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Hormone Therapy and Stroke: Is It All About Timing?

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Opinion statement

Although women have a lower incidence of stroke than men in most age groups, women have an overall increased lifetime risk of stroke. Women also have unique risk factors for stroke, including the menopausal transition, the existence of debilitating vasomotor symptoms for some women, and the issues related to hormonal treatment for those symptoms. Although the initial studies of hormone therapy (HT) use in postmenopausal women suggested significant protection against heart disease, there was no obvious protection against stroke. Randomized trials of HT for secondary prevention showed a lack of benefit for both heart disease and stroke, and the suggestion of some early risk after initiation. However, the Women's Health Initiative (WHI), a primary prevention study of the impact of HT on women aged 50 to 79 years, showed an increased risk of stroke, whether the HT was estrogen alone or estrogen combined with progestin. Therefore, HT is not recommended for stroke prevention, and it appears to cause harm. The reason for this increased stroke risk is not understood, but some have suggested that the initiation of HT closest to the time of menopausal transition should decrease the risk. Although there was a lower risk of heart disease when HT was initiated earlier, the risk appeared to be the same for stroke regardless of the timing. This was shown in both the WHI and the Nurses' Health Study cohorts. Therefore, more research is needed to understand the mechanisms for the increased stroke risk and to identify those who may be at risk because of HT for vasomotor symptoms, atrophic vaginitis, or osteoporosis, the three remaining indications for HT use in women. Trials are under way to assess the intermediate outcomes of HT on subclinical vascular disease in perimenopausal/early postmenopausal women.

Introduction

STROKE IN WOMEN

Compared with men, women have a lower incidence of stroke until about the age of 85 years or older [1]. However, because women live longer, their lifetime risk of stroke is actually higher (1 in 5 chance) than men's (1 in 6) [2]. In general, the incidence of ischemic stroke in women in the United States is 3 in 1000 between ages 55 and 65, 5.6 in 1000 from 65 to 74 years, 12.5 in 1000 from 75 to 84 years, and 20 in 1000 over age 85 [1] (also see systematic review for more epidemiologic data [3]).

IS MENOPAUSE A RISK FACTOR FOR STROKE?

The risk of stroke in women nearly doubles between age 55 and 65 years [1], corresponding to at least 10 years after the average age for menopause. During the menopausal transition period, estradiol levels decline by about 60% [4]. After menopause, estradiol levels continue

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to decline but then plateau after 1 to 3 years. Overall, estradiol levels decrease by seven- to 10-fold between pre- and postmenopause [5]. In contrast to the rapid decline in estradiol, circulating testosterone levels decrease more gradually during this period [6]. This combination leads to a relative androgen excess during the menopausal transition [6].

The menopausal shifts in hormonal levels and ratios of estrogens to androgens are important because these sex steroids appear to have opposite effects on vascular risk. Estrogens have multiple beneficial effects on the cardiovascular system, including improving vasodilation and arterial compliance [7] by decreasing cerebral vascular tone and increasing cerebral blood flow [8]. This occurs in part because estrogen facilitates production and sensitivity to vasodilatory factors, most importantly endothelial nitric oxide synthase. Conversely, androgens have a detrimental effect on cerebral blood vessels by increasing arterial tone. They also lead to a proatherogenic profile in women by decreasing high-density lipoprotein and increasing triglycerides, low-density lipoprotein, and total cholesterol [6].

Only a few studies have examined the relationship between age at menopause and stroke [9,10,11]. A study from Norway focused on stroke mortality in 3561 women over a 37-year follow-up period. The investigators found no significant relationship between age at menopause and stroke mortality, regardless of ischemic or hemorrhagic stroke type [9]. Similarly, an analysis of the Nurses' Health Study (NHS) found no relationship between age at menopause and stroke incidence (ischemic or hemorrhagic types) [11].

A study from Spain examined the lifetime exposure to estrogen rather than just the age at menopause. Using standardized questionnaires, investigators interviewed postmenopausal women regarding their age at menarche and age at menopause. The number of years between these two events was defined as the lifetime exposure to estrogens, or the duration of ovarian activity [10]. The researchers examined this variable in cases (postmenopausal women with stroke or transient ischemic attack [TIA]) and age-matched controls. They found that estrogen exposure less than 34 years (odds ratio [OR], 1.51; 95% CI, 1.13–2.03) and age at menarche less than 13 years (OR, 1.49; 95% CI, 1.15–1.92) were independently associated with an increased risk of ischemic stroke [10]. Consistent with other studies, the age at menopause was not significant. Other significant variables in the logistic regression model included hypertension, diabetes, and hyperlipidemia, whereas obesity was protective (OR, 0.73; 95% CI, 0.56–0.95) [10]. The results of this study may be interpreted in multiple ways. First, regardless of age at menopause, stroke risk is increased when lifetime exposure to endogenous estrogens is less than 34 years (eg, menarche begins at age 13 and menopause at age 47). This finding supports the evidence that endogenous estrogens likely protect against stroke. However, if menarche begins before age 13, then this early exposure could be deleterious [10]. It is important to note that women with cardioembolic stroke were excluded, menopause was defined as the cessation of menstrual bleeding, and there may be regional, geographic, and racial/ethnic differences in menstrual histories; therefore, these results may not be generalizable beyond the region in which the data were collected.

Hormone therapy and stroke

Observational studies

- The first investigations into the possible benefits of hormone therapy (HT) for cardiovascular disease prevention were performed with epidemiologic cohort studies. A systematic review of these studies showed a strong and generally consistent association between HT use and an approximate 50% reduction in coronary heart events [12]. A similar protection against stroke, however, was not clearly demonstrated [12]. The reasons for the discrepancy between stroke and heart disease are still poorly understood but could be related to the heterogeneity of

stroke types and etiologies. We now know that HT seems to be associated with ischemic but not hemorrhagic stroke [13,14••]. Combining these two stroke types may have confounded the effect in some studies. A summary of observational cohort studies reporting the relationship between hormone replacement therapy and stroke is given in Table 1 [15–28]. Notable studies are described individually in the following text.

- The Framingham Study is worth highlighting because the results of its analysis of postmenopausal women, cardiovascular disease, and HT were contrary to most of the other observational studies published in the same era (Table 1). This study showed that cerebrovascular disease events and ischemic stroke in particular were increased more than twofold among HT users [20]. There also was a 50% increase in risk of cardiovascular morbidity, but among nonsmokers, estrogen use was associated only with an increased incidence of stroke ($P < 0.05$) [20]. The analysis, however, was limited by a lack of details regarding continuation of HT after specific examination dates, the dosage or duration of use, and the small number of cases (45 with cerebrovascular disease and 21 with ischemic stroke). Despite the general sentiment at the time that HT provides multiple vascular benefits, this report was an early warning of things to come nearly 15 years later.
- Another important cohort to highlight is the NHS because it has provided some of the most detailed epidemiologic data related to stroke type and estrogen dose. Since 1976, 121,700 female nurses aged 30 to 55 years completed mail questionnaires regarding their medical histories, cardiovascular risks, postmenopausal HT use, diet, and physical activity. This cohort maintains a follow-up greater than 90%. One of the more recent analyses included follow-up questionnaires through June 2004, with more than 485,987 person-years of follow-up for women who never used HT and 409,629 person-years of follow-up among current HT users [29]. There was a significantly increased risk of stroke in current users compared with never-users (estrogen alone: relative risk [RR], 1.39; 95% CI, 1.18–1.63 and estrogen plus progestin: RR, 1.27; 95% CI, 1.04–1.56) [29]. With regard to stroke subtype, the most significant risk was shown for ischemic stroke (estrogen alone: RR, 1.43; 95% CI, 1.17–1.74 and estrogen plus progestin: RR, 1.53; 95% CI, 1.21–1.95). There was a trend toward an increased risk for hemorrhagic stroke in users of estrogen alone (RR, 1.37; 95% CI, 0.98–1.91), but there was no association with estrogen plus progestin users (RR, 0.87; 95% CI, 0.55–1.39) [29]. Similar to previous analyses of this cohort [25], the recent analysis also showed a positive correlation between increasing dose of estrogen and increasing stroke risk (RR, 0.93 for 0.3 mg; RR, 1.54 for 0.625 mg; and RR, 1.62 for 1.25 mg; P for trend < 0.001) [29]. The attributable risk for HT was approximately an additional two cases of stroke per 10,000 women per year taking hormones [29]. Overall, the NHS demonstrated a risk of stroke that was of a similar magnitude to the Women's Health Initiative (WHI; discussed later).

Randomized trials of hormone therapy

- Because of the generally positive results of observational cohorts in favor of HT's protection against heart disease, randomized trials were performed to test this hypothesis. Randomization eliminates much of the bias associated with observational studies, although these trials also have important limitations.
- The first randomized trial of HT for secondary prevention of coronary heart disease (CHD) was the Heart Estrogen–Progestin Replacement Study (HERS). Women with a documented history of CHD were randomly assigned to receive conjugated equine estrogen (CEE), 0.625 mg, and continuous medroxyprogesterone acetate

(MPA), 2.5 mg, daily or placebo. Multiple secondary outcomes were reported, including TIAs and fatal and nonfatal ischemic and hemorrhagic strokes. There were no overall differences in the rates of any of these stroke types, but there were relatively few of these events, thereby limiting the statistical power to detect a difference (Table 2) [30].

- The next randomized trial of HT and stroke was designed to determine whether 17- β estradiol, the physiologic form of estrogen, is efficacious for secondary prevention of stroke. The Women's Estrogen for Stroke Trial (WEST) randomly assigned 664 women with a recent history of stroke or TIA to 1 mg of 17- β estradiol daily versus placebo [31]. Women without a uterus were monitored for endometrial hyperplasia, and if this was documented by transvaginal ultrasound, an endometrial biopsy was performed. As an alternative to transvaginal ultrasound, women with a uterus could also take a 12-day course of MPA, 5 mg, annually. Over a mean follow-up period of 2.8 years, there was no significant difference in rates of stroke or death, the primary end point, between the two groups (RR, 1.1; 95% CI, 0.8–1.4). However, post hoc analysis showed a twofold increased risk of fatal or nonfatal stroke in the estradiol group during the first 6 months after randomization (RR, 2.3; 95% CI, 1.1–5.0; $P = 0.03$). Overall, there also was a trend toward a higher risk of fatal strokes in women using estrogen (RR, 2.9; 95% CI, 0.9–9.0) [31]. It is important to point out that the average age of the study participants was 71 years, and about 75% of the women had hypertension at baseline. Therefore, this group was older and at higher risk than the women who typically would be prescribed HT. However, this was one of the few trials to use the formulation of estradiol that is physiologically relevant; progesterone was used only if necessary, and when used, it was given cyclically. WEST reinforced the HERS results, suggesting that estrogen does not protect women from recurrent strokes or death and that there may be an early risk of stroke following initiation of treatment.
- The first study to evaluate whether HT is an effective strategy for preventing vascular disease in healthy women was the WHI. The WHI included an observational study as well as randomized trials with multiple end points important for women's health. The primary outcome was the earliest CHD event (nonfatal myocardial infarction [MI] and CHD death), and the primary adverse outcome was invasive breast cancer. Stroke was included in the overall global index for the earliest events occurring during the follow-up period [32]. Women without a significant cardiovascular disease history were randomly assigned to receive CEE, 0.625 mg, and MPA, 2.5 mg, continuously versus placebo. Women were excluded if they had a history of acute MI, stroke, or TIA in the previous 6 months. After a mean of 5.2 years, there was a 30% increased risk of CHD events (RR, 1.29; 95% CI, 1.02–1.63) and a 40% increased risk of stroke (RR, 1.41; 95% CI, 1.07–1.85) in the CEE/MPA group [32]. This trial was stopped early because of this increase in cardiovascular events as well as an increase in the rates of breast cancer among treated women. A more detailed analysis of the stroke events showed that the risk was primarily for ischemic and not hemorrhagic stroke and that there was no significant difference in most of the relevant stroke outcomes between groups [13].
- Several subgroup analyses have been performed to determine whether women with certain risk factors or characteristics would be at increased risk of ischemic stroke with CEE alone or CEE/MPA. There have been no characteristics identifying women at increased or decreased risk of stroke based on these analyses and no significant trends based on age by decade [13,14••]. However, when stroke risk was adjusted for adherence in the estrogen-alone trial, the hazard ratio (HR) for African

American women increased to 3.48 (95% CI, 1.12–10.80) whereas the risk for Caucasians was relatively unchanged (HR, 1.67; 95% CI, 1.12–2.50) [14•]. Despite the large number of women in the study overall, the smaller numbers of stroke cases in these subgroups limited the power to detect any significant relationships with HT use.

- The other important result of the WHI estrogen-alone arm was a divergence in the risk for different types of cardiovascular events. For example, there was no difference in CHD events between the CEE and placebo groups, but there was an increased risk for stroke with CEE (RR, 1.37; 95% CI, 1.09–1.73), a magnitude similar to that seen in the CEE/MPA arm of the trial [14•]. The women in the CEE group were more likely to suffer an ischemic stroke (HR, 1.55; 95% CI, 1.19–2.01) than hemorrhagic stroke (HR, 0.64; 95% CI, 0.35–1.18), also similar to the study's other arm [14•]. The reason for the lack of increase in CHD events with treatment is uncertain but suggests that ischemic stroke risk is related to estrogen rather than to progestin [14•].
- Another clinical trial of CEE/MPA and health outcomes in women was conducted in Estonia. The Estonian trial of postmenopausal HT consisted of two arms: a blinded HT group with a corresponding blinded placebo group, and a nonblinded HT group with a corresponding control group [33]. The stroke outcomes were based on International Classification of Disease (ICD)-10 codes for stroke (cerebrovascular diseases), and these were further categorized into stroke only. Very few events occurred during follow-up, and although the statistical power was limited, the combined blind and nonblind HT groups showed a nonsignificant increase in cerebrovascular disease (HR, 1.24; 95% CI, 0.85–1.82) and stroke only (HR, 1.61; 95% CI, 0.38–6.77; Table 2) [33].
- Few studies have led to the major shift in clinical practice brought about by the WHI. HT prescriptions fell dramatically in the year following the WHI's publication in 2002 [34]. In addition, amid the media frenzy surrounding the WHI, many women stopped taking HT on their own, although they were not well informed about the study's findings [35,36]. Despite this very dramatic response to one clinical trial, it is important to remember that the absolute risk for stroke in the WHI was low. In the estrogen-alone arm, the risk was 13 strokes per 10,000 women per year of use, and 8 per 10,000 women for the combination [14•].
- Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene, are nonsteroidal drugs that are antiestrogenic in mammary tissue, and as such they have been used as adjuvant or preventive treatment for breast cancer. Studies to determine the risk of stroke with tamoxifen have been conflicting. A meta-analysis of breast cancer prevention and treatment trials showed an increased risk of ischemic stroke but not all strokes [37]. A large case-control study of the Kaiser Permanente Southern California database of women with breast cancer showed that chemotherapy was associated with stroke, but tamoxifen alone was not [38].
- Raloxifene also has been studied prospectively for its impact on cardiovascular events. The Raloxifene Use for the Heart (RUTH) trial, a randomized, placebo-controlled trial of 60 mg of raloxifene, reported no significant effect on the incidence of CHD events or nonfatal stroke [39]. However, there was an increase in venous thromboembolism and fatal strokes with raloxifene. A detailed post hoc analysis of fatal stroke events showed that this risk was evident only after 3 years of follow-up, and no specific characteristics were associated with the risk of fatal stroke [40].

- The Study of Tamoxifen and Raloxifene (STAR) trial was designed to compare these two SERMs in the prevention of invasive breast cancer and for other cardiovascular events. This study reported no difference in stroke events between these two treatments [41].
- Tibolone, a drug with metabolites that have estrogenic, progestogenic, and androgenic activities, is used to treat menopausal symptoms as well as osteoporosis in more than 90 countries. The Long-term Intervention on Fractures with Tibolone (LIFT) study was a randomized, double-blind, placebo-controlled clinical trial of tibolone, 1.25 mg daily, versus placebo [42•]. The trial showed that the drug significantly reduced the risk of vertebral (relative hazard, 0.55; 95% CI, 0.41–0.74) and nonvertebral fractures (relative hazard, 0.74; 95% CI, 0.58–0.93; $P = 0.01$). However, the trial was stopped prematurely because the tibolone group had an increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14–4.23; $P = 0.02$), although there was no significant risk of CHD or venous thromboembolism [42•].

How does hormone therapy increase the risk of stroke in postmenopausal women?

- The mechanism(s) by which exogenous estrogens lead to an increased risk of stroke is not known despite multiple secondary analyses of the WHI cohort and ancillary studies. The leading hypothesis has been the timing hypothesis, that is, that estrogen is protective against cardiovascular disease when women are younger and the vessels are healthy, but after menopause or in the setting of early-onset atherosclerosis, estrogen is harmful because of its effects on accelerating atherosclerosis and an increased risk of thrombosis. This evidence was shown in a monkey model of atherosclerosis and estrogen treatment [43]. Another possible explanation, the unified hypothesis, proposes that combination HT increases the risk of plaque erosion/rupture with early exposure but that there is a long-term reduction in plaque formation and antagonism of the vasculoprotective effects of estrogens by progesterone [44]. This hypothesis, however, was formulated only for the possible mechanism of CHD risk, and not stroke.
- The possibility of time since menopause as a risk factor for events was studied in the WHI through a secondary analysis of events in women grouped by years since menopause began. There was a decreased risk of CHD in women at less than 10 years (HR, 0.76; 95% CI, 0.50–1.16), no significant effect in women at 10 to 19 years (HR, 1.10; 95% CI, 0.84–1.45), and an increased risk in women at 20 years or more since menopause onset (HR, 1.28; 95% CI, 1.03–1.58; P value for trend, 0.02) [45]. However, for stroke, there was no change in the risk based on years since menopause began or on age. The NHS also reported no association between the timing of initiation of HT and the risk of stroke [29].
- Data from multiple sources highlight the fact that the risk projections of coronary disease cannot be applied universally to stroke in women. This was true with the observational studies that did not show protection against stroke with postmenopausal HT use, whereas the heart disease protection was robust. Also, the timing of initiation in relation to menopause has no relevance for stroke risk, whereas it may for CHD risk. In addition, neither the unified hypothesis nor the timing hypothesis appears to accurately reflect the pattern of stroke risk with HT based on observational and randomized trial data.
- Regardless of the timing, at least one of the pitfalls of the WHI was the lack of measurement of subclinical vascular disease at the start of the trial, despite the investigators' claim of enrolling primarily healthy women. For example, if women are known to have significantly increased carotid artery intimal medial thickness (a

risk factor for future cardiovascular disease) or evidence of coronary artery calcium, then these women have more advanced atherosclerosis, which might put them at higher risk of stroke with estrogen exposure, especially if they are more than 5 years past menopause. Without the subclinical information, the designation of “healthy” may not be accurate.

- To put the risk into clinical perspective, the North American Menopause Society [46], the American College of Obstetrics and Gynecology Hormone Therapy Task Force [47], and the American Heart Association’s 2007 update of its guidelines for cardiovascular disease prevention in women [48] all recommend against menopausal HT and SERMs for primary or secondary prevention of cardiovascular disease (class III, level A).

New directions for hormone therapy research

- Although the WHI has provided a vast amount of information on health outcomes in women, there are many unanswered questions. Women with debilitating vasomotor symptoms will continue to seek the most effective therapy, which is still estrogen replacement. Therefore, there is still a need to find better risk markers that could identify women at risk before initiating HT. These risk markers may be different for stroke than for coronary disease, based on the differences in risk with years from menopause onset.
- At least two ongoing studies of early initiation of HT in women who are perimenopausal or early postmenopausal will help address some of the unanswered questions raised by the WHI. The Kronos Early Estrogen Protection Study (KEEPS) is a randomized trial of low-dose CEE (0.45 mg) and transdermal estradiol (50 µg), both in combination with cyclic oral micronized progesterone (200 mg) for 12 days of each month, HT regimens that have not yet been studied for cardiovascular disease [49]. The primary outcomes are progression of carotid intimal medial thickness and accrual of coronary artery calcium [49]. KEEPS began enrollment in 2005 and anticipates completion in 2010.
- The Early Versus Late Intervention Trial With Estradiol (ELITE) is enrolling women less than 6 years and more than 10 years post menopause. Similar to KEEPS, ELITE is designed to test the hypothesis of timing of initiation of estrogen therapy to prevent progression of subclinical atherosclerosis but is also assessing for cognitive decline (www.usc.edu/medicine/aru) [50].
- Another ongoing study, Sex Aging and Variation in Vascular Functionality (SAVVY), is being conducted in middle-aged women and men to specifically determine the impact of endogenous hormones on subclinical vascular disease, measured with carotid intimal medial thickness, and on endothelial function, measured with brachial artery flow-mediated dilation. In the SAVVY study, men are age matched to an equal number of pre-/perimenopausal and postmenopausal women. This study also will measure biomarkers that reflect endothelial activation, inflammation, and thrombosis, which can then be correlated with endogenous hormones and the vascular measures (clinicaltrials.gov, NCT00681681).
- Although HT clearly is not recommended for stroke prevention because of the increased risk, there are multiple gaps in knowledge that need to be filled to understand the mechanism of harm and the divergence in risk between stroke and heart disease related to timing of initiation and influence of progestins, and to identify women who are at low or high risk for cardiovascular disease although they appear healthy.

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Table 1

Risk of stroke in observational studies of hormone therapy

Study	Cohort	Study design	Patients, n	Duration of exposure	HT type	Stroke type	RR	95% CI
Lokkegaard et al. [15]	Danish Nurse Study	Cohort	13,122 total, 3674 HT users	6 y (range, 0–43 y)	Estrogen (alone or combined)	IS (fatal and nonfatal)	1.00, 1.63	0.98–2.70
Petitti et al. [16]	Northern CA Kaiser	Case-control	349 cases, 349 controls	Cases, 8.2 y; controls, 7.7 y	Estrogen (alone or combined)	Nonfatal IS	1.03	0.65–1.65
Sourander et al. [17]	Turku, Finland	Cohort	7944 total, 988 HT users	?	Estrogen	Nonfatal IS	0.86	0.42–1.75
Pfeffer and Van Den Noort [18]	CA retirement community	Case-control	1278 total	Use > 12 mo in 46% of cases, 44.8% of controls	All estrogens	Any stroke	1.12	0.79–1.57
Pederson et al. [19]	Danish National Patient Register	Case-control	4593 total	?	Estrogen (alone or combined)	IS (fatal and nonfatal)	Estrogen, 1.24; HT, 1.27	0.91–1.70; 1.00–1.62
Wilson et al. [20]	Framingham Heart Study	Case-control	1234 total, 302 HT users	?	Estrogen (alone or combined)	Cerebrovascular disease and IS	2.27, 2.6	NA
Fung et al. [21]	Rancho Bernardo, CA	Cohort	1031 total, 278 HT users	Estrogen users, 8.76 y; nonusers, 8.66 y	Estrogen (alone or combined)	Stroke (fatal and nonfatal)	Nonfatal, 3.02; fatal, 0.92	0.70–13.08; 0.34–2.49
Falkeborn et al. [22]	Uppsala, Sweden	Cohort	Total cohort = 2,179,174 person-years; total of 23,088 HT users	Estrogen users, median 3.5 y	Estrogen (alone or combined)	IS (fatal and nonfatal)	0.78, 0.91	0.59–1.01; 0.76–1.09
Rosenberg et al. [23]	Northern CA Kaiser	Case-control	198 cases, 396 controls	Estrogen users, 1–7.14 y	Estrogen (alone or combined)	IS (fatal and nonfatal)	1.16	0.75–1.77
Lenaitre et al. [24]	Group Health, Seattle, WA	Case-control	726 cases, 2525 controls	Controls, 3.7 y; IS, 3.3 y; ICH, 3.1 y	Estrogen (alone or combined)	IS (fatal and nonfatal)	0.97	0.69–1.37
Grodstein et al. [25]	Nurses' Health Study	Cohort	Nonusers, 485,987 person-years; HT users, 409,629 person-years	?	Estrogen (alone or combined)	IS (fatal and nonfatal)	1.43, 1.53	1.17–1.74; 1.21–1.95
Finucane et al. [26]	National Health and Nutrition Examination Survey	Cohort	1910 total (397 HT users, 1513 nonusers)	?	HT	Any stroke (fatal and nonfatal)	Nonfatal stroke, 0.68; fatal stroke, 0.41	0.47–0.98; 0.17–1.03
Lindstrom et al. [27]	Copenhagen City Heart Study	Cohort	4716 total (238 stroke events)	?	HT	Any stroke	HT/smoker, 0.57; HT/nonsmoker, 1.01	0.29–1.13; 0.55–1.84

Study	Cohort	Study design	Patients, <i>n</i>	Duration of exposure	HT type	Stroke type	RR	95% CI
Angeja et al. [28]	National Registry of MI	Cohort	114,724 total (7353 HT users, 107,371 nonusers)	?	HT	IS (fatal and nonfatal)	0.89	0.66–1.18

HT—hormone therapy; ICH—intracerebral hemorrhage; IS—ischemic stroke; NA—not available; RR—relative risk.

Table 2

Risk of stroke in randomized controlled trials of hormone therapy

Study	Cohort	Patients, n	Average follow-up, y	HT type	Stroke type	RR	95% CI
Simon et al. [30]	HERS	HT, 1380; placebo, 1383	4.1	CEE/MPA	Ischemic	1.18	0.83–1.67
					Fatal	1.61	0.73–3.55
					Nonfatal	1.18	0.83–1.66
Viscoli et al. [31]	WEST	Estrogen, 337; placebo, 327	2.8	17 β -estradiol	Stroke or death	1.10	0.80–1.40
					Nonfatal	1.00	0.70–1.40
					Ischemic	4.4	0.90–20.2
					Fatal	2.90	0.90–9.00
Wassertheil-Smoller et al. [13]	WHI	HT, 8506; placebo, 8102	5.6	CEE/MPA	Ischemic	1.44	1.09–1.90
					Fatal	1.20	0.58–2.50
Hendrix et al. [14•]	WHI	CEE, 5310; placebo, 5429	7.1	CEE	All	1.37	1.09–1.73
					Ischemic	1.55	1.19–2.01
Veerus et al. [33]	Estonian Trial	Blind HT, 404; open HT, 494; control, 507; placebo, 373	2–5*	CEE/MPA	Cerebrovascular diseases (ICD-10 I60–I69)	1.24	0.85–1.82
					Stroke only	1.61	0.38–6.77
						1.61	0.38–6.77

* Median follow-up was not given.

CEE—conjugated equine estrogen; HERS—Heart Estrogen-Progestin Replacement Study; HT—hormone therapy; ICD-10—International Classification of Diseases, 10th revision; MPA—medroxyprogesterone acetate; RR—relative risk; WEST—Women's Estrogen for Stroke Trial; WHI—Women's Health Initiative.