Hormone-replacement therapy, dementia and stroke

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Hormone-replacement therapy (HRT) has been used for more than 40 years to reduce perimenopausal symptoms. Estrogens may protect brain structures and functional systems affected by Alzheimer's disease, which suggests that maintaining high levels of hormones with HRT can protect against Alzheimer's disease. Moreover, high premenopausal estrogen concentrations are thought to be protective against stroke and, consequently, in the past, HRT was considered to be a potential protective agent against stroke. However, large clinical trials have failed to demonstrate a benefit from HRT on either cognitive performance or risk of dementia. In addition, although HRT has been associated with a reduction in the risk of heart disease in observational studies, results regarding stroke have been less clear. Recently, evidence has shown that HRT does not reduce but actually increases vascular risk. Here, the data from the most important studies are examined, concluding that HRT has no beneficial effect on dementia or stroke risk reduction in postmenopausal women.

Hormone-replacement therapy (HRT), originally used to reduce perimenopausal symptoms, such as vasomotor sweats, hot flashes and genitourinary changes, consists of estrogen therapy alone or with progesterone. Estrogens have a hypothesized role in protecting the brain structures and functional systems affected in Alzheimer's disease (AD), suggesting that maintaining high levels of hormones in women with HRT may protect against AD. Postmenopausal women have been reported to have a greater risk of developing AD than men [1]. Women appear to be protected from heart disease and stroke before menopause. One explanation could relate to women's lower endogenous estrogen levels after menopause [2]. Stroke is a major contributor to long-term disability and is the third leading cause of death among postmenopausal women in developed countries, after coronary heart disease (CHD) and cancer. Stroke occurs at an older age in women compared with men, and women have poorer reported outcomes from stroke than men. In both sexes, stroke is the second leading cause of dementia, after AD. Cerebral vascular and coronary artery disease have common AD risk factors: hypertension, hyperlipidemia, elevated homocysteinemia serum levels and vascular factors [3].

Keywords: dementia, estrogen, hormone-replacement therapy, menopause, stroke, women

Dementia & women

It is estimated that, by 2050, approximately 13 million men and women worldwide will be affected by AD. To date, however, treatment has failed to produce any significant benefits. With this reality, a better understanding of the risk factors responsible for cognitive impairment is an utmost public health priority.

The prevalence of AD is greater for women than men [4], in large part due to longevity and survival differences favoring women. Even so, some studies have suggested that incidence rates may also be higher for women [5]. However, women have a higher risk of developing AD than men [6,7] and their age-specific prevalence of AD is twice as high [8].

One hypothesis for this is that women have lower endogenous estrogen levels after menopause [2]. Natural menopause occurs at a median age of approximately 51 years; the incidence of AD increases with age but is very low for women in their 50s [6,7,9,10]. In addition, postmenopause women have much lower gonadal hormone levels than men [11].

Estrogens have a potential role in maintaining brain structures and protecting functional systems that are compromised in AD, suggesting that maintaining high levels of hormones in women with HRT protects against AD. However, recent reviews have reported findings contradictory to this thinking. Specifically, the most widely used HRT, premarin, failed to protect against the progression of AD or treat its symptoms [12–14].

Stroke & women

Women are believed to be protected from stroke and heart disease before menopause because of the protective effects of ovarian hormones. These

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protective effects could hold indications for preventing stroke and ischemic vascular disease. The idea of using estrogen as a stroke therapy is based on certain lines of evidence: the observation that ischemic stroke caused by atherosclerosis is uncommon in women before menopause; this is thought to be because of the protective effects of ovarian hormones. Animal data suggest that HRT may have beneficial effects for the prevention of vascular disease. Human studies document beneficial effects. Most epidemiological studies on cardiac disease suggest that women using HRT have 25–50% lower rates of cardiovascular disease [15].

Population-based studies have demonstrated that women of any age have a lower risk of stroke compared with men. In addition, women are less likely to have conventional vascular risk factors [16]. Finally, there are stroke risk factors specifically associated with women, which include pregnancy [17], oral contraceptive use [18,19] and the use of exogenous hormonal treatment for menopausal symptoms. However, since the risk of stroke increases with age and women on average currently live 5–10 years longer than men, their overall burden of stroke is higher. Lifetime epidemiological studies have consistently reported increases in stroke severity and fatal stroke in women, leading to death in one in six women compared with one in 12 men [20–23].

Even after factoring in an adjustment for age, women have reported poorer outcomes compared with men and both a higher incidence of pre- and post-stroke disabilities and a much higher likelihood of being admitted to nursing facilities [23].

After AD, stroke is the second leading cause of dementia when women and men are considered together; however, in the subgroup of elderly women aged 85 years and over it ranks as the first cause, before AD [24].

Role of estrogens & experimental studies

Estrogens are essential for normal reproductive function and exert diverse nonreproductive actions on multiple tissues, such as neuroprotective effects, vasodilatation, improved vascular reactivity, angiogenic effects, anti-thrombotic effects, enhanced neurogenesis and axonal sprouting after injury, and lipid-lowering effects. Moreover, the brain is a recognized target for estrogen and other gonadal steroids. In fact, subsets of neurons possess intranuclear receptors for estrogen [25].

Estrogens are neuroprotective against numerous insults (oxidative stress, excitatory neurotoxicity and ischemia) [26,27] and can promote the growth of nerve processes [28] and modulate synaptic plasticity [29]. Other benefits include an improvement in cerebral blood flow [30], enhanced glucose transport into the brain [31] and a reduction in β-amyloid formation [32]. Furthermore, estrogens are able to positively enhance neurotransmitter functions, which are known to decline with ageing and dementia [33–35]. In addition, they can foster the outgrowth of dendritic spines [36,37] and protect neurons against oxidative stress, both directly and indirectly via actions on the vascular system [38–40]. However, this evidence supporting the neuroprotecting benefit of estrogens has come principally from studies on animals.

Experimental evidence from these studies indicates that estrogen modulates production of endothelium-derived factors, including nitric oxide, angiotensin-converting enzyme, cyclooxygenase metabolites of arachidonic acid (prostacylcin and thromboxane), endothelin-1, endothelium-derived hyperpolarizing factor, natriuretic peptides, superoxide radicals and tissue factor pathway inhibitor [41]. These varied actions of estrogen on the endothelium may, in part, explain the differences in the efficacy of cardiovascular prophylactic therapies, such as aspirin and angiotensin-converting enzyme inhibitors, between men and women [42]. This is plausible given that the modulation of endothelium-derived growth factor production induced by estrogen favors vasodilatory and antimitogenic factors [43].

Results from numerous studies using animal models and *in vitro* cell and explant cultures, observational studies performed with human populations and clinical trials have led to the belief that ovarian hormones play an important role in protecting against neurodegenerative diseases. However, these benefits related to HRT in postmenopausal women have come under attack because of the seemingly contradictory results reported by the Women's Health Initiative (WHI) [44–47].

In contrast to their apparent neuroprotection, estrogens (with or without progestin) increase inflammation, which is a proposed stroke risk mechanism. Furthermore, opponents of estrogen therapy hold that the accumulation of estrogens in the liver induces metabolic modifications comparable to those during pregnancy [48,49]. These modifications are increased triglycerides, linked to a decrease in the size of low-density lipoprotein particles, higher levels of C-reactive protein and activation of coagulation [48–55].

Thus, there is a risk that oral administration reduces, not increases, the anti-atherogenic effects of estradiol, thereby increasing the risk of venous and arterial thromboembolism. According to this hypothesis, the main source of hormone-dependent cardiovascular benefits is not the hepatocyte but the arterial endothelium, which is estradiol dependent in women [56–62]. Given this, the choice of progestin is important, not so much for the control of the hepatic metabolism of cholesterol but for the progestin estradiol agonistic or antagonistic effects on endothelial function that are also progesterone dependent [63–69]. In addition, there is an increased risk of venous thromboembolism in postmenopausal women [44,70–72]. Several studies have associated the incidence of stroke with an increased concentration of C-reactive protein [73]. However, concentrations of these inflammatory markers were not significantly increased by the use of HRT in women with heart disease. At low doses, estrogen has been reported to have an anti-inflammatory effect, while at the standard replacement doses, it is believed to have a proinflammatory effect [74].

Regarding cognition, estrogen receptors are expressed in the forebrain cholinergic neurons, which are involved in learning and memory and are specifically affected by pathological changes in AD. Luine evidenced an increased choline acetyltransferase activity after estrogen treatment in female rats [35]. This could point to a potential protective estrogen effect from hormonal treatment able to improve dementia symptoms and/or reduce AD risk. On the other hand, some estrogen actions might be harmful. In fact, proinflammatory effects could be deleterious [75] and prothrombotic properties of some estrogens could adversely affect the cerebral vasculature [76].

Hormone-replacement therapy

HRT, consisting of estrogen therapy with or without progesterone, was originally used to relieve symptoms of menopause, such as hot flashes and genitourinary changes. Additional benefits were subsequently observed, including the reduced risks of osteoporosis, CHD and AD [77,78]. HRT has been increasingly promoted over the last 40 years to improve quality of life and to reduce the risks of osteoporotic fractures and CHD.

However, in recent years, observational studies, randomized trials and systematic reviews of such trials have shown that HRT does not reduce, but actually increases, vascular risk. HRT increases the relative risks of venous thromboembolism (twofold) and of fatal or disabling stroke (by 50%). Although the use of HRT is associated with a roughly 50% reduction in the risk of heart disease in observational studies, the results regarding stroke have been less clear.

The rational for HRT in preventing stroke was originally based upon the following facts: women have a lower risk of stroke before menopause, atherosclerosis strokes are rarer before menopause and estrogens have protective effects on lipids and vascular tone. All of this was thought to be correlated with the elevated levels of estrogen in women before menopause [79–83]. The findings from both arms of the WHI suggest that oral HRT, whether combined or unopposed, is thrombogenic, not only in the venous circulation, but also in the arterial circulation [47,84].

Gray and Bath have recently carried out a systematic review of data from 11 randomized, controlled trials of HRT, involving 23,310 subjects [85]. Here, HRT was associated with an increase in stroke risk, with an odds ratio (OR) of 1.30 (95% confidence interval [CI]: 1.09–1.54). More importantly, for fatal or disabling stroke, the OR was 1.56 (95% CI: 1.11–2.20; three trials). This HRT-associated stroke risk was confined to ischemic stroke, while hemorrhagic stroke was not observed. There was no reported heterogeneity among studies and the effect sizes appeared similar for opposed and unopposed HRTs.

Observational studies have suggested that postmenopausal HRT may improve cognitive function, but data from randomized clinical trials have been inconclusive. The effects of HRT on dementia and mild cognitive impairment (MCI) were assessed in a subgroup of the Women's Health Initiative Memory Study (WHIMS), a multicenter, randomized, double-blind, placebo-controlled clinical trial [46]. Conjugated equine estrogens (CEEs) with or without medroxyprogesterone acetate (MPA) did not show any protection against dementia, but instead a substantial increase due to any cause or cognitive decline. The incidence of probable dementia in the estrogen-alone trial was statistically similar to that of the estrogen plus progestin trial. When data from both trials were pooled, the overall risk for probable dementia was increased by 76% (hazard ratio [HR]: 1.76; 95% CI: 1.19–2.60; $p = 0.005$). A second report from WHIMS suggested that cognitive decline in women aged 65 years and older was greater in those receiving HRT than in those receiving placebo (HR: 1.25; 95% CI: 0.97–1.60).

Observational studies

In one of the first observational studies investigating the effects of HRT on stroke risk in postmenopausal women, Grady *et al.* derived a summary relative risk (RR) of stroke in estrogen-replacement therapy (ERT) users of 0.96 (95% CI: 0.82–1.13) and went on to point out that there was evidence of statistical heterogeneity among the studies reviewed [86].

Most of the initial epidemiological studies tended to group all stroke subtypes together and often the only comparison made was between users and nonusers of estrogen. Dosage duration and estrogen type were rarely specified.

Numerous epidemiological studies have reported a reduced risk of cardiovascular disease among postmenopausal women who use ERT [87]. In these studies, the risk of CHD was reported to be reduced by 30–50%, leading to speculation that estrogen may reduce stroke risk, because of the many shared risk factors between stroke and CHD. Furthermore, ovariectomy may increase the risk of both CHD and cerebrovascular disease [88].

The Framingham Heart Study investigated the effects of estrogen use on morbidity from cardiovascular disease in 1234 postmenopausal women, aged 50–83 years, and reported a significantly increased risk of stroke (RR: 2.6) in estrogen users [89]. The medication history recorded at biennial examinations eight through to 12 was used to classify the degree of estrogen exposure before 8 years of observation for cardiovascular morbidity and mortality. Despite a favorable cardiovascular risk profile and controls for the major known risk factors for heart disease, women reporting postmenopausal estrogen use at one or more examinations had over a 50% elevated risk of cardiovascular morbidity ($p < 0.01$) and more than a twofold risk of cerebrovascular disease ($p < 0.01$) after the index examination. Increased rates for myocardial infarction ($p < 0.05$) were observed, particularly among the estrogen users who smoked. Conversely, among nonsmokers, estrogen use was only associated with an increased incidence of stroke ($p < 0.05$). No benefits from estrogen use were observed in the study group. In particular, between estrogen users and nonusers, mortality from all causes and CHD did not differ. Further uncontrolled cohort studies reported a 20–50% reduced risk in HRT users [90–93], two of which were significant [92,93].

The Nurses' Health Study reported a limited association between all stroke types and the current use of oral conjugated estrogen alone (RR: 1.2), but did report a 45% significantly higher stroke risk among women receiving combined estrogen plus progestin versus those who had never taken HRT [94].

In a study by Cairu *et al.*, the risk of first-ever stroke among 16,906 middle-aged and older women taking HRT was examined and the potential factors that may modify the risk of stroke among HRT users were investigated [95]. No significant association between HRT and the risk of total stroke in women during the 10.5-year follow-up was reported. However, the preparation of estrogens and time of treatment initiation may have affected the risk of stroke.

Of the 16,906 subjects, 2148 (12.7%) took HRT. A total of 461 strokes occurred during follow-up, 48 of these in HRT users. Incidence of total stroke and ischemic subtype had no significant relation to HRT use. However, an increased risk of hemorrhagic stroke (50–70%) was found in women receiving unopposed estrogen (RR: 2.55; 95% CI: 1.03–6.35) or un-native estrogen regimens (RR: 4.27; 95% CI: 1.71–10.66). Although not significant, the risk of stroke was 33% lower in women who had started their treatment before menopause. Among HRT users, the risk of stroke was associated with advancing age, smoking, excess body weight and hypertension. Covariate-adjusted analyses showed that women using unopposed estrogen had more than a twofold increased risk of hemorrhagic stroke. Notwithstanding this, the pattern of HRT had no apparent relation to ischemic stroke. The risk of stroke was lower among women who had initiated therapy before menopause compared with nonusers (RR: 0.67; 95% CI: 0.28–1.62). Furthermore, this risk of stroke was higher in the women who had started treatment after menopause. The risk factors for stroke were examined among HRT users and the risk of first-ever stroke was seen to be significantly associated with advancing age, waist circumference, BMI and current smoking. Compared with users with normal blood pressure, the risk of stroke showed a fivefold increase in those with blood pressure 160/110 mmHg or higher. Furthermore, no significant association between HRT and risk of total stroke in women over the 10.5-year follow-up was observed.

Initial studies reported a positive association between exogenous estrogen and cognitive performance in older women with dementia. Meta-analyses of the potentially protective effects of estrogen against dementia reported a risk reduction of 29 [96] and 34% [97].

However, evidence of estrogen deficiency in women with dementia and cognitive dysfunction has been inconsistent. Nevertheless, epidemiological studies have suggested that HRT protects against the development of clinically diagnosed AD. In the early 1990s, there was a great belief in the potential of HRT for the treatment of AD and cognitive ageing. However, currently, this opinion is losing favor.

Postmenopausal women have much lower levels of gonadal hormones than men [11]. This could suggest that maintaining high level of hormones in women with HRT may protect against AD.

Most observational studies carried out to date have shown a decrease in the risk of developing AD in HRT users [96], along with demonstrating positive treatment effects related to HRT in AD. In spite of this, recently controlled trials have not shown any significant HRT effects in AD subjects [12–14]. To date, three prospective observational studies have suggested that HRT reduces the risk of AD by 39–50% [98–100].

The Hogervost meta-analysis examined the results of numerous studies to determine the validity of reports investigating HRT effects on cognition in elderly women [101]. Specifically, this meta-analysis sought to both discover the reasons for the inconsistencies present in the data and identify crucial questions that could form the basis of future research. This meta-analysis, along with the Yaffe meta-analysis [96], suggests an overall AD risk reduction of approximately 29–44%.

In conclusion, Hogervost *et al.* evidenced small but inconsistent effects related to HRT on several aspects of cognitive function in healthy women: memory, attention, reaction time speed and abstract reasoning. These effects do not seem to be explicable by the alleviation of depression or climacteric symptoms, or the use of combination therapy.

A possible bias of the epidemiological results that have shown more positive effects because of HRT, compared with experimental studies, is probably not related to sample size. Women who start HRT are generally healthier and usually belong to a higher socioeconomic status and therefore commonly have a better vascular risk control compared with those who do not use HRT.

A recent review has investigated whether age at assessment and duration of HRT had a moderating effect on the influence of HRT in cognition [102]. HRT may impact on cognition through two pathways: by acting directly on brain systems and structures, or by acting indirectly on the brain through the cardiovascular system. Low and Anstey evidenced that:

- There was some evidence for a positive association between HRT and verbal memory in cross-sectional data, although not in longitudinal or randomized, controlled trials;
- There was no consistent association between HRT use and visual memory;
- HRT did not have a consistent association with speed of performance;
- Cross-sectional studies reported a positive association between HRT and executive function that was not detected in longitudinal and randomized trials. This did not allow for conclusions to be drawn on the relationship between HRT and executive function;
- There was contradictory evidence between observational and randomized trials on the effects of HRT and performance on the cognitive screening instruments. Overall, it would appear that there is no positive effect and there may even be a small negative effect of HRT on cognitive screening instruments;
- The observational studies, particularly longitudinal studies, provided evidence that HRT reduced the risk of dementia, but this was in contradiction to the results of the randomized, controlled trials, which found increased risk of dementia.

Low and Anstey found that there were many nonsignificant results, although the positive results tended to favour HRT users over controls. However, no consistent positive association between HRT use and cognition in any cognitive domain was found.

Trials

The effects of HRT on dementia and MCI were assessed in a subgroup of WHIMS, aged 65 years or over [103]. There were two study arms, one included 4532 postmenopausal women who received continuous CEE plus MPA or placebo, while the second included 2947 hysterectomized women randomized to continuous unopposed CEE or placebo.

CEE with or without MPA did not protect against dementia but instead substantially increased its risk. Incidence of probable dementia in the estrogen-alone trial was statistically similar to that seen in the estrogen plus progestin trial. When pooled together, the data from both trials evidenced that the overall risk for probable dementia was increased by 76% (HR: 1.76;

95% CI: 1.19–2.60; p = 0.005). A second report from WHIMS suggested that cognitive decline in women aged 65 years and over was greater in those receiving HRT than in those receiving placebo (HR: 1.25; 95% CI: 0.97–1.60). The WHIMS results clearly indicate that CEE with or without MPA should not be used to prevent dementia or enhance cognition in women older than 65 years.

In order to investigate the possible effects of HRT on stroke risk, randomized, controlled trials of cardio- and/or cerebrovascular disease prevention in women have been designed.

In the Heart and Estrogen/Progestin Replacement Study (HERS), women with established cardiovascular disease were randomized to either oral CEE plus medroxyprogesterone or placebo [104]. Although stroke was a secondary end point, after an average follow-up of 4 years, nonsignificant increases were observed in the incidence of fatal stroke (HR: 1.61; 95% CI: 0.73–3.55) and nonfatal stroke (HR: 1.18; 95% CI: 0.83–1.66), although no increase in the incidence of transient ischemic attack in women receiving combination HRT was found (HR: 0.90; 95% CI: 0.57–1.42). This study did not evidence any difference between the myocardial infarction or coronary death rate (HR: 0.99; 95% CI: 0.80–1.22) and the stroke rate.

In the Women Estrogen Stroke Trial (WEST), women were randomized to oral 17-β estradiol or placebo within 90 days of ischemic stroke or transient ischemic attack [82]. There was no overall benefit related to 17-β estradiol in the prevention of the primary end points, death or nonfatal stroke over a follow-up period of approximately 3 years (HR: 1.1; 95% CI: 0.8–1.4). However, *post hoc* analysis revealed an increase in the number of fatal and nonfatal strokes in the 17-β estradiol group 6 months after randomization (HR: 2.3; 95% CI: 1.1–1.5), suggesting an early adverse effect related to HRT use. In this study, as with HERS, there was evidence of an increased early risk among those subjects randomized to HRT. In the first 6 months following randomization, three fatal and 18 nonfatal strokes were reported in the estradiol group compared with one fatal and eight nonfatal strokes in the placebo group (RR: 2.3; 95% CI: 1.1–5.0). Besides this, there was no clear evidence that women randomized to estradiol had more severe recurrent strokes. Among those subjects with recurrent nonfatal strokes, complete or near complete recovery was half as likely to occur among those randomized to estrogen therapy compared with those on placebo (19 vs 33%; p = 0.12).

Assessment of the effect of estrogen on cognitive function was a defined secondary study aim, while global and domain-specific measures of cognitive function were assessed [105].

Additionally, this study assessed whether estrogen therapy reduces the risk of cognitive decline in women with cerebrovascular disease. The Mini-Mental State Examination (MMSE) and five domain measures were recorded at baseline and exit. Among 461 women withdrawn alive without stroke, estrogen therapy did not have a significant effect on cognitive measures after an average of 3 years (RR of MMSE decline: 0.74; 95% CI: 0.49–1.13). In women with normal MMSE at entry, estrogen was associated with less decline (RR: 0.46; 95% CI: 0.24–0.87). In this study, estradiol did not have significant effects on cognitive measures. However, in women with normal function at baseline, there may have been a benefit related to estrogen therapy use in reducing the risk of cognitive decline.

The WHI randomized, controlled trial has been the most recent primary prevention study to investigate the effect of postmenopausal HRT on cardiovascular disease in healthy women, with stroke as a secondary outcome [44]. The trial reported a 40% increased risk of stroke and 30% increased risk of first CHD with combined therapy. The combination HRT (oral CEE plus medroxyprogesterone) group was terminated early (after ~5 years of follow-up) due to unacceptable increased risks of invasive breast cancer and stroke (RR: 1.4; 95% CI: 1.1–1.8), although the risk of nonfatal stroke (HR: 1.50; 95% CI: 1.08–2.08) was higher than the risk of fatal stroke (HR: 1.20; 95% CI: 0.58–2.50). However, when adjustments for multiple comparisons were made, these differences were no longer statistically significant.

The global index also indicated a net adverse effect related to hormonal therapy (19 per 10,000 person-years). Beneficial effects were seen (six fewer colorectal cancers and five fewer hip fractures per 10,000 person-years); however, these benefits were offset by an increase in other negative consequences (seven more coronary events, eight more strokes, eight more pulmonary emboli [PE] and eight more invasive breast cancers per 10,000 person-years) [44].

The second report investigated women who had had a hysterectomy [47]. Among these women, estrogen alone (CEE) was used as the active therapy. The results obtained were similar to those obtained in the estrogen plus

progestin group. The increased risk of stroke was reported to be 1.39 (95% CI: 1.10–1.77). In the WHI trial of combination HRT, an absolute excess risk (in their global index) of 19 out of 10,000 person-years was reported.

The WHI study differed in both design and purpose from HERS and WEST, in that HERS and WEST focused on secondary prevention and WHI assessed primary prevention.

Therefore, HERS and WEST subjects were at a higher risk of stroke at baseline compared with women in the WHI study. Specifically, approximately 68 and 75% of HERS and WEST subjects, respectively, had hypertension compared with only 30% in WHI. Moreover, WHI women were younger (mean age: 63 years) than those in either HERS (mean age: 66 years) or WEST (mean age: 71 years). In addition, only 20% of WHI subjects were reported to be taking aspirin at baseline compared with 80% in HERS.

Despite these baseline differences, none of these studies were able to demonstrate a stroke risk reduction with HRT use. Although the increased number of strokes in HERS did not reach significance and there was a neutral risk in WEST, the WHI study, which sought to enrol the healthiest subjects, reported a 40% increased risk of stroke in HRT users from unadjusted analysis.

These WHI results are now reflected in national guidelines. That is, HRT should not be initiated to prevent vascular disease in postmenopausal women [106].

HRT trial & cognition

Numerous studies have suggested that estrogen therapy in postmenopausal women may prevent or retard cognitive function decline. A meta-analysis of observational studies concluded that estrogen therapy was associated with a 34% decrease in the risk of dementia (OR: 0.66; 95% CI: 0.53–0.82) [107].

Results of randomized, controlled trials, however, have not shown a consistent trend for cognitive improvement with estrogen treatment.

Recently reported results from two large clinical trials (HERS-WHIMS) have failed to demonstrate a beneficial effect of daily estrogen and progestin treatments on cognitive performance or risk of dementia [108,109].

WHIMS, a substudy of the WHI, was a randomized, double-blind, placebo-controlled trial assessing 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone in postmenopausal dementia-free women aged 65 years or older. Its aim was to evaluate the impact of estrogen plus progestin on the incidence of dementia and MCI in healthy women enrolled in the WHI. The primary outcome was incidence of probable dementia, while the secondary outcome was the development of MCI with a planned 8.5-year duration. The study was terminated after 5.6 years because of an increased risk of heart disease, stroke, PE and breast cancer on active drug. Average age was 69 years and nearly 20% of subjects were aged 75 years or over. In total, 1% had previous cerebrovascular accidents, 7% diabetes, 10% were on statins and nearly 30% were regular acetylsalicylic acid users.

The mean time between date of randomization and the last Modified Mini-Mental Status Exam was 4 years. A total of 61 women were diagnosed with probable dementia, of which 66% were on active treatment. Estrogen/progestin was associated with a RR of 2.05, or 45 versus 22 per 10,000 person-years for placebo ($p = 0.01$). Treatment effects on MCI did not differ between groups. The risk of probable dementia from therapy became evident at the first year, persisted over the 5 years of follow-up and was present after controlling for adherence. Estrogen plus progestin therapy increased the risk of probable dementia in postmenopausal women aged 65 years or older and did not prevent MCI. These data, coupled with the previous reports from WHI, support the conclusion that the risk of estrogen plus progestin outweighs the benefits. The absolute risk increase for AD was relatively small, an additional 23 cases per 10,000 women. Added together, the risk of a major adverse outcome from estrogen/progestin was approximately 0.01 per 10,000 women [46].

Furthermore, the results from WHIMS showed a near doubling of the risk for all-cause dementia [103]. One explanation for this could be that the late use of HRT, after age 65 years, confers a cognitive risk. A secondary analysis examined HRT effects on MCI, considered to be an early 'preclinical' indicator of AD [110]. For women assigned to HRT, MCI risk was modestly, but not significantly, elevated [46,103].

WHIMS subjects who had used HRT in the past were less likely to develop dementia than never-users, regardless of treatment allocation. However, trial findings did not vary significantly by baseline differences in age, education, cognitive score, history of hypertension or stroke, or prior HRT use. Increased risk was apparent within several years of randomization. Older

women and those with low cognitive test scores at baseline were more likely to develop dementia in both treatment arms.

In conclusion, WHIMS demonstrated that, contrary to earlier research suggesting a protective effect of estrogen on the brain, estrogen plus progestin had a damaging effect and the risk of dementia, along with global cognitive deterioration, increased with estrogen plus progestin compared with placebo in this group of postmenopausal women aged over 65 years.

It is not known how HRT elevates dementia risk. Given that HRT increases stroke incidence in some populations [47,84] and given that vascular factors are implicated in AD pathogenesis [3], one hypothesis is that the HRT effects on vascular disease could account for the WHIMS findings on dementia.

Secondary prevention clinical trials have not demonstrated any benefit of HRT in slowing the progression of dementia [96,111].

Most of the research examining the effects of estrogen on cognition in demented persons has focused on Alzheimer's dementia. The characteristic brain pathologies in AD are the gradual and insidious accumulation of both neuritic plaques and neurofibrillary tangles. Failure of HRT to lessen the impact of AD may mean that, once it has begun, HRT cannot arrest or reverse these neuropathologies [112].

An alternative hypothesis is that an increased risk of dementia among women in the early stages of AD occurs when estrogen provokes neurovascular disease (small strokes), a second pathology in the brain that leads to cognitive decline and, ultimately, dementia [113].

Moreover, epidemiological studies have suggested that there is a window of biological opportunity when benefit from estrogen can be realized [100].

In fact, women who reported taking HRT during perimenopausal and early postmenopausal periods had better global cognitive scores and a lower incidence of dementia than either those who had never taken HRT or those who had started well after the menopausal transition. This prospective, observational study by Zandis *et al.* had predicted the WHIMS findings of increased dementia in women initiating HRT after age 65 years.

The Women's International Study on Long-Duration Oestrogen After Menopause (WISDOM) trial, a randomized, placebo-controlled trial, compared combined estrogen and progestogen versus placebo, and estrogen alone versus combined estrogen and progestogen in 226,282 women aged 50–69 years [114]. The trial sought to randomize 22,300 postmenopausal women and treat them for 10 years. The interventions were: conjugated equine estrogens 0.625 mg orally daily; conjugated equine estrogens plus medroxyprogesterone acetate 2.5/5.0 mg orally daily; or matched placebo. Primary outcome measures were major cardiovascular disease, osteoporotic fractures, breast cancer and dementia. Secondary outcomes were other cancers, all causes of death, venous thromboembolism and cerebrovascular disease. The trial was prematurely closed during recruitment, following the publication of early results from the WHI. At the time of closure, 56,583 women had been screened, 8980 entered run-in and 5694 (26% of target of 22,300) were randomized. Randomized women had received a mean of 1 year of therapy, mean age was 62.8 years and total follow-up time was 6491 person-years. When combined HRT (n = 2196) was compared with placebo (n = 2189), there was a significant increase in the number of major cardiovascular events (7 vs 0; p = 0.016) and venous thromboembolisms (22 vs 3; HR: 7.36; 95% CI: 2.20–24.60). There were no statistically significant differences in numbers of breast or other cancers (22 vs 25; HR: 0.88; 95% CI: 0.49–1.56), cerebrovascular events (14 vs 19; HR: 0.73; 95% CI: 0.37–1.46), fractures (40 vs 58; HR: 0.69; 95% CI: 0.46–1.03) and overall deaths (8 vs 5; HR: 1.60; 95% CI: 0.52–4.89). Comparison of combined HRT (n = 815) versus estrogen therapy (n = 826) outcomes revealed no significant differences. In conclusion, HRT increases cardiovascular and thromboembolic risk when started many years after the menopause. These results are consistent with the findings of the WHI and secondary prevention studies [115].

The Kronos Early Estrogen Prevention Study (KEEPS) is an ongoing, prospective, randomized, placebo-controlled study comparing oral and transdermal estrogens with pulsed progestin in women shortly after menopause. The primary outcome is vascular disease measured by progression of carotid intimal medial thickness and coronary artery calcification [116]. This study is matching the characteristics of women who might benefit from postmenopausal hormone treatment. In addition, it is studying the formulation of hormones that might reduce risk.

Conclusion

Currently, there is no convincing evidence that combination HRT reduces primary or secondary stroke risk in postmenopausal women and

there seems to be no protective effect on dementia. However, the trials performed in the past were not designed for women at the physiological age for HRT and the therapy was not administered following the cyclic hormone metabolism but was instead administered continuously. The trials had shown that the longer the time between menopause and treatment beginning, the greater the risk of sides effects. Thus, the target women should be those close to menopause, as suggested by the KEEPS trial.

Future perspective

The incidence of AD is believed to increase in the next years. In fact, it is estimated that in 2050, approximately 13 million men and women worldwide will be affected by this disease. The prevalence of AD is greater for women than men. With this reality, a better understanding of the risk factors responsible for cognitive impairment is an utmost public health priority.

Probably, the HRT may provide benefit if it is administered in a window of time following the loss of ovarian function. Future research should be designed to identify when and how long this therapy could be administered to protect women against the negative effects of menopause without harming as shown by randomized trials. However, at present the data about dementia/stroke prevention with HRT are contradictory. Being so, the results of the un-going research and the future of HRT are unpredictable and its rule in dementia and stroke prevention is uncertain.

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Executive summary

- High premenopausal estrogen concentrations are thought to be protective against stroke and may protect brain structures and functional systems affected by Alzheimer's disease.
- Hormone-replacement therapy (HRT) reduces the risks of osteoporotic fractures and coronary heart disease, but a recent trial failed to demonstrate any benefit in women with established coronary heart disease.
- There is no convincing evidence that combination HRT reduces primary or secondary stroke risk in postmenopausal women.
- There is no convincing evidence that combination HRT protects against dementia.
- Trials have shown that the longer the time between menopause and the beginning of treatment, the greater the risk of side effects.
- It seems that the greatest benefit from HRT comes from initiating such treatment as close to the onset of menopause as possible.
- Previous trials were not designed for women in the physiological age for HRT.
- In previous trials, therapy was not administered following the cyclic hormone metabolism.

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