Association between hormone replacement therapy and subsequent stroke: a meta analysis.

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All authors declare that the answer to the questions on your competing interest form (http://bmj.com/cgi/content/full/317/7154/291/DC1) are all No and therefore have nothing to declare

ABSTRACT

Objectives: To review systematically completed trial evidence assessing hormone replacement therapy (HRT) to subsequent stroke risk, in particular assessing stroke by pathological type, severity and outcome.
Data sources: Randomised controlled trials of HRT were identified from the Cochrane Library, reviews and reference lists of relevant papers.
Review methods: Rates for cerebrovascular events were extracted, combined and analysed using a random effects model. Sensitivity analyses were defined to explain any heterogeneity, including phase of prevention (primary, secondary), type of HRT (mono/unopposed oestrogen, dual/opposed), type of oestrogen (estradiol, conjugated equine oestrogen), size of trial (<5000, >5000 patients), length of follow-up (≤3 years, >3 years), and gender.
Results: Fourteen trials (t), involving 34,976 subjects, were identified. HRT was associated with significant increases in total stroke, odds ratio (95% confidence intervals) 1.29 (1.12-1.47, t=14), non-fatal stroke 1.23 (1.06-1.44, t=11) stroke leading to death or disability/dependency 1.56 (1.11-2.20, t=4), ischaemic stroke 1.28 (1.06-1.56, t=5), and a trend to more fatal stroke 1.28 (0.87-1.88, t=12). HRT was not associated with haemorrhagic stroke 1.06 (0.64-1.75, t=5), or transient ischaemic attack 1.00 (0.75-1.33, t=6). No heterogeneity was present in any analysis.
Conclusions: HRT is associated with an increased risk of stroke, particularly of ischaemic type. Subjects having a stroke on HRT appear to have a worse outcome. HRT cannot be recommended for the prevention of stroke.

INTRODUCTION

Sex steroid hormones are believed to provide women with endogenous protection against cerebrovascular events. Pre-menopausal women have a lower risk of stroke relative to men of the same age [1 2] whilst the incidence of stroke increases rapidly following the menopause, [3] coincident with diminished circulating levels of oestrogen and progesterone. As a result, hormone replacement therapy (HRT) has been used widely for vascular prophylaxis in parallel with its known effects in reducing menopausal symptoms and bone loss. Longitudinal observational studies have suggested that HRT may reduce cardiovascular and cerebrovascular disease. [4] However, a review of these studies (which also included two randomised trials) found that the number of strokes was increased. [5] Furthermore, the results of randomised controlled trials (RCT) have given conflicting results with studies either finding no benefit or even apparent hazard. A recent non-systematic review of RCTs found that treatment with HRT was associated with an increased risk of stroke. [6]

The aim of this study was to review systematically completed trial evidence relating HRT to subsequent stroke risk, in particular assessing stroke by pathological type, severity and outcome.

METHODS

Searching

Publications were identified from searches of The Cochrane Library, Embase and Medline (from 1966 to May 2004), in addition the reference lists of previous reviews [7-9] and reference the identified articles were made.

Selection

All completed and published randomised controlled trials of HRT against a control group reporting stroke events were included. Publications not reported in English or where event numbers were given for stroke or transient ischaemic attack and not separately were excluded. Trials were found which included both males and females, and in one case males exclusively. It was decided to include both genders in the review but to analyse those trials which included males separately to those which included females only. From the search 18 trials were identified, of which fourteen met our criteria for inclusion. Four trials did not meet our inclusion criteria (table 1).

Quality assessment

Studies were assessed in five areas, including method of randomisation, blinding, reporting of withdrawals, generation of random numbers and allocation concealment. Trials scored one point for each area addressed, therefore receiving a score between 0-5, with 5 reflecting the highest level of quality. [10]

Data abstraction

All data were independently extracted by the two authors (LG and PB). Disparities were resolved by consensus.

Study characteristics

Information on trial size, treatment regimen (oestrogen $\pm$ progesterone), length of follow-up and outcome were recorded. Outcomes included stroke events (fatal and non fatal), type of stroke (ischaemic, haemorrhagic, not known), functional outcome (combined death and disability/dependency), and case fatality. Where available, data were also collected on the number of transient ischaemic attacks, but these were not included in the overall stroke outcome. Where obtainable, data related to intention-to-treat analyses.

Quantitative data synthesis

Data were analysed using Stata (version 7) and Cochrane Review Manager (version 4). The effect of HRT on dichotomous outcomes was assessed using the odds ratio calculated using a random effects model since the trials were expected to be heterogeneous. Pre-specified sensitivity analyses were defined to explain any heterogeneity, including phase of prevention (primary, secondary), type of HRT (mono/unopposed oestrogen, dual/opposed), type of oestrogen (estradiol, conjugated equine oestrogen), size of trial (<5000,

>5000 patients), length of follow-up (≤3 years, >3 years), gender (females only) and quality (those scoring 5/5 only). Interactions between subgroups and treatment were assessed. Publication bias was examined using Eggers test.[11]

RESULTS

Study characteristics

Fourteen trials were identified for inclusion involving 34,976 subjects (table 1, figure 1). The trials varied in size between 134 [12] and 16,608. [13] The trials included four investigating primary vascular prevention [13-16] and nine in patients with prior vascular events: stroke [17-19], ischaemic heart disease [20-23] and venous thromboembolism. [24] The average age of the patients varied between 55 and 71; three trials not only included post menopausal women but also included men, with one trial including men exclusively. [12 18 19] Two trials required that women should not have had a hysterectomy.[13 21] Follow-up varied between 0.9 and 6.8 years. Mono-HRT (oestrogen alone) was studied in seven trials and dual (or opposed) HRT in the others. Both mono and dual comparison arms of the 'Women's Health Initiative Trial' were terminated prematurely due to HRT treatment being associated with hazard.[13 15] All trials, apart from two [23 25], were placebo controlled.

Data quality

Quantitative data synthesis

Stroke occurred in 2.3% of the participants randomised to no HRT and was significantly increased by one-third in those randomised to HRT (figure 2). This increase in stroke resulted from excess ischaemic strokes but not primary intracerebral haemorrhage, as also seen in WHI dual alone.[13] An early increase in stroke occurred during the first 6 months of treatment in the WEST trial of secondary stroke prevention,[17] analogous to the early increase in CHD events seen in the HERS trial of secondary CHD prevention.[21]

A poor outcome after stroke, judged as combined death and dependency, was increased by half with HRT; a non-significant increase in fatal stroke was also seen. This relationship between HRT and severe stroke was present individually in three trials – HERS, WEST, WHI dual (figure 3).[13 21 26] HRT did not alter the rate of transient ischaemic attack (table 2). No statistical heterogeneity was seen for any of the stroke outcomes.

Pulmonary embolism was increased by three-quarters in those randomised to HRT (table 2). In contrast, CHD events were not more frequent with HRT. No statistical heterogeneity was observed for either PE or CHD.

Sensitivity analyses were performed on several prognostic factors for the total stroke outcome (table 3). The results of these analyses appear to be driven by the large WHI dual study and significant results are seen for the sub groups which contain this study. However, significant heterogeneity was not present between trials examining primary versus secondary prevention, mono versus dual HRT, CEE versus estradiol, shorter versus longer follow-up, smaller versus larger trials, and those including women and men versus women alone. No significant publication bias was found for the all stroke outcome (Eggers test p=0.24).

DISCUSSION

This systematic review supports the results of individual trials and previous reviews finding that HRT does not reduce the risk of stroke in post-menopausal women. Indeed, HRT was associated with an overall increase in the risk of stroke of 27%. This effect was driven by an increase in ischaemic but not haemorrhagic stroke. Importantly, the severity of stroke was increased since the frequency of a poor functional outcome, judged as combined death and disability/dependency, was 56% higher in those randomised to HRT. Similarly, fatal stroke was non-significantly increased.

Why HRT should increase ischaemic stroke and its severity when biological plausibility and previous observational studies suggested it might protect against cerebrovascular events remains unclear. This discrepancy between observational and intervention studies is not unique; for example, whilst antioxidant vitamins might on biological grounds have been expected to protect against vascular disease with observational studies supporting this hypothesis, several large RCTs involving antioxidant vitamins found no beneficial effect.[27] A number of possible explanations exist for why HRT promoted stroke. First, it is possible that the results of the RCTs are wrong although this is unlikely since none of the studies were positive, i.e. HRT did not reduce stroke in any study, with 11 trials being neutral and 3 negative. The absence of a beneficial effect on stroke was mirrored for VTE and CHD. If the trials are correct then the observational studies must have been falsely positive. Second, the trials involved either mono or dual HRT. Whilst long-term unopposed oestrogen therapy can promote cause uterine cancer, this would not explain an increase in stroke. In contrast, adding a progestogen could have had detrimental effects since this class of drugs can promote atherogenesis and vasoconstriction.[28] This is particularly true for medroxyprogesterone acetate which was used in most of the trials involving dual HRT. Nevertheless, no heterogeneity between trials of mono and dual HRT was present suggesting that oestrogen itself, given as oestradiol or CEE, might be the culprit. Third, within-class differences in HRT may mean that the most appropriate type of oestrogen has yet to be tested adequately; the RCTs assessed either conjugated equine oestrogens or estradiol but not other types such as phytoestrogen.[29] However, there was no evidence for statistical heterogeneity between the trials with respect to type of oestrogen.

Fourth, the dose of oestrogen (and progestogen if present) may have been too high. The usually starting dose of CEE and estradiol in the UK in older women are 0.625 mg and 1 mg respectively, although the dose may then be titrated up if menopausal vasomotor symptoms persist. These doses are below those used in several of the trials. Fifth, the delivery route may be important since important pharmacological differences exist between oral and transdermal administration of oestrogen, especially relating to first pass liver metabolism. Sixth, several of the trials may have been too short with a median length of less than 3 years contrasting with the earlier observational studies. Of note, both HERS and WEST found an early vascular hazard which disappeared later.[21 26] The hazard during the first year of treatment appears to reflect the development of a thrombophilic state which may not persist. This raises the possibility that an extended follow-up would have

revealed long term benefit. An analogous situation exists with statin therapy whereby benefit was found in trials with longer rather than shorter follow-up.[30] Nevertheless, the largest two of the HRT trials, WHI dual and WHI mono, had follow-up for more than 5 years and yet found no beneficial effect on stroke risk.

In summary we have found that the use of HRT is associated with an increased risk of stroke, typically ischaemic in type and severe in nature. HRT cannot be recommended for the primary or secondary prevention of stroke. Extrapolation of the data suggest that patients at high risk of stroke, e.g. those with previous stroke, coronary heart disease, or multiple vascular risk factors, should cease taking it unless there is a strong contrary medical reason.

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TABLE 1

Randomised controlled trials excluded from the review

Trial & year	Indication	Subjects	Intervention (daily dose)	Reason for exclusion
WISDOM [31]	Healthy	5,664	CEE + MPA CEE	Trial completed but not reported at time of writing
De Kleijn et al, 1999 [32]	Healthy	121	E2 (1.5 mg) +DG (0.15 mg), or CEE (0.625 mg) + N (0.15 mg)	No stroke events reported
Herrington et al, 2000 [33]	Coronary disease	309	CEE (0.625 mg), or CEE (0.625 mg + MPA (2.5 mg)	Numbers only given for stroke or TIA and not separately
Clarke et al, 2002 [34]	IHD	255	E2 (2.5 mg) or E2 (3 mg) + NG (4 mg)	Numbers only given for stroke or TIA and not separately

TABLE 1

Randomised controlled trials of hormone replacement therapy in the primary and secondary prevention of vascular disease included in the meta analysis.

Trial & year	Indication	Subjects	Age (years)	Female (%)	Ethnicity white (%)	Uterus present (%)	Follow-up (years)	Stroke rate (control group, %/year)	Intervention (daily dose)	Compliance (%)	Quality score (0-5)
Marmorston, 1965 [19]	Cerebral thrombosis	200	62.1	37	?	?	?	?	Females: CEE (0.625mg) Males: CEE (0.625-2.5 mg)	?	2
Veterans Administration Cooperative, 1966 [18]	Cerebrovascular disease	592	?	0	79.2	?	1.4	7.72	CEE (1.25 mg) after 1 year CEE (2.5 mg)	94	5
McDowell et al, 1967 [12]	Non-embolic cerebral infarction	134	64	25	?	?	Treated 0.9, control 1.2	0	CEE (1.25mg)	84	3
PEPI Writing Group, 1995 [14]	Healthy	875	56	100	?	68	3	0	CEE ± MPA or MP	76	5
Simon et al, 1998 [21]	IHD	2,763	67	100	?	100	4.1	1.18	CEE (0.625 mg) + MPA (2.5 mg)	78	5
Høibraaten et al, 2000 [24]	VTE	140	56	100	?	?	1.3	1.11	E2 (2mg) + NTA (1mg)	76	5
Hodies et al, 2001 [16]	Healthy	222	62	100	58	62	2.0	0	E2 (1 mg)	94	5
Angerer et al, 2001 [23]	Carotid athero	264	?	100	?	?	1	0	E2 (1 mg) + GG (0.025 mg)	98	4
Viscoli et al, 2001 [26]	Stroke	664	71	100	?	55	2.7	6.34	E2 (1 mg)	66	5
The ESPRIT team, 2002 [20]	MI	1,017	62.3/62.9	100	?	?	2.0	0.59	E2 (2 mg)	53	5
Waters et al, 2002 [22]	IHD	423	65	100	?	41	2.8	0.67	CEE (0.625 mg) ± MPA (2.5 mg) †	69	5
Wassertheil-Smoller et al,	Healthy	16,608	63	100	84	100	5.6	0.24	CEE (0.625 mg) + MPA (2.5 mg)	60	5

2003 [13]											
Holmberg et al, 2004 [25]	Breast cancer	345	55	100	?	?	2.1	0	No specified treatment	?	3
WHI Steering Committee, 2004 [15]	Healthy	10,739	63.6	100	75.3	0	6.8	0.32	CEE (0.625 mg)	46.2	5

CEE, 'conjugated equine estrogen'; DG: desogestrel; E2, 17ß-estradiol; GG: gestogene; IHD: ischaemic heart disease; MI: myocardial infarction; MPA: medroxyprogesterone acetate; NG: norgestrel; NTA: northisterone acetate; VTE: venous thromboembolic. † progesterone given if no hysterectomy

TABLE 2

Effect of hormone replacement therapy on stroke, its type and outcome. Odds ratio (95% confidence intervals) using random effects model, and heterogeneity

	Trials	Subjects	Events	Control event rate (%)	Odds ratio (95% CI)	p	Heterogeneity p
Stroke, all	14	34,976	916	2.32	**1.29 (1.12 – 1.47)**	**0.0003**	0.46
Ischaemic	5	20,510	442	1.91	**1.28 (1.06 -1.56)**	**0.01**	0.46
Haemorrhagic	5	20,510	63	0.30	1.06 (0.64 -1.75)	0.82	0.56
Transient ischaemic attack	6	5,451	203	4.08	1.00 (0.75 – 1.33)	1.00	0.71
Outcome							
Fatal	12	33,718	129	0.33	1.28 (0.87 – 1.88)	0.21	0.39
Non-fatal	11	33,518	710	1.93	**1.23 (1.06 – 1.44)**	**0.007**	0.45
Death or dependency	4	17,733	145	0.65	**1.56 (1.11 – 2.20)**	**0.01**	0.93

TABLE 3

Sensitivity analyses of the effect of hormone replacement therapy on total stroke

	Trials	Subjects	Control event Rate %	Odds ratio (95% CI)	χ^2 Interaction
Stroke, all	14	34976	2.32	**1.29 (1.12 – 1.47)**	
Prevention					0.32
Primary	5	28789	1.61	**1.36 (1.14 – 1.61)**	
Secondary	9	6187	5.59	1.17 (0.90 – 1.52)	
HRT					0.75
Oestrogen alone	7	13558	3.18	1.20 (0.90 – 1.62)	
Oestrogen & progesterone	7	21418	1.75	**1.31 (1.08 – 1.60)**	
Type of oestrogen †					0.59
Estradiol	5	2307	5.71	1.15 (0.80 – 1.65)	
Conjugated equine oestrogens	8	32669	2.09	**1.29 (1.06 – 1.55)**	
Trial size					0.31
Small (<5000)	12	7629	4.87	1.17 (0.94 – 1.44)	
Large (>5000)	2	27347	1.66	**1.36 (1.14 – 1.61)**	
Length of follow-up					0.35
Shorter, <3 years	11	4866	4.88	1.14 (0.83 – 1.56)	
Longer, >3 years	3	30110	1.96	**1.33 (1.14 – 1.55)**	
Gender					-
Females only ‡	12	34133	2.18	**1.30 (1.13 – 1.50)**	

Quality		
Score of 5 only	10	**1.28 (1.12 – 1.46)**
Score 0-4	4	2.11 (0.14 – 32.18)

† Habits [25] not included as type of oestrogen left to investigators judgement

‡ Including women only from Marmorston [19]

FIGURE 1

Flow diagram of search strategy

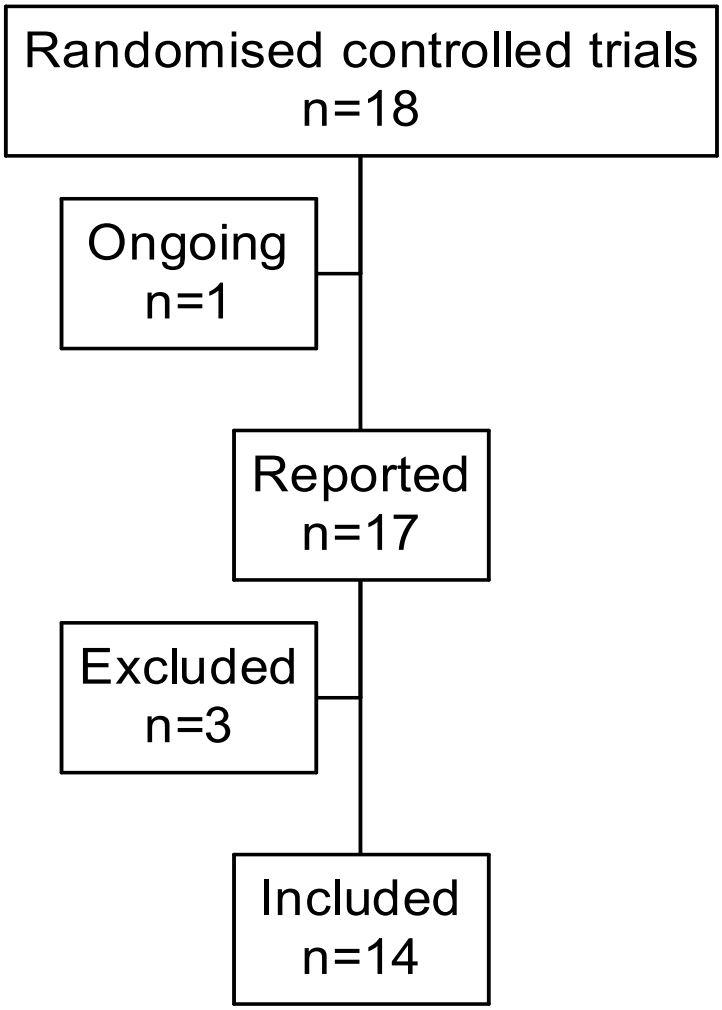

FIGURE 2

Forrest plot of randomised controlled trials of hormone replacement therapy in the primary and secondary prevention of stroke, coronary heart disease and pulmonary embolism