Postmenopausal Hormone Therapy and Risk of Stroke

The Heart and Estrogen-progestin Replacement Study (HERS)

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Background—Observational studies have shown that postmenopausal hormone therapy may increase, decrease, or have no effect on the risk of stroke. To date, no clinical trial has examined this question. To investigate the relation between estrogen plus progestin therapy and risk of stroke among postmenopausal women, we analyzed data collected from the Heart & Estrogen-progestin Replacement Study (HERS), a secondary coronary heart disease prevention trial.

Methods and Results—Postmenopausal women (n=2763) were randomly assigned to take conjugated estrogen plus progestin or placebo. Primary outcomes for these analyses were stroke incidence and stroke death during a mean follow-up of 4.1 years. The number of women with strokes was compared with the number of women without strokes. A total of 149 women (5%) had 1 or more strokes, 85% of which were ischemic, resulting in 26 deaths. Hormone therapy was not significantly associated with risk of nonfatal stroke (relative hazard [RH] 1.18; 95% CI 0.83 to 1.66), fatal stroke (RH 1.61; 95% CI 0.73 to 3.55), or transient ischemic attack (RH 0.90; 95% CI 0.57 to 1.42). Independent predictors of stroke events included increasing age, hypertension, diabetes, current cigarette smoking, and atrial fibrillation. Black women were at increased risk compared with white women, and unexpectedly, body mass index was inversely associated with stroke risk.

Conclusions—Hormone therapy with conjugated equine estrogen and progestin had no significant effect on the risk for stroke among postmenopausal women with coronary disease. **(*Circulation*. 2001;103:638-642.)**

Key Words: cerebrovascular disorders ■ hormones ■ stroke

Strokes are an important cause of disability and death among older women. Because many women use hormone therapy for the control of perimenopausal symptoms and to prevent osteoporosis after menopause, establishing whether such therapy has other health effects is of considerable clinical importance. A decision to use hormone therapy for osteoporosis could be influenced, for example, by effects it might have on other medical conditions, such as the risk of heart disease and stroke.

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Based on observational studies, the effect of postmenopausal hormone therapy on the risk of stroke is uncertain. Recent case-control studies and cohort studies have reported that postmenopausal hormone therapy increases,[1] decreases,[2–6] or has no significant effect[7–15] on stroke risk. Because observational studies of postmenopausal hormone therapy may be confounded by differences in the characteristics of women who use postmenopausal hormones, eg, women who use postmenopausal hormones tend to be healthier than nonusers,[16,17] clinical trial data are essential for discerning the unconfounded relation between postmenopausal hormone therapy and risk of stroke.

To examine the relation of postmenopausal hormone therapy to risk of stroke and transient ischemic attack (TIA), we analyzed data collected from the Heart & Estrogen-progestin Replacement Study (HERS), a secondary coronary heart disease (CHD) prevention study among postmenopausal women with known coronary artery disease.[18] Stroke and TIA were prespecified secondary outcomes. HERS is the first clinical trial of postmenopausal hormone therapy to examine whether such therapy affects the risk of TIAs and stroke.

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Methods

Subjects

Between February 1993 and October 1994, 2763 postmenopausal women with CHD were recruited from 20 clinical centers across the United States for a randomized, blinded study of the effect of hormone therapy with conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) on recurrent CHD events. Baseline data were collected during the screening and randomization visits and included demographic characteristics, medical history, risk factors for CHD, physical examination, and laboratory data. Participants were monitored by phone interview 3 times per year and were seen in clinic yearly for a physical examination and for evaluation of interval events. Details of the study rationale, design, and recruitment procedures have been described elsewhere.[18] HERS was approved by the institutional review board at each clinical center, and informed consent was obtained from all participants before enrollment.

Measurements

Baseline data included self-reported information on participants' age, ethnicity, marital status, highest grade or year of school completed, number of pregnancies, past use of postmenopausal estrogen therapy, level of physical activity, alcohol consumption, smoking habits, and history of diabetes mellitus and hypertension. Women with a history of gestational diabetes were not classified as having diabetes mellitus. Data were also obtained on all current prescription and nonprescription medications and vitamin preparations. Participants were considered to have hypertension based on self-reported history, a baseline systolic blood pressure >140 mm Hg, or a baseline diastolic blood pressure >90 mm Hg. Women with a history of thrombotic events or with uncontrolled hypertension or diabetes were not enrolled. Details regarding the questionnaires, physical examination, and laboratory procedures used in HERS have been published previously.[18]

Outcome Adjudication

Outcome adjudication for stroke and TIA events was conducted after a careful review of medical records by 2 physician adjudicators at the coordinating center who were blinded to treatment status. Stroke events were defined as the rapid onset of a neurological deficit attributed to an obstruction or rupture of the arterial system not known to be caused by a brain tumor, infection, or other cause. The neurological deficit had to last >24 hours or be confirmed by a lesion compatible with an acute stroke on CT or MRI of the brain. Stroke events were further classified as fatal or nonfatal and as ischemic or hemorrhagic based on a review of brain imaging studies. A total of 10 strokes (6 nonfatal and 4 fatal) could not be classified as either ischemic or hemorrhagic because of the absence of imaging documentation. Adjudication of these strokes was based on a review of all other available medical records. These events were excluded from the analyses that examined the relation of hormone therapy to type of stroke (ie, hemorrhagic versus ischemic) but were included in the analyses of fatal and nonfatal stroke. TIA events were defined as the rapid onset of a neurological deficit attributed to an embolus or obstruction of the arterial system not known to be caused by a brain tumor, infection, or other cause. Adjudication of TIA events was based on documented neurological symptoms that lasted <24 hours and the lack of an acute stroke on CT or MRI scan of the brain. The main study results published in 1998 were based on the near-final data available at the time.[18] This article includes the updated and final HERS results for cerebrovascular disease events.[19]

Statistical Methods

We used unpaired 2-tailed t tests to compare continuous variables and χ^2 tests to compare categorical variables. To analyze the association between hormone therapy and incident stroke events, we used Cox proportional hazards models. To examine the predictors of stroke, treatment assignment and variables that were associated with stroke at the $P \leq 0.20$ significance level were entered into each multivariate model. We used stepwise regression procedures to retain variables associated with stroke at $P \leq 0.05$. We calculated the hazard ratio and 95% CI to estimate the risk of TIA and stroke (categorized as ischemic versus hemorrhagic and fatal versus nonfatal). Participants who were judged to have had TIAs during the study were not excluded from the analyses of stroke incidence. However, women who suffered >1 nonfatal stroke ($n=9$) were excluded from the analyses of nonfatal stroke after their first stroke event. Women who had ≥ 1 nonfatal stroke followed by a subsequent fatal stroke ($n=7$) were included in analyses of predictors of fatal stroke. We also performed survival analysis using Kaplan-Meier curves to compare time to all incident stroke events (nonfatal and fatal stroke). Log-rank tests were used to compare differences in survival curves.

Results

The baseline characteristics of the HERS participants had similar distributions in the 2 randomized study arms (Table 1). HERS participants were on average 67-year-old white, married women with a high likelihood of being hypertensive and using aspirin. A total of 165 strokes occurred in 149 participants over of the course of the study. As expected, most (85%) of the strokes were ischemic; 8% were hemorrhagic strokes, and 6% could not be classified. A total of 139 nonfatal strokes and 26 fatal strokes occurred over a mean follow-up of 4.1 years. The incidence rates for any stroke event were 12/1000 person-years among women taking placebo and 15/1000 person-years among women taking postmenopausal hormone therapy.

In analyses that examined the relation of hormone therapy to risk of stroke, we found that hormone therapy was not significantly associated with either risk of nonfatal stroke events (relative hazard [RH] 1.18; 95% CI 0.83 to 1.66) or fatal stroke events (RH 1.61; 95% CI 0.73 to 3.55) (Table 2). Kaplan-Meier survival curves display the cumulative percentage of strokes for both hormone therapy and placebo groups over the entire duration of follow-up (Figure). By the end of the study, $\approx$7% of women assigned to the hormone therapy group experienced a fatal or nonfatal stroke compared with 5% of women in the placebo group. This 2% absolute difference in stroke risk, however, was not statistically significant ($P=0.20$). The relation between hormone therapy and risk of stroke was similar for ischemic or hemorrhagic strokes, neither of which was significantly associated with the use of hormone therapy (Table 2). Postmenopausal hormone therapy had no discernible effect on risk of TIAs (RH 0.90; 95% CI 0.57 to 1.42), nor was it associated with the risk for all combined cerebrovascular disease events (any stroke or TIA) (RH 1.09; 95% CI 0.84 to 1.43).

Using multivariable stepwise regression models, we examined predictors of stroke events adjusting for treatment assignment (Table 3). A number of variables were significantly associated with risk of stroke. As expected, older women and participants with hypertension, atrial fibrillation, or diabetes, as well as current smokers, were at increased risk for stroke. Black women had approximately twice the risk of stroke as white women. Increasing body mass index was associated with a decreased risk for stroke; a 1-unit increase in body mass index was independently associated with a 4% decrease in stroke risk. Additional multivariate models that included all the variables noted in Table 1 also found body

TABLE 1. Selected Baseline Characteristics of Women in HERS

Variable	Estrogen-Progestin Therapy (n=1380)	Placebo (n=1383)
Age, y*	67 (7)	67 (7)
Race, %		
White	88	90
Black	8	7
Other	4	3
Body mass index, kg/m^2*	29 (6)	29 (6)
Education, y*	13 (3)	13 (3)
Exercises >3 times/wk, %	39	38
Hypertension, %	68	68
Pack-year history of smoking*	32 (26)	32 (26)
Current smoking, %	13	13
Alcohol consumption, drinks/wk*	1 (3.7)	1 (3.6)
Diabetes mellitus, %	23	22
Past estrogen replacement therapy, %	24	23
Aspirin use, %	79	79
Atrial fibrillation, %	1	1
Warfarin use, %	4	4
Lipid-lowering medication use, %	46	48
Vitamin C supplement use, %	16	16
Vitamin E supplement use, %	19	19
Serum LDL cholesterol, mmol/L*	3.75 (0.98)	3.75 (0.96)
Serum HDL cholesterol, mmol/L*	1.29 (0.34)	1.29 (0.34)

*Values denote means (SD). Unpaired 2-tailed *t* tests were used to compare continuous variables and χ^2 tests were used to compare categorical variables.

mass index inversely associated with risk of stroke. Baseline atrial fibrillation was the strongest predictor of stroke among HERS participants and conferred a 6.5-fold increased risk of stroke, even after controlling for the effects of aspirin and warfarin therapy. Among participants with baseline atrial fibrillation, stroke incidence did not differ by treatment assignment. We examined whether statin use might affect the risk of stroke or TIA and found no relation with either cerebrovascular disease outcome.

With the exception of level of education, there were no statistically significant interactions with postmenopausal hormone therapy. Additional adjustment for level of education and level of education×treatment assignment produced similar findings.

Discussion

Postmenopausal Hormone Therapy and Stroke

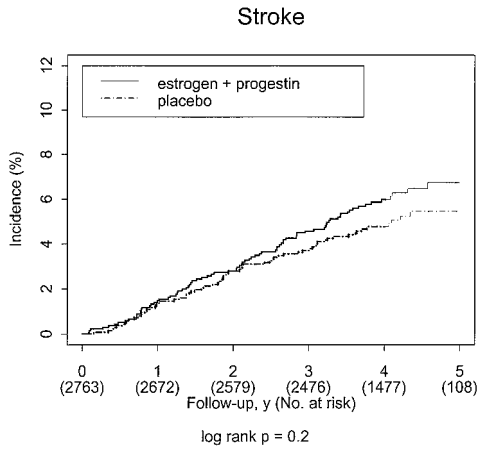
Our main finding was the absence of any significant beneficial or detrimental effect of hormone therapy on the risk of cerebrovascular disease events among postmenopausal women with coronary disease followed up for a mean of 4.1 years. Compared with a stroke incidence rate of 4/1000 person-years among populations of white women aged 45 to 84 years,[20] HERS participants had a higher incidence rate. Unlike the pattern observed for myocardial infarction and CHD death in the original HERS report,[18] there was no early increase in risk of stroke in the hormone-treated group followed by a later decrease. HERS was not designed to detect differences in the rate of stroke events. However, the 149 women who experienced a stroke event provided enough power to observe a modest protective effect, and the confidence interval of 0.89 to 1.70 makes it unlikely that we missed a true reduction exceeding 11%.

HERS is important because it is the first large randomized clinical trial to examine the effect of hormone therapy on risk of strokes, a predesignated secondary outcome of interest. Our findings concur with many recent observational studies that reported no significant association between postmeno-

TABLE 2. Risk of Cerebrovascular Disease Events in HERS

Outcome	Number of Women With Event*		RH (95% CI)
	Placebo	Estrogen+Progestin	
Fatal stroke	10	16	1.61 (0.73–3.55)
Nonfatal stroke	60	70	1.18 (0.83–1.66)
TIA	44	35	0.90 (0.57–1.42)
Hemorrhagic stroke	5	8	1.65 (0.47–5.72)
Ischemic stroke	59	69	1.18 (0.83–1.67)
Any stroke	67	82	1.23 (0.89–1.70)
Any stroke or TIA	103	112	1.09 (0.84–1.43)

*A total of 4 fatal and 6 nonfatal strokes could not be classified as ischemic or hemorrhagic, and 7 participants were censored after their initial nonfatal stroke event.



Kaplan-Meier estimate of cumulative incidence of stroke events. Number of women observed at each year of follow-up and still free from stroke events is provided in parentheses; lines become thinner when this number drops below half of the cohort. Log-rank *P* value is 0.20.

pausal hormone therapy and stroke risk.[7–15] However, some studies examining the relation between postmenopausal hormone therapy and stroke have reported that hormone therapy decreases stroke risk,[2–6] and the Framingham Heart Study reported that it increased risk of stroke, at least among smokers.[1] Our findings do not support the Framingham observation of an adverse interaction between postmenopausal hormone therapy and stroke among smokers. Because women who use postmenopausal hormone therapy tend to be more health-conscious than nonusers, it is possible that the ostensible beneficial effects of hormone therapy on risk of stroke reported in some observational studies may have resulted from such confounding.

Other Predictors of Stroke

Similar to the findings of others, we found that increasing age, hypertension, diabetes, and cigarette smoking were important independent risk factors for stroke events.[21–24] Black women in HERS experienced an increased risk for stroke events, even after controlling for other factors. These findings also are similar to those of other investigators and largely remain unexplained.[21,22] Baseline atrial fibrillation was the strongest predictor of stroke events. The risk of a thromboembolic stroke in the presence of untreated atrial fibrillation is 5% per year.[21] Among the 29 women (≈1% of HERS participants) identified with atrial fibrillation at baseline, 55% of whom were given warfarin for anticoagulation, we found a 6.5-fold increased risk of stroke, independent of anticoagulation with warfarin and other risk factors. These estimates concur with those from other studies that range from 6- to 18-fold.[22] The risk of stroke for women with atrial fibrillation did not differ by treatment assignment, in contrast with the findings of Hart et al,[25] who reported that postmenopausal hormone therapy conferred a 3-fold additional increased risk of ischemic stroke in women with atrial fibrillation enrolled in the Stroke Prevention in Atrial Fibrillation (SPAF) III trial. However, HERS enrolled so few women with atrial fibrillation that there was little power to observe such an association.

Although obesity is a less-well-documented risk factor for stroke, it is associated with established stroke risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, and may therefore be on the causal pathway to stroke.[21] Whereas a number of recent studies have found no association between obesity and risk of stroke in women,[8,26,27] some earlier studies reported obesity to be a stroke risk factor, either independent of[28,29] or as related to hypertension or diabetes.[30–32] In contrast, we found an inverse association between body mass index and stroke. This finding may have occurred by chance or may possibly reflect residual confounding by other risk factors, such as smoking. Of note, the Tecumseh study[33] reported a higher risk of cardiovascular mortality (including stroke) among lean hypertensive individuals even after adjustment for smoking. We controlled for differences in hypertension, but like the Tecumseh investigators, we do not have an explanation for the observation of decreased risk among heavier women.

There were a number of limitations to our study. HERS was restricted to postmenopausal women with CHD, and therefore our findings may not be generalizable to other

TABLE 3. Predictors of Incident Stroke in HERS

	RH (95% CI)*	
Variable	Simple Model	Multivariate Model†
Age (10 y)	1.83 (1.41–2.38)	1.93 (1.45–2.55)
Race (black vs white)	1.86 (1.16–2.98)	1.91 (1.18–3.10)
Hypertension (yes vs no)	1.97 (1.32–2.96)	1.67 (1.10–2.53)
History of diabetes mellitus (yes vs no)	2.57 (1.85–3.56)	3.03 (2.12–4.32)
Cigarette smoking (current vs never)	1.45 (0.95–2.22)	2.01 (1.28–3.15)
Atrial fibrillation (yes vs no)	7.18 (3.66–14.09)	6.45 (3.25–12.82)
Body mass index (kg/m^2)	0.98 (0.95–1.01)	0.96 (0.93–0.99)

*All RH estimates are adjusted for treatment assignment.

†Stepwise regression was used to adjust for variables nominally associated with stroke at a *P* value of ≤0.20. In addition to the variables noted in Table 3, marital status, level of education, alcohol consumption, cigarette smoking (past vs never), aspirin use, warfarin use, use of lipid-lowering medication, and level of lipoprotein(a) were also entered into the multivariate model. Only variables associated with stroke at a *P* value of ≤0.05 were retained.

groups of women. Using data from HERS, we cannot separate the effects of estrogen from those of progestin. Much of the baseline data were obtained by self-report; hence, misclassification of some variables, such as diabetes mellitus, likely occurred. However, the magnitude of the risk for stroke associated with age, diabetes, and atrial fibrillation was similar to risk estimates from other studies. Because the main HERS trial did not collect data on dietary intake, markers of inflammation, or hemostasis, we are unable to comment on several other possible predictors of stroke. However, HERS was a randomized, blinded trial, and it is unlikely that our principal findings regarding the relation of estrogen plus progestin to stroke and TIA were affected by confounding or bias.

In conclusion, HERS is the first large randomized clinical trial to examine the effect of hormone therapy on risk of strokes. Our findings indicate that there is no significant association between postmenopausal hormone therapy and risk of stroke among postmenopausal women followed up for a mean of 4.1 years.

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