Stroke risk in women: the role of menopause and hormone therapy

Lynda Lisabeth, Cheryl Bushnell

Lancet Neurol 2012; 11: 82–91

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on December 22, 2011

Department of Epidemiology, University of Michigan School of Public Health, Ann Arbour, MI, USA (L Lisabeth PhD); and Wake Forest School of Medicine, Wake Forest University, Winston-Salem, NC, USA (C Bushnell MD)

Correspondence to: Dr Cheryl Bushnell, Wake Forest Baptist Stroke Center, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157, USA
cbushnel@wakehealth.edu

Although women have a lower risk of stroke during middle age than men, the menopausal transition is a time when many women develop cardiovascular risk factors. Additionally, during the 10 years after menopause, the risk of stroke roughly doubles in women. Endogenous oestrogen concentrations decline by 60% during the menopausal transition, leading to a relative androgen excess, which could contribute to the increased cardiovascular risk factors in women. Earlier onset of menopause might affect the risk of stroke, but the data are not clear. Because of the stroke risk associated with it, hormone therapy is recommended only for treatment of vasomotor symptoms, and some formulations might be safer than others. More research is needed to understand which women are at greatest stroke risk during midlife and to identify the safest formulation, dose, and duration of hormone therapy that can be used to treat vasomotor symptoms without increasing the risk of stroke.

Introduction

Stroke is the fourth leading cause of death and a major cause of disability.[1] The risk of stroke increases with age. Although overall age-adjusted risk of stroke is higher in men than in women, more strokes occur in women because of their longer life expectancy combined with the very high stroke rates in the oldest age groups. Strokes in women, therefore, account for 60% of all stroke events.[2] Results from studies have consistently shown that women have less favourable functional outcomes after stroke than do men including greater disability at the time of hospital discharge and more physical impairments and limitations in activities during the recovery period after a stroke.[3–7] Discussing issues related to stroke in women is important because of the predicted epidemic of stroke in women as the population ages.[2] Recognition of risk factors for stroke and treatment for the modifiable risks are essential and should not be delayed until older age. In fact, acceleration of midlife risk factors for women seems to be associated with the menopausal transition,[8,9] so this is the ideal time frame to focus on prevention in women. The reason for the higher risk profile after menopause than before it is not entirely understood but is likely to be influenced by endogenous sex steroid hormones, especially estradiol.

Our hypothesis is that stroke risk in women is related to menopause, partly because of hormonal changes and the acceleration of risk factors. To investigate this hypothesis, we have combined the observational data related to stroke in midlife and the influence of menopause and hormone therapy (the "what") with physiological evidence related to hormones and atherosclerosis (the "why"), which could help practitioners to understand the reasons to focus on early and appropriate treatment to prevent stroke in women. We highlight the evidence to guide clinical practice, but also focus on gaps in knowledge and on where future research is needed.

Epidemiology of stroke in women during midlife

Incidence

Ischaemic stroke is quite uncommon in premenopausal women, but risk increases with advancing age. Several population-based epidemiological studies have reported estimates of stroke incidence in women during midlife (45–64 years) including the age range when most women experience menopause (table 1). Estimates of stroke incidence (including ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage) in white women aged 45–54 years range from 0·59 to 1·02 per 1000 women per year (table 1). As an example, Petrea and colleagues[10] analysed 56 years of follow-up data from the Framingham Heart Study (FHS) and reported a stroke incidence of 0·82 per 1000 person-years in white women aged 45–54 years. Stroke rates roughly double in women aged 55–64 years.[10–12,14–16]

Age-specific data on incidence of stroke for women in minority groups are scarce. In Mexican American women aged 45–59 years, stroke incidence has been estimated to be 1·94 per 1000 per year.[12] In African American women aged 45–54 years, it has been estimated to be 2·47 per 1000 per year.[14] These data point to higher stroke incidence for women of minority groups than for white women during midlife.

Over the life course, age-adjusted stroke risk is higher in men than in women.[10] During midlife specifically, most but not all studies suggest that men have greater stroke risk than women do. For example, stroke incidence in those aged 45–54 years from the FHS was 1·16 per 1000 person-years in men and 0·82 per 1000 person-years in women.[10] Other population-based US studies,[14,15] as well as a population-based study from Sweden,[11] also report greater stroke incidence in men aged 45–54 years compared with women of the same age (table 1).

After midlife, sex differences in stroke risk can decrease or reverse with advancing age.[2] However, findings across studies have not been consistent with regard to patterns of sex differences in stroke risk varying with age.[2,10,11,13,17,18] Data from the FHS[10] show that white women aged 45–84 years have lower stroke risk than white men do, but above the age of 85 years women have a higher stroke risk than men. Similarly, a population-based study in Sweden[11] reported a lower incidence of stroke for women than for men at ages 55–64 years but, at 75–85 years of

	Study design	Time frame	Incident events only	Stroke endpoint	Stroke rate	
					Women	Men
Framingham Heart Study[10]	Cohort	1948–2005	Yes	IS, ICH, SAH	0·82 per 1000 person-years	1·16 per 1000 person-years
Riks-Stroke, Sweden[11]	Population-based surveillance	2000–02	Yes	IS, ICH, unspecified stroke	1·02 per 1000 women/year	1·48 per 1000 men/year
Brain Attack Surveillance In Corpus Christi Project*[12]	Population-based surveillance	2000–06	No	IS, ICH	0·97 per 1000 women/year (white population); 1·94 per 1000 women/year (Mexican American population)	NR
Oxford Vascular Study[13]	Population-based surveillance	2002–05	No	IS, ICH, SAH, TIA	1·25 per 1000 women/year	1·37 per 1000 men/year
Greater Cincinatti/Northern Kentucky Stroke Study[14]	Population-based surveillance	1993–94	Yes	IS, ICH, SAH, unspecified stroke, TIA	0·59 per 1000 women/year (white population); 2·47 per 1000 women/year (black population)	0·95 per 1000 men/year (white population); 2·26 per 1000 men/year (black population)
Northern Manhattan Stroke Study[15]	Population-based surveillance	1993–96	Yes	IS, ICH, SAH	0·76 per 1000 women/year (white, black, and Hispanic population)	1·75 per 1000 men/year
Rochester, MN[16]	Population-based surveillance	1985–89	Yes	IS, ICH, SAH, unspecified stroke	0·64 per 1000 women/year	0·61 per 1000 men/year

IS=ischaemic stroke. ICH=intracerebral haemorrhage. SAH=subarachnoid haemorrhage. NR=not reported. TIA=transient ischaemic attack. *Risk is among those aged 45–59 years.

Table 1: **Studies reporting stroke rates in men and women aged 45–54 years**

age, this association reversed and the incidence was higher in women than in men.[11] Other studies, however, report excess stroke risk in men compared with women that persists after midlife or diminishes, but does not reverse with age.[13,17,18]

Prevalence

Data for stroke prevalence in women during midlife and on sex differences in stroke prevalence are limited. Towfighi and colleagues[19] reported a prevalence of 2·5% in women aged 45–54 years with data from the National Health and Nutrition Examination Survey (NHANES) for the time period 1999–2004. In this study,[19] women aged 45–54 years had a higher odds of having had a stroke than did men of the same age (odds ratio [OR] 2·39 [95% CI 1·32–4·33]), whereas no sex differences were noted in the younger (35–44 years) and older (55–64 years) age groups.[19] In a more recent wave (2005–06) of NHANES data, women also had a higher prevalence of stroke than men at the age of 45–54 years.[20] By contrast, data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study suggest that fewer women than men in the 45–54 year age range have had a stroke and that this sex difference decreases with age and is reversed in those older than 85 years.[2]

If stroke prevalence is greater in women than in men during midlife, we would expect to see supporting epidemiological data with regard to sex differences in incidence, mortality, or both. For example, if stroke incidence in women in this age range is greater than that for men this could result in increased prevalence; however, existing data do not support this hypothesis, with most studies reporting greater incidence in men in midlife as described here. Alternatively, a post-stroke survival benefit in women compared with men during midlife could result in an increased prevalence in women in this age range. Considering US national vital statistics data, women aged 45–74 years have a lower risk of stroke mortality (ie, stroke deaths divided by person-time), on a magnitude of 25–35%, than do men of the same age, but this trend is driven partly by the lower incidence in women in this age range.[2,21] Case fatality and post-stroke mortality rates in women compared with men during midlife would more directly answer this question. In an analysis of data from the Nationwide Inpatient Sample, Towfighi and colleagues[22] reported that for the most recent time period (2005–06), women aged 45–54 years were less likely to die in hospital from stroke than their male counterparts even after adjustment for demographics, clinical factors, treatment with alteplase, and hospital factors (OR 0·91 [95% CI 0·82–1·00]).[22] Sex differences in the 45–54 years age range were also reported for the 2001–02 period; however, absolute differences in in-hospital mortality were quite small (ie, 4·88% in women and 5·15% in men in 2005–06).[22] Recent findings from The Registry of the Canadian Stroke Network[23] showed no sex differences in case fatality for stroke in those aged 45–64 years.

Menopause and stroke

Menopause: hormonal changes and risk factors for early onset

The menopause is defined as the absence of menstrual periods for 12 consecutive months. The average age of menopause is 51 years, with a range of 40–60 years.[24] The menopausal transition is associated with significant hormonal changes—most importantly, a decline of estradiol levels by about 60%.[25] After menopause, the levels continue to decrease and then plateau after 1–3 years. Altogether, estradiol levels decrease by seven to

ten times between pre-menopause and post-menopause.[26] During this time, circulating testosterone levels decrease more gradually as compared with the rapid decline in estradiol, such that the menopausal transition is associated with a relative androgen increase.[27] Accurate measurement of estradiol and testosterone is dependent on the concurrent measurement of sex hormone-binding globulin (SHBG), which binds both estradiol and testosterone. This is because less than 2% of the biologically active estradiol and testosterone is free in the circulation. SHBG concentrations also decrease in the menopausal transition,[25] and low concentrations are used to assess androgen excess by calculating the free androgen index, which equates to total testosterone divided by SHBG in molar concentrations. This same method can be used to calculate the free estradiol index.[28] SHBG concentrations increase in the setting of exogenous oestrogens and thyroid replacement.[29]

Early decline in estradiol levels related to early age at menopause could be detrimental to the health of bones and blood vessels. Cigarette smoking, malnutrition, and lower socioeconomic status have been associated with earlier menopause, but heredity seems to be the most important determinant of age at menopause. A study of sister pairs[30] showed that about 85% of the phenotypic variation in age at menopause was genetically determined.

Primary ovarian insufficiency (the term preferred over premature ovarian failure) is defined as amenorrhea for at least 4 months, sex steroid deficiency, and two measurements of follicle-stimulating hormone (FSH) concentrations of more than 40 IU/L at least 1 month apart in a woman younger than 40 years.[31] Because of the normal distribution of age at menopause, 40 years or less is used because it represents greater than two standard deviations below the mean age of menopause.[32] The most recognised cause of primary ovarian insufficiency is Turner's syndrome (45,X). The loss of all or part of the X chromosome leads to oocyte dysfunction because these cells require two active X chromosomes to allow differentiation. Therefore, oocytes are depleted by the age of 10 years.[33] Other known causes include cytotoxic drugs (cyclophosphamide, ifosfamide, and chlormethine) and autoimmune disorders (autoimmune lymphocytic oophoritis, polyglandular autoimmune syndrome).[32] A continuous effort exists to better understand this disorder because of the implications for bone health, as well as the risk for cardiovascular disease and stroke.

Menopause and risk factors for stroke

Menopause is associated with an increase in various risk factors for stroke. Cohort studies of healthy women moving through the menopausal transition have shown an increase in abdominal obesity, an increase in triglycerides, total cholesterol, and LDL cholesterol, a decrease in HDL cholesterol, increased fasting glucose and other measures of insulin resistance, increased body-mass index, and increased blood pressure.[34] Low SHBG (and free androgen index) has been associated with increased cardiovascular risk factors during the menopausal transition.[8,35] Additionally, women have an increase in evidence of subclinical vascular disease early after menopause, measured with carotid intimal medial thickness and adventitial diameter.[9,36] The accumulation of these risk factors are probably attributable to the androgen excess and decrease in oestrogen,[8] and might explain the doubling of stroke risk in the 10 years after menopause. Therefore, it is imperative to focus on recognition and treatment of these risk factors in women during midlife since menopause is often evident when amenorrhea or vasomotor symptoms are present, but also in those aged 51–55 years without previous surgical hysterectomy. It is unknown whether measurement of these hormones or screening for subclinical disease in midlife would affect cardiovascular disease and stroke prevention strategies, although this is an active area of research.[37] An analysis of the Study of Women Across the Nation (SWAN)[38] was done to investigate the risk factors associated with menopause versus chronological ageing. These results showed that total cholesterol, LDL cholesterol, and apolipoprotein B substantially increased within 1 year of the last menstrual period, whereas the changes in other risk factors were more suggestive of chronological ageing (table 2).[38] A separate analysis of risk factor and carotid atherosclerosis changes across the menopausal transition in the Healthy Women Study is also shown in table 2.[34]

Endogenous hormones and stroke

Observational studies have shown that younger, premenopausal women are protected from ischaemic stroke compared with their male counterparts of a similar age, and that this protection might be lost with advancing age. Because of these findings, as well as supportive evidence from studies in animals, exposure to endogenous oestrogen has been postulated to be protective for stroke in premenopausal women. To date, no study has investigated the relation between endogenous hormones and stroke in premenopausal women or in women as they transition to menopause. The studies that have investigated the association between endogenous hormones and stroke, cardiovascular disease, or death have been limited to post-menopausal women. The Study of Osteoporotic Fractures[28] investigated free estradiol index and stroke in women older than 65 years. In age-adjusted analyses, a linear relation between free estradiol and ischaemic stroke risk was noted, such that those with the highest free estradiol index had more than double the risk of ischaemic stroke (comparing highest to lowest quartiles). An early analysis of the Women's Health Study (women aged 55 years or older) showed that, in non-users of hormone therapy, those with cardiovascular events had a lower concentration of SHBG ($p=0\cdot03$) and higher free androgen index ($p=0\cdot008$) than did those

	Risk factors	Findings	Comments
Matthews et al[34]	(1) CVD risk factors; (2) carotid atherosclerosis (CIMT and plaque)	(1) Increased SBP, pulse pressure, LDL-C, triglycerides, fasting glucose, and BMI from 1st to 5th year post-menopause; (2) increasing CIMT associated with SBP, increasing pulse pressure from pre-menopause to 1st year post-menopause, and increasing CIMT between 1st and 5th year post-menopause associated with glucose change	An analysis of the Healthy Women Study showed no significant change in risk factors from pre-menopause to 1st year post-menopause, but changes from the 1st to 5th year post-menopause were significant
Matthews et al[38]	TC, LDL-C, Apo-B, HDL-C, triglycerides, insulin, glucose, Lp(a), fibrinogen, factor VIIc, tPA-ag, PAI-1, CRP, BMI, SBP, DBP	TC, LDL-C, and Apo-B were the only risk factors substantially increased around the FMP	The Study of Women Across the Nation analysed the slope of change in risk factors during the year around the FMP; other CVD risk factors were associated with chronological ageing rather than the menopausal transition

CVD=cardiovascular disease. CIMT=carotid intimal medial thickness. SBP=systolic blood pressure. LDL-C=low-density lipoprotein cholesterol. BMI=body-mass index. TC=total cholesterol. Apo-B=apolipoprotein-B. HDL-C=high-density lipoprotein cholesterol. Lp(a)=lipoprotein (a). tPA-ag=tissue plasminogen activator antigen. PAI-1=plasminogen activator inhibitor-1. CRP=C-reactive protein. SBP=systolic blood pressure. DBP=diastolic blood pressure. FMP=final menstrual period.

Table 2: **Association between menopause, final menstrual period, and cardiovascular risk factors[34,38]**

without cardiovascular events.[39] Women in the lowest quartile of SHBG were 2·25 times (95% CI 1·03–4·91) more likely to have a cardiovascular event in the adjusted analysis. However, there was no difference in SHBG or free androgen index in women using hormone therapy, whether or not an event had occurred.[39] Lastly, the InChianti Study[40] in Italy reported that women with higher total estradiol had a higher likelihood of age-adjusted mortality (hazard ratio [HR] 1·03 [95% CI 1·01–1·06]), although the cause-specific mortality, such as from stroke, could not be identified.[40] Given the logistical difficulty in measuring endogenous hormones over the life course, the focus from an epidemiological perspective has been on the association between proxies for exposure to endogenous hormones, such as age at menopause and number of reproductive years, and stroke risk. The relation between previous use of oral contraceptive pills and the risk of stroke during menopause is unknown, although present use is associated with stroke in young women.[41,42]

Age at menopause and stroke

A handful of cohort studies have been done in various countries to consider the association between age at menopause and stroke mortality, with findings suggestive of a null association so far. de Kleijn and colleagues,[43] using 20 years of follow-up data from a population-based cohort study in the Netherlands, reported that age at menopause analysed in quartiles of the distribution (≤44, 45–48, 49–51, >51 years) was not associated with stroke mortality when adjusting for age, hormone-replacement therapy, hypertension, body-mass index, and socioeconomic status.[43] Jacobsen and colleagues[44] similarly reported no association between age at natural menopause modelled in 3-year age categories and stroke mortality in a large Norwegian cohort study. Data from two prospective cohort studies[45,46] of US adults also support no association between age at natural menopause and stroke mortality. Finally, in a Japanese cohort study,[47] age at menopause was not associated with stroke mortality, with the exception that women with menopause at 47–48 years had increased risk of death due to stroke compared with women with menopause after the age of 50 years.

Studies of the association between age at menopause and risk of incident stroke are rare and somewhat inconsistent in findings. Hu and colleagues[48] showed that age at natural menopause, modelled in 5-year age categories or in a continuous manner (ie, 1-year decrease in age at menopause), was not associated with risk of total stroke, ischaemic stroke, or haemorrhagic stroke in individuals who had never used hormone therapy in the Nurse's Health Study. In a cohort study of post-menopausal Korean women who had never used hormone therapy,[49] Choi and colleagues showed no association between age at natural menopause (<40, 40–44, 45–49, 50–54, ≥55 years) and risk of total stroke, ischaemic stroke, or haemorrhagic stroke, although the number of events in some categories was small. By contrast, Lisabeth and colleagues,[50] using data from the Framingham Heart Study, showed that women with natural menopause before the age of 42 years had twice the risk of ischaemic stroke compared with women with natural menopause at the age of 42 years and older when adjusting for age, stroke risk factors, and oestrogen use after menopause (HR 2·03 [95% CI 1·16–3·56]; figure 1).[50] Results from a Japanese cohort study[51] also suggested that women who underwent menopause before the age of 40 years were more than twice as likely to have an ischaemic stroke as those with menopause between the ages of 50 and 54 years when adjusting for age and risk factors; however, this study[51] included women with both natural and surgical menopause, and findings were driven by those with surgical menopause. In a case-control study[52] done in Spain, age at menopause (>53 years *vs* ≤53 years) was not associated with the odds of non-cardioembolic stroke accounting for age and stroke risk factors.

Interestingly, in this same study,[52] lifetime exposure to oestrogen of less than 34 years, defined as age at menarche to age at menopause, was associated with an increased odds of non-cardioembolic stroke (OR 1·51 [95% CI 1·13–2·03]). This finding raises the hypothesis that longer exposure to endogenous hormones might be protective for stroke, and measures related to age at menopause might not necessarily be indicative of this exposure. However, a Japanese study[47] showed no association between reproductive years and stroke mortality. Alternative measures of lifetime exposure to endogenous oestrogens, which include additional information on pregnancies and breastfeeding, have also been proposed, although their association with stroke has not been studied.[43] Furthermore, anti-Mullerian hormone concentrations have been shown to be highly predictive of age at menopause,[53] and might therefore be a reasonable surrogate for studying hormonal exposure and stroke in younger women, especially those with established high risks, such as existing cardiovascular disease, diabetes, cigarette smoking, and hypertension.

Hormone therapy and stroke

Completed clinical trials

Data from randomised clinical trials show that use of oestrogen plus progestin as well as oestrogen alone taken orally increases stroke risk in healthy post-menopausal women.[54,55] The Women's Health Initiative (WHI), a randomised trial of 16 608 post-menopausal women, reported that oestrogen plus progestin increased the risk of ischaemic stroke by 44%, with no effect on haemorrhagic stroke.[55] In the WHI trial, of 10 739 post-menopausal women with a hysterectomy, conjugate equine oestrogen alone increased risk of ischaemic stroke by 55% and no significant effect was noted on haemorrhagic stroke.[54] Meta-analyses of existing trials have confirmed these findings suggesting an increased total stroke risk of roughly 30% with use of hormone-replacement therapy compared with no use.[56–58] LaCroix and colleagues[59] reported long-term health outcomes for the WHI Estrogen-Alone Trial participants. Participants were followed up for an average of 10·7 years with a median use of conjugate equine oestrogen of 5·9 years. In this study,[59] stroke risk was no longer increased during the post-intervention period (HR 0·89 [95% CI 0·64–1·24]).

In post-menopausal women with known coronary heart disease, results from the Heart and Estrogen/Progestin Replacement Study (HERS)[60] showed that oestrogen plus progestin did not reduce the risk of non-fatal or fatal strokes. Results from the Women's Estrogen for Stroke Trial (WEST)[61] showed that oestrogen alone in post-menopausal women with recent stroke or transient ischaemic attack had no effect on recurrent stroke (fatal and non-fatal combined), although there was an early onset of stroke events in the estradiol group in the first 6 months after randomisation.

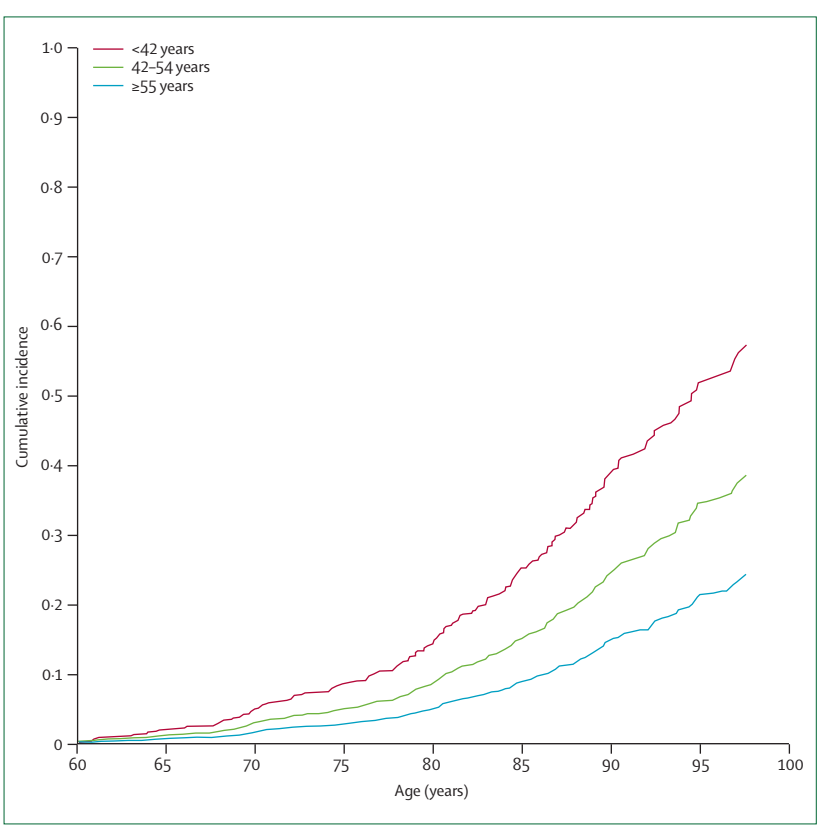

Figure 1: **Kaplan-Meier event curve for stroke risk associated with age at menopause in the Framingham cohort**[50]
Reproduced from Lisabeth and colleagues,[50] by permission of the American Heart Association.

Clinical trials in progress

Currently, there are two trials in progress that might help to clarify the association between hormone-replacement therapy and stroke. The Kronos Early Estrogen Prevention Study (KEEPS)[37] is a randomised placebo-controlled clinical trial comparing 0·45 mg of oral oestrogen, a transdermal oestrogen skin patch, and progesterone with placebo in healthy, recently post-menopausal women (ie, within 3 years of menopause). The primary outcome of this study is rate of change in carotid intimal medial thickness. The Early Versus Late Intervention Trial with Estradiol (ELITE; ClinicalTrials.gov number NCT00114517) is a second randomised placebo-controlled clinical trial in progress that aims to examine the effects of oestrogen (1 mg 17β-estradiol daily) taken orally on the progression of early subclinical atherosclerosis and cognitive decline in healthy post-menopausal women. The design of this study includes randomisation of women according to their years since menopause (less than 6 years or 10 years or more) to receive either oestrogen or placebo. Although not designed to specifically consider stroke, these trials should provide evidence for or against the role of hormone-replacement therapy, including issues surrounding timing and route of administration, in the progression of atherosclerosis and whether a larger trial

powered for hard cardiovascular outcomes, including heart disease and stroke, could be warranted.

Route of administration

Transdermal oestrogen has been postulated to be safer than oral oestrogen with respect to stroke risk because it involves no exposure to first-pass liver metabolism and no increase in clotting factors and inflammatory markers when delivered across the skin.[62] Few observational data exist about the different routes of administration of oestrogen and the risk of stroke. In a nested case-control study[63] of post-menopausal women in the UK's General Practice Research Database, present use of oral oestrogen was suggested to be associated with a greater risk of transient ischaemic attack (OR 1·47 [95% CI 1·09–1·97] compared with non-use) than that with present use of transdermal patches (OR 0·86 [0·43–1·73] compared with non-use), although the authors report that there were only a few users of transdermal patches (actual number not reported).[63] Results were not reported for ischaemic or haemorrhagic stroke because of small numbers. In a more widespread and updated nested case-control study of the same database,[64] Renoux and colleagues reported an adjusted rate ratio (RR) of stroke of 0·95 (95% CI 0·75–1·20) comparing present users of transdermal hormone-replacement therapy with non-users.[64] This association was modified by dose such that stroke risk was not increased for users of low-dose (≤50 μg) oestrogen patches (RR 0·81 [95% CI 0·62–1·05]) but was increased for users of high-dose (>50 μg) patches (RR 1·89 [1·15–3·11]) compared with non-users. For comparison, present users of oral hormone-replacement therapy had a higher risk of stroke than did non-users (RR 1·28 [1·15–1·42]), which was not modified by dose of the oral hormone therapy. The authors also provided a direct comparison of stroke risk for users of transdermal versus oral therapies. The results suggest that stroke risk is roughly 25% lower in those who use transdermal hormone-replacement therapy than in those who use oral hormone-replacement therapy (RR 0·74 [0·58–0·95]).[64] Of note, these observational studies were focused on women who were on average 10–20 years post-menopause (average age 62 years[63] and 70 years,[64] respectively) rather than younger, recently menopausal women, who are the target of the KEEPS and ELITE studies in progress.

Dose of hormone therapy

Oestrogenic dose (low dose *vs* high dose) can depend on the type (oestradiol *vs* congregated equine estrogen) and dose of oestrogen used. As existing clinical trials were based on single regimens of hormone-replacement therapy, no trial data directly comparing stroke risk with varying types and doses of oestrogen are available; however, some observational data exist on this subject. In the nested case-control study by Renoux and colleagues,[64] the associations of oral and transdermal hormone-replacement therapy with stroke were reported for low-dose and high-dose oestrogen formulations. Considering the transdermal route, the authors showed that stroke risk was not increased with present use of low-dose patches, but was increased with present use of high-dose (>50 μg) patches compared with no use (RR 1·89 [95% CI 1·15–3·11]). By contrast, stroke risk was increased to a similar extent in present users of low-dose (≤0·625 mg equine oestrogen or ≤2 mg of estradiol; RR 1·25 [1·12–1.40]) and high-dose (>0·625 mg equine oestrogen or >2 mg of estradiol; RR 1·48 [1·16–1·90]) oral therapies.[64] In the earlier analysis of the same dataset, Arana and colleagues[63] also reported a dose-response association between hormone-replacement therapy and odds of transient ischaemic attack. Current users of medium-dose hormone-replacement therapy, defined as oral conjugate equine oestrogen of 0·625–1·24 mg or 50 μg of transdermal oestrogen, had a 50% greater likelihood of transient ischaemic attack (OR 1·48 [1·12–1·96]), whereas present users of high-dose hormone-replacement therapy, defined as oral conjugate equine oestrogen of 1·25 mg, or more, or 100 μg of transdermal oestrogen, had a two-times increased likelihood of transient ischaemic attack (OR 1·96 [95% CI 1·34–2·87]) compared with non-users after accounting for confounding factors. No association with stroke was noted in users of low-dose hormone-replacement therapy.[63] Although not new, these results are in general agreement with results from the Nurse's Health Study, in which Grodstein and colleagues[65] also showed a dose-response relation between oral conjugate equine oestrogen and risk of stroke. Compared with never users, post-menopausal women taking 0·625 mg or more of conjugate equine oestrogen were 35% more likely to develop a stroke (relative risk 1·35 [1·08–1·68]) and women taking 1·25 mg or more were 63% more likely to develop a stroke (relative risk 1·63 [1·18–2·26]) after accounting for age and risk factors. Women taking 0·30 mg did not have an increased risk of stroke (relative risk 0·54 [0·28–1·06]).[65]

Monotherapy versus dual therapy

Clinical trial results show that the use of either oestrogen plus progestin or oestrogen alone (taken orally) increases stroke risk in post-menopausal women.[54,55] Newer observational data by Renoux and colleagues from their nested case-control study[64] also support the conclusion that the association of hormone-replacement therapy, taken orally, with stroke did not differ between individuals having monotherapy or dual therapy.[64] The odds of stroke were 1·35 (95% CI 1·16–1·58) for users of monotherapy and 1·24 (1·08–1·41) for users of dual therapy. In users of transdermal therapy, stroke risk was not increased for users of monotherapy (RR 1·02 [0·78–1·34]) or dual therapy (0·76 [0·47–1·22]).[64] Although not significant, similar results for transient ischaemic attack were reported by Arana and colleagues[63] combining data on route of administration.

The timing hypothesis for hormone therapy and stroke

One of the most important lessons learned from the clinical trials of hormone therapy in post-menopausal women is that 10 years or more after menopause, the main effect from exogenous estrogens or progesterone seems to be harm rather than benefit. The absence of benefit was shown in a study of mice deficient in apolipoprotein E, in which treatment with oestrogen for mice with mature plaques did not lead to inhibition of progression of the plaques.[66] However, for vessels with less advanced atherosclerosis, oestrogen treatment was associated with fewer fatty streaks, the initial sign of atherosclerosis.[66] Endothelial dysfunction can be improved or reversed with oestrogen replacement at physiological concentrations during the early stage of atherosclerosis. However, with more advanced atherosclerotic lesions, the cellular biology differs such that the response to late initiation of exogenous hormone therapy is likely to lead to inflammatory and haemostatic abnormalities, which promote progression or instability of the lesion.[67] Figure 2 shows a summary of the beneficial and harmful effects of hormone therapy.[67]

The WHI secondary analysis[68] of women classified by the number of years since menopause showed that timing was important for the risk of coronary artery disease events. No significant benefit from hormone therapy was noted in women 10 years or less after menopause (HR 0·76 [95% CI 0·50–1·16]) or 10–19 years after menopause (1·10 [0·84–1·45]), but the risk was increased in women 20 years or more after menopause (1·28 [1·03–1·58]; p value for trend 0·02). Interestingly, this trend was not seen in women who had stroke events, since there was a risk of stroke with treatment regardless of age at enrolment or years since menopause.[68] Results from the Nurses' Health Study showed a similar pattern of increased risk with use of hormone therapy, regardless of age or timing of initiation.[65] In a medical records study[69] of more than 50 000 women in the UK General Practice Research Database, for women younger than 55 years at the time of exposure to oestrogen, the adjusted HR for stroke was 1·52 (95% CI 1·11–2·08), whereas the effect of oestrogen exposure on myocardial infarction was neutral (0·91 [0·69–1·20]). Although age and timing of start of hormone therapy might have a role in the risk-benefit ratio for heart disease, women seem to be at the same risk for stroke regardless of age at initiation.

The reasons for the differences in risk by age for stroke and heart disease are poorly understood. One potential explanation is that the prothrombotic properties of hormone therapy also increase the risk for venous thromboembolism,[69,70] which could then lead to ischaemic stroke via paradoxical embolism through a patent foramen ovale or other right-to-left cardiac shunt. In fact, a longitudinal study[71] showed that increased thrombin generation at baseline was associated with the risk for ischaemic stroke, but not for coronary heart disease, and

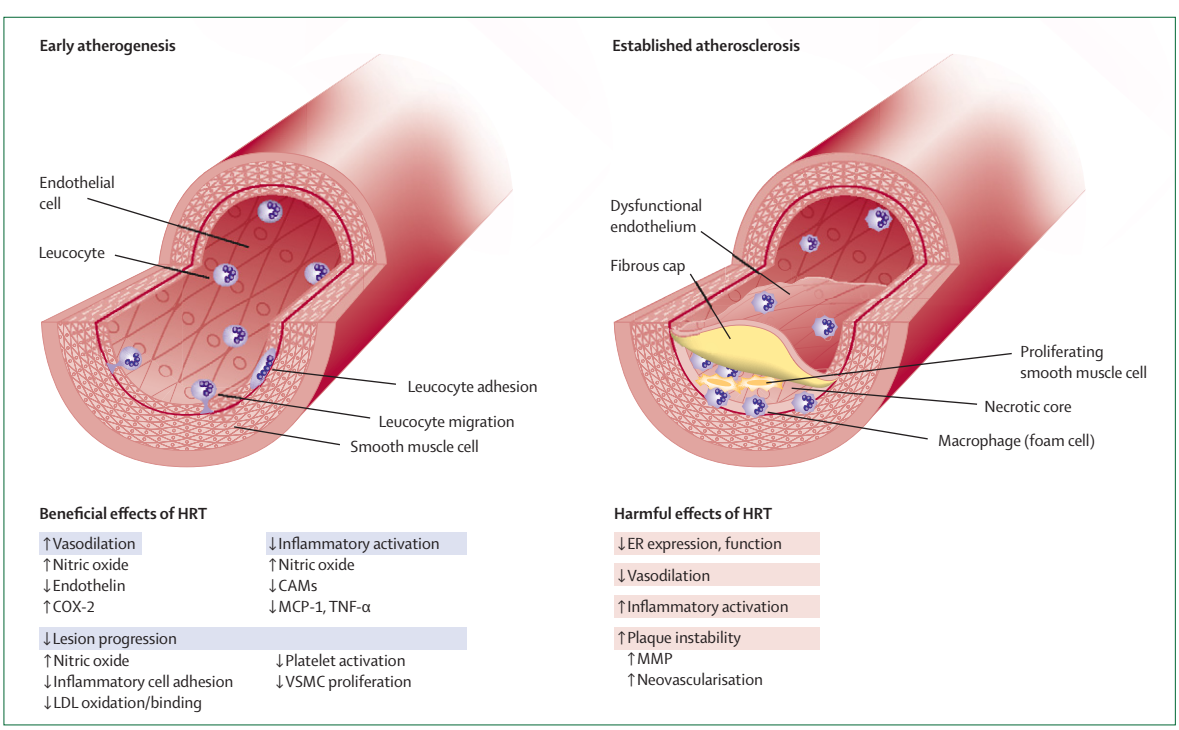

Figure 2: **Beneficial and harmful vascular effects of oestrogens depending on the degree of atherogenesis**
HRT=hormone-replacement therapy. CAMs=cell adhesion molecules. COX-2=cyclooxygenase-2. MCP-1=monocyte chemotactic protein 1. TNF-α=tumor necrosis factor α. VSMC=vascular smooth muscle cell. LDL=low-density lipoprotein. ER=oestrogen receptor. MMP=matrix metalloproteinase protein. Reproduced from Mendelsohn and Karas,[67] by permission of the American Association for the Advancement of Science.

Search strategy and selection criteria

We searched PubMed with the terms "incidence or prevalence AND stroke", "menopause AND stroke", "primary ovarian insufficiency", "premature ovarian failure", "sex steroids or sex hormone-binding globulin or hormone therapy or estrogens AND stroke" and references cited in identified articles from 1966 to August 2011. We included studies with multivariable adjusted analyses to identify the risk of stroke on the basis of age at menopause, and observational or post-hoc studies of treatment with hormone therapy focused on age or timing or initiation, published between 2000 and August 2011. We also included other original studies that met inclusion criteria identified from bibliographies of other search results, as well as reviews relevant to the topic of this Review. We excluded case reports, case series, or studies with fewer than 30 patients, or with too small a sample size to do adjusted analyses.

that this effect was mainly seen in women, but not men. The causes of stroke are rarely reported in sufficient detail in large cohorts, clinical trials, or database studies to allow speculation about causation with exposure to hormone therapy. Additionally, the causes of stroke are heterogeneous and in about 35% of patients are undetermined (ie, no identifiable cause).[72]

Clinical guidelines for hormone therapy

The American Heart Association guidelines specifically state that hormone therapy should not be prescribed for prevention of heart disease or stroke.[73–75] The European Menopause and Andropause Society released a position statement for women with known coronary heart disease, which recommends that women who are experiencing menopausal symptoms should be individually assessed for their baseline risk of developing breast cancer, venous thromboembolism, and coronary heart disease recurrence. After weighing the risks of these events against quality of life, "the lowest effective estrogen dose should be used for the shortest possible time."[76] Also, for women at increased risk of coronary heart disease, transdermal hormone therapy should be the first choice over oral formulations.[76]

Conclusions and future directions

Although women have a lower incidence of stroke than men during midlife, their risk doubles in the decade after menopause, emphasising the need to screen for and manage risk factors that increase during this period. Women with very early onset of menopause might also be at increased risk, but whether they should receive hormone-replacement therapy is unknown. Although the risk of stroke is low and early age of menopause is uncommon, further research is needed for optimum prevention of cardiovascular events. Hormone therapy is still the most effective treatment for menopausal symptoms, but there is no timing for exposure in midlife that seems to protect women from stroke, whereas for heart disease, the risk seems lowest in the early post-menopausal time frame. More research is needed to identify the safest and most effective formulation, dose, and duration of hormone therapy that can be used to treat vasomotor symptoms without increasing the risk of stroke. The KEEPS and ELITE studies in progress will shed light on the association between hormone-replacement therapy, including information on route of administration and timing of initiation, and progression of atherosclerosis—information that should inform the design of future clinical trials. In the meantime, it is important for women to maximise a healthy lifestyle throughout midlife to reduce the overall risk for stroke and cardiovascular disease.[77]

Contributors

Both authors did the literature search, drafted an equal distribution of sections in the Review, and reviewed and edited the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

CB receives funding support from the National Institute of Neurological Disorders and Stroke (NINDS) K02 NS058760. LL receives funding support from NINDS R01 NS38916, R01 NS062675, R01 NS070941, and NHLBI R01 HL098065.

References

1 Roger V, Go A, Lloyd-Jones D, et al. Heart Disease and Stroke Statistics 2011 Update: A report from the American Heart Association. *Circulation* 2010; **123:** e18–e209.

2 Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol* 2008; **7:** 915–26.

3 Roquer J, Rodriguez A, Gomis M. Sex differences in first-ever acute stroke. *Stroke* 2003; **34:** 1581–85.

4 Kapral MK, Fang J, Hill MD, et al. Sex differences in stroke care and outcomes. Results from the registry of the Canadian Stroke Network. *Stroke* 2005; **36:** 809–14.

5 Gargano J, Reeves M. Sex differences in stroke recovery and stroke-specific quality of life. *Stroke* 2007; **38:** 2541–48.

6 Gargano JW, Wehner S, Reeves MJ. Sex differences in acute stroke care in a statewide stroke registry. *Stroke* 2008; **39:** 24–29.

7 Martínez-Sánchez P, Fuentes B, Fernández-Domínguez J, et al. Young Women Have Poorer Outcomes than Men after Stroke. *Cerebrovasc Dis* 2011; **31:** 455–63.

8 Sutton-Tyrrell K, Wildman RP, Matthews KA, et al. Sex hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). *Circulation* 2005; **111:** 1242–49.

9 Sutton-Tyrrell K, Lassila HC, Meilahn EN, Bunker C, Matthews KA, Kuller LH. Carotid atherosclerosis in premenopausal and postmenopausal women and its association with risk factors measured after menopause. *Stroke* 1998; **29:** 1116–21.

10 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:** 1032–37.

11 Lofmark U, Hammarstrom A. Evidence for age-dependent education-related differences in men and women with first-ever stroke. Results from a community-based incidence study in northern Sweden. *Neuroepidemiology* 2007; **28:** 135–41.

12 Lisabeth LD, Smith MA, Sanchez BN, Brown DL. Ethnic disparities in stroke and hypertension among women: the BASIC project. *Am J Hypertens* 2008; **1:** 778–83.

13 Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005; **366:** 1773–83.

14 Kissela B, Schneider A, Kleindorfer D, et al. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke* 2004; **35:** 426–31.

15 Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol* 1998; **147:** 259–68.

16 Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996; **27:** 373–80.

17 Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* 2003; **74:** 317–21.

18 Vega T, Zurriaga O, Ramos JM, et al. Stroke in Spain: epidemiologic incidence and patterns; a health sentinel network study. *J Stroke Cerebrovasc Dis* 2009; **18:** 11–16.

19 Towfighi A, Saver J, Engelhardt R, Ovbiagele B. A midlife stroke surge among women in the United States. *Neurology* 2007; **69:** 1898–904.

20 Towfighi A, Markovic D, Ovbiagele B. Persistent sex disparity in midlife stroke prevalence in the United States. *Cerebrovasc Dis* 2011; **31:** 322–28.

21 Ayala C, Croft J, Greenlund K, et al. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995–1998. *Stroke* 2002; **33:** 1197–201.

22 Towfighi A, Tai W, Markovic D, Ovbiagele B. Sex-Specific Temporal Trends in In-Hospital Mortality After Stroke Among Middle-Age Individuals in the United States. *Stroke* 2011; **42:** 2740–45.

23 Kapral M, Degani N, Hall R, et al. Gender differences in stroke care and outcomes in Ontario. *Womens Health Issues* 2011; **21:** 171–76.

24 Te Velde E, Pearson P. The variability of female reproductive aging. *Hum Reprod Update* 2002; **8:** 141–54.

25 Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. *Maturitas* 1995; **21:** 103–13.

26 McKinlay SM. The normal menopause transition: an overview. *Maturitas* 1996; **23:** 137–45.

27 Liu Y, Ding J, Bush T, et al. Relative androgen excess and increased cardiovascular risk after menopause: a hypothesized relation. *Am J Epidem* 2001; **154:** 489–94.

28 Lee JS, Yaffe K, Lui LY, et al. Prospective study of endogenous circulating estradiol and risk of stroke in older women. *Arch Neurol* 2010; **67:** 195–201.

29 Selby C. Sex hormone binding globuling: origin, function, and clinical significance. *Ann Clin Biochem* 1990; **27:** 532–41.

30 de Bruin J, Bovenhuis H, van Noord P, et al. The role of genetic factors in age at natural menopause. *Hum Reprod* 2001; **16:** 2014–18.

31 Coulam C, Adamson S, Annegers J. Incidence of premature ovarian failure. *Obstet Gynecol* 1986; **67:** 604–06.

32 De Vos M, Devroey P, Fauser P. Primary ovarian insufficiency. *Lancet* 2010; **376:** 911–21.

33 Sybert V, McCauley E. Turner's Syndrome. *N Engl J Med* 2004; **351:** 1227–38.

34 Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang Y-F. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. *Stroke* 2001; **32:** 1104–11.

35 Mudali S, Dobs AS, Ding J, Cauley JA, Szklo M, Golden SH. Endogenous postmenopausal hormones and serum lipids: the Atherosclerosis Risk in Communities Study. *J Clin Endocrinol Metab* 2005; **90:** 1202–09.

36 Wildman R, Colvin A, Powell L, et al. Associations of endogenous sex hormones with the vasculature in menopausal women: the Study of Women's Health Across the Nation (SWAN). *Menopause* 2008; **15:** 414–21.

37 Harman S, Brinton E, Cedars M, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005; **8:** 3–12.

38 Matthews K, Crawford S, Chae C, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol* 2009; **54:** 2366–73.

39 Rexrode KM, Manson JE, Lee I-M, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. *Circulation* 2003; **108:** 1688–93.

40 Maggio M, Ceda G, Lauretani F, et al. Relationship between higher estradiol levels and 9-year mortality in older women: the Invecchiare in Chianti Study. *J Am Geriatr Soc* 2009; **57:** 1810–15.

41 Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives. A meta-analysis. *JAMA* 2000; **284:** 72–78.

42 Chan W-S, Ray J, Wai EK, et al. Risk of stroke in women exposed to low-dose oral contraceptives. A critical evaluation of the evidence. *Arch Intern Med* 2004; **164:** 741–47.

43 de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002; **155:** 339–45.

44 Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. *Stroke* 2004; **35:** 1548–51.

45 Cooper GS, Sandler DP. Age at natural menopause and mortality. *Ann Epidemiol* 1998; **8:** 229–35.

46 Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *Am J Epidemiol* 2005; **162:** 1089–97.

47 Cui R, Iso H, Toyoshima H, et al. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol* 2006; **16:** 177–84.

48 Hu FB, Grodstein F, Hennekens CH, et al. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med* 1999; **159:** 1061–66.

49 Choi SH, Lee SM, Kim Y, Choi NK, Cho YJ, Park BJ. Natural menopause and risk of stroke in elderly women. *J Korean Med Sci* 2005; **20:** 1053–58.

50 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:** 1044–49.

51 Baba Y, Ishikawa S, Amagi Y, Kayaba K, Gotoh T, Kajii E. Premature menopause is associated with increased risk of cerebral infarction in Japanese women. *Menopause* 2010; **17:** 506–10.

52 de Lecinana MA, Egido JA, Fernandez C, et al. Risk of ischemic stroke and lifetime estrogen exposure. *Neurology* 2007; **68:** 33–38.

53 Broer S, Eijkemans M, Scheffer G, et al. Anti-Mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. *J Clin Endocrinol Metab* 2001; **96:** 2532–39.

54 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.

55 Wassertheil-Smoller S, Hendrix SL, 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.

56 Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; **330:** 342.

57 Sare GM, Gray LJ, Bath PM. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur Heart J* 2008; **29:** 2031–41.

58 Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. *BJOG* 2006; **113:** 5–14.

59 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.

60 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.

61 Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *NEJM* 2001; **345:** 1243–49.

62 Hemelaar M, van der Mooren M, Rad M, Kluft C, Kenemans P. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review. *Fertil Steril* 2008; **90:** 642–72.

63 Arana A, Varas C, Gonzalez-Perez A, Gutierrez L, Bjerrum L, Garcia Rodriguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. *Menopause* 2006; **13:** 730–36.

64 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.

65 Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133:** 922–41.

66 Rosenfeld M, Kauser K, Martin-McNulty B, Polinsky P, Schwartz S, Rubanyi G. Estrogen inhibits the initiation of fatty streaks throughout the vasculature but does not inhibit intra-plaque hemorrhage and the progression of established lesions in apolipoprotein E deficient mice. *Atherosclerosis* 2002; **164:** 251–59.

67 Mendelsohn M, Karas R. Molecular and cellular basis of cardiovascular gender differences. *Science* 2005; **308:** 1583–87.

68 Rossouw J, Prentice R, Manson J, et al. postmenopausal hormone therapy and risk of cardiovascular disase by age and years since menopause. *JAMA* 2007; **297:** 1465–77.

69 Weiner MB, Barnhart K, Xie D, Tannen RL. Hormone therapy and coronary heart disease in young women. *Menopause* 2008; **15:** 86–93.

70 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy post-menopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.

71 Carcaillon L, Alhenc-Gelas M, Bejot Y, et al. Increased thrombin generation is associated with acute ischemic stroke but not with coronary heart disease in the elderly. The Three-City Cohort Study. *Arterio Thromb Vasc Biol* 2011; **31:** 1445–51.

72 Kolominsky-Rabas P, Weber M, Gefeller O, Neundoerfer B, Heuschmann P. Epidemiology of ischemic stroke subtypes according to TOAST criteria. Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. *Stroke* 2001; **32:** 2735–40.

73 Mosca L, Benjamin E, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: A guideline from the American Heart Association. *Circulation* 2011; **123:** 1243–62.

74 Goldstein L, Bushnell C, Adams R, et al. Guidelines for the primary prevention of stroke. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; **42:** 517–84.

75 Furie K, Kasner S, Adams R, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; **42:** 227–76.

76 Schenck-Gustafsson K, Brincat M, Erel C, et al. EMAS position statement: Managing menopause in the context of coronary heart disease. *Maturitas* 2011; **68:** 94–97.

77 Lloyd-Jones D, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010; **121:** 586–613.