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# Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials

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## ABSTRACT

Principal 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 one-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 ($\leq$50 μg/day) 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 two 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.

## INTRODUCTION

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 countries[1]. Although stroke incidence has declined steadily in recent decades in high-income countries[1], stroke remains the leading cause of prolonged adult disability and the third leading cause of death among women[2]. In many developing countries, stroke mortality and disability exceed those of ischemic heart disease[3]. 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 A1[4].

The incidence of stroke increases steadily with age[5]. At least until late-old age, the age-specific incidence remains lower for women than for men[6]. However, because of longer life 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 life[7], as might be early surgical menopause[8]. The mean age of first stroke occurs 4 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

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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 malformation[9]. Other classifications have been proposed[10]. 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 disease[11].

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 women[12]. This conclusion contrasted with other observational evidence that implied that hormone therapy could benefit postmenopausal women at risk for coronary heart disease[13]. Before the 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 disease[14]. 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 1[15]), 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 days[16]. 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 arms[16].

## 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 status[17]. 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

**Table 1** Stroke risk in large randomized, placebo-controlled trials of hormone therapy or raloxifene in postmenopausal women*

| *Trial, year* | *Clinical population (hysterectomy status)* | *Number contributing to analysis* | *Active intervention* | *Type of stroke* | *Number of events* | | *Hazard ratio (95% confidence interval)* |
|---|---|---|---|---|---|---|---|
| | | | | | *Active group* | *Placebo group* | |
| *Hormone therapy* | | | | | | | |
| HERS, 2001[14] | coronary heart disease (uterus) | 2763 | CE + MPA | any | 82 | 67 | 1.2 (0.9–1.7) |
| | | | | ischemic | 69 | 59 | 1.2 (0.8–1.7) |
| | | | | fatal | 16 | 10 | 1.6 (0.7–3.6) |
| WEST, 2001[16] | recent stroke or transient ischemic attack (uterus or no uterus) | 664 | estradiol† | any | 63 | 56 | 1.1 (0.8–1.6) |
| | | | | ischemic | 56 | 51 | 1.1 (0.8–1.5)‡ |
| | | | | fatal | 12 | 4 | 2.9 (0.9–9.0) |
| WHI, 2003[20] | generally healthy (uterus) | 16608 | CE + MPA | any | 151 | 107 | 1.3 (1.0–1.7) |
| | | | | ischemic | 125 | 81 | 1.4 (1.1–1.9) |
| | | | | fatal | 12 | 11 | 1.0 (0.5–2.6)‡ |
| WHI, 2006[21] | generally healthy (no uterus) | 10739 | CE | any | 168 | 127 | 1.4 (1.1–1.7) |
| | | | | ischemic | 142 | 95 | 1.6 (1.2–2.0) |
| | | | | fatal | 17 | 15 | 1.2 (0.6–2.3)‡ |
| *Raloxifene* | | | | | | | |
| MORE, 2002[33] | osteoporosis | 5133 | raloxifene** | any | 22 | 32 | 0.7 (0.4–1.2) |
| | | | | fatal | 3 | 6 | 0.5 (0.1–2.0) |
| RUTH, 2006[34] | coronary heart disease or coronary risk | 10101 | raloxifene** | any | 249 | 224 | 1.1 (0.9–1.3) |
| | | | | ischemic | 198 | 171 | 1.2 (0.9–1.4) |
| | | | | fatal | 59 | 39 | 1.5 (1.0–2.2) |

CE, conjugated estrogens, 0.625 mg/day; HERS, Heart and Estrogen/progestin Replacement Study[14]; MORE, Multiple Outcomes of Raloxifene Evaluation trial[33]; MPA, medroxyprogesterone acetate, 2.5 mg/day; RUTH, Raloxifene Use for The Heart trial[34]; WEST, Women's Estrogen for Stroke Trial[16]; WHI, Women's Health Initiative trial for women with a uterus (CE + MPA)[20] or without a uterus (CE)[21]

*, Trials with at least 25 events. Table adapted from reference 15; †, the oral estradiol dose was 1 mg/day. Women with a uterus received annually medroxyprogesterone acetate, 5 mg/day for 12 days; ‡, unadjusted relative risks and confidence intervals are estimates from published data; **, results are for raloxifene 60 mg/day; hysterectomy status is not shown

calcium plus vitamin D dietary supplements[17]. Participants in these trials were community-dwelling postmenopausal women aged 50–79 years at baseline (mean age 63 years). Principal 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 + progestogen trial, women were studied over an average duration of 5.6 years[20]. The estrogen-alone trial followed women for an average follow-up of 7.1 years[21]. 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 Heart and Estrogen/progestin Replacement Study and the Women's Estrogen for Stroke Trial. The excess risk in the WHI corresponded to about nine additional cases of stroke per 10 000 person-years of hormone use[22]. 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 65–79 years at study onset, underwent magnetic resonance brain imaging[23]. Scans were obtained on average 3 years (estrogen + 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 + 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 3-year post-intervention relative risk for prior allocation to estrogen + progestogen was 1.2 (95% confidence interval (CI) 0.8–1.6)[24]; for estrogen alone, the post-intervention relative risk over a 4-year period was 0.9 (95% CI 0.6–1.2)[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 1.1–1.5)[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 + progestogen versus estrogen alone) or type of estrogen (conjugated estrogens versus estradiol)[26]. Stroke outcomes seemed worse among women who received hormone therapy[26].

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 the 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 therapy[27]. These analyses involved 121 700 women aged 30–55 years at baseline in 1976 and followed through 2004. For estrogen + progestogen, risks were increased for any stroke (relative risk (RR) 1.3, 95% CI 1.0–1.6) and for ischemic stroke (RR 1.5, 95% CI 1.2–2.0). For estrogen alone, relative risks were similar (any stroke: RR 1.4, 95% CI 1.2–1.6; ischemic stroke: RR 1.4, 95% CI 1.2–1.7). The population-based General Practice Research Database in the United Kingdom identified 15 710 cases of stroke between 1987 and 2006 among women aged 50–79 years[28]. For women using oral estrogens, the relative of risk of stroke was 1.3 (95% CI 1.2–1.4); 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/day) – unlike higher doses – were unassociated with stroke risk (RR 0.9, 95% CI 0.6–1.4)[27]. In the General Practice Research Database, however, 'low-dose' conjugated estrogens (defined as $\leq 0.625$ mg; note that 0.625 mg/day is usually viewed as standard dose) – like higher doses – were still linked to increased risk (RR 1.3, 95% CI 1.1–1.4)[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 disease[22]. 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 50–59 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 – although based on small numbers – were similar to risks for other women allocated to receive hormone therapy[22]. The WHI was not designed to detect modest age-related differences, but findings are similar from the observational Nurses' Health Study[27]. Here, comparisons were between women who initiated hormone therapy between ages 50 and 59 years or after age 60 years and between women who initiated hormone therapy within 4 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 women[31]. 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 estrogens[32]. In the General Practice Research Database, lower doses of transdermal estrogen ($\leq$ 50 μg/day estradiol) were not significantly associated with stroke (RR 0.8, 95% CI 0.6–1.1), although risks were elevated for higher doses ($>$ 50 μg/day) of transdermal estrogen as well as for oral estrogens[28].

## 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 non-steroidal 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 osteoporosis[33] or coronary heart disease[34], 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 1.1–1.7) and ischemic stroke (RR 1.8, 95% CI 1.4–2.4) in women with breast cancer, although absolute risks were small[36]. 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 1.1–4.2)[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 0.2–1.4)[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 one-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 ($\leq$ 50 μg/day) may not elevate stroke risk, but evidence is limited[28]. Other limited evidence suggests that low-dose oral conjugated estrogens (0.3 mg/day) are not associated with elevated stroke risk[27].

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 50–59 years, hormone therapy caused two strokes per 10 000 person-years. Stated another way, hormone therapy used for 5 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

**Table 2** Key points: hormone therapy and stroke

- For healthy postmenopausal women, standard-dose hormone therapy increases stroke risk by about one-third*
- Stroke risk is not modified by age of hormone initiation or use, or by temporal proximity to menopause
- Stroke risks are similar for estrogen + progestogen and for unopposed estrogen
- Limited evidence suggests that lower doses of transdermal estradiol ($\leq$ 50 μg/day) or low-dose oral conjugated estrogens (0.3 mg/day) may not alter stroke risk
- For women aged $<$ 60 years, the absolute risk of stroke from standard-dose oral hormone therapy is about two additional strokes per 10 000 person-years, equivalent to one additional stroke among 1000 women using hormone therapy for 5 years. The risk is considerably greater for older women

*, High quality of evidence based on consistent findings from well-performed randomized trials[39]. Evidence for other key points is of lower quality

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 mid-life women and their physicians when discussing hormone therapy initiation and maintenance for treatment of vasomotor symptoms.

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## References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8:355–69
2. Lethbridge-Çejku M, Vickerie J. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2003. *Vital and Health Statistics* 2005;10(225)
3. Kim AS, Johnston SC. Global variation in the relative burden of stroke and ischemic heart disease. *Circulation* 2011;124: 314–23
4. O'Donnell MJ, Xavier D, Liu L, *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376: 112–23
5. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;2:43–53
6. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke* 2009;40: 1032–7
7. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. *Stroke* 2009;40:1044–9
8. Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD Jr. Premature menopause or early menopause and risk of ischemic stroke. *Menopause* 2011 Oct 6. Epub ahead of print
9. Mohr JP, Caplan LR, Melski JW, *et al*. The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology* 1978;23: 754–62
10. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovasc Dis* 2009;27:493–501
11. Ruiz VC, Soler EP. Epidemiology and risk factors of cerebral ischemia and ischemic heart disease: similarities and differences. *Curr Cardiol Rev* 2010;6:138–49
12. Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? *Maturitas* 2002;38:243–61
13. Grady D, Rubin SM, Petitti DB, *et al*. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–37
14. Simon JA, Hsia J, Cauley JA, *et al*. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638–42
15. Henderson VW. Alzheimer's disease and other neurological disorders. *Climacteric* 2007;10(Suppl 2):92–6
16. Viscoli CM, Brass LM, Kernan WN, Sarrel SM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–9
17. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–109
18. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
19. Anderson GL, Limacher M, Assaf AR, *et al*. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
20. Wassertheil-Smoller S, Hendrix S, Limacher M, *et al*. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; 289:2673–84
21. Hendrix SL, Wassertheil-Smoller S, Johnson KC, *et al*. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006;113:2425–34
22. Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77
23. Coker LH, Hogan PE, Bryan NR, *et al*. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology* 2009;72:125–34
24. Heiss G, Wallace R, Anderson GL, *et al*. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036–45
25. LaCroix AZ, Chlebowski RT, Manson JE, *et al*. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–14
26. Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; 330:342
27. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008;168:861–6
28. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519
29. Umetani M, Domoto H, Gormley AK, *et al*. 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen. *Nat Med* 2007;13:1185–92
30. Clarkson TB. Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause* 2007;14:373–84
31. Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* 2011; 18:237–40
32. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2011;18:1052–9

33. Barrett-Connor E, Grady D, Sashegyi A, *et al*. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287: 847–57
34. Barrett-Connor E, Mosca L, Collins P, *et al*. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006;355:125–37
35. Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the Framingham stroke risk score. *Am J Med* 2009;122:754–61
36. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004;63:1230–3
37. Cummings SR, Ettinger B, Delmas PD, *et al*. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359: 697–708
38. Renoux C, Dell'aniello S, Garbe E, Suissa S. Hormone therapy use and the risk of stroke. *Maturitas* 2008;61:305–9
39. Santen RJ, Allred DC, Ardoin SP, *et al*. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95(Suppl 1):s1–66