Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women

The Women's Health Initiative: A Randomized Trial

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Context The Women's Health Initiative (WHI) trial of estrogen plus progestin was stopped early because of adverse effects, including an increased risk of stroke in the estrogen plus progestin group.

Objective To assess the effect of estrogen plus progestin on ischemic and hemorrhagic stroke and in subgroups, and to determine whether the effect of estrogen plus progestin was modified by baseline levels of blood biomarkers.

Design Multicenter double-blind, placebo-controlled, randomized clinical trial involving 16608 women aged 50 through 79 years with an average follow-up of 5.6 years. Baseline levels of blood-based markers of inflammation, thrombosis, and lipid levels were measured in the first 140 centrally confirmed stroke cases and 513 controls.

Interventions Participants received 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate (n=8506) or placebo (n=8102).

Main Outcome Measures Overall strokes and stroke subtype and severity were centrally adjudicated by stroke neurologists.

Results One hundred fifty-one patients (1.8%) in the estrogen plus progestin and 107 (1.3%) in the placebo groups had strokes. Overall 79.8% of strokes were ischemic. For combined ischemic and hemorrhagic strokes, the intention-to-treat hazard ratio (HR) for estrogen plus progestin vs placebo was 1.31 (95% confidence interval [CI], 1.02-1.68); with adjustment for adherence, the HR was 1.50 (95% CI, 1.08-2.08). The HR for ischemic stroke was 1.44 (95% CI, 1.09-1.90) and for hemorrhagic stroke, 0.82 (95% CI, 0.43-1.56). Point estimates of the HRs indicate that excess risk of all stroke was apparent in all age groups, in all categories of baseline stroke risk, and in women with and without hypertension, prior history of cardiovascular disease, use of hormones, statins, or aspirin. Other risk factors for stroke, including smoking, blood pressure, diabetes, lower use of vitamin C supplements, blood-based biomarkers of inflammation, higher white blood cell count, and higher hematocrit levels did not modify the effect of estrogen plus progestin on stroke risk.

Conclusions Estrogen plus progestin increases the risk of ischemic stroke in generally healthy postmenopausal women. Excess risk for all strokes attributed to estrogen plus progestin appeared to be present in all subgroups of women examined.

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STROKE IS A MAJOR HEALTH issue for women.[1,2] Cerebrovascular diseases are the third leading cause of death in the United States[3] and are the leading cause of adult disability. The Women's Health Initiative (WHI), beginning in the early 1990s was designed to examine a number of factors affecting the health of postmenopausal women.[4] Recently 1 arm of the WHI, the clinical trial of estrogen plus progestin, was terminated 3 years before its planned completion date because its harmful effects outweighed its benefits.

See also pp 2651, 2663, and 2717.

The overall results in this randomized double-blind clinical trial indicated that women in the estrogen plus progestin group had a 41% increase in locally adjudicated strokes over 5.2 years compared with women in the placebo group.[5] Our report provides results over an additional 4 months (average follow-up 5.6 years) on subtypes of stroke, based on central adjudication of stroke events by neurologists, additional data on the effects of estro-

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gen plus progestin in various subgroups of women, and data on the effect of lipid levels and biomarkers of inflammation and thrombosis.

A relationship between stroke and hormone use was suggested in early studies showing that oral contraceptive users had higher stroke rates than those not taking oral contraceptives.[6] However, results of subsequent epidemiologic studies have been inconsistent and had small numbers of stroke cases. The WHI is the first randomized trial to show that estrogen plus progestin increases risk of stroke in generally healthy women.[5] Stroke is a heterogeneous condition, with differing types, mechanisms, and outcomes. Most prior observational studies and randomized clinical trials reported that stroke risk generally encompassed both hemorrhagic and ischemic strokes without consideration of subtype and mechanism although in more recent studies hemorrhagic and ischemic strokes have been reported separately.[7-9] By refined classification of stroke type, it may be possible to elucidate better the mechanism of the increased incidence of stroke in the WHI randomized clinical trial of estrogen plus progestin vs placebo.

The mechanism through which these hormones act has not yet been established, but it has been hypothesized to be through inflammatory or thrombotic effects. The interactions of other risk factors with estrogen and progestin use may enhance or diminish these effects. Although a well-studied set of risk factors (including age, blood pressure, diabetes mellitus, and cigarette smoking)[10,11] may permit reasonably accurate predictions of an individual's future risk of ischemic stroke, 40% or more of strokes may remain unexplained after these known risk factors are taken into account.[12,13] Even among patients with severe stenosis of the large cerebral arteries, approximately half of all strokes do not originate from lesions in the large arteries.[14,15] Exposures that may affect risk of ischemic stroke, which may act through the pathways of inflammation and thrombosis, are smoking,[16] hypertension,[17] overweight, insulin resistance,[18] and physical exertion.[19] Therapies known or hypothesized to modify risk of stroke, such as aspirin,[20] antihypertensive medications,[17] antioxidants,[21] oral anticoagulants,[22] and omega-3 fatty acids,[23] are also associated with changes in biomarkers of inflammation or thrombosis. Our report examines in more detail the effects of estrogen plus progestin on ischemic and hemorrhagic stroke, including a consideration of risk factors and medical therapies that may modify the effect of estrogen plus progestin on stroke.

METHODS

Study Population

Details of the WHI design are reported elsewhere.[4] Postmenopausal women aged 50 through 79 years who gave written informed consent were enrolled in the WHI at 40 clinical centers in the United States. Women were considered postmenopausal if they were between the ages 50 and 54 years and had no vaginal bleeding for at least 12 months or were aged 55 through 79 years and had no bleeding in the prior 6 months. To be eligible for the trial of estrogen plus progestin, women had to have an intact uterus. Exclusions were participation in other randomized trials, predicted survival of less than 3 years, alcoholism, drug dependency, diagnosed mental illness, dementia, or other conditions suggesting that a woman would not be adherent to study medicines or other procedures.

Exclusions for safety reasons included prior diagnosis of breast cancer or other cancers within the past 10 years (except nonmelanoma skin cancer). Women with systolic blood pressure (SBP) of 200 mm Hg or higher or diastolic blood pressure (DBP) of 105 mm Hg or higher were advised to see their physician within a specified period depending on blood pressure level and were temporarily excluded from the clinical trials until their blood pressure was determined to be under control. Most women had never taken hormone therapy prior to enrollment. Those who were taking hormones were required to have a 3-month washout period before their baseline visit.

Study Pills

Treatment consisted of combined estrogen and progestin, provided as 1 tablet taken daily, containing 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth Ayerst, Philadelphia, Pa), or matching placebo. Details of randomization have been published .[4,5] The trial reported herein consists of 8506 participants randomized to take the estrogen plus progestin and 8102 randomized to be in the placebo group. Participants were followed up for an average of 5.6 years.

Study medication was discontinued permanently by protocol for women who developed breast cancer; endometrial hyperplasia not responsive to treatment; atypia or cancer; deep-vein thrombosis or pulmonary embolism; malignant melanoma; meningioma; triglyceride level greater than 1000 mg/dL (11.3 mmol/L); or prescription of estrogen, testosterone, or selective estrogen-receptor modulators by their personal physicians. Medications were temporarily discontinued for participants who had acute myocardial infarction, stroke, fracture, or major injury requiring hospitalization, surgery involving use of anesthesia, or any illness resulting in immobilization for more than 1 week.

Follow-up and End Point Determination

Women were required to come to the clinic annually and have semiannual contacts in the clinic or by telephone. At each semiannual contact, a standardized interview asked them about symptoms, safety, adherence to study pills, and potential outcome events. When a potential outcome was identified, medical records and death certificates were obtained as necessary. Physician adjudicators at clinical sites reviewed the information to determine the cause of the event. Third-party reports directly given to clinic staff were also followed up by obtaining the requisite records. Transient ischemic attacks requiring hospi-

talization were ascertained and records obtained. One of 3 stroke neurologists centrally adjudicated locally determined strokes, transient ischemic attacks, and women's self-reports of stroke that had been not confirmed by local adjudicators after careful review of the medical records. Of locally adjudicated strokes, 94.5% were confirmed by the central adjudicators. Of centrally adjudicated strokes, 93.8% had been classified as strokes by the local adjudicators. This article presents stroke data centrally confirmed by neurologists. Local and central adjudicators were blinded to treatment assignment.

Stroke diagnosis requiring and/or occurring during hospitalization was based on rapid onset of a neurological deficit attributable to an obstruction or rupture of an arterial vessel system. The deficit was not known to be secondary to brain trauma, tumor, infection, or other cause and must have lasted more than 24 hours unless death supervened or a lesion compatible with acute stroke was evident on computed tomography or magnetic resonance imaging scan. Strokes were classified as ischemic or hemorrhagic based 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 a cardioversion or invasive cardiovascular procedure.

The 6 categories of stroke were (1) subarachnoid hemorrhage not resulting from a procedure; (2) intracerebral hemorrhage not resulting from a procedure; (3) other or unspecified intracranial hemorrhage not resulting from a procedure (nontraumatic epidural hemorrhage or subdural hemorrhage); (4) occlusion of cerebral or pericerebral arteries with infarction not resulting from a procedure (cerebral thrombosis, cerebral embolism, lacunar infarction); (5) acute, but ill defined, cerebrovascular disease not resulting from a procedure (this option is used only if the adjudicator was unable to code it as hemorrhagic or ischemic); (6) and central nervous system complications during or resulting from a procedure. For analysis purposes, categories 1, 2, and 3 were combined as hemorrhagic strokes; category 4 was classified as ischemic stroke; and categories 5 and 6 were combined as other stroke.

Ischemic strokes were further classified by the central neurologist adjudicators according to the Oxfordshire[24] and Trial of Org 10172 Acute Stroke Trial (TOAST)[25] criteria to examine stroke subtypes. The TOAST classification focuses on the presumed underlying stroke mechanism; requires detailed investigations (such as brain computed tomography, magnetic resonance imaging, angiography, carotid ultrasound, and echocardiography); and distinguishes 5 categories of stroke, which include large-artery atherothrombosis, cardioembolic, lacunar (small vessel), other, and undetermined mechanism. However, even with the extensive work-up, 39% of strokes were of undetermined mechanism, including cryptogenic stroke (no cause found on work-up), incomplete evaluation to make a determination, and 2 or more causes identified. This classification, the best currently available, shows moderate to good interobserver reliability with training.[26-28]

For the purpose of analyses, stroke subtypes judged probable or possible are combined. The Oxfordshire classification[24] is based on clinical assessment of the patient in whom a computed tomographic brain scan has excluded cerebral hemorrhage and classifies patients into total anterior circulation infarct, partial anterior circulation infarct, lacunar infarct, and posterior circulation infarct. This scale has the advantage that virtually all patients can be classified; it shows a correlation with outcome and severity and has a moderate-to-good interobserver reliability for the classification in practice.[28] The Glasgow Outcome Scale score was ascertained by clinical information available at the time of hospital discharge to provide an assessment of stroke outcome.[29,30]

Definition of Variables

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

Physical activity was assessed by asking about the frequency and duration of walking at various intensities and 3 other types of recreational activity classified by intensity (strenuous, moderate, or light). Data were summarized into episodes per week of moderate or strenuous activity (as defined by a metabolic equivalent score of at least 4.0 as indicated by Ainsworth and colleagues[31] of at least 20 minutes' duration). One metabolic equivalent is the amount of energy expended sitting quietly at rest adjusted to body weight, equal to 1 kcal/kg per hour. Women reporting some recreational activity but of shorter duration and/or lesser intensity were classified as engaging in some activity. Vasomotor symptoms were assessed from responses to questions on the presence of hot flashes or night sweats. A 12-lead electrocardiogram was performed at baseline and every 3 years.

Statistical Analyses

Baseline characteristics between placebo and estrogen plus progestin groups were compared using the χ^2 test. 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.

Outcome comparisons were made from Cox proportional hazards analyses and Kaplan-Meier curves for the entire population. Additional analyses examined effects of estrogen plus progestin in 11 subgroups of special clinical interest: by age group, race or ethnicity, years since menopause, prior

Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants by Randomization Assignment*

Characteristics	No. (%) Estrogen + Progestin (n = 8506)	No. (%) Placebo (n = 8102)	*P* Value†
Age group at screening, y			
50-59	2839 (33.4)	2683 (33.1)	.80
60-69	3853 (45.3)	3657 (45.1)	
70-79	1814 (21.3)	1762 (21.8)	
Race or ethnicity			
White	7140 (83.9)	6805 (84.0)	.33
Black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.6)	416 (5.1)	
American Indian	26 (0.3)	30 (0.4)	
Asian/Pacific Islander	194 (2.3)	169 (2.1)	
Unknown	125 (1.5)	107 (1.3)	
Smoking status			
Never	4178 (49.1)	3999 (49.4)	.85
Past	3362 (39.5)	3157 (39.0)	
Current	880 (10.4)	838 (10.3)	
Hormone usage status			
Never	6277 (73.8)	6020 (74.3)	.48
Past	1671 (19.6)	1588 (19.6)	
Current	554 (6.5)	491 (6.1)	
Hormone use duration, y			
Never used	6277 (73.8)	6020 (74.3)	.30
<5	1539 (18.1)	1470 (18.1)	
5 to <10	427 (5.0)	356 (4.4)	
≥10	263 (3.1)	255 (3.2)	
Supplement use			
Ascorbic acid	4186 (49.2)	4028 (49.7)	.52
Vitamin E	4257 (50.1)	4111 (50.7)	.38
Potassium	2741 (32.2)	2596 (32.0)	.80
Selected medication use			
Statin	578 (6.8)	533 (6.6)	.58
Aspirin	1623 (19.1)	1631 (20.1)	.09
NSAID	1273 (15.0)	1255 (15.5)	.35
Treated diabetes	374 (4.4)	360 (4.4)	.40
History of CVD	406 (4.8)	419 (5.2)	.22
Hypertension‡	3039 (35.7)	2949 (36.4)	.47
Myocardial infarction ever	139 (1.6)	157 (1.9)	.14
Stroke ever	61 (0.7)	77 (1.0)	.10
History of transient ischemic attack	115 (1.4)	143 (1.8)	.03
ECG atrial fibrillation	7 (0.1)	15 (0.2)	.07
LVH, Minnesota code	402 (4.7)	432 (5.3)	.07
Carotid endarterectomy/angioplasty ever	15 (0.2)	19 (0.2)	.40
Framingham stroke risk			
Low risk, first tertile	3049 (35.9)	2814 (34.7)	.16
Medium risk, second tertile	3171 (37.3)	3014 (37.2)	
High risk, third tertile	2286 (26.9)	2274 (28.1)	
	Mean (SD)		
Body-mass index§	28.5 (5.8)	28.5 (5.9)	.66
Blood pressure, mm Hg			
Systolic	127.6 (17.6)	127.8 (17.5)	.51
Diastolic	75.6 (9.1)	75.8 (9.1)	.31
Pulse pressure	51.9 (14.7)	52.0 (14.7)	.87

Abbreviations: CVD, cardiovascular disease; ECG, electrocardiograph; LVH, left ventricular hypertrophy; NSAID, nonsteroidal anti-inflammatory drug.
*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.
‡Hypertension was defined as taking medication or having high systolic or diastolic blood pressure.
§Body mass index is calculated as weight in kilograms divided by the square of height in meters.

history of cardiovascular disease, hypertensive status, duration of prior hormone use, statin and aspirin use, vasomotor symptoms at baseline, vasomotor symptoms within the youngest group, and by tertile of Framingham scores for stroke risk. Framingham risk scores reflect the probability of stroke within 10 years for women aged 55 to 84 years, based on use of antihypertensive medications, as well as SBP, age, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy by electrocardiogram.[32] In addition, 16 biomarkers were examined, resulting in a total of 27 subgroups. At the .05 level of significance, 1 of 20 comparisons may be statistically significant by chance. Nominal confidence intervals (CIs) are presented throughout, except for stroke outcome, which was 1 of 7 outcomes monitored by the data and safety monitoring board, so we also present the adjusted CIs in this instance.

All primary analyses of time-to-first stroke were based on the intention-to-treat principle. The effect modification of stroke risk with estrogen plus progestin by potential risk factors was assessed by first-fitting univariate Cox proportional hazards models. Variables showing a marginal relationship with stroke ($P<.25$) were all included in a multivariate Cox model with estrogen plus progestin. Statistical significance of the interaction between estrogen plus progestin and these variables was explored 1 at a time using the score test. All Cox models were stratified on age, prior stroke, and randomization assignment in the dietary modification trial and were adjusted for race or ethnicity. The proportional hazards assumption was verified by testing the interaction of time and estrogen plus progestin and through visual inspection of the survival function.

Secondary analyses were performed to account for participant adherence, to determine if any risk conferred by estrogen plus progestin could not be explained by increases in SBP and if risk differed by stroke type. In the adher-

ence-adjusted analyses, participants' event histories were censored 6 months after they became nonadherent (stopped taking study drugs, were using <80% of study drugs, or, if in the placebo group, started hormone therapy). A Cox model that included follow-up SBP as a time-dependent covariate was used to estimate the additional risk of estrogen plus progestin unrelated to its effect on SBP. 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. Analysis were performed by SAS statistical software version 8.02 (SAS Inc, Cary, NC).

The protocol included a blood draw at baseline after a minimum 10-hour fast. Serum and plasma specimens were maintained at 4°C until separated, aliquoted, and frozen at –70°C, until they were shipped on dry ice to the laboratory (Medical Research Laboratories, Highland Heights, Ky), for analysis. All lipid and lipoprotein fractions were analyzed on EDTA-treated plasma, using methods described elsewhere.[33-37] Fibrinogen and factor VIII were measured in frozen citrated plasma using a clot-based turbidometric detection system (MLA Electra 1400c, Pleasantville, NY). Human interleukin 6 (IL-6) was quantitated using a high-sensitivity sandwich enzyme-linked immunoassay (R&D Systems, Minneapolis, Minn). Soluble endothelial leukocyte adhesion molecules (E-selectin) was measured by enzyme-linked immunosorbent assay (R&D Systems). High-sensitivity C-reactive protein was measured using an ultrasensitive rate immunonephelemetric method (Dade-Behring, Marburg, Germany). Matrix metalloproteinase 9 (MMP-9) was quantitated using an enzyme-linked immunosorbent assay procedure (Quantikine human MMP-9, R&D Systems).

Associations of biomarkers with stroke by randomization group were assessed using logistic regression models on available case-control data. Cases were the first 140 strokes that were locally adjudicated as stroke before February 2001 and later confirmed centrally. There were 513 controls: a control with an intact uterus was selected for each case, matched on age, randomization year, and presence of baseline stroke. Additional controls that had been selected for women who developed coronary heart disease and venous thrombosis were included in these analyses.

RESULTS

Baseline Characteristics

Baseline characteristics of the estrogen plus progestin and placebo groups

Table 2. Diagnosis, Classification, and Severity of Centrally Adjudicated Stroke in the Women's Health Initiative Estrogen Plus Progestin Trial Participants by Randomization Assignment*

Variables	No. (%) Estrogen + Progestin (n = 8506)	No. (%) Placebo (n = 8102)	*P* Value†
Stroke Diagnosis			
Hemorrhagic stroke‡	18 (11.9)	20 (18.7)	.46
Subarachnoid	5 (3.3)	5 (4.7)	
Intraparenchymal	13 (8.6)	14 (13.1)	
Other or unspecified intracranial	0	1 (0.9)	
Ischemic stroke§	125 (82.7)	81 (75.7)	
Other stroke¶	2 (1.3)	1 (0.9)	
Report of cerebrovascular death only	6 (3.9)	5 (4.7)	
Total	**151** (100)	**107** (100)	
TOAST Classification of Ischemic Stroke			
Large artery atherosclerosis	16 (12.8)	12 (14.8)	.77
Cardioembolism	12 (9.6)	12 (14.8)	
Small-vessel occlusion	36 (28.8)	22 (27.1)	
Stroke of other determined origin	9 (7.2)	6 (7.4)	
Stroke of undetermined origin	52 (41.6)	29 (35.8)	
≥2 Causes identified	1 (0.80)	1 (1.2)	
Negative evaluation	22 (17.6)	12 (14.8)	
Incomplete evaluation	29 (23.2)	16 (19.8)	
Total	**125** (100)	**81** (100)	
Oxfordshire Classification of Ischemic Stroke			
Total anterior circulation infarct	8 (6.4)	4 (4.9)	.37
Partial anterior circulation infarct	57 (45.6)	28 (34.6)	
Lacunar infarct	42 (33.6)	34 (41.9)	
Posterior circulation infarct	18 (14.4)	15 (18.5)	
Total	**125** (100)	**81** (100)	
Glasgow Outcome Scale‖			
Missing	1 (0.7)	0	.52
Good recovery	42 (27.8)	38 (35.5)	
Moderately disabled	45 (29.8)	33 (30.8)	
Severely disabled	35 (23.1)	18 (16.8)	
Vegetative survival	3 (1.9)	2 (1.8)	
Death	12 (7.9)	11 (10.3)	
Unable to categorize outcome	13 (8.6)	5 (4.7)	
Total	**151** (100)	**107** (100)	

Abbreviation: TOAST, Trial of Org 10172 Acute Stroke Trial.
*Data as of July 7, 2002. Percentages may not sum to 100 due to rounding.
†Categorical variables are based on χ^2 tests and continuous variables are based on *t* tests.
‡Subarachnoid, intracerebral, or other or unspecified intracranial hemorrhage (nontraumatic subdural or extradural hematomas).
§Occlusion of cerebral arteries with infarction.
¶Acute but ill-defined cerebrovascular disease or procedure-related stroke.
‖*P* value for 1-sided Cochran-Armitage test for trend is .20.

are shown in TABLE 1. Both groups were similar with respect to baseline demographic and risk factor characteristics with no significant differences between the 2 groups on any of the variables except for history of transient ischemic attack, which was higher in the placebo group ($P=.03$) than in the treatment group. The average participant age was 63.3 years; 33% of women were in the 50 through 59 year age group. Before WHI enrollment, 74.3% of participants never used hormones. Ninety-five percent had no history of cardiovascular disease.

Table 3. Annualized Percentage of Stroke Events and Hazard Ratios of the Women's Health Initiative Estrogen Plus Progestin Trial Participants by Randomization Assignment and in Selected Subgroups*

Variables	No. (%) Estrogen + Progestin (n = 8506)	No. (%) Placebo (n = 8102)	Hazard Ratio† (95% CI)
Follow-up time, mean (SD), y	5.65 (1.35)	5.57 (1.27)	
All stroke	151 (0.31)	107 (0.24)	1.31 (1.02-1.68)
Ischemic	125 (0.26)	81 (0.18)	1.44 (1.09-1.90)
Hemorrhagic	18 (0.04)	20 (0.04)	0.82 (0.43-1.56)
Age, y‡			
50-59	24 (0.14)	15 (0.10)	1.46 (0.77-2.79)
60-69	68 (0.32)	47 (0.23)	1.35 (0.93-1.96)
70-79	59 (0.61)	45 (0.48)	1.26 (0.86-1.86)
Race or ethnicity			
American Indian or Alaskan Native	0 (0.00)	0 (0.00)	
Asian or Pacific Islander	5 (0.48)	2 (0.22)	2.12 (0.41-10.96)
Black	17 (0.55)	7 (0.22)	2.52 (1.05-6.08)
Hispanic	2 (0.08)	5 (0.22)	0.34 (0.07-1.78)
White	126 (0.31)	89 (0.23)	1.33 (1.01-1.74)
Unknown	1 (0.15)	4 (0.72)	0.21 (0.02-1.90)
Years since menopause‡			
<5	8 (0.10)	5 (0.07)	1.45 (0.48-4.45)
5 to <10	14 (0.17)	9 (0.11)	1.57 (0.68-3.63)
10 to <15	24 (0.27)	14 (0.17)	1.67 (0.87-3.24)
≥15	84 (0.48)	73 (0.42)	1.13 (0.83-1.55)
Prior history of CVD§			
No	137 (0.30)	93 (0.22)	1.31 (1.01-1.70)
Yes	11 (0.50)	13 (0.59)	1.14 (0.46-2.82)
Hypertension status			
No	54 (0.21)	41 (0.16)	1.29 (0.86-1.94)
Yes	78 (0.47)	61 (0.38)	1.22 (0.87-1.71)
Duration of prior hormone use, y			
Never	117 (0.33)	80 (0.24)	1.37 (1.03-1.82)
<5	17 (0.19)	17 (0.20)	0.96 (0.49-1.88)
5-10	10 (0.41)	7 (0.36)	1.04 (0.40-2.73)
≥10	7 (0.49)	3 (0.22)	2.17 (0.56-8.40)
Statin use			
No	138 (0.31)	98 (0.23)	1.32 (1.02-1.71)
Yes	13 (0.43)	9 (0.32)	1.21 (0.52-2.83)
Aspirin use			
No	115 (0.29)	81 (0.22)	1.31 (0.99-1.74)
Yes	36 (0.40)	26 (0.29)	1.31 (0.79-2.18)
Mild, moderate, severe vasomotor symptoms‖			
No	108 (0.37)	78 (0.29)	1.30 (0.97-1.74)
Yes	41 (0.22)	27 (0.15)	1.37 (0.84-2.23)
Framingham stroke risk			
Low risk, first tertile	16 (0.09)	10 (0.06)	1.40 (0.64-3.09)
Medium risk, second tertile	50 (0.28)	38 (0.23)	1.20 (0.79-1.83)
High risk, third tertile	85 (0.70)	59 (0.49)	1.42 (1.02-1.99)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.
*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 diabetes mellitus randomization assignment.
‡From Cox regression model stratified by previous stroke and diabetes mellitus randomization assignment.
§From Cox regression model stratified by age and diabetes mellitus randomization assignment.
‖Symptoms were night sweats, hot flashes, or both.

Stroke and Stroke Subtype Events

There were 151 strokes in the estrogen plus progestin group (1.8%) and 107 in the placebo group (1.3%) as of July 7, 2002, after an average of 5.6 years of follow-up; all women had been enrolled for a minimum of 3.7 years and a maximum of 8.6 years. Ischemic strokes accounted for 79.8% of all strokes (82.8% estrogen plus progestin; 75.7% placebo), and hemorrhagic strokes accounted for 14.8% of strokes (11.9% estrogen plus progestin; 18.6% placebo, TABLE 2). Three strokes were not classified as ischemic or hemorrhagic, 1 of which resulted from a surgical procedure. Of 38 hemorrhagic strokes, 10 (26.3%) were due to subarachnoid hemorrhage.

Of 206 ischemic strokes in both groups, 24 (11.7%) were cardioembolic; 28 (13.6%), large artery; and 58 (28.2%), small vessel. There were 23 stroke deaths, 12 in the estrogen plus progestin and 11 in the placebo groups; 11 of these were reports of cerebrovacular deaths only (6 estrogen plus progestin; 5 placebo) without classification of type. Distributions of ischemic stroke subtypes by Oxfordshire and TOAST classifications did not differ significantly between the 2 treatment groups nor did severity of stroke differ on the Glasgow Outcome Scale.

The hazard ratio (HR) for all stroke subtypes combined was 1.31 (nominal 95% CI, 1.02-1.68). Because 7 end points were monitored by the data and safety monitoring board and examined to assess the global risk vs benefit of estrogen plus progestin,[5] the conservative Bonferroni adjusted 95% CI was (0.93-1.84). The HR for ischemic stroke was 1.44 (95% CI, 1.09-1.90), and for

hemorrhagic stroke, it was 0.82 (95% CI, 0.43-1.56; TABLE 3).

Subgroup Analyses

Hazard ratios for all stroke subtypes combined were similar across age groups (Table 3). Women who never used hormones before randomization had a 37% excess risk of stroke with estrogen plus progestin (HR, 1.37; 95% CI, 1.03-1.82). Use of statins or aspirin at baseline did not modify the effect of estrogen plus progestin, and the findings remained similar when participants with prior cardiovascular disease were excluded (n=24) from the analysis (data not shown). The effect of estrogen plus progestin on stroke risk was similarly increased in women with and without vasomotor symptoms at baseline. Thirteen women taking estrogen plus progestin and 5 women taking placebo who were aged 50 through 59 years and who had vasomotor symptoms had experienced a stroke. Point estimates of HRs were higher for estrogen plus progestin in virtually all subgroups examined and did not differ from the overall HR of 1.31 for total strokes.

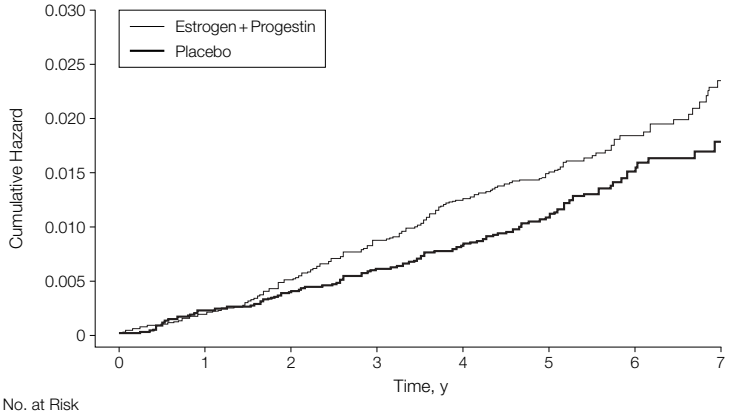
Time Trends

Kaplan-Meier cumulative hazard of stroke (all types of stroke combined) begins to diverge between 1 and 2 years after randomization (FIGURE 1). Cumulative hazards within each of the 3 age groups (50-59, 60-69, 70-79 years), for normotensive and hypertensive women, and within low, medium, and high stroke–risk tertiles as determined from the Framingham equations, indicate that within each of these groups there was an adverse effect of estrogen plus progestin compared with placebo, but the adverse effect of estrogen plus progestin was delayed in the low-risk tertile compared with the middle or highest tertile of Framingham stroke risk and in normotensive compared with hypertensive women (data not shown).

Other Stroke Risk Factors

Black women were 75% more likely to have a stroke than white women (HR, 1.75; 95% CI, 1.14-2.68). Risk of stroke, adjusted for race or ethnicity, was significantly associated with current smoking (HR, 2.31; 95% CI, 1.61-3.31), hypertension (HR, 1.85; 95% CI, 1.42-2.42), higher baseline SBP (HR, 1.22; 95% CI, 1.14-1.30 per 10 mm Hg increase), or DBP (HR, 1.21; 95% CI, 1.06-1.38 per 10 mm Hg increase), having left ventricular hypertrophy at baseline (HR, 1.73; 95% CI, 1.13-2.66), having diabetes (HR, 2.23; 95% CI, 1.47-3.38), and with Framingham stroke risk score (HR, 6.36; 95% CI, 3.76-10.76 for highest tertile compared with lowest tertile of Framingham stroke risk). Increased white blood cell count ($P<.001$) and higher hematocrit levels ($P<.001$) were also significantly related to stroke risk. Reduced risk was associated with taking vitamin C supplements (HR, 0.74; 95% CI, 0.58- 0.95) and physical activity (HR, 0.65; 95% CI, 0.44-0.97 for participants who reported 4 or more episodes a week of moderate or strenuous activity). Prior oral contraceptive use was not related to stroke risk.

Figure 1. Estimates of Cumulative Hazards for Strokes



No. at Risk								
Estrogen + Progestin	8505	8395	8309	8214	7992	5818	3063	1337
Placebo	8102	8012	7932	7846	7653	5486	2737	994

Multivariate Analyses

We ran Cox regression models including as independent variables those univariately related to stroke with $P<.05$ as noted above, plus additional variables with $P>.05$ and $P<.25$ (data not shown). To examine potential interactions of variables from this core set with estrogen plus progestin, we included each interaction term 1 at a time. There were no significant interactions ($P>.05$) of estrogen plus progestin with any of these variables or with the Framingham risk score, which is a composite of some of these variables. Other analyses indicated no significant interactions of estrogen plus progestin with age or use of aspirin, nonsteroidal anti-inflammatory drugs, statins, or prior oral contraceptives.

Use of estrogen plus progestin was not associated with an increase in DBP, but it was associated with an increase in SBP (average <2 mm Hg).[5]

For women taking estrogen plus progestin, the unadjusted HR was 1.31 (95% CI, 1.02-1.68, TABLE 4). Adjustment for race or ethnicity and baseline SBP did not affect the risk of stroke for those taking estrogen plus progestin, nor did further adjustments for multiple covariates affect stroke risk. Adjustment for SBP as a time-dependent variable did not appreciably change the HR. Thus, the effect of estrogen plus progestin on SBP did not explain the excess risk of stroke associated with estrogen plus progestin. In an analysis that adjusted for adherence, the HR was higher than in the intention-to-treat analysis (HR, 1.50; 95% CI, 1.08-2.08), and higher HRs were found in all models tested.

Table 4. Risk of Stroke With Estrogen Plus Progestin vs Placebo

Variables	Hazard Ratio of Estrogen + Progestin vs Placebo (95% CI)
Intention-to-treat analysis*	
No covariates	1.31 (1.02-1.68)
Race, baseline SBP	1.32 (1.03-1.69)
Race, time-dependent SBP	1.27 (0.99-1.63)
Race, baseline SBP, plus other covariates†	1.29 (1.01-1.65)
Race, Framingham Risk by tertiles, plus other covariates‡	1.32 (1.03-1.69)
Adjusted for adherence§	
No covariates	1.50 (1.08-2.08)
Race, baseline SBP	1.52 (1.09-2.10)
Race, baseline SBP, plus other covariates†	1.50 (1.08-2.08)
Race, Framingham Risk by tertiles, plus other covariates‡	1.51 (1.09-2.10)

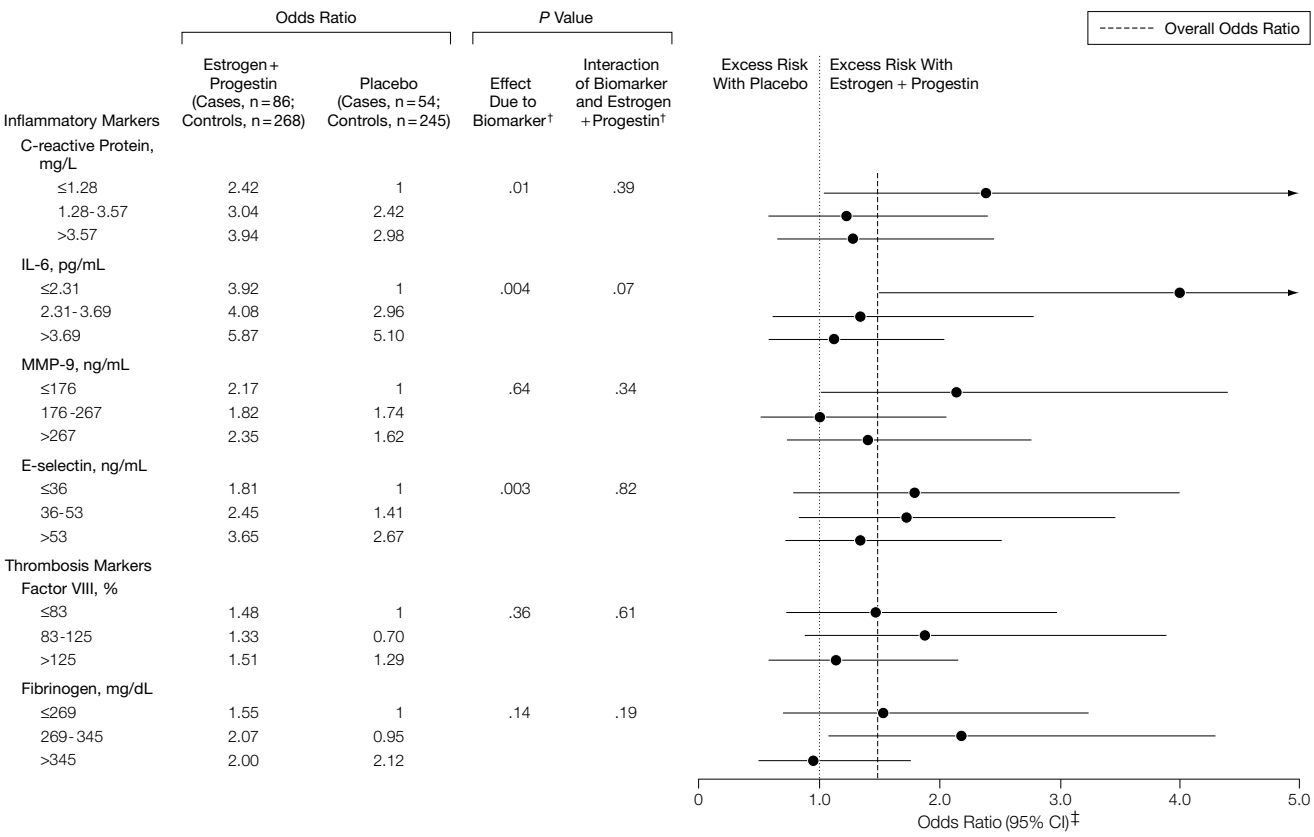
Abbreviation: CI, confidence interval SBP, systolic blood pressure.
*Stratified by age, prior stroke, and diabetes mellitus randomization status.
†Smoking, supplement use of ascorbic acid, supplement use of vitamin E, supplement use of potassium, history of transient ischemic attack, baseline left ventricular hypertrophy, history of coronary heart disease, duration of prior hormone use, treated diabetes, white blood count, and hematocrit level.
‡Supplement use of ascorbic acid, supplement use of vitamin E, supplement use of potassium, duration of prior hormone use, white blood cell count, hematocrit level.
§Censored a woman's event history 6 months after becoming nonadherent (using <80% of hormone group stopping study drugs or placebo group starting hormone replacement therapy).

Blood Biomarkers

In a substudy of blood biomarkers to examine the effects of lipid levels, inflammatory markers, and thrombotic factors on the excess risk associated with estrogen plus progestin, the first 140 stroke cases that were locally adjudicated and centrally confirmed were compared with 513 controls who had no stroke, myocardial infarction, or venous thromboembolism up to that time. The overall odds ratio of estrogen plus progestin in this case-controlled substudy is 1.47 (95% CI, 1.00-2.16).

The odds ratios for each biomarker tertile in relation to the lowest tertile in the placebo group are shown in FIGURE 2 and FIGURE 3. Inflammatory markers (C-reactive protein, IL-6, and

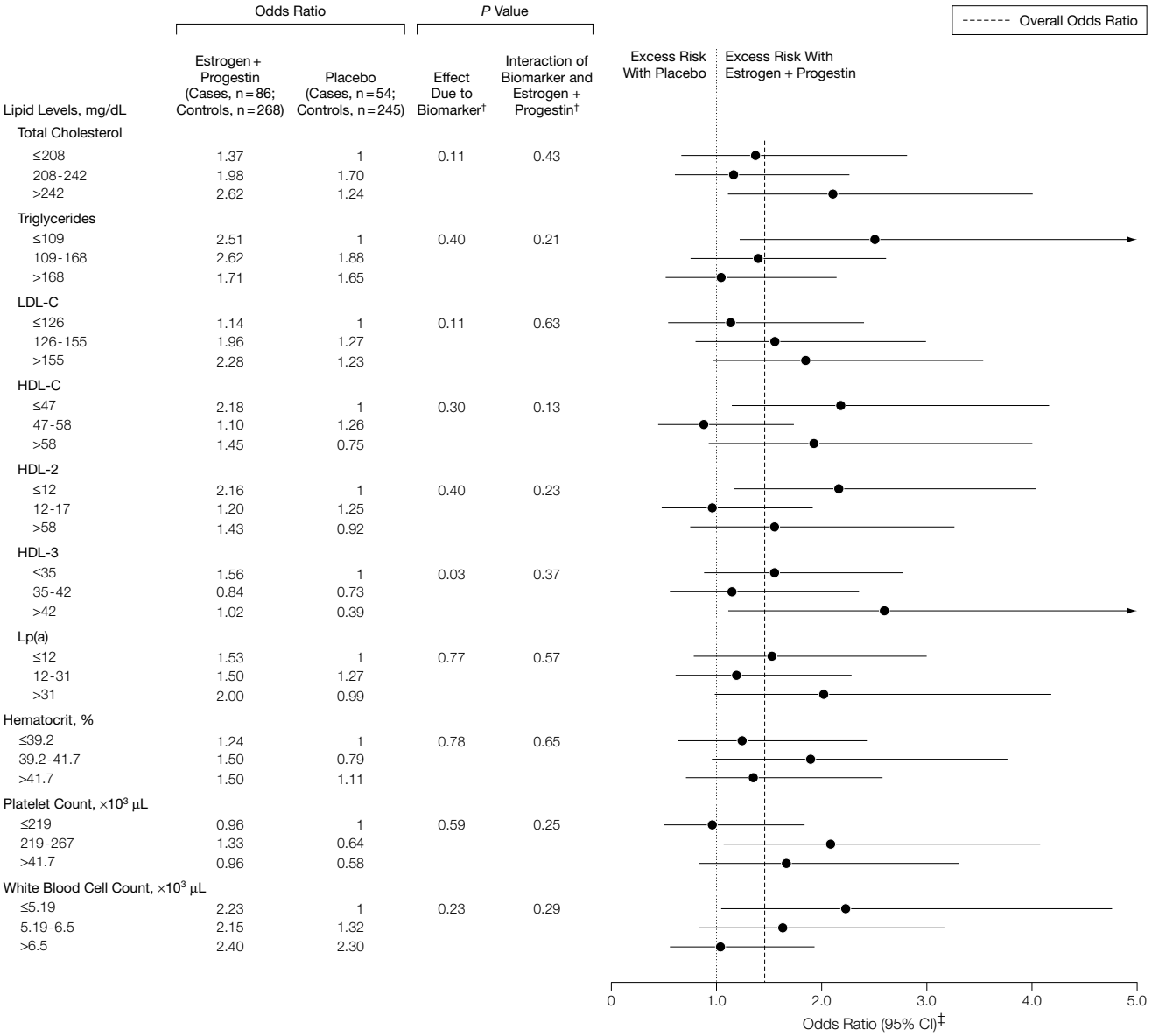
Figure 2. Odds Ratios for Blood Inflammatory Markers and Stroke Risk



*Odds ratios for all biomarkers use placebo lowest tertile of that biomarker as the reference group. In the display of confidence intervals, the odds ratios pertain to the effect of estrogen plus progestin within each tertile of biomarker.
†Based on a 2-degree-of-freedom likelihood ratio statistic.
‡Placebo group within each tertile is used as the reference group for odds ratios and corresponding 95% confidence intervals (CIs), which are presented as error bars.
IL-6 indicates interleukin 6; MMP-9, matrix metalloprotein 9. To convert fibrinogen from mg/dL to µmol/L, multiply by 0.0294

E-selectin) were associated with increased risk of stroke. For example women in the highest tertile of C-reactive protein in the placebo group had 3.0 times the risk of stroke as those in the lowest tertile, whereas women in the highest tertile of C-reactive protein in the estrogen plus progestin group had 3.9 times the risk of stroke as those in the lowest tertile of the placebo group. However, there were no significant interactions of baseline inflammatory markers and estrogen plus progestin, indicating that the increased risk associated with higher levels of inflammatory markers held true in both placebo and estrogen plus progestin. Factor VIII coagulant activity and fibrinogen concentration were not associated with stroke risk. Of the lipids, only high-density lipoprotein-3 was statistically

Figure 3. Odds Ratios for Blood Biomarkers and Stroke Risk



To convert total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (LDL-C), HDL-2, and HDL-3 from mg/dL to mmol/L, multiply by 0.0259; lipoprotein(a) (Lp[a]), multiply by 0.0357; and triglycerides from mg/dL to mmol/L, multiply by 0.0113.
*Odds ratios for all biomarkers use placebo lowest tertile of that biomarker as the reference group. In the display of confidence intervals, the odds ratios pertain to the effect of estrogen plus progestin within each tertile of biomarker.
†Based on a 2-degree-of-freedom likelihood ratio statistic.
‡Placebo group within each tertile is used as the reference group for odds ratios and corresponding 95% confidence intervals (CIs), which are presented as error bars.

significantly related to stroke risk with higher levels being protective. Similarly, there were no significant interactions between estrogen plus progestin and lipid levels or thrombosis markers. All odds ratios for estrogen plus progestin vs placebo do not differ significantly from the overall odds ratio of 1.47 in the case-control substudy (Figure 2 and Figure 3).

COMMENT

In this clinical trial involving 16608 postmenopausal women, those taking estrogen plus progestin had an approximate 31% increase in total stroke risk compared with those taking placebo. This increased risk was significant for ischemic but not hemorrhagic stroke although there were too few hemorrhagic strokes to draw conclusions about the risk of estrogen plus progestin for this subtype. The increase was unrelated to a number of other risk factors, including age and a prior history of cardiovascular disease, hormone use, or hypertension. Furthermore, no interaction was observed between estrogen plus progestin and any stroke risk factor that might allow identification of women at the highest risk of stroke when taking estrogen plus progestin. The increase in risk did not appear until after the first year of treatment. The results extend those published in the first WHI report,[5] with the use of central adjudication of strokes, the addition of new cases (from 212 to 258), data on the effects of estrogen plus progestin in various subgroups of women, and assessment of biomarker levels and stroke risk.

Prior case-control, observational studies and randomized clinical trials of postmenopausal hormone therapy have given conflicting results in relation to stroke risk,[38] with some showing decreased risk[39-42] others showing no effect,[43-45] and, yet, others[46] including the Framingham study, showing increased risk.[47] A recent meta-analysis also reported increased risk.[48] Two prior randomized controlled trials have evaluated the effect of estrogen with or without progestin on stroke risk. The Heart and Estrogen/progestin Replacement Study (HERS)[9] was a secondary coronary heart disease prevention trial using a combination of 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate. Of the 2763 women with known coronary heart disease, whose mean age was 67 years and who were followed up for a mean of 4.1 years, 149 had strokes. Hormone therapy in HERS was not significantly associated with risk of all strokes (HR, 1.23; 95% CI, 0.89-1.70), and results were similar for ischemic and hemorrhagic strokes. The Women's Estrogen for Stroke Trial (WEST)[8] was a secondary stroke prevention trial in which 664 women with a mean age of 71 years using estrogen alone (1 mg of 17B-estradiol), who were followed up for a mean of 2.8 years, had a total of 192 strokes. No difference in the combined end point of recurrent stroke and fatality rate was found; however, there was an increased rate of fatal stroke and an early increase in overall stroke rate in the first 6 months, but this was not sustained.

In WHI, 79.8% of all strokes were ischemic while 14.7% were hemorrhagic. The increased risk with estrogen plus progestin is related to ischemic stroke. Because the numbers of hemorrhagic strokes were very low, no definitive conclusion can be drawn about how or whether hormone therapy affects the risk of hemorrhagic stroke. The distributions of stroke subtypes and stroke severity were similar in the estrogen plus progestin and placebo groups. Determination of ischemic stroke subtype was made from chart review. While chart documentation was adequate for most patients, evaluation was incomplete for some patients. The time trend for stroke differed from WEST, in which the early increase in stroke risk observed in the first 6 months disappeared over time as it did in HERS, in which an early increase in the coronary event rate in the estrogen plus progestin group was reported in the first year of follow-up. Both WEST and HERS were secondary prevention trials involving women at high risk of stroke.

In contrast, WHI is a trial involving predominantly healthy women with only 5% having a history of cardiovascular disease. Their low-baseline risk is illustrated by the fact that even though the WHI cohort was much larger (N=16608) than the other 2 studies, only 258 strokes occurred during the 5.6-year follow-up. When considering ischemic stroke, estrogen has been believed to have a neuroprotective effect through perfusion-dependent and independent mechanisms and so may be associated with less severe strokes and better stroke outcome[49]; however, in our study there were no differences in stroke outcome as classified by the Glasgow Outcome Scale. In prior observational studies, the increased risk involved nonfatal rather than fatal strokes. Similarly in WHI most of the increased elevation was in nonfatal strokes, with only 23 stroke-related deaths occurring in both groups combined.

The WHI trial used a specific combination of hormones: 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate taken daily. The WHI trial studying the effect of estrogen alone on women with no uterus is continuing and is scheduled to be completed in 2005. The question of whether giving estrogen plus progestin to younger women when they first reach menopause would confer the same risks has been raised. Our study does not address the issue of short-term hormone use for postmenopausal symptoms or perimenopausal use of hormones. However, in our youngest age group (50-59 years), the results were similar, if not more extreme than in older women, showing about a 46% increase in risk of stroke. There was no indication that estrogen plus progestin had a different effect in the younger women (aged 50-59 years) who experienced vasomotor symptoms (hot flashes or night sweats). These women showed an HR of 2.42 (95% CI, 0.86- 6.80), but the number of events in this subgroup was very small. Additionally, the effect of estrogen plus progestin did not vary according to years since menopause. Furthermore, defining short-term is problematic. In our study, the excess

stroke risk became apparent by the second year. The rates of discontinuation of medication, while similar in both treatment groups, were high (approximately 40%) although comparable with what has been reported in practice. However, our results of excess risk of stroke with estrogen plus progestin in the intention-to-treat analysis were confirmed and strengthened by the per protocol analyses that indicated a relative risk of 1.50 (95% CI, 1.08-2.08).

The case-control substudy of inflammatory, thrombogenic, and lipid biomarkers indicated that inflammation plays a role in increasing stroke risk, but does not do so differentially in women who received estrogen plus progestin than in those who received placebo. Inflammation has been shown to be a risk factor for coronary heart disease,[50,51] and our findings demonstrate that it is also a risk factor for stroke. Whether changes brought about by estrogen plus progestin play a role remains to be determined in future analyses of postbaseline biomarker levels.

In summary, the results from this large randomized, double-blind clinical trial, conducted in multiple centers among a generally healthy, ethnically diverse group of postmenopausal women indicate that combined estrogen plus progestin use poses a significant increase in risk of stroke, in particular ischemic stroke, overall, and provide no indication that any of the multiple subgroups examined had a different risk. This increased risk is not accounted for by an increase in blood pressure. Together with other findings reported from WHI[5] of increased risk of invasive breast cancer, myocardial infarction, and venous thrombosis, the stroke data indicate that the risks of estrogen plus progestin outweigh the potentially beneficial effects.

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