

# Hormone therapy and cerebrovascular events: a population-based nested case-control study

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## ABSTRACT

**Objective:** The relationship between postmenopausal hormone therapy (HT) and cerebrovascular disease has been examined in several epidemiological studies and clinical trials with conflicting results. The authors aimed to evaluate the association between the use of HT and the incidence of first cerebrovascular event.

**Design:** The study cohort comprised 158,031 women 50 to 69 years old registered in the U.K. General Practice Research Database between 1991 and 1997. The authors conducted a nested case-control analysis using all 920 confirmed cases of cerebrovascular events identified during the follow-up (536 of transient ischemic attack [TIA]; 259 of ischemic stroke; 125 of hemorrhagic stroke) and 10,000 controls.

**Results:** The odds ratios of TIA, ischemic stroke, and hemorrhagic stroke among women currently using HT were 1.48 (95% CI, 1.17-1.87), 1.12 (95% CI, 0.78-1.59) and 1.21 (95% CI, 0.76-1.93), respectively, compared to never users. The overall risk estimate for having a cerebrovascular event was 1.34 (95% CI, 1.11-1.61). The risk of TIA was greater (1.96) among women using high doses of estrogen (95% CI, 1.34-2.87).

**Conclusion:** Overall, a small increased risk of stroke associated with HT use of comparable magnitude to the one observed in recent clinical trials was found. The increased risk was more apparent for TIA than for stroke and was greater at higher doses.

**Key Words:** Hormone therapy – Cerebrovascular event – Stroke – Menopause – Pharmacoepidemiology.

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Coronary heart disease and cerebrovascular disease are the leading causes of death worldwide,<sup>1</sup> and all projections indicate that they will remain first and second in the year 2020.<sup>2</sup> In the case of stroke, the lifetime risk

of death has been reported to be greater in women than in men with about 16% of women and 8% of men expected to die of stroke.<sup>3</sup>

The relationship between postmenopausal hormone therapy (HT) and cerebrovascular disease has been examined in several epidemiological studies<sup>4-13</sup> and clinical trials.<sup>14-20</sup> The results from observational studies among postmenopausal women without a history of cerebrovascular disease suggest that HT does not affect the risk of hemorrhagic stroke. However, results on the risk of ischemic stroke are conflicting, with a tendency toward an increased risk reported in some studies.<sup>7-9,13</sup> Early epidemiologic studies primarily assessed the risk of stroke in association with the use of estrogen therapy (ET). More recent studies evaluating the risk of

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cerebrovascular events with estrogen plus progestogen therapy (EPT) have indicated that the addition of progesterone increases the risk.<sup>9</sup> Similarly, the majority of the randomized clinical trials, either in primary or secondary prevention, consistently suggested that HT increases the risk of stroke. Still, there are some questions that remain unanswered: the effect of HT on the different subtypes of stroke, the influence of the route of administration, and the effect of preparations other than EPT.

As part of a comprehensive safety evaluation of the effects of HT in postmenopausal women, we conducted a population-based cohort study with a nested case-control analysis to evaluate the association between the use of this therapy and the incidence of first cerebrovascular event in a European population using oral and transdermal estrogens.<sup>21</sup> Estimates of risk by duration, dose, regimen, and route are also presented.

## MATERIALS AND METHODS

### Study population

A cohort of women, 50 to 69 years old, from the general population in the United Kingdom was identified through registration status in the General Practice Research Database maintained by the Boston Collaborative Drug Surveillance Project<sup>22</sup> between January 1991 and December 1997. Women with a history of cardiovascular diseases (coronary heart disease, cerebrovascular disease, and arrhythmias), neoplasms, coagulopathies, vasculitis, and alcohol-related diseases were excluded. The resulting study cohort consisted of 158,031 women who were followed until the occurrence of the first recorded code of transient ischemic attack (TIA) or cerebrovascular event, any of the exclusion criteria as listed above, reaching 70 years of age, death, or the end of the study period (December 31, 1997), whichever occurred first. The study protocol was approved by the General Practice Research Database Scientific and Ethical Advisory Group.

### Data source

More than 1,500 general practitioners (GPs) use the General Practice Research Database to register health care and medical information about their patients in a standardized manner.<sup>23</sup> The registered information includes demographic data, all medical diagnoses, consultant and hospital referrals, and a record of all prescriptions issued. Practitioners generate prescriptions directly from the computer, ensuring its automatic recording. Several validation studies have shown that more than 90% of information present in the manual

medical records of the GPs, and more than 95% of newly prescribed drugs are recorded in the database.<sup>24,25</sup> The GP may also record laboratory results and other medical data in a free text comment field.

### Definition and ascertainment of cases

We used specific and nonspecific codes to ascertain all cerebrovascular accidents (CVAs) recorded on the computer files. A total of 1,264 potential cases of first ischemic stroke, hemorrhagic stroke, or TIA were originally identified. Manual review of all patient profiles was performed to characterize them as "probable" cases of stroke (ischemic, TIA, hemorrhagic) or "doubtful" based on the recorded medical information. A hospital admission was required for ischemic and hemorrhagic stroke but not for TIA. To validate the case status, a questionnaire was sent to the GPs requesting all available medical information related to the event of interest, including hospital discharge letters, reports of diagnostic procedure results (CT scan, magnetic resonance imaging, lumbar puncture), autopsy reports, and death certificates. We requested this information for a random sample of "probable" cases (119 of 649 cases). The response rate was about 95%. Overall, 86% of the "probable" cases were confirmed (ischemic 76%, hemorrhagic 100%, TIA 87%). All remaining "probable" cases for whom we did not send a questionnaire were included in the final analysis. The validation process was applied to all "doubtful" cases, and only those confirmed based on the information sent by the GPs (56%) were included in the analysis. The index date was defined as the earliest date of symptom onset (when available), date of hospital admission, or date of death.

### Selection of controls

We used a time incidence sampling method to select controls.<sup>26</sup> A random date within the study period was generated for each of the women of the cohort. All women with a random date included in their person-time period of observation (from study entry to end of follow-up) were eligible as controls. This procedure takes into account the amount of person-time contributed by each woman. Thus, we ensure that our control selection will yield a comparison group whose relevant exposure characteristics accurately reflect those of the source population for cases. The same exclusion criteria used to ascertain the cases were applied to all eligible controls using each woman's random date as her index date. A sample of 10,000 controls were identified, frequency-matched by age to cases.

### Exposure and other risk factors assessment

A list of all medications containing estrogens and/or progestogens recommended for HT and available in the United Kingdom during the study period was extracted from the British National Formulary. These drugs were grouped into the following regimens: (1) oral estrogens (76% were EPT with equine estrogens); (2) transdermal estradiol; (3) estradiol implant; and (4) tibolone. In addition, oral estrogens and transdermal estradiol were classified as opposed or unopposed depending on whether a progestogen was supplied along with estrogens. For each woman, the date of the last issued prescription for each of the regimens before the index date was identified. We defined a nonuser as a woman who never had a prescription for HT recorded in the database, a current user as a woman who used HT at any time in the 6-month period before the index date; a recent user as a woman who used HT from 6 to 12 months before the index date, and, finally, a past user was a woman who stopped therapy more than 1 year before the index date. The time period corresponding to consecutive prescriptions was used to define duration of HT. The daily dose of estrogens, type of regimen, and route of administration was obtained from the last prescription. Duration was categorized as (1) 1 year or less of use or (2) more than 1 year.

Estrogen prescribed doses were categorized as follows: (1) low dose: less than 0.625 mg of oral estrogens or 25 µg of transdermal estradiol; (2) medium dose: 0.625 to 1.24 mg of oral estrogens or 50 µg of transdermal estradiol; and (3) high dose: 1.25 mg or more of oral estrogens or 100 µg of transdermal estradiol.

Information on risk factors for CVA and drug utilization (including use of low-dose aspirin, lipid-lowering drugs, and anticoagulant drugs) was obtained from the database. Overweight was defined as recorded history of obesity and/or individual body mass index greater than 27 kg/m<sup>2</sup>. Menopause was considered surgical when a bilateral oophorectomy was recorded with or without hysterectomy. Comorbidity was categorized as single if there was only one recorded code of a disease in the following systems (nervous, cardiovascular, respiratory, renal, osteo-articular) or diabetes, or multiple if more than one.

### Statistical analysis

Person-time of follow-up was calculated for all cohort members by age and was used as the denominator to obtain incidence rates of CVAs.

Odds ratios (ORs) were used as the measure of association. Adjusted ORs and 95% CIs were estimated using unconditional logistic regression in STATA 8.2 (Stata Corporation, College Station, TX). Adjusted ORs were obtained by recency of HT use compared to nonuse. The effect of duration was assessed among current/recent users. The effect of oral and transdermal therapy (when numbers permit), unopposed, and opposed therapy was assessed in current/recent users with duration longer than 1 year compared to nonusers. The effect of estrogen dose was also assessed in long-term users of oral estrogens and transdermal estradiol, unopposed or opposed, aggregated in a single group of users.

## RESULTS

A total of 920 cases of incident stroke or TIA were identified: 536 cases of TIA, 259 cases of ischemic stroke, and 125 cases of hemorrhagic stroke. Overall, the incidence rate was 1.3 (95% CI, 1.2-1.4) cases per 1,000 person-years. The incidence in women younger than 60 years of age was 0.7 (95% CI, 0.6-0.8), and among women aged 60 years and older, it was 2.3 (95% CI, 2.1-2.5). These estimates are in line with other reports.<sup>27</sup> Mean age was the same among cases and controls (62 years).

Use of HT in the past 6 months was found in 215 cases (23.4%) and 2,005 controls (20.1%). Women who had ever used HT tended to be younger but had similar stroke risk profile as those women who never used HT (data not shown). Use of HT was inversely related to age. In the age group 50 to 59, 35% of controls used HT in the past 6 months compared with 12% among controls aged 60 to 69 years.

Overall, the occurrence of cerebrovascular events was positively associated with a history of smoking, diabetes, hypertension, obesity, and comorbidity (Table 1). After controlling for potential confounding factors, women who were currently using HT had an OR of 1.34 (95% CI, 1.11-1.61), whereas recent users had an OR of 1.47 (95% CI, 0.90-2.39) compared with nonusers. Further adjustment for antihypertensive drugs yielded virtually the same results (data not shown). In a supplementary analysis, we redefined "current use" as use in the month before the index date, resulting in an OR of 1.36 (95% CI, 1.12-1.65). When we stratified women according to a history of hypertension, we observed similar results (OR 1.29; 95% CI, 0.93-1.78 among hypertensive women and OR 1.36; 95% CI, 1.09-1.71 among nonhypertensive women).

**TABLE 1.** Association of cerebrovascular events with hormone therapy and other risk factors

	Cases (n = 920)	Controls (n = 10,000)	Age-adjusted OR	CI LL	CI UL	Multivariate OR <sup>a</sup>	CI LL	CI UL
Use of HT								
Never	636	7,186	1.0			1.0		
Current	215	2,005	1.21	1.02	1.42	1.34	1.11	1.61
Recent	20	176	1.28	0.80	2.05	1.47	0.90	2.39
Past	49	633	0.87	0.64	1.18	0.91	0.66	1.25
Smoking history								
Nonsmoker	365	5,192	1.0			1.0		
Smoker	258	1,664	2.21	1.86	2.61	2.43	2.04	2.90
Ex-smoker	57	537	1.51	1.12	2.02	1.52	1.13	2.05
Unknown	240	2,607	1.31	1.10	1.55	1.62	1.31	2.01
Diabetes								
No	850	9,723	1.0			1.0		
Yes	70	277	2.89	2.20	3.79	2.26	1.68	3.03
Hypertension								
No	583	7,689	1.0			1.0		
Yes	337	2,311	1.92	1.66	2.21	1.66	1.41	1.95
Obesity								
No	349	4,499	1.0			1.0		
Yes	304	2,573	1.52	1.30	1.79	1.38	1.17	1.64
Unknown	267	2,928	1.17	0.99	1.38	1.12	0.92	1.37
Comorbidity <sup>b</sup>								
No	243	3,539	1.0			1.0		
Single	337	3,901	1.25	1.06	1.49	1.04	0.87	1.24
Multiple	340	2,560	1.93	1.62	2.29	1.27	1.03	1.56

OR, odds ratio; CI LL, 95% confidence interval lower limit; CI UL, 95% confidence interval upper limit; HT, hormone therapy.

<sup>a</sup>ORs were estimated from a logistic model including all variables in this table in addition to hypercholesterolemia, family history of coronary heart disease, surgical menopause, cardioprophylactic use of aspirin, lipid-lowering drug use, anticoagulant drug use, and age.

<sup>b</sup>Comorbidity was present if there were one or more (2+) computer diagnoses of the following disease areas: nervous, cardiovascular, respiratory, renal, and osteoarticular.

When we analyzed separately the risk of TIA, we found that current use of HT was associated with an increased risk (OR 1.48; 95% CI, 1.17-1.87) (Table 2). The estimate associated with current HT

use was slightly larger during the first year of use (OR 1.94; 95% CI, 1.34-2.74). The OR associated with medium dose was 1.48 (95% CI, 1.12-1.96) and 1.96 (95% CI, 1.34-2.87) with a high dose. HT use

**TABLE 2.** Risk of cerebrovascular events by type and use of hormone therapy by duration, regimen, route of administration, and dose

HT use	Ischemic CVA				Hemorrhagic CVA				TIA			
	Cases/ controls	Multivariate <sup>a</sup> OR	CI LL	CI UL	Cases/ controls	Multivariate <sup>a</sup> OR	CI LL	CI UL	Cases/ controls	Multivariate <sup>a</sup> OR	CI LL	CI UL
Nonuse	187/7,186	1.0			88/7,186	1.0			361/7,186	1.0		
Past	14/633	0.86	0.48	1.54	5/633	0.58	0.23	1.49	30/633	1.02	0.68	1.53
Recent	7/176	1.80	0.81	4.01	2/176	0.80	0.19	3.38	11/176	1.53	0.81	2.89
Current	51/2,005	1.12	0.78	1.59	30/2,005	1.21	0.76	1.93	134/2,005	1.48	1.17	1.87
By duration												
≤1 y	14/534	1.23	0.69	2.19	6/534	0.92	0.39	2.18	45/534	1.94	1.38	2.74
>1 y	37/1,471	1.11	0.75	1.64	24/1,471	1.25	0.76	2.05	89/1,471	1.34	1.03	1.75
By estrogen dose <sup>b</sup>												
Low	7/178	1.65	0.75	3.64	1/178	0.45	0.06	3.29	7/178	0.82	0.38	1.78
Medium	29/1,195	1.09	0.71	1.67	16/1,195	1.06	0.60	1.89	77/1,195	1.48	1.12	1.96
High	11/422	1.16	0.61	2.23	11/422	1.87	0.94	3.69	36/422	1.96	1.34	2.87
By regimen												
Unopposed	10/521	0.79	0.40	1.54	10/521	1.54	0.76	3.12	33/521	1.36	0.92	2.01
Opposed	23/701	1.54	0.95	2.47	11/701	1.22	0.63	2.39	41/701	1.34	0.94	1.91

OR, odds ratio; CI LL, 95% confidence interval lower limit; CI UL, 95% confidence interval upper limit; HT, hormone therapy.

<sup>a</sup>Individual models for each variable adjusted for age, past use of HT, history of smoking, hypertension, diabetes, obesity, hypercholesterolemia, family history of cardiovascular disease, surgical menopause, lipid-lowering drug use, anticoagulant drug use, and cardioprophylactic use of aspirin.

<sup>b</sup>Dose: low: less than 0.625 mg for oral estrogens and 25 µg for transdermal estradiol; medium: 0.625 to 1.24 mg for oral estrogens and 50 µg for transdermal estradiol; high: 1.25 mg or higher for oral estrogens and 100 µg for transdermal estradiol.

was similarly associated with TIA irrespective of the type of regimen used (unopposed regimen, OR 1.36; 95% CI, 0.92-2.01; opposed regimen, OR 1.34; 95% CI, 0.94-1.91). There was, however, a suggestion of a greater risk associated with oral preparations (OR 1.47; 95% CI, 1.09-1.97) than with transdermal patches (OR 0.86; 95% CI, 0.43-1.73), although this comparison was based on a small number of users of transdermal preparations. The risk of having an incident TIA associated with 0.625 mg or higher of oral estrogens was 1.57 (95% CI, 1.16-2.11) and 1.02 (95% CI, 0.51-2.06) with 50 µg or more of transdermal estradiol compared to women who never used HT.

Current use of HT was associated with a non-significant slightly increased risk of ischemic CVA (Table 2). No estrogen dose-response relationship was observed. Opposed therapy was associated with an increased risk of ischemic CVA (OR 1.54; 95% CI, 0.95-2.47) as compared to women who never used HT.

Based on only 30 exposed cases, current use of HT conferred a 20% increase (OR 1.21; 95% CI, 0.76-1.93) in the risk of hemorrhagic CVA (Table 2). No clear treatment duration pattern was observed. There was a suggestion of an estrogen dose effect because HT at high dose was associated with an OR of 1.87 (95% CI, 0.94-3.69). No clear patterns were observed by regimen.

## DISCUSSION

Our cohort of relatively healthy postmenopausal women presented a 34% increase in the risk of cerebrovascular events associated with current use of HT. This association was more apparent for TIA, which represented more than one half of our cases, whereas the risk of ischemic and hemorrhagic stroke was only slightly elevated and not statistically significant. In the particular case of TIA, we found that the increased risk was estrogen dose dependent. Also the risk of TIA was greater with oral therapy than with transdermal patches, although there were few women exposed to transdermal therapy. Baseline differences in risk factors for CVA, such as age, history of smoking, hypertension, diabetes, obesity, family history, comorbidity, and use of aspirin, lipid-lowering drugs, or anticoagulant drugs did not explain these apparent differences in relative risk estimates.

The impact of HT on CVA risk has been controversial. Most of the early observational studies conducted in women without a history of CVA

reported no association, except the Framingham Heart Study that reported a 2.6-fold increase in the risk of ischemic CVA in women who used HT compared with those who never used HT.<sup>4-8,11,28-33</sup>

More recently, the Nurses' Health Study, a relatively homogeneous cohort of healthy postmenopausal women who have been followed more than 20 years, reported a 26% increase in the risk of ischemic CVA among current users of HT after controlling for a number of risk factors.<sup>9</sup> This risk was also stronger in women using EPT and was estrogen dose dependent. More recently, a meta-analysis of observational studies with HT reported a pooled relative risk estimate of 1.12 (95% CI, 1.01-1.23) for overall stroke and of 1.20 (95% CI, 1.01-1.40) for thromboembolic subtype.<sup>34</sup> Finally, our overall risk estimate is in line with the results from a recent meta-analysis of 28 randomized clinical trials where the authors reported an increase of 29% in stroke among users of HT.<sup>35</sup>

In our cohort of women, the risk of TIA and to a lesser extent ischemic stroke was more marked during the first year of therapy, which could suggest that women with some underlying characteristics may be particularly predisposed to (or at high risk of) developing thromboembolic conditions.<sup>36</sup> However, these results should be interpreted with caution because CIs across categories of duration clearly overlapped. The overall effect of HT on hemostasis is still unclear. Potentially adverse effects on coagulation may be balanced by potentially beneficial anti-coagulatory and profibrinolytic effects.<sup>37</sup> However, the net effect of HT on coagulation and fibrinolysis could depend on the specific type of estrogen, the dose and the duration of therapy, and the type of progestin used if the regimen is opposed.<sup>38</sup>

To the best of our knowledge, our study is the first to examine the association between the route of the HT and the risk of CVA. In TIA, the OR for oral therapy was higher than the one for transdermal therapy, although this result is compatible with no difference between routes of administration. However, the small number of observations hampered the evaluation of the effect of transdermal therapy in TIA and precluded a similar assessment in ischemic and hemorrhagic stroke.

It has been suggested that users of HT in observational studies are healthier and present with a better premenopausal cardiovascular risk factor profile than nonusers.<sup>39,40</sup> The healthy women bias, if present in our study, would underestimate the risk of CVA among users of HT. However, the study was

restricted to women with no history of cardiovascular and other chronic diseases, and the comorbidity index was greater for women exposed than for women not exposed to HT. Also, we adjusted the analysis for recorded known risk factors. In a previous study using the same source population, no differences were observed in social class and self-reported health indicators between HT users and nonusers.<sup>41</sup> Although our results are of the same magnitude as those from randomized, controlled trials immune to this selection bias, a small remaining healthy user effect cannot be completely discarded. On the other hand, women taking HT might be subject to referral or diagnostic bias that would tend to overestimate the risk of cerebrovascular disease and particularly TIA.<sup>42</sup>

In our study, the daily dose of estrogens, type of regimen, and route of administration were obtained from the last prescription of HT. This could introduce some minor degree of misclassification in the exposure variable as some women change HT preparations over time. This misclassification, if present, is unlikely to be associated with case status (nondifferential) and consequently would tend to slightly dilute any observed effect in some of our analyses.

Nondifferential misclassification could also be present if women not truly having cerebrovascular disease were included as cases, independent of their exposure status. However, in our study, the validation sample resulted in a high percentage of definite cases according to our diagnostic classification. When we used definite and nondefinite events as separate endpoints, the estimates of risk were similar (data not shown). Consequently, the misclassification present in our study is unlikely to have distorted our results to a great extent.

## CONCLUSION

We estimated an increased risk of CVA associated with HT use of comparable magnitude to the one observed in the Heart and Estrogen-Progestin Replacement Study and Women's Health Initiative trials, and in the extended follow-up of the Nurses' Health Study. Among subtypes of CVA, the risk of TIA was the most affected by HT use, whereas the risk of ischemic and hemorrhagic stroke was only modestly increased, not reaching statistical significance. The association was also slightly more apparent during the first year of use and greater at higher doses.

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