Oestrogen plus progestin increased risk of stroke and probable dementia in postmenopausal women

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.*

Shumaker SA, Legault C, Rapp SR, et al. ***Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial.*** *JAMA 2003;**289**:2651–62.*

Rapp SR, Espeland MA, Shumaker SA, et al. ***Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial.*** *JAMA 2003;**289**:2663–72.*

QUESTIONS:

(1) In postmenopausal women 50–79 years of age, does hormone replacement therapy (HRT) increase the risk of stroke?

(2) In postmenopausal women ≥65 years of age, does HRT increase the risk of probable dementia or protect global cognitive function?

Design

The Women's Health Initiative (WHI) hormone therapy study of oestrogen plus progestin was a randomised (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee),* placebo controlled trial with a mean follow up period of 5.6 years. The Women's Health Initiative Memory Study (WHIMS) was an ancillary study to the larger WHI hormone trial with a mean follow up of 4.2 years.

Setting

39 of 40 WHI US clinical centres also participated in WHIMS.

Participants

16 608 community dwelling postmenopausal women 50–79 years of age (mean age 63 y) who had an intact uterus participated in the WHI trial of oestrogen plus progestin. Exclusion criteria included participation in other trials, predicted survival <3 years, alcoholism, drug dependence, diagnosed mental illness, and dementia. WHI follow up was 100%. 4532 women enrolled in WHI who were ≥65 years of age and free of probable dementia were recruited to participate in WHIMS. WHIMS follow up was 97%.

Intervention

Women were allocated to HRT consisting of conjugated equine oestrogen, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg daily (n=8506 and 2229 for WHI and WHIMS, respectively) or placebo (n=8102 and 2303 for WHI and WHIMS, respectively).

Main outcome measures

WHI: incidence of overall stroke and stroke subtypes centrally adjudicated by stroke neurologists. WHIMS: incidence of dementia and global cognitive function both measured annually by the Modified Mini-Mental State Examination (3MSE) (range 0–100, higher score reflecting better cognitive functioning).

Main results

Analysis was by intention to treat. WHI: The incidence of ischaemic and hemorrhagic strokes combined, and of ischaemic stroke alone were greater in the HRT group than in the placebo group (table). The groups did not differ for incidence of haemorrhagic stroke (0.2% *v* 0.2%; hazard ratio 0.82, 95% CI 0.43 to 1.56). Subgroup analysis showed that the excess risk for all stroke was apparent in all age groups; all categories of baseline stroke risk; and in women with and without hypertension, and history of cardiovascular disease, use of hormones, statins, or aspirin. WHIMS: The incidence of probable dementia was greater in the HRT group than in the placebo group (table). Increase from baseline in global cognitive function (3MSE scores) was lower in the HRT group than in the placebo group (table). The results (effect of HRT on global cognitive function) were not altered by sensitivity analysis that consisted of removing women by censoring them after adjudicated dementia, mild cognitive impairment, stroke, or non-adherence to study protocol. The results were also not influenced by previous HRT use or timing of previous HRT initiation with respect to the final menstrual period.

Conclusions

(1) In postmenopausal women 50–79 years of age, hormonal replacement therapy was associated with an increased risk of stroke. (2) In postmenopausal women ≥65 years of age, hormone replacement therapy increased the risk of probable dementia.

*See glossary.

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Hormone replacement therapy (HRT) v placebo in community dwelling postmenopausal women at 5.6 years†

Outcomes	Trial	HRT	Placebo	RRI (95% CI)	NNH (CI)
All stroke	WHI	1.8%	1.3%	31% (2 to 68)	220 (120 to 1265)
Ischaemic stroke	WHI	1.5%	1.0%	44% (9 to 90)	213 (124 to 743)
Probable dementia	WHIMS	1.8%	0.9%	105% (21 to 248)	114 (63 to 461)
				Difference between groups (CI)	
Mean 3MSE scores at baseline	WHIMS	95.5	95.63	–0.13 (–0.37 to 0.11)	
Mean rate of increase in 3MSE scores per year	WHIMS	0.149	0.213	–0.063 (–0.120 to –0.006)‡	

†WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; 3MSE = Modified Mini-Mental State Examination. Other abbreviations defined in glossary; RRI, NNH, and CI calculated from data in article.

‡Statistically significant difference favours placebo.

COMMENTARY

The 3 studies by Wassertheil-Smoller *et al*, Shumaker *et al*, and Rapp *et al*, respectively, extend the string of bad news from the WHI.[1] Since the early termination of the oestrogen plus progestin arm, a possible benefit of preventing cognitive impairment seemed to be the last best hope for long term HRT. Unfortunately, rather than the hoped for summer blockbuster, these reports look more like a rerun of the disappointing findings linking oestrogen plus progestin and heart disease. The expectations of a protective effect against dementia were based on a compelling combination of basic science and epidemiology. In animal studies, oestrogen has favourable effects on neurotransmission, cell growth, and prevention of β amyloid accumulation and oxidative damage.[2] Most observational studies reported substantially lower risk of dementia among women who had used HRT.[3] Yet, as with heart disease, WHI observed worse outcomes among women in the HRT group than in the placebo group.

Neither the stroke nor cognitive function findings from these studies are a complete surprise. The 31% increase in total stroke risk is compatible with a 12% increase in a recent meta-analysis[4] and with known prothrombotic effects of HRT. In the Heart and Estrogen/progestin Replacement Study (HERS) trial, however, the same regimen produced only a non-significant 9% increase in stroke and transient ischaemic attacks, possibly because of the high rate of aspirin use (80%) in the HERS patients, all of whom had heart disease. HERS also found no benefit of oestrogen plus progestin on global cognitive function after 4 years of treatment.[5] In some earlier short term trials, oestrogen alone improved some cognitive measures such as number recall, but benefits were not consistent across different measures and were largely confined to younger women with postmenopausal symptoms.[3]

Most surprising are the findings of a small increase in clinically important declines in cognitive function and a 2 fold increase in probable dementia among women >65 years of age who received oestrogen plus progestin. The reasons for this are unknown but may relate to small subclinical cerebral thromboses.[2]

Is it possible that HRT was given too late in WHI to protect against dementia? This scenario seems unlikely given that identical effects were seen in the 20% of women who had used HRT before the study. Furthermore, many of the earlier studies reported benefits in a broad spectrum of HRT users—current and past, short and long term. It seems more plausible that earlier studies fell prey to the same biases that affected studies of HRT and heart disease.[3] The protective effects observed in non-randomised studies may have resulted not from HRT itself but from other characteristics of the women who were prescribed HRT, for example, better education and better health, 2 factors that substantially reduce risk of dementia.

The last remaining hope is that unopposed oestrogen will prove safer and more effective than oestrogen plus progestin. In one cohort study, current oestrogen plus progestin users were the only group of HRT users whose cognitive scores declined.[3] The oestrogen only arms of WHI and the WHIMS substudy are continuing, indicating that neither significant benefits nor significant harms have been observed so far. Until those results are available, these reports reinforce the original messages from WHI. For women without menopausal symptoms, the harms of oestrogen plus progestin exceed benefits. HRT remains a suitable option for women with bothersome menopausal symptoms, but women should understand that there are some risks involved and should regularly reassess their need for treatment with their physician. It is prudent to use the lowest effective dose for the shortest possible period, but we should not assume that different formulations or lower doses of HRT will avoid all the risks observed in WHI.

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2 Yaffe K. Hormone therapy and the brain: déjà vu all over again? [editorial]. *JAMA* 2003;**289**:2717–9.
3 LeBlanc ES, Janowsky J, Chan BK, *et al*. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001;**285**:1489–99.
4 Nelson HD, Humphrey LL, Nygren P, *et al*. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;**288**:872–81.
5 Grady D, Yaffe K, Kristof M, *et al*. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002;**113**:543–8.

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