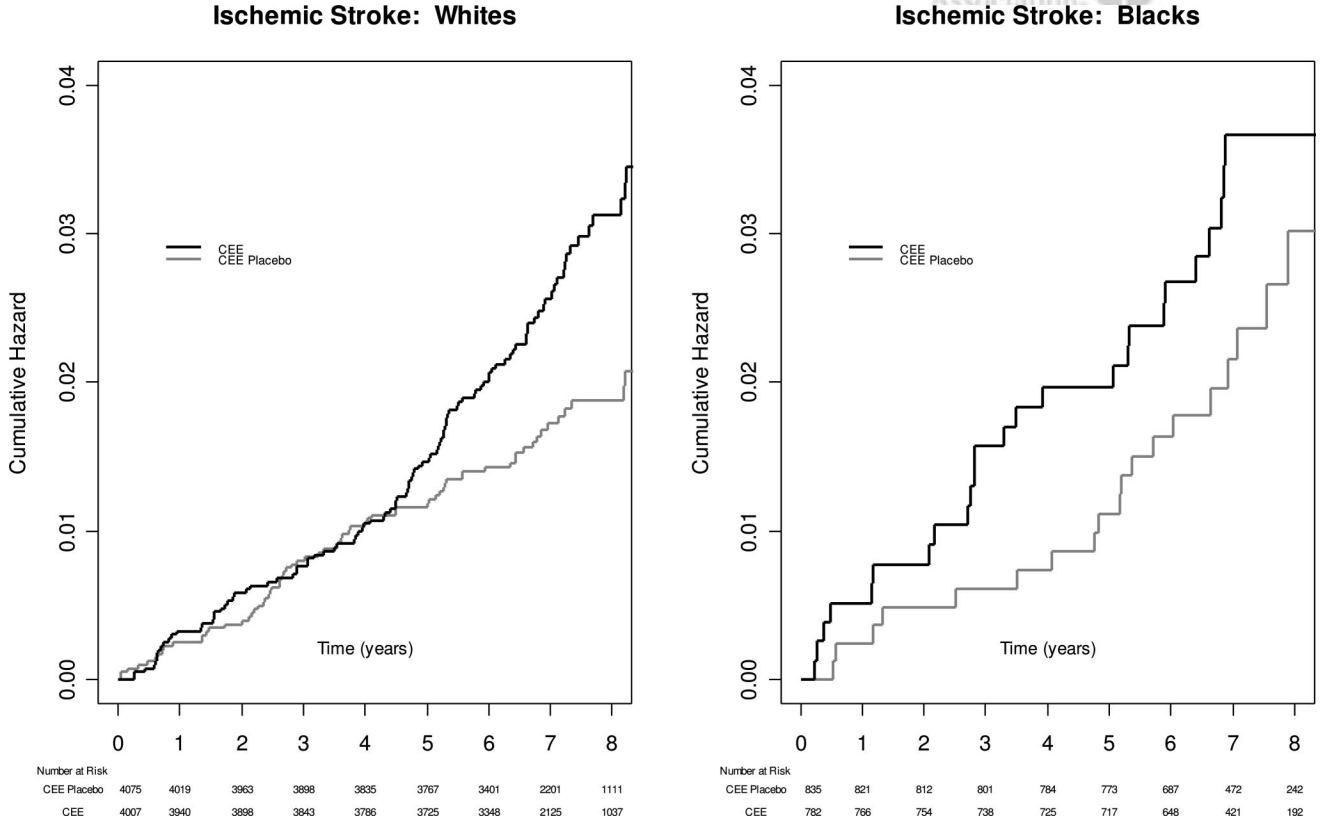

Figure 1. Ischemic stroke by race.

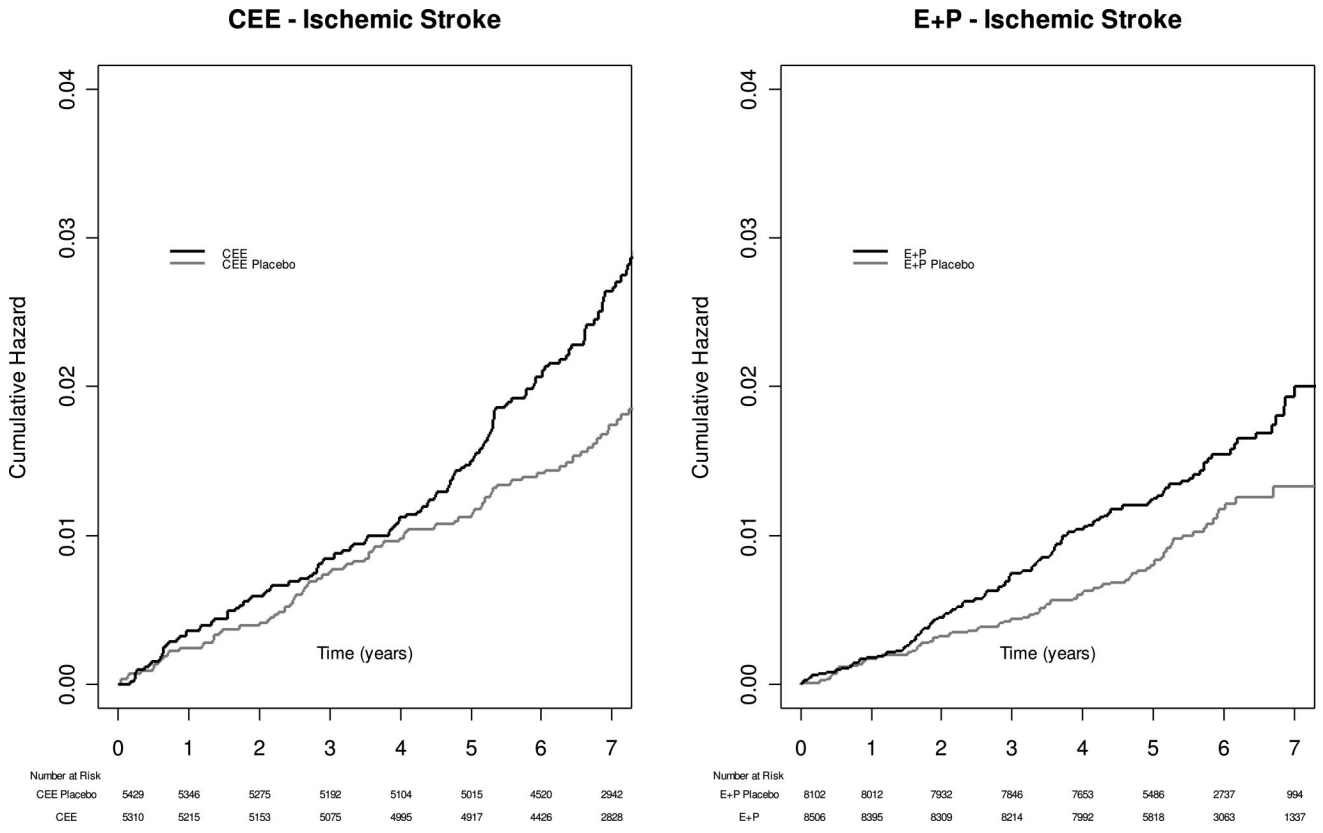

Figure 2. Ischemic stroke risk by WHI hormone trial.

examined, but absolute risk may be increased in the presence of underlying risk factors. Even though the incidence of stroke is somewhat higher in men than in women in most age groups, women live longer than men, and the net result is that the lifetime absolute risk for stroke is higher for women than for men. Many women, particularly those who have had a hysterectomy, use estrogen-only therapy for menopausal symptom relief, often for many years. Therefore, determining stroke risk with use of this medication is of considerable clinical importance in the prescribing practices of clinicians. A decision to prescribe or use menopausal estrogen therapy for its approved indications should take into consideration the risk of stroke along with the other known risks and benefits.

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CLINICAL PERSPECTIVE

Postmenopausal women without a uterus who take estrogen for symptoms normally take it without progestin. In the 2002 report of the Women's Health Initiative hormone trial, estrogen with progestin increased the risk for stroke in postmenopausal women. That study did not address the effects of estrogen alone on stroke risk. In the Estrogen Alone trial, 10 739 women with prior hysterectomy, aged 50 to 79 years, were assigned to conjugated estrogens (Premarin) 0.625 mg daily or to placebo. The study was stopped ahead of schedule in February 2004 by the National Institutes of Health because of increased stroke risk with estrogen. Further evaluation revealed conjugated equine estrogen use caused a significant increase in the risk of ischemic stroke but not hemorrhagic stroke, although the numbers were too small to be definitive. There was no indication that the risk of estrogen use was different in any subgroup examined, but absolute risk may be increased in the presence of underlying risk factors. The similarity in the results in the 2 independent trials (1 with estrogen with progestin and 1 with estrogen alone) substantially strengthens the evidence that ischemic stroke risk is elevated and implicates estrogen (as opposed to progestin) as the more likely cause of stroke. The annualized rates per 10 000 women were 38 for conjugated estrogens and 25 for placebo, which yielded an excess risk of 13 strokes. A decision to prescribe or use menopausal estrogen therapy for its approved indications should consider the risk of stroke along with the other known risks and benefits.