

Menopause and ischaemic stroke: basic, clinical and epidemiological considerations. The role of hormone replacement

Amos Pines^{1,4}, Nathan M. Bornstein² and Itzhak Shapira³

Departments of ¹Medicine 'T', ²Neurology and ³Cardiology, Tel Aviv Souraski Medical Center, Tel-Aviv, and the ¹Menopause Clinic, Ramat-Marpe Hospital, Ramat-Gan, Israel

⁴To whom correspondence should be addressed at: Department of Medicine 'T', Ichilov Hospital, 6 Weizman Street, Tel-Aviv 64239, Israel. E-mail: apines@netvision.net.il

Stroke is a leading cause of disability and death in women, despite progress in its prevention and treatment. As with coronary artery disease, the incidence of stroke rises after the menopause, in parallel with metabolic changes that add up to create an unfavourable risk factor profile for cardiovascular disease. The menopause metabolic syndrome, which includes weight gain and changes in lipids, insulin resistance, endothelial dysfunction, increased levels of homocysteine, lipoprotein (a) and several coagulation factors, may in part be attributable to estrogen deficiency, and may be reversible with hormone replacement therapy (HRT). As for blood pressure, a major detrimental risk factor for stroke, it is probably not affected by either the menopause *per se* or by HRT. Abundant experimental data exist indicating that estrogens have both anti-atherosclerotic and neuroprotective effects. The width or thickness of the carotid wall is a good indicator of carotid atherosclerosis; it increases after the menopause transition, and decreases with HRT. Estrogens may enhance cerebral blood flow and reduce vascular resistance. In animal models of stroke, estrogen induced anti-ischaemic effects. Several large-scale epidemiological studies have verified the concept of primary protection of stroke by HRT, though others have failed to do so. In light of these contradictory data, several recent reports were highly significant (Nurses' Health Study, HERS Study, Cancer Prevention II Trial, WEST Trial). Despite the known neural and vascular benefits of estrogen, it is uncertain whether HRT is associated with stroke protection. At present, prevention of stroke should involve proven risk reduction strategies.

Key words: cerebrovascular disease/hormone replacement therapy/menopause/stroke

TABLE OF CONTENTS

Menopause and risk of stroke
HRT and risk factors for stroke
HRT and neuroprotection
HRT and carotid/cerebral blood flow
HRT and carotid atherosclerosis
Epidemiological data on HRT and stroke: primary prevention
Secondary prevention of stroke by HRT
Recent data from major epidemiological studies
Conclusions
Acknowledgements
References

Menopause and risk of stroke

Stroke remains a leading cause of disability and death in women, despite progress in its prevention and treatment. A 50-year-old white woman in the USA has a 20% lifetime probability of

developing stroke, and an 8% probability of dying from the condition (Grady *et al.*, 1992). One study in the USA claimed that one in six American women would die from stroke (Bonita, 1992). Thus, although cerebrovascular diseases are as important as coronary artery disease and breast cancer in women's health, they somehow have not received sufficient public attention in the context of menopause medicine, despite many articles on this issue.

Basically, stroke is a disease of old age, the incidence increasing from age 65 years onward (Brown *et al.*, 1996; Manolio *et al.*, 1996). Ischaemic stroke is rare in premenopausal women however, and the few cases of stroke in young women are mainly attributed to either embolism or haemorrhage. Before the age of 65 years, women demonstrate strikingly less cerebral atherosclerosis than men, but later on the incidence is comparable (Flora *et al.*, 1968; Sacco *et al.*, 1997). Interestingly, and very similar to coronary artery disease, once a woman has had a stroke, the course of the disease and her prognosis is worse than that in a

man (Bousser, 1999). The main risk factors for stroke in women, as in men, are age, hypertension and metabolic alterations that induce accelerated atherosclerosis (Bronner *et al.*, 1995; Rosenthal and Oparil, 2000).

Hypertension

The lifetime risk for hypertension in a 50-year-old woman exceeds 60% (Cummings *et al.*, 1989). Epidemiological studies agree that under the age of 40 years, systolic pressures are higher in men than in women, but by 60 years they are higher in women (Miall and Lovell, 1977; Sigurdsson, 1983; Landahl *et al.*, 1986). Diastolic pressures increase less steeply, and to a similar degree, with age in both sexes (Wilson *et al.*, 1985). Data on changes in blood pressure during the menopause transition are contradictory, but in summary there appears to be no interaction (Hjortland *et al.*, 1976; Lindquist, 1982; Staessen *et al.*, 1989). In a recent longitudinal study (Matthews *et al.*, 2001), the systolic blood pressure and the pulse pressure increased significantly from the first to the fifth year post menopause, whereas a small increase in blood pressure from premenopause values to first year post menopause did not reach statistical significance. Hypertension is an important risk factor for stroke: according to the Framingham study, women with blood pressure values of 160/95 mmHg or higher had an age-adjusted relative risk of 2.9 for stroke (Elkind and Sacco, 1998). On the other hand, treatment of hypertension in menopausal women reduces the risk for stroke by 40% (Collins *et al.*, 1990; SHEP Cooperative Research Group, 1991). The National Stroke Association thus recommended that, apart from optimizing blood pressure control, blood pressure should be measured at every visit to the clinic, and should also be monitored by the patients themselves at home (Gorelick *et al.*, 1999).

Smoking

The Nurses' Health study analysed the impact of cigarette smoking on stroke risk in a huge cohort of middle-aged women. Those who smoked more than 25 cigarettes per day had a 2.7-fold increased relative risk for thromboembolic stroke and 10-fold increased risk for subarachnoid haemorrhage as compared with non-smokers (Colditz *et al.*, 1988). A meta-analysis on the association of smoking and stroke in women showed that the pooled relative risk was 1.72, and that the number of cigarettes per day correlated positively with risk. Interestingly, among smokers the younger the woman, the higher was the risk for stroke: below age 55 years the risk was 2.9, but above age 75 it was similar to that in non-smokers (Shinton and Beevers, 1989). Cessation of smoking as a stroke prevention measure is highly advised, as the risk returns to the level observed in non-smokers within a few years.

Diabetes mellitus

Diabetes mellitus, a major risk factor for atherosclerosis and cardiovascular diseases in women, increases the risk for stroke by a factor of at least 2 to 3, especially in older women (Billir and Love, 1993). Stroke risk is higher in cases with increased insulin resistance or hyperinsulinaemia without hyperglycaemia (Shinozaki *et al.*, 1996). In view of data showing that tight control of both glycaemia and blood pressure may reduce the vascular complications of diabetes, including stroke (UK PDS Group, 1998), and may decrease mortality rate after stroke (Wang

et al., 2000), such measures are highly recommended (NAMS Consensus Opinion, 2000). In the Nurses' Health Study, the relative risk for stroke in women with type 2 diabetes was 5.4, and was even higher in those who were also smokers (Manson *et al.*, 1991). Ten years after cessation of smoking, the cardiovascular mortality risk was decreased to a value comparable with that in non-smoking diabetic women (Al-Delaimy *et al.*, 2001).

Menopause metabolic syndrome and hypercholesterolaemia

In recent years, the concept of a 'menopause metabolic syndrome' has gained popularity (Spencer *et al.*, 1997). This refers to a series of alterations, related to estrogen deficiency, which become evident in post-menopausal women and add up to create an unfavourable risk factor profile for cardiovascular disease. The main features of the syndrome include weight gain and changes in lipid profile [raised low-density lipoprotein (LDL) cholesterol; lowered triglycerides (TG)], insulin resistance, endothelial dysfunction, increased levels of homocysteine, lipoprotein (a) and several coagulation factors as well as fibrinolytic factors. Unlike the case with coronary artery disease, the relationship between serum cholesterol and stroke risk is unclear, and most data have so far shown no correlation (Prospective Studies Collaboration, 1995). Although an analysis of earlier studies on the effect of lipid-lowering medications on stroke risk showed no association (Herbert *et al.*, 1995), recent studies on women with statins revealed some beneficial results, especially in patients with coronary artery disease (Amarengo, 2001).

The net result of all the above-mentioned metabolic changes is an increased risk for cardiovascular diseases and atherosclerosis. Indeed, the width or thickness of the carotid wall, which is considered to be a good indicator of carotid atherosclerosis, increases after the menopause. Premenopausal women have thinner intima-media values and fewer carotid focal plaques than their post-menopausal counterparts (Dobs *et al.*, 1999). Women having an early menopause demonstrate thicker intima-media than women entering menopause at a relatively late age (Joakimsen *et al.*, 2000). Others (Matthews *et al.*, 2001) found that the increase in intima-media thickness observed between premenopause and the fifth year post menopause correlated with the cardiovascular risk factor profile of the study participants, mainly blood pressure, lipids, fasting glucose and body mass index.

HRT and risk factors for stroke

The overall effect of hormone replacement therapy (HRT) on blood pressure is considered to be negligible. A 3-year follow-up in the PEPI trial did not show any difference in blood pressure between the placebo group and the hormone group, although a small increase in blood pressure was recorded in all groups (this may have been due to either the effect of ageing or of weight gain) (Writing Group for the PEPI Trial, 1995). However, several small-scale studies were able to demonstrate favourable changes in blood pressure in hypertensive women taking HRT, either during exercise or in 24-h ambulatory blood pressure recordings (Mercuro *et al.*, 1997; Pines *et al.*, 1998). Apart from a suggestion of preference for the transdermal route in diabetic patients, a broad-based recommendation for the use of hormones in diabetics cannot be made (NAMS, 2000). However, both the Nurses'

Health Study (Grodstein *et al.*, 1996) and a study from Turku, Finland (Sourander *et al.*, 1998) pointed at a larger cardiovascular benefit for hormone users with several risk factors (smoking, hypertension, hyperlipidaemia or diabetes mellitus).

As for the menopause metabolic syndrome, most of the metabolic changes related to menopause are reduced, or even reversed after the administration of estrogen (Manolio *et al.*, 1993; Mendelsohn and Karas, 1999; Davidson *et al.*, 2000). Estrogen treatment led to the lowering of LDL cholesterol and elevation of high-density lipoprotein (HDL) cholesterol, a decrease in insulin resistance, and an improvement in endothelial function (through both the vasodilatory and vasoconstrictory mediators). It should be mentioned that adverse metabolic changes might also occur, such as an increase in triglycerides. Concern has also been expressed about the prothrombotic effects of estrogen (Teede *et al.*, 2000), and these could be relevant to the increase in incidence of stroke related to oral contraceptives (Gillum *et al.*, 2000), or to a higher dosage of post-menopausal estrogen replacement (Grodstein *et al.*, 2000). Nevertheless, most of the above estrogen-induced alterations and reactions seem beneficial and may be the basic explanation for a cardiovascular protective effect of estrogen.

HRT and neuroprotection

Abundant experimental data exist which indicate that estrogens have a neuroprotective effect (Hurn and Macrae, 2000; McEwen, 2001; Wise *et al.*, 2001). Estrogen has both receptor-dependent and -independent brain actions, mainly affecting neuronal viability and cerebral blood flow. Estrogen has been mentioned in the context of maintaining memory, cognition and mood, and is believed to attenuate the extent of acute brain injury (i.e. during stroke). Recent data, however, have raised some doubts with regard to these effects (see below). Some studies have suggested that physiological concentrations of estradiol protect through estrogen receptor-dependent mechanisms that lead to the transcription of critical genes that ultimately promote cell survival. Estrogen receptor α has an important role (Dubal *et al.*, 2001), although high-dose estradiol seems to protect neurones that do not express estrogen receptors. Among the potential mechanisms investigated in experimental models in the context of neuroprotection by estrogen were the following: endothelial effects that induce vasodilation; anti-oxidant activity; various signalling effects through estrogen receptors; interaction with the *bcl-2* proto-oncogenes (involved in cell survival); interaction with neuronal growth factors; alteration of the glutamatergic and γ -aminobutyric acid (GABA) neuronal activity; stimulation of neuronal regeneration; and secretion of neurotransmitters.

In a middle-cerebral-artery-occlusion model, the volume of induced infarcts was smaller in fertile female rats with intact ovaries and normal estrogen secretion than that in castrated female rats or in male rats (Alkayed *et al.*, 2000). The administration of low physiological levels of estradiol 1 week before permanent occlusion of the middle cerebral artery in ovariectomized rats, led to a dramatic decrease in the size of cortical infarction (Dubal *et al.*, 1998). Higher doses of estradiol were equally efficient. The same effect was seen in young rats (3–4 months) and in middle-aged rats (9–12 months) (Dubal and Wise, 2001).

HRT and carotid/cerebral blood flow

A substantial volume of the brain mass consists of blood vessels. Numerous studies have determined that carotid and cerebral blood flows each react to estrogens in the same way, and via the same mechanisms as the coronary or peripheral arteries. Thus, the end result of estrogen deficiency states might be a decrease in flow and increase in resistance, whereas the effect of estrogen on the cerebral arterial tree is the opposite. The following are examples of such studies: comparing the ophthalmic artery blood flow and resistance in non-pregnant, pregnant and post-menopausal women showed a correlation with estrogen status, namely the lowest flow and highest resistance were recorded in the post-menopausal women, while highest flow and lowest resistance was seen in pregnancy (Belfort *et al.*, 1995). In a small-scale study (Gangar *et al.*, 1991), an association was demonstrated between time since menopause and carotid artery pulsatility index, a parameter which correlates negatively with blood flow. In the above two studies, after the initiation of estrogen supplementation, a significant positive effect on blood flow was recorded. On the other hand, drug-induced hypoestrogenism during GnRH therapy was not associated with any changes in carotid or middle cerebral artery flows (Penotti *et al.*, 1996a). As for the effect of HRT on cerebral vasculature, many studies have indicated a clear vasoreaction. When long-term hormone users were compared with age-matched non-users, lower carotid vascular resistance was recorded in the users (Naessen and Bakos, 2001). Another group who measured whole cerebral and cerebellar blood flow by single-photon emission computed tomography were able to detect a significant increase in brain perfusion following several weeks of conjugated estrogen (Ohkura *et al.*, 1995). Penotti and colleagues published several studies on the interaction of HRT and carotid/cerebral blood flow. In the first study (Penotti *et al.*, 1993), it was shown that the pulsatility index was reduced in both arteries after 6 weeks of transdermal estradiol at 50 μ g/day. Interestingly, cyclical medroxyprogesterone acetate supplementation (12 days per cycle, 10 mg per day) did not modify this positive effect. In a later study from the same investigators (Penotti *et al.*, 1999), cyclical medrogestone acetate (12 days per month, at 5 mg/day) added to continuous conjugated equine estrogen at 0.625 mg/day gave similar results. These authors also demonstrated that the pulsatility index rapidly increased to pre-treatment values following the suspension of hormone therapy (Penotti *et al.*, 1996b). Others (Darj *et al.*, 1999) used a different hormonal combination consisting of oral estradiol and cyclical norethisterone acetate, but could not show any important differences in common, internal or external carotid blood flow between the treated women and a control group. In summary, it is possible that estrogens may enhance cerebral blood flow and reduce vascular resistance, though there are studies in which such an effect was either marginal or not present.

HRT and carotid atherosclerosis

The intima-media thickness, evaluated by B-mode ultrasonography, is considered a good marker for atherosclerosis. Many studies which have investigated stroke risk or myocardial infarction risk, used this parameter. The Healthy Women Study assessed a possible association between menopause and carotid

artery atherosclerosis (Matthews *et al.*, 2001). Women were followed from the premenopausal period until several years post menopause. Premenopausal values of blood pressure, lipids and body mass index predicted intima-media thickness and carotid plaque score 5–8 years after menopause. Two large surveys, one from the United States (Atherosclerosis Risk in Community) (Dobs *et al.*, 1999) and the other from Norway (Joakimsen *et al.*, 2000), demonstrated that menopause is associated with thickened carotid artery walls. The Norwegian study also showed an inverse relationship between age at menopause and carotid atherosclerosis, namely that women having a late menopause had relatively less atherosclerosis than women entering menopause at an early age. Clearly, this effect on the structure of the arterial wall was considered as another aspect of the vascular damage inflicted by estrogen deficiency. The importance of estrogen status has also been demonstrated while comparing hormone users with non-users. In all those studies, HRT was associated with thinner intima-media (Baron *et al.*, 1998; Dobs *et al.*, 1999; Joakimsen *et al.*, 2000). In one study, the adjusted odds ratio for carotid atherosclerosis in ever-users of estrogen was 0.75 as compared with never-users, a very significant preventive effect (Joakimsen *et al.*, 2000). A thinner intima-media was also observed in a cohort of women aged 65 years or older who used HRT (Manolio *et al.*, 1993). The above data point to a protective effect of hormones, possibly through retardation of atheroma formation. The studies of Clarkson and colleagues on monkeys should also be mentioned in this respect (Clarkson *et al.*, 2001). Animals were fed an atherogenic diet and developed arterial plaques that could be measured. Some were also given estrogen, and this resulted in a substantial decrease in plaque size. Interestingly, soy protein extract containing phytoestrogens had the same beneficial effect as estrogen. Few data exist on the effect of progestins. An early release from the Atherosclerosis Risk in Communities study (Nabulsi *et al.*, 1996), and data from the Cardiovascular Health Study (Jonas *et al.*, 1996), as well as more recent studies (McGrath *et al.*, 1998; Griewing *et al.*, 1999), showed that progestins did not impact on the effect of estrogen.

Another group (Angerer *et al.*, 2001) investigated the effect of oral hormone therapy on the progression of carotid atherosclerosis in healthy women with established intima-media thickening (>1 mm) at baseline. At the end of 48 weeks of follow-up, changes in wall thickness were similar for estrogen plus cyclical monthly progestin, estrogen plus tri-monthly progestin, and a control group of hormone non-users. In a similar study on women with an LDL-cholesterol level of at least 130 mg/dl or with diabetes mellitus (fasting glucose <200 mg/dl) but no history of cardiovascular disease, the carotid artery intima-media thickness was not considered an inclusion criteria (Hodis *et al.*, 2001). In this study, the mean basal values were ~0.75 mm, far less than those in the above-mentioned study (Angerer *et al.*, 2001). In contrast with the results of that study, the progression of subclinical carotid atherosclerosis during 2-year follow-up was significantly slower in estradiol users than in the placebo group. As a matter of fact, the hormone users even demonstrated some regression in thickness. Interestingly, the average rate of progression did not differ between hormone and placebo recipients who took lipid-lowering medications. Thus, at this point it seems that, much like the case of the coronary arteries, HRT may retard the development of carotid atherosclerosis, but

once a woman has established carotid thickening treatment with estrogen probably has a minor or no effect on the progression of atherosclerosis.

Epidemiological data on HRT and stroke: primary prevention

Despite all the above encouraging data of possible mechanisms for neuroprotection by estrogens, what really matters of course is whether or not post-menopausal HRT changes the risk for stroke. Overviews of the relevant data were published in 1995 and 2001 (Paganini-Hill, 1995, 2001). The 1995 analysis included six case-control studies, six uncontrolled cohort studies and 14 controlled studies. The results of those trials were inconsistent, although the preponderance of the evidence suggested that women taking HRT were at a decreased risk of stroke. The 2001 article summarized eight publications of case-control studies, seven of uncontrolled cohort studies, and 25 of internally controlled cohort studies. On this occasion, the conclusion was that 'although several observations suggest that HRT might protect women from stroke, most studies in the past 25 years have produced no conclusive evidence of a beneficial effect. The lack of consistency in stroke endpoints, definition of HRT user, estrogen preparation, and influence of combined regimen might account in part for the unclear association between HRT and risk of stroke.' Also, the definition of a cerebrovascular event usually includes ischaemic stroke, haemorrhagic stroke and subarachnoid bleeding. Those three entities are different in pathogenesis and risk factors, and therefore should be evaluated separately. Table I, which shows data from selected major studies on HRT and stroke risk, clearly demonstrates the inconsistency and wide variability in their methodology and results (Pfeffer, 1978; Wilson *et al.*, 1985; Falkeborn *et al.*, 1993; Finucane *et al.*, 1993; Folsom *et al.*, 1995; Pederson *et al.*, 1997; Schairer *et al.*, 1997; Petitti *et al.*, 1998; Sourander *et al.*, 1998; Fung *et al.*, 1999; Grodstein *et al.*, 2000; Rodriguez *et al.*, 2001).

A non-traditional approach was used in two recent relevant trials: the Cardiovascular Health Study performed brain magnetic resonance imaging (MRI) scans on 2100 healthy women aged over 65 years (Luoto *et al.*, 2000). Although MRI scans identified infarcts (mostly small and asymptomatic) in about 30% of the cohort, the prevalence of MRI infarcts did not differ among current users, past users or never-users of hormones. White matter changes were associated with the score of the Mini Mental State Exam, but not with hormone use. Another study investigated a possible correlation between hormone use at the time of stroke and stroke severity (according to the Canadian Neurological Scale score) (Bushnell *et al.*, 2001). The score was 10 for hormone users and 9.5 for matched non-users, interpreted by the authors as a non-significant trend toward lesser stroke severity in hormone users. However, multivariate analysis showed no independent effect of hormone therapy.

Secondary prevention of stroke by HRT

There is very little information available on this issue. In a trial of aspirin and HRT in women who suffered a transient ischaemic attack (TIA), hormone users had a RR for stroke of 0.23 compared with non-users (Persantine aspirin trial; The American-

Table I. Selected studies on primary prevention of stroke by HRT

Reference (year)	Type	Description
Falkeborn <i>et al.</i> (1993)	UCCS	23 088 HRT users, mean observation 5.8 yrs. 361 first strokes versus 403 expected. RR for acute stroke = 0.85*, for age <60 = 0.61*. Same RR for E only or E+P users.
Schairer <i>et al.</i> (1997)	UCCS	23 346 HRT users for average 8.6 yrs. 172 stroke fatalities. No effect of HRT, except for marked reduction in risk for intracranial haemorrhage.
Pfeffer (1978)	CCS	257 cases, 1245 controls. No effects of HRT on fatal or non-fatal stroke risk.
Pedersen <i>et al.</i> (1997)	CCS	1422 cases, 3171 controls. No effect of HRT (E or E+P) on non-fatal stroke risk, but RR for TIA in ERT users = 2.1*.
Petitti <i>et al.</i> (1998)	CCS	349 cases, 349 controls. No effect of HRT (E or E+P) on ischaemic stroke risk, but RR for haemorrhagic stroke = 0.33*.
Wilson <i>et al.</i> (1985)	ICCS	1234 women, 45 strokes/TIA during 8 years observation. RR in HRT users = 2.3.
Finucane <i>et al.</i> (1993)	ICCS	1910 women, 250 strokes during average follow-up of 12 yrs. RR for all strokes in HRT users = 0.69, RR for fatal stroke = 0.37*.
Folsom <i>et al.</i> (1995)	ICCS	41 837 women, 90 fatal strokes during 6 yrs follow-up. RR in HRT users = 1.3.
Sourander <i>et al.</i> (1998)	ICCS	7944 women, 111 strokes during 8 yrs follow-up. RR in ERT users = 0.86.
Fung <i>et al.</i> (1999)	ICCS	1031 older women, 57 strokes/TIA during 8.8 yrs follow-up. RR for stroke death in HRT users = 0.92, RR for non-fatal stroke and TIA = 3.0.
Rodriguez <i>et al.</i> (2001)	ICCS	290 827 women, 2390 stroke fatalities during 12 yrs follow-up. RR for stroke death in HRT users = 0.82 (borderline significance).
Grodstein <i>et al.</i> (2000)	ICCS	70 533 women, 767 strokes during 20 yrs follow-up. RR for HRT users = 1.13, but increased with dosage of E (0.54 for the 0.3 mg CEE, 1.35 for the 0.625 mg, 1.63 for the 1.25 mg). RR for ischaemic stroke in current users = 1.26*. RR for CEE only = 1.18; RR for CEE+Progestin = 1.45*.

UCCS = Uncontrolled cohort study; CCS = Case-controlled study; ICCS = Internally controlled cohort study. * $P < 0.05$.
CEE = conjugated equine estrogen; E = estradiol; P = progesterone; RR = relative risk; TIA = transient ischaemic attack.

Canadian Co-operative Study Group, 1986). Others (Viscoli *et al.*, 2001) recently published data from the Women's Estrogen for Stroke Trial (WEST). A total of 652 post-menopausal women with stroke/TIA within 90 days of entry were randomized to estradiol at 1 mg/day or placebo. The follow-up period was 3 years, and drug compliance was 76% at year 1. Non-fatal stroke, death rate and adverse events were similar for both groups. The relevant results on stroke obtained in the HERS trial (Simon *et al.*, 2001) will be mentioned later, as this was a secondary prevention trial in women with known coronary artery disease at baseline, but no history of cerebrovascular disease. A recent Medline and web search on HRT in stroke patients was largely unproductive because of a paucity of information (Damczyk and Gardner, 2000). The authors concluded that there are no data available which specifically examine the value and safety of HRT use in women with a history of stroke.

Recent data from major epidemiological studies

It should be noted that the characteristics of a cohort, its sample size and methodology differed from study to study on stroke risk and HRT in the menopause, and this perhaps explains the diversity of results obtained in those trials. To resolve this uncertainty about a possible benefit of HRT in the

prevention of cerebral events, one of the following two investigations would be needed: either a very long-term observational study on a very large cohort; or (preferably) a double-blind, placebo-controlled study. Fortunately, three reports have been published during the past 12 months, which may fit the above specifications.

The first summarizes the latest experience from the Nurses' Health Study, which is a primary prevention observational trial (Grodstein *et al.*, 2000). The data were derived from biennial questionnaires filled by more than 70 000 female nurses who were followed-up since 1976. This study is unique in its scope, as 767 strokes were identified during a 20-year follow-up. The main findings of the study were as follows:

1. Overall, there was little association between current use of hormone and stroke risk, but the relative risk for ischaemic stroke was 1.23.

2. Relative risk correlated with dosage of conjugated equine estrogen: 0.54 for the 0.3 mg daily dose, 1.35 for the standard 0.625 mg daily dose, and 1.63 for the 1.25 mg daily dose. This means that only the low-dose estrogen was protective, while most of the women were exposed to a higher risk of stroke because of HRT.

3. Relative risk for the use of estrogen only was 1.18, whereas relative risk for combined estrogen-progestin was 1.45. It should

be noted that the cardioprotective effect of estrogen was similar for both the small and standard doses.

The Cancer Prevention Study II addressed cardiovascular mortality in healthy post-menopausal women (Rodriguez *et al.*, 2001). Women with significant diseases or incomplete data regarding their menopause were excluded. The cohort was huge (about 290 000 participants) and the follow-up period was 12 years. There were 12% ever-users of hormones and 22% past users. During follow-up, about 31 000 women died, 2390 from stroke; hormone use was associated with a 19% reduction in stroke risk.

The above two studies were primary prevention observational trials. A recent publication from the HERS Study, a secondary prevention double-blind, placebo-controlled trial, investigated women in late menopause with proven coronary artery disease during a follow-up period of 4.1 years (Simon *et al.*, 2001). Women who were included in the hormone treatment arm were assigned to receive a continuous combined regimen of conjugated equine estrogen at 0.625 mg plus medroxyprogesterone acetate at 2.5 mg daily. A total of 149 women suffered a stroke, and 85% of the strokes were ischaemic. Although increasing age, hypertension, atrial fibrillation and current smoking were risk factors for stroke, HRT was not significantly associated with risk for stroke. However, there were six more fatal strokes and 10 more non-fatal strokes among hormone users, leading to a 2% absolute difference in stroke risk between the hormone and placebo groups. One additional study was of interest (Angeja *et al.*, 2001) in which the occurrence of in-hospital strokes immediately following acute myocardial infarction in women was examined. The cohort included 114 724 women aged 55 years or older, of whom 0.9% suffered an ischaemic stroke. When stratified by hormone use, the rate was similar for both users and non-users.

Conclusions

During the past year, the issue of post-menopausal hormone use and stroke risk was discussed in an overview (Paganini-Hill, 2001), an editorial (Tolbert and Oparil, 2001), and two statements from the American Heart Association (Goldstein *et al.*, 2001; Mosca *et al.*, 2001). All of these authors reached the same conclusions. It seems that, despite ample animal data being available on neuroprotection by estrogen, plus the beneficial effects of estrogen on risk profile for cardiovascular disease, plus the vasodilatory properties due to endothelial and non-endothelial mechanisms, the conclusion remains somewhat unclear, disappointing and confusing because of the non-uniform results in the major studies. In addition, there is a lack of high-quality, randomized, double-blind studies on this important issue. The data on primary prevention are derived from observational studies, which are subject to bias. Despite the large numbers of women evaluated in those studies, modern epidemiology is looking for results from evidence-based medicine. Although it is felt that observational trials are valuable, the paucity of controlled studies unfortunately leaves unanswered the question of whether HRT reduces the risk of stroke. At early stages, the development of carotid and cerebral atherosclerosis might be influenced by hormones, and so long-term hormone users might have fewer ischaemic strokes. Also, there is no clear basis for an assumption that HRT affects the progression of established carotid athero-

sclerosis or changes the risk in women who have already suffered cerebrovascular events. Recent studies on coronary artery disease and cerebrovascular disease point at a possible role for the type and dosage of hormone regimens. We support the current consensus of opinion that HRT should not be considered as a specific measure for primary or secondary prevention of stroke. Protection from ischaemic stroke should comprise proven risk reduction strategies, such as aggressive treatment of blood pressure, prescribing aspirin, tight glycaemic control and cessation of smoking (Goldstein *et al.*, 2001).

Acknowledgements

The authors acknowledge Prof. Henry Burger, Monash Medical Centre, Melbourne, for his valuable comments while preparing the manuscript.

References

- Al-Delaimy, W.K., Willett, W.C., Manson, J.E. *et al.* (2001) Smoking and mortality among women with type 2 diabetes. The Nurses' Health study cohort. *Diabetes Care*, **24**, 2043–2048.
- Alkayed, N.J., Murphy, S.J., Traystman, R.J. *et al.* (2000) Neuroprotective effects of female gonadal steroids in reproductively senescent female rats. *Stroke*, **31**, 161–168.
- Amarenco, P. (2001) Hypercholesterolemia, lipid lowering agents, and the risk for brain infarction. *Neurology*, **57** (Suppl. 2), S35–S44.
- Angeja, B.G., Shlipak, M.G., Go, A.S. *et al.* (2001) Hormone therapy and the risk for stroke after acute myocardial infarction in postmenopausal women. *J. Am. Coll. Cardiol.*, **38**, 1297–1301.
- Angerer, P., Stork, S., Kothny, W. *et al.* (2001) Effect of oral postmenopausal hormone replacement on progression of atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.*, **21**, 262–268.
- Baron, Y.M., Galea, R. and Brincat, M. (1998) Carotid artery wall changes in estrogen-treated and -untreated postmenopausal women. *Obstet. Gynecol.*, **91**, 982–986.
- Belfort, M.A., Saade, G.R., Snabes, M. *et al.* (1995) Hormonal status affects the reactivity of cerebral vasculature. *Am. J. Obstet. Gynecol.*, **172**, 1273–1278.
- Biller, J. and Love, B.B. (1993) Diabetes and stroke. *Med. Clin. North Am.*, **77**, 95–110.
- Bonita, R. (1992) Epidemiology of stroke. *Lancet*, **339**, 342–344.
- Bousser, M.G. (1999) Stroke in women. The 1997 Paul Dudley White International Lecture. *Circulation*, **99**, 463–467.
- Bronner, L.L., Kanter, D.S. and Manson, J.E. (1995) Primary prevention of stroke. *N. Engl. J. Med.*, **333**, 1392–1400.
- Brown, R.D., Jr, Wisnant, J.P., Sicks, J.R.D. *et al.* (1996) Stroke incidence, prevalence and survival. *Stroke*, **27**, 373–380.
- Bushnell, C.D., Samsa, G.P. and Goldstein, L.B. (2001) Hormone replacement therapy and ischemic stroke severity in women: case-control study. *Neurology*, **22**, 1304–1307.
- Clarkson, T.B., Anthony, M.S. and Morgan, T.M. (2001) Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens. *J. Clin. Endocrinol. Metab.*, **86**, 41–47.
- Colditz, G.A., Bonita, R., Stampfer, M.J. *et al.* (1988) Cigarette smoking and risk of stroke in middle-aged women. *N. Engl. J. Med.*, **318**, 937–941.
- Collins, R., Peto, R., MacMahon, S. *et al.* (1990) Blood pressure, stroke, and coronary heart disease, part 2: short-term reduction in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet*, **335**, 827–838.
- Cummings, S.R., Black, D.M. and Rubin, S.M. (1989) Lifetime risks of hip, Colles, or vertebral fracture and coronary heart disease among white postmenopausal women. *Arch. Intern. Med.*, **149**, 2445–2448.
- Damczyk, M.P. and Gardner, D.M. (2000) Risk of hormone replacement therapy in stroke patients. *J. Clin. Pharm. Ther.*, **25**, 239–241.
- Darj, E., Bakos, O., Naessen, T. *et al.* (1999) Ultrasonographic blood flow measurement in the carotid arteries in postmenopausal women. *Gynecol. Obstet. Invest.*, **47**, 20–25.
- Davidson, M.H., Maki, K.C., Marx, P. *et al.* (2000) Effects of continuous estrogen and estrogen-progestin replacement regimens on cardiovascular

- risk markers in postmenopausal women. *Arch. Intern. Med.*, **160**, 3315–3325.
- Dobs, A.S., Nieto, F.J., Szklo, M. *et al.* (1999) Risk factors for popliteal and carotid wall thickness in the Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Epidemiol.*, **150**, 1055–1067.
- Dubal, D.B. and Wise, P.M. (2001) Neuroprotective effects of estradiol in middle-aged female rats. *Endocrinology*, **142**, 43–48.
- Dubal, D.B., Kashon, M.L., Pettigrew, L.C. *et al.* (1998) Estradiol protects against ischemic injury. *J. Cereb. Blood Flow Metab.*, **18**, 1253–1258.
- Dubal, D.B., Zhu, H., Yu, J. *et al.* (2001) Estrogen receptor α , not β , is a critical link in estradiol-mediated protection against brain injury. *Proc. Natl. Acad. Sci. USA.*, **98**, 1952–1957.
- Elkind, M.S. and Sacco, R.L. (1998) Stroke risk factors and stroke prevention. *Semin. Neurol.*, **18**, 429–439.
- Falkeborn, M., Persson, I., Terent, A. *et al.* (1993) Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. *Arch. Intern. Med.*, **153**, 1201–1209.
- Finucane, F.F., Madans, J.H., Bush, T.L. *et al.* (1993) Decreased risk of stroke among postmenopausal hormone users. Results from a national cohort. *Arch. Intern. Med.*, **153**, 73–79.
- Flora, G.C., Baker, A.B., Loewenson, R.B. *et al.* (1968) A comparative study of cerebral atherosclerosis in males and females. *Circulation*, **38**, 859–869.
- Folsom, A.R., Mink, P.J., Sellers, T.A. *et al.* (1995) Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am. J. Public Health*, **85**, 1128–1132.
- Fung, M.M., Barrett-Connor, E. and Bettencourt, R.R. (1999) Hormone replacement therapy and stroke risk in older women. *J. Women's Health*, **8**, 359–364.
- Gangar, K.F., Vyas, S., Whitehead, M. *et al.* (1991) Pulsatility index in internal carotid artery in relation to transdermal oestrogen correlates with time since menopause. *Lancet*, **338**, 839–842.
- Gillum, L.A., Mamidipudi, S.K. and Johnston, S.C. (2000) Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA*, **284**, 72–78.
- Goldstein, L.B., Adams, R., Becker, K. *et al.* (2001) Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation*, **103**, 163–182.
- Gorelick P.B., Sacco R.L., Smith, D.B. *et al.* (1999) Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*, **281**, 1112–1120.
- Grady, D., Rubin, S.M., Petiti, D.B. *et al.* (1992) Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann. Intern. Med.*, **117**, 1016–1037.
- Griewing, B., Romer, T., Spitzer, C. *et al.* (1999) Hormone replacement therapy in postmenopausal women: carotid intima-media thickness and 3-D volumetric plaque quantification. *Maturitas*, **32**, 33–40.
- Grodstein, F., Stampfer, M.J., Manson, J.E. *et al.* (1996) Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N. Engl. J. Med.*, **335**, 453–461.
- Grodstein, F., Manson, J.E., Colditz, G.A. *et al.* (2000) A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann. Intern. Med.*, **133**, 933–941.
- Herbert, P.R., Gaziano, J.M. and Hennekens, C.H. (1995) An overview of trials of cholesterol lowering and risk of stroke. *Arch. Intern. Med.*, **155**, 50–55.
- Hjortland, M.C., McNamara, P.M. and Kannel, W.B. (1976) Some atherogenic concomitants of menopause: the Framingham study. *Am. J. Epidemiol.*, **103**, 304–311.
- Hodis, H.N., Mack, W.J., Lobo, R.A. *et al.* (2001) Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.*, **135**, 939–953.
- Hurn, P.D. and Macrae, I.M. (2000) Estrogen as a neuroprotectant in stroke. *J. Cereb. Blood Flow Metab.*, **20**, 631–652.
- Joakimsen, O., Bonna, K.H., Stensland-Bugge, E. *et al.* (2000) Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis. The Tromsø study. *J. Clin. Epidemiol.*, **53**, 525–530.
- Jonas, H.A., Kronmal, R.A., Psaty, B.M. *et al.* (1996) Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. *Ann. Epidemiol.*, **6**, 314–323.
- Landahl, S., Bengtsson, C., Sigurdsson, J.A. *et al.* (1986) Age-related changes in blood pressure. *Hypertension*, **8**, 1044–1049.
- Lindquist, O. (1982) Intraindividual changes of blood pressure, serum lipids, and body weight in relation to menstrual status: results from a prospective population study of women in Goteborg, Sweden. *Prev. Med.*, **11**, 162–172.
- Luoto, R., Manolio, T., Meilahn, E. *et al.* (2000) Estrogen replacement therapy and MRI-demonstrated cerebral infarcts, white matter changes, and brain atrophy in older women: the Cardiovascular Health Study. *J. Am. Geriatr. Soc.*, **48**, 467–472.
- Manolio, T.A., Furberg, C.D., Shemanski, I. *et al.* (1993) Association of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. *Circulation*, **88**, 2163–2171.
- Manolio, T.L., Kronmal, R.A., Burke, G.L. *et al.* (1996) Short-term predictors of incident stroke in older adults. *Stroke*, **27**, 1479–1486.
- Manson, J.E., Colditz, G.A., Stampfer, M.J. *et al.* (1991) A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch. Intern. Med.*, **151**, 1141–1147.
- Matthews, K.A., Kuller, L.H., Sutton-Tyrrell, K. *et al.* (2001) Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. *Stroke*, **32**, 1104–1111.
- McEwen, B.S. (2001) Invited review. Estrogens effects on the brain: multiple sites and molecular mechanisms. *J. Appl. Physiol.*, **91**, 2785–2801.
- McGrath, B.P., Liang, Y.L., Teede, H. *et al.* (1998) Age-related deterioration in arterial structure and function in postmenopausal women: impact of hormone replacement therapy. *Arterioscler. Thromb. Vasc. Biol.*, **18**, 1149–1156.
- Mendelsohn, M.E. and Karas, R.H. (1999) The protective effects of estrogen on the cardiovascular system. *N. Engl. J. Med.*, **340**, 1801–1811.
- Mercurio, G., Zoncu, S., Pilia, I. *et al.* (1997) Effects of acute administration of transdermal estrogen on postmenopausal women with systemic hypertension. *Am. J. Cardiol.*, **80**, 652–654.
- Miall, W.E. and Lovell, H.G. (1977) Relation between change of blood pressure and age. *Br. Med. J.*, **2**, 660–664.
- Mosca, L., Collins, P., Herrington, D.M. *et al.* (2001) AHA Scientific Statement. Hormone replacement therapy and cardiovascular disease. *Circulation*, **104**, 499–503.
- Nabulsi, A.A., Folsom, A.R., Szklo, M. *et al.* (1996) No association of menopause and hormone replacement therapy with carotid intima-media thickness. *Circulation*, **94**, 1857–1863.
- Naessens, T. and Bakos, O. (2001) Carotid vascular resistance in long-term estrogen users. *Obstet. Gynecol.*, **97**, 327–332.
- NAMS Consensus Opinion (2000) Effects of menopause and estrogen replacement therapy or hormone replacement therapy in women with diabetes mellitus: consensus opinion of the North American Menopause Society. *Menopause*, **7**, 87–95.
- Ohkura, T., Teshima, Y., Isse, K. *et al.* (1995) Estrogen increases cerebral and cerebellar blood flow in postmenopausal women. *Menopause*, **2**, 13–18.
- Paganini-Hill, A. (1995) Estrogen replacement and stroke. *Prog. Cardiovasc. Dis.*, **38**, 223–242.
- Paganini-Hill, A. (2001) Hormone replacement therapy and stroke: risk, protection or no effect? *Maturitas*, **38**, 243–261.
- Pederson, A.T., Lidsgaard, O., Kreiner, S. *et al.* (1997) Hormone replacement therapy and risk of nonfatal stroke. *Lancet*, **350**, 1277–1283.
- Penotti, M., Nencioni, T., Gabrielli, L. *et al.* (1993) Blood flow variations in internal carotid and middle cerebral arteries induced by postmenopausal hormone replacement therapy. *Am. J. Obstet. Gynecol.*, **169**, 1226–1232.
- Penotti, M., Farina, M., Gabrielli, L. *et al.* (1996a) Gonadotropin-releasing hormone agonist-induced hypoestrogenism and blood flow in cerebral arteries. *Fertil. Steril.*, **66**, 240–243.
- Penotti, M., Farina, M., Castiglioni, E. *et al.* (1996b) Alteration in the pulsatility index values of the internal carotid and middle cerebral arteries after suspension of postmenopausal hormone replacement therapy: a randomized crossover study. *Am. J. Obstet. Gynecol.*, **175**, 606–611.
- Penotti, M., Sironi, L., Castiglioni, E. *et al.* (1999) Blood flow in the internal carotid and middle cerebral arteries: effect of continuous conjugated equine estrogens administration with monthly progestogen supplementation on postmenopausal women. *Menopause*, **6**, 225–229.
- Petititi, D.B., Sidney, S., Quesenberry, C.P., Jr *et al.* (1998) Ischemic stroke and the use of estrogen and estrogen/progestogen as hormone replacement therapy. *Stroke*, **29**, 23–28.
- Pfeffer, R.I. (1978) Estrogen use, hypertension and stroke in postmenopausal women. *J. Chron. Dis.*, **31**, 389–398.
- Pines, A., Fisman, E.Z., Drory, Y. *et al.* (1998) The effects of sublingual estradiol on left ventricular function at rest and exercise in postmenopausal women: an echocardiographic assessment. *Menopause*, **5**, 79–85.
- Prospective Study Collaboration (1995) Cholesterol, diastolic blood pressure and stroke: 13000 strokes in 450,000 people in 45 prospective cohorts. *Lancet*, **346**, 1647–1653.

- Rodriguez, C., Calle, E.E., Patel, A.V. *et al.* (2001) Effect of body mass on the association between estrogen replacement therapy and mortality among elderly US women. *Am. J. Epidemiol.*, **153**, 145–152.
- Rosenthal, T. and Oparil, S. (2000) Hypertension in women. *J. Hum. Hypertens.*, **14**, 691–704.
- Sacco, R.L., Benjamin, E.J., Broderick, J.P. *et al.* (1997) American Heart Association Prevention Conference IV: prevention and rehabilitation of stroke: risk factors. *Stroke*, **28**, 1507–1517.
- Schairer, C., Adami, H.-O., Hoover, R. *et al.* (1997) Cause-specific mortality in women receiving hormone replacement therapy. *Epidemiology*, **8**, 59–65.
- SHEP Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older patients with isolated systolic hypertension. *JAMA*, **265**, 3255–3264.
- Shinozaki, K., Naritomi, H., Shimizu, T. *et al.* (1996) Role of insulin resistance associated with compensatory hyperinsulinism in ischemic stroke. *Stroke*, **27**, 37–43.
- Shinton, R. and Beevers, G. (1989) Meta-analysis of relation between cigarette smoking and risk of stroke in middle-aged women. *Br. Med. J.*, **298**, 789–794.
- Sigurdsson, J.A. (1983) High blood pressure in women: a cross-sectional and a longitudinal follow-up study. *Acta Med. Scand.*, **669** (Suppl.), 1–39.
- Simon, J.A., Hsia, J., Cauley, J.A. *et al.* (2001) Postmenopausal hormone use and the risk of stroke. The Heart and Estrogen/progestin Replacement Study (HERS). *Circulation*, **103**, 638–642.
- Sourander, L., Rajala, T., Raiha, I. *et al.* (1998) Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). *Lancet*, **352**, 1965–1969.
- Spencer, C.P., Godsland, I.F. and Stevenson, J.C. (1997) Is there a menopausal metabolic syndrome? *Gynecol. Endocrinol.*, **11**, 341–355.
- Staessen, J., Bulpitt, C.J., Fagard, R. *et al.* (1989) The influence of menopause on blood pressure. *J. Hum. Hypertens.*, **3**, 427–433.
- Teede, H.J., McGrath, B.P., Smolich, J.J. *et al.* (2000) Postmenopausal hormone replacement therapy increases both coagulation activity and fibrinolysis. *Arterioscler. Thromb. Vasc. Biol.*, **20**, 1404–1409.
- The American-Canadian Co-Operative Study Group (1986) Persantine aspirin trial in cerebral ischemia – Part III: risk factors for stroke. *Stroke*, **17**, 12–18.
- Tolbert, T. and Oparil, S. (2001) Hormone replacement therapy and stroke: are the results surprising? *Circulation*, **103**, 620–622.
- UK PDS Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UK PDS 38. *Br. Med. J.*, **317**, 703–713.
- Viscoli, C.M., Brass, L.M., Kernan, W.M. *et al.* (2001) Estrogen after ischemic stroke: effect of estrogen replacement on risk of recurrent stroke and death in the Women's Estrogen for Stroke Trial (WEST). *Stroke*, **32**, 329 (abstract).
- Wang, S.L., Pan, W.H., Lee, M.C. *et al.* (2000) Predictors of survival among elders suffering strokes in Taiwan: observation from a nationally representative sample. *Stroke*, **31**, 2354–2360.
- Wilson, P.W., Garrison, R.J. and Castelli, W.P. (1985) Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: The Framingham Study. *N. Engl. J. Med.*, **313**, 1038–1043.
- Wise, P.M., Dubal, D.B., Wilson, M.E. *et al.* (2001) Minireview: Neuroprotective effects of estrogen – new insights into mechanism of action. *Endocrinology*, **142**, 969–973.
- Writing Group for the PEPI Trial (1995) Effects of estrogen and estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA*, **273**, 199–208.

Submitted on October 3, 2001; accepted on January 11, 2002