Hormone Replacement Therapy and Associated Risk of Stroke in Postmenopausal Women

Rozenn N. Lemaitre, PhD, MPH; Susan R. Heckbert, MD, PhD; Bruce M. Psaty, MD, PhD; Nicholas L. Smith, PhD; Robert C. Kaplan, PhD; W. T. Longstreth, Jr, MD, MPH

**Background:** There is little information about the risk of stroke in relation to time since initiation of hormone therapy and in relation to estrogen dose.

**Methods:** We conducted a population-based case-control study at Group Health Cooperative (GHC), a health maintenance organization in the greater Seattle (Wash) area, to assess the association of hormone replacement therapy with the risks of incident ischemic and hemorrhagic stroke. Cases were all postmenopausal women with incident stroke at GHC during July 1989 through December 1998 (726 ischemic strokes and 213 hemorrhagic strokes). Controls were randomly selected from GHC enrollees and frequency matched to cases on age and calendar year (n = 2525). Hormone use was assessed from computerized pharmacy data. We reviewed the medical record to confirm eligibility and assess other risk factors.

**Results:** After risk factor adjustment, ischemic stroke was not associated with current use of estrogen with progestin (odds ratio [95% confidence interval]: 0.97 [0.69-1.37]) or without (0.94 [0.72-1.23]) compared with never use. Similarly, hemorrhagic stroke was not associated with current use of estrogen with progestin (0.74 [0.43-1.28]) or without (1.06 [0.71-1.56]). However, the risks of ischemic stroke and hemorrhagic stroke were increased 2-fold during the first 6 months of hormone use (ischemic stroke: 2.16 [1.04-4.49], hemorrhagic stroke: 2.20 [0.83-5.81]). Risk of ischemic stroke also increased with estrogen dose ($P$ for trend = .03).

**Conclusion:** The transitory increase in risks of ischemic stroke and hemorrhagic stroke associated with initiation of hormone replacement therapy merits further investigation.

*Arch Intern Med. 2002;162:1954-1960*

---

**The Possibility** that initiation of hormone replacement therapy (HRT) might be associated with a transitory increase in risk of stroke was raised by a recent report from the Women’s Estrogen for Stroke Trial (WEST).1 In the WEST trial, therapy with 17β-estradiol did not prevent strokes among postmenopausal women with previous stroke or transient ischemic attack.1,2 Furthermore, estrogen therapy appeared to actually increase stroke risk during the first 6 months of therapy. Early harm from HRT has been observed previously in another secondary prevention trial. In the Heart and Estrogen/progestin Replacement Study (HERS), HRT appeared to increase the risk of coronary events in the first year of therapy.3 While the HERS study investigators did not report an early increase in stroke, only a small number of stroke events were observed in HERS.4 Primary prevention trials of HRT and cardiovascular disease among healthy women have yet to be reported. Observational studies provide conflicting evidence on the overall association of HRT and stroke.5-16 These studies relied largely on the self-report of hormone use, and the only study that addressed the possibility of early harm from HRT could not assess HRT use of less than 1 year’s duration.3 Furthermore, whether stroke risk varies with the dose of estrogen used or with other characteristics of HRT has received limited attention, although a dose-related hazard has been hypothesized17 and was suggested by a prospective study.3

We investigated the possible association of HRT with the risk of incident ischemic stroke and incident hemorrhagic stroke in a population-based case-control study using detailed computerized information on hormone use. Our objective was to investigate the association of current use of estrogen and estrogen plus progestin with the risks of incident ischemic stroke and incident hemorrhagic stroke among postmenopausal women. In addition, the detailed assessment of HRT...
use up to the date of stroke events allowed us to investigate the association of recency of HRT initiation, as well as dose of estrogen used, with the risk of stroke.

METHODS

DESIGN AND SETTING

This was a population-based case-control study conducted at Group Health Cooperative (GHC), a large health maintenance organization that serves approximately 370000 enrollees in western Washington State.

STUDY SUBJECTS

Cases were all female GHC enrollees aged 30 to 79 years who experienced an incident fatal or nonfatal stroke between July 1, 1989, and December 31, 1998. Cases were identified from GHC hospitalization discharge diagnosis databases and from the results of a match between Washington State death records and the membership list of GHC. Controls were a random sample of GHC female enrollees, frequency matched to cases on calendar year and age (by decade). The ratio of controls to cases was at least 2 to 1. We excluded women who had a prior stroke and women who were not postmenopausal. In addition, we excluded women who had been a member at GHC for less than a year or who had fewer than 4 visits prior to their index date because we might not have found adequate risk factor information in their records.

Classification of an event as an ischemic stroke required the rapid onset of a neurologic deficit that persisted at least 24 hours or evidence of infarction on brain imaging studies, at surgery, or at autopsy. Strokes were defined as hemorrhagic if there was evidence of blood in the subarachnoid space or ventricles or dense intraparenchymal blood on brain imaging studies. In the absence of test results, strokes were defined as hemorrhagic if there was rapid onset of neurologic deficit followed by death within 24 hours. We excluded stroke cases that could not be categorized as ischemic or hemorrhagic due to insufficient information (64 of 1003 identified strokes).

INDEX DATES

The index date was the date of hospitalization for hospitalized cases or the date of death for out-of-hospital fatal cases. For controls, the index date was a randomly assigned date within the calendar year for which they were sampled as controls.

DATA COLLECTION

We reviewed the ambulatory medical record to determine eligibility and to collect information on key covariates for the period before the index date. We collected information on medical history, including angina, hypertension, diabetes, congestive heart failure, myocardial infarction, transient ischemic attack, and peripheral vascular disease, and information on traditional risks factors such as blood pressure and smoking status. Angina was defined as probable or definite based on the notes of the primary care physician and consultants and the results of diagnostic tests. Diabetes mellitus was defined as treatment with oral hypoglycemic medication and/or insulin or a history of diabetes. Hypertension was defined as treatment with antihypertensive medications. Blood pressure was the blood pressure measured during the most recent visit before the index date. Cardiovascular disease was defined as any of the following conditions: prior myocardial infarction, angina, angioplasty, coronary artery bypass, carotid endarterectomy, peripheral vascular disease procedure, transient ischemic attack, claudication, congestive heart failure, or atrial fibrillation. We also performed a telephone interview of consenting survivors to assess risk factors such as smoking status, education, and race.

EXPOSURE ASSESSMENT

We used the GHC computerized pharmacy database to assess current and past use of estrogen and estrogen plus progestin as of the index date. Since 1976, the GHC pharmacy database includes a record of all prescriptions dispensed to GHC enrollees. In a previous case-control study of HRT and myocardial infarction, we found that 97% of both myocardial infarction cases and controls filled all or almost all their prescriptions at a GHC pharmacy. Current users of hormone therapy were defined as women who received at least 1 estrogen prescription before the index date with enough estrogen pills to last until the index date, assuming at least 80% compliance with prescribing instructions. Past users of hormone therapy were defined as women who received at least 2 estrogen prescriptions before the index date and were not current users at the index date.

To determine the duration of estrogen use, we calculated the number of days that each prescription would last using prescribing instructions and assuming 80% compliance. If an estrogen prescription was filled out before another one run out, we assumed that the extra pills were not taken. Duration of use was obtained by summing the duration of exposure for each estrogen prescription, with or without progestin, recorded in the GHC database since 1976. All estrogen prescriptions were counted whether they provided continuous or intermittent estrogen exposure. As a measure of recency of HRT initiation, we calculated the time elapsed between the first estrogen prescription ever recorded in the GHC pharmacy database and the index date. This measure was computed for all current users, whether the exposure to estrogen between the initiation of HRT use and the index date was continuous or interrupted with periods of nonuse. To determine the dose of estrogen used, we assumed that the following doses were equivalent: 0.625 mg of conjugated estrogens, 0.625 mg of esterified estrogens, 1 mg of estriopipate, 1 mg of micronized estradiol, 1 mg of estradiol valerate, and 0.05 mg of ethinyl estradiol. All estrogen doses are given as equivalents of conjugated estrogens.

STATISTICAL ANALYSES

Statistical analyses were performed using STATA 7.0 (Stata Corp, College Station, Tex). We compared the risk factor distribution in stroke cases and controls using descriptive analyses. We defined 4 mutually exclusive categories of hormone use as of the index date: current use of estrogen without progestin, current use of estrogen with progestin, past use of estrogen (with or without progestin), and never use of estrogen. To compare the distribution of risk factors across categories of hormone use among the controls, we used analyses of variance for the continuous variables and $\chi^2$ tests for categorical variables. Because there were differences in age across the hormone use categories, the analyses of variance and means and proportions across the categories were adjusted for age.

To investigate the association of hormone use with ischemic and hemorrhagic stroke we performed unconditional logistic regression analyses. Using never users of estrogen as reference, we obtained odds ratios (ORs) and 95% confidence intervals (CIs) associated with the 3 categories of hormone use in logistic regression analyses with indicator variables for each category. The statistical significance associated with the addition of a variable to the models was based on the likeli-
We identified 726 incident ischemic stroke cases, 213 incident hemorrhagic stroke cases, and 2525 controls during the study period. Women in the study were on average 68 years old and were long-time enrollees at GHC (Table 1). Ischemic stroke cases were older on average than hemorrhagic stroke cases. Further, as expected in this type of study, cardiovascular risk factors were more prevalent among cases than controls. Systolic blood pressure was higher and current smoking and cardiovascular disease were more prevalent in both types of stroke cases than in controls. Ischemic stroke cases also had higher mean cholesterol levels and weight and higher prevalence of diabetes than controls.

Thirty-eight percent of ischemic stroke cases, 45% of hemorrhagic stroke cases, and 47% of controls had used estrogen at some time, alone or in combination with progestin, while 22% of ischemic stroke cases, 27% of hemorrhagic stroke cases and 28% of controls were current users (Table 1). Among controls, never users were older than estrogen users, and current users of estrogen with progestin were younger than other users (Table 2). After adjustment for age, current HRT users were less likely to have diabetes, while current users of estrogen with progestin were less likely to be current smokers and had lower average systolic and diastolic blood pressure, weight, and total cholesterol levels (Table 2).

In unadjusted analyses, ever use of estrogen was associated with a decreased risk of incident ischemic stroke (OR, 0.71; 95% CI, 0.60-0.84). However, after adjustment for age, index year, diabetes, systolic blood pressure, cardiovascular disease, and current smoking, the association was weak (OR, 0.93; 95% CI, 0.76-1.12). Likewise, current use of estrogen, current use of estrogen in combination with progestin, and past use of HRT were not associated with ischemic stroke after adjustment for potential confounders (Table 3). In addition, we found no evidence that diabetes, cardiovascular disease, current smoking, treated hypertension, or age modified the association of HRT with ischemic stroke. Use of HRT was not associated with the risk of incident hemorrhagic stroke in both unadjusted and adjusted analyses (Table 4).

The median duration of HRT use among ever users was 3.7 years for controls, 3.3 years for ischemic stroke cases, and 3.1 years for hemorrhagic stroke cases. Duration of estrogen use was not associated with incident ischemic stroke (ORs, adjusted for risk factors, corresponding to quartiles of increasing duration: 1.0, 0.9, 0.9, and 0.8; P for trend = .27) and was not associated with incident hemorrhagic stroke (ORs corresponding to quartiles of increasing duration: 1.0, 1.1, 0.9, and 0.7; P for trend = .26).

We explored the possibility that recent HRT initiation might be associated with an increased risk of incident stroke. Compared with never use of HRT, current use initiated within 6 months of the index date appeared associated with about 1.8-fold increase in risk of

---

Table 1. Characteristics of Cases and Controls*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ischemic Stroke Cases (n = 726)</th>
<th>Hemorrhagic Stroke Cases (n = 213)</th>
<th>Controls (n = 2525)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.3 (7.4)†</td>
<td>67.9 (9.2)†</td>
<td>68.1 (8.1)</td>
</tr>
<tr>
<td>White race, %</td>
<td>89.1†</td>
<td>87.1†</td>
<td>91.1</td>
</tr>
<tr>
<td>Time in GHC, y</td>
<td>19.3 (12.1)</td>
<td>18.4 (12.0)†</td>
<td>19.9 (11.5)</td>
</tr>
<tr>
<td>No. of physician visits in last year</td>
<td>8.7 (7.8)†</td>
<td>6.6 (6.1)†</td>
<td>5.9 (5.6)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>61.9†</td>
<td>43.7‡</td>
<td>35.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148.0 (22.7)†</td>
<td>143.9 (22.5)‡</td>
<td>136.8 (19.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.4 (11.1)†</td>
<td>83.2 (12.2)‡</td>
<td>79.1 (10.1)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL§</td>
<td>243.6 (47.7)†</td>
<td>236.9 (50.8)‡</td>
<td>234.6 (41.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.0 (17.5)</td>
<td>68.0 (15.8)‡</td>
<td>71.4 (16.3)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31.4†</td>
<td>32.9‡</td>
<td>22.0</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>52.5†</td>
<td>32.9‡</td>
<td>22.0</td>
</tr>
<tr>
<td>Angina, %</td>
<td>20.7†</td>
<td>12.7†</td>
<td>9.9</td>
</tr>
<tr>
<td>Transient ischemic attack, %</td>
<td>15.2†</td>
<td>13.2‡</td>
<td>3.3</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>20.1†</td>
<td>13.2‡</td>
<td>8.5</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>12.8†</td>
<td>4.7†</td>
<td>3.5</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>18.7†</td>
<td>24.4‡</td>
<td>13.9</td>
</tr>
<tr>
<td>Ever use of hormone replacement therapy, %</td>
<td>38.2†</td>
<td>45.1†</td>
<td>46.5</td>
</tr>
<tr>
<td>Current use of hormone replacement therapy at index date, %</td>
<td>22.2‡</td>
<td>27.2†</td>
<td>27.8</td>
</tr>
</tbody>
</table>

*Numbers are mean (SD) unless indicated otherwise. Information was missing on time in Group Health Cooperative (GHC) (9 controls, 8 ischemic strokes, 1 hemorrhagic stroke); number of visits (6 controls, 1 hemorrhagic stroke); history of myocardial infarction (1 ischemic stroke, 1 hemorrhagic stroke); cholesterol levels (162 controls, 57 ischemic strokes, 23 hemorrhagic strokes), weight (4 controls), and race (313 controls, 83 ischemic strokes, 19 hemorrhagic strokes).

†P < .05 for the ischemic stroke/control comparison.
‡P < .05 for the hemorrhagic stroke/control comparison.
§To convert to millimoles per liter, multiply by 0.02586.
Table 2. Characteristics of Controls According to Estrogen Use

<table>
<thead>
<tr>
<th>Current Use</th>
<th>Past Use, Estrogen ± Progestin (n = 470)</th>
<th>Never Use (n = 1352)</th>
<th>Odds Ratio (95% CI) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.8 (60.0-65.2)</td>
<td>67.7 (65.0-70.5)</td>
<td>0.70 (.63-0.77)</td>
</tr>
<tr>
<td>Time in GHC, y</td>
<td>22.1 (17.7-26.4)</td>
<td>21.5 (19.1-23.9)</td>
<td>.19 (.09-.35)</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>19.8 (16.4-23.4)</td>
<td>22.0 (19.3-24.8)</td>
<td>.46 (.30-.68)</td>
</tr>
<tr>
<td>Angina, %</td>
<td>8.3 (6.4-10.2)</td>
<td>9.8 (7.8-11.8)</td>
<td>.30 (.19-.44)</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>8.3 (6.4-10.2)</td>
<td>8.2 (6.4-10.2)</td>
<td>.47 (.27-.80)</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>2.8 (1.9-3.6)</td>
<td>2.0 (1.3-2.9)</td>
<td>.19 (.09-.40)</td>
</tr>
<tr>
<td>Transient ischemic attack, %</td>
<td>2.6 (1.9-3.3)</td>
<td>3.7 (2.9-4.6)</td>
<td>.70 (.48-1.00)</td>
</tr>
<tr>
<td>Claudication, %</td>
<td>2.0 (1.6-2.5)</td>
<td>2.5 (2.1-3.0)</td>
<td>.84 (.59-1.19)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>6.7 (5.7-7.8)</td>
<td>8.5 (7.4-9.7)</td>
<td>.02 (.01-.05)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>133.1 (127.8-138.7)</td>
<td>135.6 (131.3-140.0)</td>
<td>.02 (.01-.05)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.3 (73.9-80.7)</td>
<td>79.4 (75.8-83.0)</td>
<td>.01 (.00-.02)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL †</td>
<td>226.1 (215.5-236.7)</td>
<td>236.0 (225.5-246.5)</td>
<td>.04 (.00-.006)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.9 (65.6-70.2)</td>
<td>71.9 (69.6-74.2)</td>
<td>.02 (.01-.03)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>8.6 (7.4-9.9)</td>
<td>11.5 (10.1-13.0)</td>
<td>.06 (.04-.09)</td>
</tr>
</tbody>
</table>

*Except for values of age, the values shown in the table are age adjusted. GHC indicates Group Health Cooperative. †To convert to micromoles per liter, multiply by 0.02586.

Both incident ischemic stroke (OR, 1.86; 95% CI, 0.91-3.79) and hemorrhagic stroke (OR, 1.70; 95% CI, 0.66-4.40) (Table 5, top). There was no increase in risk associated with current HRT use initiated earlier (Table 5, top). Since current HRT users appeared healthier than never users (Table 2), we also performed analyses confined to current users. When current users of HRT initiated within 6 months were compared with other current users, the stroke risk increases were slightly more pronounced (Table 5, bottom). Current HRT use initiated within 6 months was associated with a 2-fold increase in risk of ischemic stroke (OR, 2.16; 95% CI, 1.04-4.49), and hemorrhagic stroke (OR, 2.20; 95% CI, 0.83-5.81), compared with current use initiated earlier.

Among current users who had initiated HRT use within 6 months of their index date, 7 ischemic stroke cases (50%) and 25 controls (68%) used estrogen in combination with progestin. Current HRT use initiated within 6 months appeared associated with increased risk of ischemic stroke among both users of estrogen alone (OR, 3.31; 95% CI, 1.16-9.43) and users of estrogen combined with progestin (OR, 1.55; 95% CI, 0.51-4.69) with the difference in the point estimates well within chance (P for interaction = .22). Of the 6 hemorrhagic stroke cases who were recent current HRT users, 5 used progestin in combination with estrogen and 1 used estrogen alone. Owing to small numbers, we could not meaningfully investigate if progestin use modified the association of recently initiated current HRT use with hemorrhagic stroke.

Among current HRT users, 78% of controls, 76% of ischemic stroke cases, and 74% of hemorrhagic stroke cases used a modal dose of estrogen (equivalent to 0.625 mg of conjugated estrogen). Dose of estrogen used was associated with the risk of ischemic stroke among current users. Compared with use of low-dose estrogen (equivalent to 0.3 mg of conjugated estrogen), use of the modal estrogen dose was associated with an OR of 1.44 (95% CI, 0.81-2.61) and use of higher doses (median 1.25 mg of conjugated estrogen) was associated with an OR of 2.41 (95% CI, 1.09-5.35) (P for trend = .03) (Table 6). Exclusion of women who had initiated HRT within 6 months of the index date did not change the point estimates. In contrast to the association with ischemic stroke, dose of estrogen was not associated with hemorrhagic stroke (P for trend = .89).

We could not investigate whether recent initiation of HRT with low-dose (0.3 mg) estrogen was also associated with increased risk of stroke because 88% of ischemic stroke cases and 100% of hemorrhagic stroke cases who initiated...
HRT within 6 months of index date used the modal dose equivalent to 0.625 mg of conjugated estrogen.

Further adjustment for body weight, angina or myocardial infarction, history of transient ischemic attack, atrial fibrillation, hypertension, total cholesterol and glucose levels, added one at a time to the models, did not change any of the results.

**COMMENT**

Overall, among the postmenopausal women in this case-control study, ever use of estrogen, past use of estrogen, current use of estrogen alone, and current use of estrogen plus progesterin were not associated with the risk of incident ischemic stroke or the risk of incident hemorrhagic stroke after adjustment for cardiovascular risk factors. Nonetheless, the risk of both types of stroke appeared to be transiently increased after initiation of HRT.

Compared with current HRT use of longer duration, there was a 2-fold increase in risk of first ischemic stroke and a 2-fold increase in risk of first hemorrhagic stroke during the first 6 months after initiating HRT. In addition, the association between current HRT and ischemic stroke differed depending on the dose of estrogen used. Compared with use of 0.3 mg of estrogen, use of 0.625 mg of estrogen was associated with a 1.4-fold increase in risk of incident ischemic stroke and use of higher estrogen doses was associated with a 2.4-fold increase in risk.

The strengths of our study include the population-based study design, the objective assessment of hormone use, and control for many potential confounders of the association of estrogen with stroke. While cases were identified after their event, the assessment of HRT exposure and other stroke risk factors was based on information accrued prospectively in a computerized database and in the medical record, thereby avoiding all possibility of recall bias. In addition, the computerized pharmacy records on HRT use provided detailed information on combination therapy, timing of HRT use and dose of estrogen.

The main limitation of the study is the small number of study subjects who recently initiated HRT use and the small number of users of estrogen doses other than the modal dose. For this reason, we were not able to investigate if initiation of low estrogen dose was also associated with increased risk of incident stroke in the first 6 months after initiating HRT. Another limitation was the observational study design from which cause and effect cannot be concluded. We did not know if the study subjects took the estrogen pills prescribed to them. Although we took into account many potential risk factors, residual confounding by unmeasured participant characteristics, such as compliance, cannot be eliminated.

The study results are similar to those of the WEST trial, a randomized trial of estrogen therapy among postmenopausal women with a history of stroke or...
transient ischemic attack. In WEST, therapy with 1 mg/d of 17β-estradiol did not prevent strokes (relative risk of stroke compared with placebo, 1.1; 95% CI, 0.8-1.6). However, post hoc analysis suggested an increased risk of stroke in the first 6 months of estradiol therapy (relative risk, 2.3; 95% CI, 1.1-5.0). In the HERS trial, a secondary prevention trial conducted among postmenopausal women with coronary heart disease, therapy with 0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone did not prevent strokes either (relative risk, 1.23; 95% CI, 0.89-1.70). Furthermore, early harm from HRT was also suggested in the HERS trial. In post hoc analyses, an increased risk of coronary events was observed during the first year of HRT therapy. In HERS, the risk of stroke did not appear to increase with the initiation of HRT; however, the power to find an early risk of stroke may have been limited.

There have been no clinical trials of HRT for the prevention of stroke in healthy women. Results from observational studies have been inconsistent, in part due to differences in outcome, exposure, and study design. A healthy user bias might explain the decreased risk of stroke associated with HRT in some of the observational studies. In our study, the apparent association of HRT use (ever, current, past, with or without progestin) with decreased risk of ischemic stroke appeared to be explained by other cardiovascular risk factors. The lack of benefits of current use of estrogen and current use of estrogen with progestin with respect to ischemic stroke is in agreement with studies that have looked at this outcome. A lack of association with HRT use with hemorrhagic stroke was also reported in the most recent, and largest studies.

Two observational studies have addressed the possibility of early risk of incident stroke with HRT use. In a case-control study of HRT and ischemic stroke, reported HRT use of less than 1 year among current users was not associated with the risk of ischemic stroke (OR, 0.75; 95% CI, 0.23-2.42). These analyses included 90 cases and 102 controls who were current users and the number of recent users was not shown but likely small. In recent analyses from the Nurses Health Study, current use of HRT of less than 1 year was not associated with increased risk of ischemic stroke (OR, 1.07; 95% CI, 0.44-2.61) or with increased risk of hemorrhagic stroke (OR, 1.56; 95% CI, 0.63-3.90). However, the duration of HRT use in that study was reportedly underestimated by an average of 1 year due to the biannual self-report assessment of HRT use. Given the imprecision of the information on time of HRT initiation and the large 95% CIs, a lack of association with early HRT use in these studies remains inconclusive.

Our finding of decreased risk of ischemic stroke with lower estrogen doses is in agreement with the report from the Nurses Health Study: using never users as reference, the relative risk (95% CI) of ischemic stroke associated with 0.3 mg of estrogen was 0.43 (0.16-1.16); with 0.625 mg of estrogen, 1.44 (1.07-1.93); and with 1.25 mg or more, 2.00 (1.32-3.05). However, there were only 4 ischemic stroke cases who used 0.3-mg estrogen. The possibility that low-dose estrogen might lower the risk of ischemic stroke compared with higher doses needs to be investigated in a clinical trial.

The mechanisms by which HRT might increase the risk of stroke are not known. The higher risk of ischemic stroke associated with higher estrogen doses might be due to prothrombotic effects of estrogen. On the other hand, the similar levels of the associations of current HRT use initiated recently with both ischemic stroke and hemorrhagic stroke do not support such a mechanism of action.

We recently reported that in the same population of postmenopausal women, current HRT use was associated with an 8-fold increase in risk of myocardial infarction among hypertensive women with the prothrombin 20210 G→A variant, while there was no association of HRT use with myocardial infarction among hypertensive women without the variant. Whether this polymorphism or other prothrombotic mutations also modify the association of HRT with stroke needs to be investigated as well.

In summary, we observed an increased risk of incident ischemic stroke and an increased risk of incident hemorrhagic stroke in the first 6 months after initiation of HRT among postmenopausal women. Further research is needed to confirm these findings and to investigate the reasons for the transitory increase in risk. We also found that the risk of ischemic stroke was inversely related to estrogen dose among current users of HRT. Until better evidence is available to guide such decisions, these findings suggest that the lowest possible dose of estrogen should be used when women receive HRT for symptoms of the menopause.

Accepted for publication January 31, 2002.

This research was supported by grants from the National Heart, Lung, and Blood Institute (HL 40628, HL 43201) and the Merck/Society for Epidemiologic Research Clinical Epidemiology Fellowships (Dr Psaty).

We wish to thank Shannon Ryan and Marian Harper for their help with the project.

Corresponding author and reprints: Rozenn N. Lemaître, PhD, MPH, University of Washington, Cardiovascular Health Research Unit, Metropolitan Park, East Tower, Suite 1360, 1730 Minor Ave, Seattle, WA 98101 (e-mail: rozenl@u.washington.edu).

REFERENCES


