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Hormone therapy and the risk of stroke: perspectives ten years after the Women's Health Initiative trials

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Abstract

Principle findings on stroke from the Women's Health Initiative (WHI) clinical trials of hormone therapy indicate that estrogen, alone or with a progestogen, increases a woman's risk of stroke. These results were not unexpected, and research during the past decade has tended to support these findings. Consistent evidence from clinical trials and observational research indicates that standard dose hormone therapy increases stroke risk for postmenopausal women by about a third; increased risk may be limited to ischemic stroke. Risk is not modified by age of hormone initiation or use, or by temporal proximity to menopause, and risk is similar for estrogen plus progestogen and for unopposed estrogen. Limited evidence implies that lower doses of transdermal estradiol (50µg/d) may not alter stroke risk. For women less than 60 years of age, the absolute risk of stroke from standard dose hormone therapy is rare, about 2 additional strokes per 10,000 person-years of use; the absolute risk is considerably greater for older women. Other hormonally active compounds — including raloxifene, tamoxifen, and tibolone — can also affect stroke risk.

Keywords

estrogen; progestogen; hormone therapy; raloxifene; tamoxifen; tibolone; review; stroke; women's health initiative

Stroke can be defined as a persistent neurological deficit caused by vascular disease affecting the brain. The age-adjusted incidence is estimated at 94 per 100,000 person-years in high-income countries, and 117 per 100,000 person-years in other countries¹. Although stroke incidence has declined steadily in recent decades in high-income countries¹, stroke remains the leading cause of prolonged adult disability and the third leading cause of death among women². In many developing countries, stroke mortality and disability exceed those of ischemic heart disease³. Risk factors for stroke include hypertension, current smoking, increased waist-to-hip ratio, unhealthy diet, less regular physical activity, diabetes mellitus, high alcohol intake, psychosocial stress or depression, atrial fibrillation and other forms of cardiac disease, and elevated ratio of apolipoprotein B to apolipoprotein A1⁴.

The incidence of stroke increases steadily with age⁵. At least until late-old age, the age-specific incidence remains lower for women than for men⁶. However, because of longer life

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expectancy, estimates from the Framingham Study indicate that women's life-time risk of stroke at age 45 years (about one in five) exceeds that of men (about one in six).

Early natural menopause is associated with elevated risk of ischemic stroke later in life⁷, as might be early surgical menopause⁸. The mean age of first stroke occurs four years later for women compared to men (75 versus 71 years)⁶. It has long been suspected that sex differences in stroke incidence might be hormonally mediated, with ovarian estrogens produced cyclically during a woman's reproductive years acting to reduce stroke risk. Estrogen actions affect neurons and glia, vascular endothelium and smooth muscle, formed elements of the blood, plasma lipids and proteins, and inflammatory pathways. These complex actions have the potential to modify stroke risk and outcomes. The magnitude and direction of potential risk modification are not necessarily obvious.

BEFORE THE WOMEN'S HEALTH INITIATIVE

Stroke is a highly heterogeneous disorder. The primary clinical distinction is between ischemia and hemorrhage. Major subtypes of ischemic stroke include atherothrombotic (often related to atherosclerosis in the carotid artery or other large extracranial artery), cardioembolic (often related to atrial fibrillation or valvular heart disease), and lacunar (often related to occlusion of small perforating arteries within the brain)⁹. Major subtypes of hemorrhagic stroke include intracerebral hemorrhage due to rupture of a small artery and subarachnoid hemorrhage due to rupture of an aneurysm or vascular malformation⁹. Other classifications have been proposed¹⁰. Given this striking etiological heterogeneity, it is not surprising that risk factors for stroke, even ischemic stroke, differ in important ways from risk factors for ischemic heart disease¹¹.

Even prior to the Women's Health Initiative (WHI), the relation between hormone therapy and stroke risk had been widely studied. In 2002, Paganini-Hill reviewed 29 observational studies, finding no clear evidence that hormone use benefited stroke risk in postmenopausal women¹². This conclusion contrasted with other observational evidence that implied that hormone therapy could benefit postmenopausal women at risk for coronary heart disease¹³. Before WHI, stroke outcomes had been investigated in two large clinical trials, both focused on women with established vascular disease. The Heart and Estrogen/progestin Replacement Study enrolled postmenopausal women with established coronary disease¹⁴. Women, who were randomly assigned to daily estrogen combined with a progestogen or to placebo, were followed for a mean of 4.1 years. There was no significant effect on risk of stroke (Table 1¹⁵), a secondary outcome in this trial. In the Women's Estrogen for Stroke Trial, eligible women were postmenopausal, and they had a mild ischemic stroke or transient ischemic attack within the preceding 90 days¹⁶. After a mean follow-up period of 2.8 years, stroke events were similar for women allocated to an estrogen or to placebo (Table 1). Among women with non-fatal stroke, neurological and functional outcomes did not differ significantly between women in the two treatment arms¹⁶.

STROKE OUTCOMES IN THE WOMEN'S HEALTH INITIATIVE

Findings from the WHI hormone therapy trials were reported soon after those from the Heart and Estrogen/progestin Replacement Study and the Women's Estrogen for Stroke Trial. The multicenter WHI included a large observational cohort and two parallel clinical trials stratified by hysterectomy status¹⁷. The dual clinical trial used a partial factorial design, with three randomized interventions: low-fat diet, hormone therapy (conjugated estrogens with or without medroxyprogesterone acetate, depending on hysterectomy status), and calcium plus vitamin D dietary supplements¹⁷. Participants in these trials were community-dwelling postmenopausal women aged 50 to 79 years at baseline (mean age 63 years). Principle findings of the WHI hormone therapy trials, published in 2002 and 2004,

did not consider the factorial design^{18,19}. Stroke was a secondary outcome in these trials^{18,19}. More detailed analyses of stroke outcomes were published later^{20,21}.

In the WHI estrogen-plus-progestogen trial, women were studied over an average duration of 5.6 years²⁰. The estrogen-alone trial followed women for an average follow-up of 7.1 years²¹. In both trials, about 80% of strokes were classified as ischemic, and in both trials the risk of stroke was increased for women in the hormone therapy arm compared to placebo (Table 1). The magnitude of increase in stroke risk — approximately one-third — was slightly higher than, but consistent with, non-significant increases seen in the Estrogen/progestin Replacement Study and the Women's Estrogen for Stroke Trial. The excess risk in WHI corresponded to about nine additional cases of stroke per 10,000 person-years of hormone use²². The increase appeared primarily to affect ischemic stroke, although the study had limited power to evaluate hemorrhagic stroke outcomes. For women with a stroke, severity assessed at the time of discharge with the Glasgow Outcome Scale did not differ between hormone and placebo arms^{20,21}.

AFTER THE WOMEN'S HEALTH INITIATIVE

Since initial WHI publications on stroke^{18,19}, there have been new reports on women who participated in the WHI trials. Other research has helped clarify WHI inferences regarding hormone therapy and stroke. It is also now evident that other hormonally active compounds are associated with increased stroke risk.

A subset of WHI hormone trial participants, 1403 women aged 65 to 79 years at study onset, underwent magnetic resonance brain imaging²³. Scans were obtained on average three years (estrogen plus progestogen) or 1.4 years (estrogen alone) after trial termination. The primary outcome was based on an automated measure of ischemic lesion volume, defined by white matter changes attributed to ischemic disease and by lacunar infarction. There were no significant differences between women who had received on-trial hormone therapy and those who had received placebo. This finding was unexpected, as hormone therapy had increased stroke incidence during the WHI trials, although white matter ischemic changes *per se* do not represent frank infarction and are not associated with stroke symptoms.

As might be expected, excess risk of stroke attributed to hormone therapy during the WHI trials tended to decline after the trials were terminated. Group differences (hormone therapy group compared to the placebo group) between the intervention and post-intervention phases were significant for estrogen alone but not for estrogen plus progestogen. In both instances, post-intervention stroke risks did not differ significantly between women formerly assigned to hormone therapy and women formerly assigned to placebo. The three-year post-intervention relative risk for prior allocation to estrogen plus progestogen was 1.2 (95% confidence interval [CI] 0.8 to 1.6)²⁴; for estrogen alone, the post-intervention relative risk over a four year period was 0.9 (95% CI 0.6 to 1.2)²⁵.

Results of the WHI hormone therapy trial have generally proved consistent with results of other clinical trials. A meta-analysis of 28 randomized controlled trials (including three trials that included men) suggested a 29% increase in stroke due to hormone use (95% CI 1.1 to 1.5)²⁶. Risk was confined to ischemic stroke. The major contributors to this meta-analysis, based on number of stroke events, are the four estrogen trials summarized in Table 1. In this meta-analysis, there was no indication that risk was modified by hormone preparation (estrogen plus a progestogen versus estrogen alone) or type of estrogen (conjugated estrogens versus estradiol)²⁶. Stroke outcomes seemed worse among women who received the hormone therapy²⁶.

Interestingly, results from the WHI observational study failed to demonstrate a clear link between hormone therapy use and stroke^{24,25}. Other recent observational findings, however, do support WHI clinical trial findings^{27,28}.

In the Nurses' Health Study, investigators compared current users of hormone therapy to women who had never used hormone therapy²⁷. These analyses involved 121,700 women aged 30 to 55 years at baseline in 1976 and followed through 2004. For estrogen plus progestogen, risks were increased for any stroke (relative risk [RR] 1.3, 95% CI 1.0 to 1.6) and for ischemic stroke (RR 1.5, 95% CI 1.2 to 2.0). For estrogen alone, relative risks were similar (any stroke: RR 1.4, 95% CI 1.2 to 1.6; ischemic stroke: RR 1.4, 95% CI 1.2 to 1.7). The population based General Practice Research Database in the United Kingdom identified 15,710 cases of stroke between 1987 and 2006 among women aged 50 to 79 years²⁸. For women using oral estrogens, the relative of risk of stroke was 1.3 (95% CI 1.2 to 1.4); risks were similar regardless of progestogen use.

The effect of dose is not clear, but some evidence points to lower stroke risks with lower doses of oral estrogens. In the Nurses' Health Study, low dose conjugated estrogens (0.3 mg/d) — unlike higher doses — was unassociated with stroke risk (RR 0.9, 95% CI 0.6 to 1.4).²⁷ In the General Practice Research Database, however, “low dose” conjugated estrogens (defined as 0.625 mg; note that 0.625 mg/d is usually viewed as standard dose) — like higher doses — was still linked to increased risk (RR 1.3, 95% CI 1.1 to 1.4)²⁸. Use of transdermal estrogen is addressed below.

Hormone therapy use as a function of age or timing

The critical window hypothesis — also referred to as the timing hypothesis or window of opportunity hypothesis — posits that effects of exogenous estrogens are modified by a woman's age or by temporal proximity to menopause. It is predicted that some clinical effects are more likely to be beneficial when hormone therapy is initiated and used by younger women closer to the menopause. A strong biological rationale underpins the critical window hypothesis for atherosclerotic vascular disease^{29,30}, and the clinical literature lends credence to the hypothesis as applied to coronary heart disease²². Contrary to prediction, however, stroke risk does not appear to be modified by a woman's age or the timing of hormone use.

In the WHI hormone therapy trials, post hoc analyses considered the relative risk for any stroke among women analyzed by age decade (the youngest being 50 to 59 years) or time since menopause (analyzed in 10 year increments, the earliest being within 10 years of menopause)²². For women randomized to receive hormone therapy, relative risks for younger women and women closer to menopause were similar to risks for other women allocated to receive hormone therapy²². WHI was not designed to detect modest age-related differences, but findings are similar from the observational Nurses' Health Study²⁷. Here, comparisons were between women who initiated hormone therapy between ages 50 to 59 years or after age 60 years and between women who initiated hormone therapy within four years of menopause or 10 or more years after menopause. There was no evidence that risks differed based on age or timing.

One suggestion for this distinction between coronary heart disease and stroke is that thrombotic mechanisms play a larger role in causing stroke than coronary heart disease in younger postmenopausal women³¹. Oral estrogens are absorbed from the digestive system into the hepatic portal system, where they induce changes in hepatic metabolism of various substrates. The net effect of these changes may be prothrombotic. Indeed, transdermal estrogen is associated with a lower risk of venous thrombosis than oral estrogens³². In the General Practice Research Database, lower doses of transdermal estrogen (50µg/d

estradiol) were not significantly associated with stroke (RR 0.8, 95% CI 0.6 to 1.1), although risks were elevated for higher doses ($>50 \mu\text{g/d}$) of transdermal estrogen as well as for oral estrogens²⁸.

Other compounds that interact with estrogen receptors

Other drugs with the ability to interact with estrogen receptors have the potential to affect stroke risk. Raloxifene, a nonsteroidal selective estrogen receptor modulator, is an option for postmenopausal women for the treatment and prevention of osteoporosis and for reduction in risk of invasive breast cancer in women with osteoporosis. In large clinical trials of postmenopausal women with osteoporosis³³ or coronary heart disease³⁴, raloxifene did not significantly increase stroke risk, but fatal strokes were more common among women with coronary heart disease at high risk for stroke^{34,35} (Table 1). Tamoxifen is a selective estrogen receptor modulator used to treat breast cancer and to reduce breast cancer incidence in high risk women. A meta-analysis of clinical trials suggested that tamoxifen increases risk of any stroke (RR 1.4, 95% CI 1.1 to 1.7) and ischemic stroke (RR 1.8, 95% CI 1.4 to 2.4) in women with breast cancer, although absolute risks were small³⁶. Tibolone, a progestogenic steroid with multiple hormonal effects, has been characterized as a selective tissue estrogenic activity regulator. It is used in many countries for treatment of vasomotor symptoms and prevention of osteoporosis. In a study of 4538 older postmenopausal women with osteoporosis followed for a median of 34 months, tibolone increased risk of any stroke compared to placebo (RR 2.2, 95% CI 1.1 to 4.2)³⁷. Contrary findings are reported from the General Practice Research Database, where tibolone use was unassociated with stroke risk (any stroke RR 1.1, 95% CI 0.2 to 1.4)³⁸.

Conclusions

Much has been learned about the relation between hormone therapy and stroke since the initial WHI publications on this topic^{18,19}. Key points based on current understanding are shown in Table 2. Clinical trials and observational studies indicate that hormone therapy in standard doses increases the relative risk of stroke by about a third, without evidence for substantial risk modification based on type of estrogen, use of a progestogen, age at use, or timing of use. Lower doses of transdermal estradiol ($50 \mu\text{g/d}$) may not elevate stroke risk, but evidence is limited²⁸. Other limited evidence suggests that low-dose oral conjugated estrogens (0.3 mg/d) is not associated with elevated stroke risk²⁷.

Because stroke incidence increases with age, the *absolute risk* of stroke associated with standard-dose hormone therapy will be less among women close to the time of menopause, the group of women more likely to consider hormone therapy for vasomotor symptoms. For women in the WHI trials aged 50 and 59 years, hormone therapy caused two strokes per 10,000 person-years. Stated another way, hormone therapy used for five years by 1000 women under age 60 would be expected to lead to one additional stroke, on average. In the Nurses' Health Study, attributable risks were almost the same (ages 55–59 years, about two additional strokes per 10,000 person-years; ages 50–54, one or two per 10,000 person-years, below age 50, one per 10,000 person-years)²⁷. These risks, which are rare but not negligible, should be considered by midlife women and their physicians when discussing hormone therapy initiation and maintenance for treatment of vasomotor symptoms.

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Table 1

Stroke risk in large randomized, placebo-controlled trials of hormone therapy or raloxifene in postmenopausal women^a

Trial, year	Clinical population (hysterectomy status)	Number contributing to analysis	Active intervention	Type of event	Number of events in active group	Number of events in placebo group	Hazard ratio (95% confidence interval)
<i>Hormone therapy</i>							
HERS, 2001 ¹⁴	Coronary heart disease (uterus)	2,763	CE+MPA	Any stroke	82	67	1.2 (0.9 to 1.7)
				Ischemic stroke	69	59	1.2 (0.8 to 1.7)
				Fatal stroke	16	10	1.6 (0.7 to 3.6)
WEST, 2001 ¹⁶	Recent stroke or transient ischemic attack (uterus or no uterus)	664	Estradiol ^b	Any stroke	63	56	1.1 (0.8 to 1.6)
				Ischemic stroke	56	51	1.1 (0.8 to 1.5) ^c
				Fatal stroke	12	4	2.9 (0.9 to 9.0)
WHI, 2003 ²⁰	Generally healthy (uterus)	16,608	CE+MPA	Any stroke	151	107	1.3 (1.0 to 1.7)
				Ischemic stroke	125	81	1.4 (1.1 to 1.9)
				Fatal stroke	12	11	1.0 (0.5 to 2.6) ^c
WHI, 2006 ²¹	Generally healthy (no uterus)	10,739	CE	Any stroke	168	127	1.4 (1.1 to 1.7)
				Ischemic stroke	142	95	1.6 (1.2 to 2.0)
				Fatal stroke	17	15	1.2 (0.6 to 2.3) ^c
<i>Raloxifene</i>							
MORE, 2002 ³³	Osteoporosis	5,133	Raloxifene ^d	Any stroke	22	32	0.7 (0.4 to 1.2)
				Fatal stroke	3	6	0.5 (0.1 to 2.0)
RUTH, 2006 ³⁴	Coronary heart disease or coronary risk	10,101	Raloxifene ^d	Any stroke	249	224	1.1 (0.9 to 1.3)
				Ischemic stroke	198	171	1.2 (0.9 to 1.4)
				Fatal stroke	59	39	1.5 (1.0 to 2.2)

CE = conjugated estrogens, 0.625 mg/d; HERS = Heart and Estrogen/progestin Replacement Study¹⁴; MORE = Multiple Outcomes of Raloxifene Evaluation trial³³; MPA = medroxyprogesterone acetate, 2.5 mg/d; RUTH = Raloxifene Use for The Heart trial³⁴; WEST = Women's Estrogen for Stroke Trial¹⁶; WHI = Women's Health Initiative trial for women with a uterus (CE+MPA)²⁰ or without a uterus (CE)²¹.

^aTrials with at least 25 events. Table adapted from reference [15].

^bThe oral estradiol dose was 1 mg/d. Women with a uterus received annually medroxyprogesterone acetate, 5 mg/d for 12 days.

^c Unadjusted relative risks and confidence intervals are estimates from published data.

^d Results are for raloxifene 60 mg/d; hysterectomy status is not shown.

Table 2

Key points: hormone therapy and stroke

<ul style="list-style-type: none">• For healthy postmenopausal women, standard dose hormone therapy increases stroke risk by about a third.^a• Stroke risk is not modified by age of hormone initiation or use, or by temporal proximity to menopause.• Stroke risks are similar for estrogen plus progestogen and for unopposed estrogen.• Limited evidence suggests that lower doses of transdermal estradiol (50µg/d) or low-dose oral conjugated estrogens (0.3 mg/d) may not alter stroke risk.• For women aged <60 years, the absolute risk of stroke from standard dose oral hormone therapy is about 2 additional strokes per 10,000 person-years, equivalent to one additional stroke among 1000 women using hormone therapy for five years. The risk is considerably greater for older women.

^aHigh quality of evidence based on consistent findings from well-performed randomized trials³⁹. Evidence for other key points is of lower quality.