Postmenopausal Hormone Therapy and Stroke

Role of Time Since Menopause and Age at Initiation of Hormone Therapy

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Background: We evaluated stroke risk associated with hormone therapy (HT) in younger women, in recently menopausal women, and in older women.

Methods: Prospective, observational analyses were performed in postmenopausal participants of the Nurses’ Health Study, from 1976 to 2004, with biennial mailed questionnaires. Proportional hazards models were used to calculate multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs).

Results: We found a significantly increased risk of stroke for women currently taking HT (estrogen alone: RR, 1.39; 95% CI, 1.18-1.63; and estrogen with progestin: RR, 1.27; 95% CI, 1.04-1.56), a finding that is nearly identical to that of the Women's Health Initiative. This increased risk was observed for women initiating HT at young ages or near menopause and at older ages or more than 10 years after menopause. Short-term (<5 years) HT initiated at younger ages was not associated with a clear increase in stroke; however, this apparently null result was based on a small number of cases. The incidence of stroke was relatively low in younger women, and the attributable risk in women aged 50 through 54 years indicated approximately an additional 2 cases of stroke per 10,000 women per year taking hormones. We found a strong relationship between dose of oral conjugated estrogen and stroke, with RRs of 0.93, 1.54, and 1.62 for doses of 0.3, 0.625, and 1.25 mg, respectively (P for trend, < .001).

Conclusions: Hormone therapy is associated with an increased risk of stroke, and this increased risk does not appear to be related to the timing of the initiation of HT. In younger women, with lower stroke risk, the attributable risk of stroke owing to hormone use is modest and might be minimized by lower doses and shorter treatment duration.

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Many controversies remain regarding the risks and benefits of postmenopausal hormone therapy (HT). In particular, there are relatively limited data regarding the effects of hormone use on stroke. A 35% increased risk of stroke with current use of HT was reported in the Nurses’ Health Study.1 The Women’s Health Initiative (WHI), a randomized trial of postmenopausal HT, also reported a 30% to 40% elevated risk of stroke for women given estrogen combined with progestin or estrogen alone.2 3 Although these risks appeared similar in the WHI for women who initiated HT at younger and older ages, the WHI included few women who were recently menopausal, when HT is most commonly initiated in clinical settings. Therefore, the stroke risk for women taking HT near menopause, in terms of both relative and absolute risks, remains unclear. Because HT is the most effective treatment for menopausal symptoms, it is important to determine whether stroke risk is an important consideration for younger women who are taking HT near the onset of menopause. Also, although national recommendations suggest taking the lowest possible HT dose to minimize risks, sparse data are available regarding the relationship between lower doses of estrogen and stroke.

In a previous publication,1 we reported results regarding the relationship of current and past HT, including HT duration and estrogen dose, to total stroke, ischemic stroke, and hemorrhagic stroke and presented the associations of HT regimen (estrogen alone vs estrogen combined with progestin) with total stroke. Therefore, in the present analyses, we examined the most critical current questions regarding stroke risk: we explored the timing of HT initiation and further examined varying estrogen doses since we had limited power to address these questions in the previous analyses. Also, given important differences in the pathogen-
esis of ischemic stroke and hemorrhagic stroke, we updated our analyses of hormone regimen to specifically address stroke type.

### METHODS

#### THE NURSES’ HEALTH STUDY COHORT

The Nurses’ Health Study began in 1976, when 121,700 female nurses, aged 30 to 55 years, returned a mailed questionnaire, including detailed information on menopause and postmenopausal hormone use as well as on diagnoses of cardiovascular disease and cardiovascular risk factors. We update health and lifestyle information with biennial follow-up questionnaires. Dietary and physical activity questionnaires were added in 1980. Cohort follow-up is more than 90%. On each biennial questionnaire, women were asked details regarding postmenopausal HT, including current use (within the last month), duration of use, type of hormones taken, and dose of oral conjugated estrogen (data on estrogen dose were first collected in 1980).

#### IDENTIFICATION OF STROKE

We identified first occurrences of nonfatal and fatal stroke between the return of the 1976 questionnaire and June 1, 2004. Nurses who reported a nonfatal stroke were asked for permission to review their medical records. Medical records were reviewed by physicians who had no knowledge of the participant’s self-reported exposure status. Nonfatal strokes for which medical records were unavailable were not included in analyses. Deaths were ascertained by reports from relatives or postal authorities and a search of the National Death Index. Only fatal stroke cases documented by medical records were included in analyses. Overall, medical records were available for 74% of reported stroke cases. In contrast, in our previous publications on stroke, we included cases confirmed by medical records as well as “probable” cases, defined as strokes for which medical records were unavailable but which required hospitalization and were corroborated by letter or interview with the subject or next of kin. However, in the current analyses, we were more interested in stroke type and therefore could not include cases without medical records. This difference in our analytic approach would have little impact on the relative risk (RR) estimates. Characteristics of the subset of cases with medical records were very similar to those of all women with stroke; eg, of those with medical records available, 46% had never taken HT, 36% used estrogen alone, and 18% used estrogen with progestin, while in the entire group of stroke cases, these figures were 48%, 35%, and 17%, respectively. However, the exclusion of probable cases decreases our estimates of absolute stroke rates and attributable risks. Therefore, for the purposes of comparison, we provide data on stroke rates and attributable risks both excluding and including the probable cases.

Incident strokes were confirmed using National Survey of Stroke criteria, which require a constellation of neurologic deficits, sudden or rapid in onset, and duration of at least 24 hours or until death. Cerebrovascular disease due to infection, trauma, or malignancy was excluded. We classified strokes as ischemic (embolic or thrombotic) and hemorrhagic (subarachnoid or intracerebral) according to standard criteria.

#### POPULATION FOR ANALYSIS

In primary analyses, women who reported stroke as well as myocardial infarction, angina, coronary revascularization, or cancer (except nonmelanoma skin cancer) on the 1976 questionnaire were excluded, because these diseases are among the most common that may have caused women to alter their hormone use. Similarly, women who reported such diagnoses on a subsequent questionnaire were censored at that point and excluded from further analysis. Therefore, at the start of each 2-year interval, the base population included no women reporting these diagnoses.

We classified women as postmenopausal from the time of natural menopause or hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for smokers and 56 years for non-smokers). The women’s reports of age at and type of menopause were highly accurate in this cohort.

We explored the effects of initiating HT at varying intervals since menopause and at different ages. A primary interest was to investigate stroke risk in younger women who are near menopause. To provide data for women initiating HT near menopause, we examined women who began hormone use within 4 years of menopause. We chose a cutoff of 4 years to define “near” menopause since our follow-up occurs in 2-year intervals, and we believed that a 2-year cutoff was excessively short but that a 6-year cutoff was too long. Moreover, most HT use in the general population occurs within 4 years of menopause onset. In these analyses, we excluded women with unknown age at menopause (eg, those with no uterus but with intact ovaries). We also compared women initiating HT at younger ages (30-59 years, or <55 years) with women who never used hormones.

### STATISTICAL ANALYSIS

For each participant, person-months were allocated to hormone categories according to the 1976 data and updated every 2 years (for estrogen dose, follow-up began in 1980). We specifically assessed dose of oral conjugated estrogen with or without oral medroxyprogesterone acetate, as these 2 were the most common regimens, as well as the hormones used in the WHI. If no data were available on hormones in a given period, women were assigned to a missing category for that period. Follow-up for a participant ended with a first diagnosis of stroke, or death, or June 1, 2004, whichever came first. In total, we included 485,987 person-years of follow-up among women who had never taken HT and 409,629 person-years of follow-up among current HT users. Compared with our previous publication with follow-up through 1996, the present data represent substantially greater power to detect effects, with a 36% increase in person-years among women who had never used HT and a 54% increase among women who were currently taking HT. The greater increase of current hormone use than “non-use” likely reflects both the aging of the population and the changing prescription patterns over the different periods.

Analyses are based on incidence rates using person-years of follow-up as the denominator. We used RR as the measure of association, defined as the incidence rate of stroke among women in various categories of hormone use divided by the rate among women who never used hormones. We computed age-specific rates using 5-year categories and calculated age-adjusted RRs using Mantel-Haenszel rate ratios, with 95% confidence intervals (CIs).

We calculated adjusted RRs with Cox proportional hazards models, controlling for age (continuous), body mass index (calculated as weight in kilograms divided by height in meters squared: <21, 21-22, 23-25, 26-29, 30-31, and ≥32), cigarette smoking (never, past, or current smoker of 1-14, 15-24, 25-34, or ≥35 cigarettes per day), history of hypertension (yes, no), diabetes (yes, no), and elevated cholesterol level (yes, no).
be incurred with hormone use.

tain rate differences, or the number of stroke cases that would come from the rate among women who never used hormones to ob-

We then subtracted the rate estimated for women taking HT from the model; in these analyses, follow-up began in 1980, when that information was first collected, and included only women who completed the diet questionnaires (approximately 80% of the subjects). Finally, adjusting for hysterectomy status had no impact on our results; therefore, we did not include this vari- able in our models.

We calculated rate differences based on the rate of total stroke among participants who had never used HT. For ease of calculation, we multiplied this rate by the overall, multivariable-adjusted RR we found for the association of current HT use and total stroke (ie, RR, 1.4), to obtain the rate of stroke for HT users. We then subtracted the rate estimated for women taking HT from the rate among women who never used hormones to obtain rate differences, or the number of stroke cases that would be incurred with hormone use.

### RESULTS

For estrogen alone, the age-adjusted RR of total stroke for current users was 1.33 (95% CI, 1.13-1.55) compared with women who never used HT (Table 1). For combined HT, this RR was generally similar (RR, 1.17; 95% CI, 0.96-1.42). After adjustment for major stroke risk factors, these estimates became slightly stronger: the RR for estrogen alone rose to 1.39, and the RR for estrogen with progestin rose to 1.27. When we further adjusted for dietary factors, physical activity, regular aspi- rin use, and vitamin supplementation (data not shown in the tables), the results did not materially change (eg, for total stroke: RR, 1.43; 95% CI, 1.19-1.71 with estrogen alone; and RR, 1.45; 95% CI, 1.18-1.80 with combined therapy); therefore, we did not include these additional covariates in the primary analyses. Relative risks were generally similar across stroke types (ie, ischemic stroke, hemorrhagic stroke, nonfatal stroke, and fatal stroke), although with the small number of hemor- rhagic strokes or fatal strokes, the CIs were wide (Table 1).

Timing of HT initiation in relation to onset of meno- pause or age (Table 2) did not appear to change the observed associations (eg, for estrogen alone: RR, 1.20; 95% CI, 1.06-1.38 initiated near menopause; and RR, 1.31; 95% CI, 1.06-1.63 initiated ≥10 years after menopause). These increases in stroke risk were consistent for women taking estrogen alone and estrogen combined with progestin (eg, for estrogen with progestin: RR, 1.22; 95% CI, 0.95-1.55 initiated near menopause; and RR, 1.18; 95% CI, 0.87- 1.60 initiated ≥10 years after menopause).

Because HT is most commonly initiated to treat meno- pausal symptoms, which generally last less than 5 years, we also examined the impact of HT duration on stroke risk; in these analyses, we focused on the very youngest women, within 4 years of menopause or younger than 55 years (data not shown in the tables). We combined women taking estrogen alone and estrogen with progestin, since both regi-
Table 2. Risk for Total Stroke Comparing Women Currently Taking Hormone Therapy (HT) With Women Who Never Used HT by Timing of HT Initiation With Respect to Onset of Menopause and Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>Person-Years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HT Initiation by Time Since Menopause</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>312</td>
<td>370,831</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td>146</td>
<td>163,092</td>
<td>1.29 (1.06-1.58)</td>
</tr>
<tr>
<td>Estrogen and progestin</td>
<td>93</td>
<td>119,912</td>
<td>1.22 (0.95-1.55)</td>
</tr>
<tr>
<td><strong>HT Initiation by Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>240</td>
<td>193,066</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td>133</td>
<td>87,038</td>
<td>1.31 (1.06-1.63)</td>
</tr>
<tr>
<td>Estrogen and progestin</td>
<td>53</td>
<td>35,909</td>
<td>1.18 (0.87-1.60)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

a Adjusted for age, body mass index, high cholesterol level, diabetes, high blood pressure, husband's education, smoking, and family history of premature myocardial infarction.

b Near menopause defined as within 4 years; data not shown for 5 to 9 years since menopause.

c Data not shown for women who initiated HT in their 40s.

Figure. Rate of total stroke among women who never used hormone therapy in the Nurses' Health Study.

Table 3

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Attributable Risk a</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.9</td>
</tr>
<tr>
<td>50-54</td>
<td>1.5</td>
</tr>
<tr>
<td>55-59</td>
<td>2.2</td>
</tr>
<tr>
<td>60-64</td>
<td>2.8</td>
</tr>
<tr>
<td>≥65</td>
<td>7.2</td>
</tr>
</tbody>
</table>

a Attributable risks were calculated assuming an RR of 1.4 for current hormone use compared with never hormone use.

For example, if 10,000 women aged 50 through 54 years used HT for 1 year—applying the RR of 1.4 for HT and stroke seen in the overall cohort to all women—one would expect an extra 1.5 cases of stroke compared with an extra 7.2 cases for women aged 65 years and older.

In alternate analyses, including both the confirmed and probable cases, absolute stroke rates were higher, ranging from 5.4 per 10,000 person-years among women aged 50 through 54 years to 10.6 per 10,000 person-years among women aged 60 through 64 years and 26.0 per 10,000 person-years among women aged 65 years and older (data not shown in the Figure). Similarly, the attributable risk of stroke resulting from current HT use was higher. For example, if 10,000 women used HT for 1 year, we would expect an extra 2.2 cases of stroke among women aged 50 through 54 years and an extra 10.4 cases among women aged 65 years and older (data not shown in the tables).

Finally, when we examined the dose of estrogen (Table 3), we found a strong trend of increasing risk of stroke with increasing dose of oral conjugated estrogen (P for trend, <.001). Specifically, for total stroke, there was a similar rate of stroke for women currently taking 0.3 mg of estrogen compared with women who had never taken HT (multivariable-adjusted RR, 0.93; 95% CI, 0.62-1.40), while there were statistically significant increases for those taking 0.625 mg (RR, 1.54; 95% CI, 1.31-1.81) and 1.25 mg (RR, 1.62; 95% CI, 1.23-2.14).

COMMENT

Overall, we found approximately a 30% to 40% increased risk of stroke for women currently taking postmenopausal HT, either estrogen alone or estrogen combined with progestin. These findings are virtually identical to those of the WHI trials. Similar to the WHI, we did not find any clear difference in the relationship of HT to stroke for women initiating therapy at younger ages vs at older ages. However, considering the low rate of stroke development in younger women, the attributable risk of stroke associated with hormone use in the younger age groups was modest. Moreover,
although CIs were wide, there was not a clear increase in the risk of stroke for the youngest women, who had used HT for less than 5 years.

Also, we found a strong trend of increasing risk of stroke with increasing dose of estrogen. At the lowest estrogen dose (0.3 mg of oral conjugated estrogen), there was not a greater risk of stroke, although the CI was fairly wide. These current findings are generally similar to our previously published data on HT and stroke,9 where we had also reported a trend of increasing stroke risk with increasing estrogen dose. However, in the previous report, with just 9 stroke cases among women taking 0.3 mg of estrogen, we had found a nearly 50% decrease in stroke rates compared with those among women who had never taken HT (RR, 0.54; 95% CI, 0.28–1.06), although the CI was wide. In these analyses, with almost 3 times as many stroke cases in the low-dose estrogen group, the RR was 0.93 (95% CI, 0.62–1.40), consistent with the previous estimate but ruling out the previously reported 50% reduction in stroke for low-dose estrogen users. Very limited additional research has been conducted on the relationship of hormone dose to risk of stroke. However, in a randomized trial, low-dose estrogen did not increase certain inflammatory or thrombotic markers to the same extent as higher doses.9 Clearly, substantially more research is needed on the cardiovascular effects of 0.3 mg of estrogen, since this dose has now become common in clinical practice.

Interestingly, in contrast to data on heart disease in both our study and the WHI,10–12 which suggest a lower risk of heart disease with HT initiation at younger ages or near menopause, the risk of stroke appeared similar regardless of the timing of HT initiation. Still, we found a low absolute rate of stroke in younger women, leading to a modest attributable risk; both the absolute rate and the attributable risk remained modest among younger women even after we included stroke cases for which we had no medical records available. Since Nurses’ Health Study participants are a select group of educated health professionals, these data on stroke rates and attributable risks likely underestimate those in the general population. However, our rates were only somewhat lower than estimates across studies of more general populations,13 especially when we included stroke cases for which we could not obtain medical records. For comparison, among women aged 55 through 64 years, the American Heart Association Statistical Committee13 reported a rate of 19.0 per 10 000 person-years for cerebral infarction and hemorrhagic strokes compared with our finding of 12.5 per 10 000 person-years in this age group when cases without medical records were excluded and 18.2 per 10 000 person-years when cases without medical records were included.

Finally, confounding is always a concern in observational studies. However, we found that adjustment for potential confounding factors did not substantially alter associations between postmenopausal HT and stroke (ranging from a 10%-20% increase in RR), indicating that the relationship would likely not be largely changed with either more accurate data on known confounding factors or additional data on currently unknown confounding factors. Our results on the relation of HT to stroke are entirely consistent with those from the WHI trials, strongly indicating that our data on stroke are valid.

In summary, our findings in the Nurses’ Health Study indicate that HT is associated with an increased risk of stroke, regardless of the hormone regimen or the timing of HT initiation. However, in younger women, who are at lower absolute risk of stroke, the attributable risk of stroke owing to hormone use is modest, and our data suggest that risk might be further minimized by lower doses and shorter duration of treatment.

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**REFERENCES**


