

Primary care

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

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Abstract

Objectives To review completed trials assessing effect of hormone replacement therapy on subsequent risk of stroke, assessing stroke by pathological type, severity, and outcome.

Design Systematic review of randomised controlled trials identified from the Cochrane Library, Embase, and Medline; reviews; and reference lists of relevant papers.

Studies reviewed 28 trials, with 39 769 subjects, were identified.

Review measures Rates for cerebrovascular events analysed with a random effects model. Sensitivity analyses for heterogeneity included phase of prevention (primary or secondary), type of hormone replacement therapy (oestrogen alone or combined with progesterone), type of oestrogen (estradiol or conjugated equine oestrogen), size of trial (<5000 or >5000 patients), length of follow up (≤ 3 years or >3 years), sex (women only or men only), and trial quality (high or low).

Results Hormone replacement therapy was associated with significant increases in total stroke (odds ratio 1.29 (95% confidence interval 1.13 to 1.47), $n=28$), non-fatal stroke (1.23 (1.06 to 1.44), $n=21$), stroke leading to death or disability (1.56 (1.11 to 2.20), $n=14$), ischaemic stroke (1.29 (1.06 to 1.56), $n=16$), and a trend to more fatal stroke (1.28 (0.87 to 1.88), $n=22$). It was not associated with haemorrhagic stroke (1.07 (0.65 to 1.75), $n=17$) or transient ischaemic attack (1.02 (0.78 to 1.34), $n=22$). Statistical heterogeneity was not present in any analysis.

Conclusions Hormone replacement therapy was associated with an increased risk of stroke, particularly of ischaemic type. Among subjects who had a stroke, those taking hormone replacement therapy seemed to have a worse outcome. Hormone replacement therapy cannot be recommended for the primary or secondary prevention of stroke.

Introduction

Sex steroid hormones are believed to provide women with endogenous protection against cerebrovascular events—premenopausal women have a lower risk of stroke than men of the same age,^{1 2} and the incidence of stroke in women increases rapidly after the menopause,³ coincident with diminished circulating

levels of oestrogen and progesterone. As a result, hormone replacement therapy has been used widely for vascular prophylaxis in parallel with its known effects in reducing menopausal symptoms and bone loss. However, two meta-analyses of observational studies have suggested that hormone replacement therapy may increase risk of stroke, especially ischaemic stroke.^{4 5} Furthermore, the results of randomised controlled trials have given conflicting results, with studies either finding no benefit or apparent hazard. A recent non-systematic review of randomised controlled trials found that hormone replacement therapy was associated with an increased risk of stroke.⁶

The aim of this study was to review systematically the evidence from completed randomised controlled trials of hormone replacement therapy and subsequent stroke risk, in particular assessing stroke by pathological type, severity, and outcome.

Methods

Literature search—We identified publications from searches of the Cochrane Library, Embase, Medline (to May 2004), previous reviews,⁷⁻¹⁰ and reference lists from identified articles.

Study selection—We included completed, published, and non-confounded randomised controlled trials that compared hormone replacement therapy with a control group and that reported stroke events, or where such events could be calculated. Trials could include participants of either sex since early studies assessed the role of hormone replacement therapy in preventing vascular events in men. We excluded publications not in English or where event numbers were given for stroke or transient ischaemic attack and not separately.

Quality assessment—We assessed studies for quality of randomisation, blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation.



Details of the search strategy used, of the trials identified in the search, and of references w1-w40 are on bmj.com



This is the abridged version of an article that was posted on bmj.com on 7 January 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38331.655347.8F>

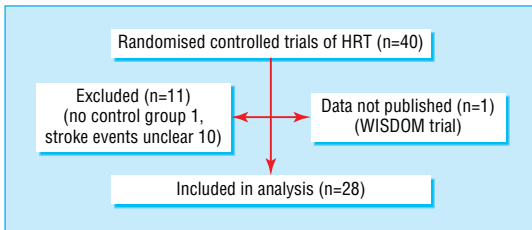


Fig 1 Results of literature search for randomised controlled trials of hormone replacement therapy (HRT) that reported stroke events

Data abstraction—All data were independently extracted by LJJ and PMWB. Disparities were resolved by discussion.

Study characteristics—We recorded information on trial size, treatment regimen (oestrogen alone or plus progesterone), length of follow up, and outcome. Outcomes included stroke events (fatal and non-fatal), type of stroke (ischaemic, haemorrhagic, not known), and functional outcome (combined death and disability or dependency). Where data were available, we also recorded the number of transient ischaemic attacks (not included in the overall stroke outcome) and data related to intention to treat analyses.

Quantitative data synthesis

We analysed data using Stata (version 7) and Cochrane Review Manager (version 4.2). We assessed the effect of hormone replacement therapy on dichotomous outcomes from the odds ratio calculated with a random effects model since we expected the trials to be heterogeneous.

We used pre-specified sensitivity analyses to explain any heterogeneity, including phase of stroke prevention (primary or secondary), type of hormone replacement therapy (oestrogen only or oestrogen plus progesterone), type of oestrogen (estradiol or conjugated equine oestrogen), size of trial (≤ 5000 or > 5000 patients), length of follow up (≤ 3 years or > 3 years), sex, and quality of trial (high (5) or low (< 5)). We assessed interactions between subgroups and treatment. We examined publication bias using Eggers test.¹¹

Results

Study characteristics

We identified 28 trials with 39 769 subjects for inclusion in our study (fig 1, table A on bmj.com).^{w1-w28} The trials varied in size between 59 subjects^{w17} and 16 608.^{w26} Follow up varied from 0.7 to 6.8 years.

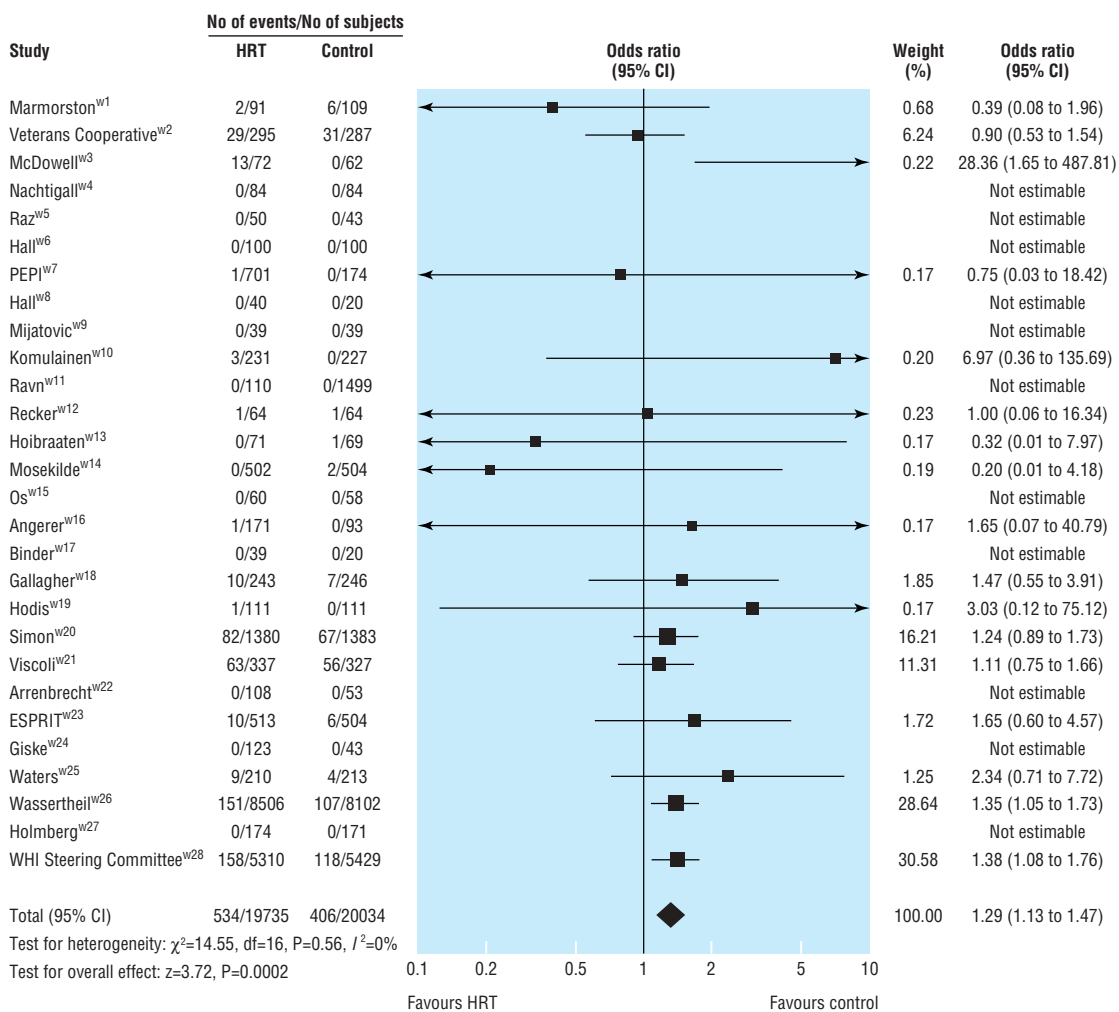


Fig 2 Effects of hormone replacement therapy (HRT) on stroke events

Effect of hormone replacement therapy on stroke and its type and outcome, and transient ischaemic attack

	No of trials	No of subjects	No of events	Control event rate (%)	Odds ratio* (95% CI), P value	Heterogeneity (P value)
Stroke:	28	39 769	940	2.03	1.29 (1.13 to 1.47), 0.0002	0.56
Ischaemic	16	23 426	443	1.59	1.29 (1.06 to 1.56), 0.01	0.59
Haemorrhagic	17	23 690	63	0.25	1.07 (0.65 to 1.75), 0.79	0.75
Transient ischaemic attack	22	10 050	233	2.13	1.02 (0.78 to 1.34), 0.86	0.86
Outcome:						
Fatal	22	36 430	129	0.29	1.28 (0.87 to 1.88), 0.21	0.39
Non-fatal	21	36 230	710	1.72	1.23 (1.06 to 1.44), 0.007	0.45
Death or dependency	14	20 445	145	0.53	1.56 (1.11 to 2.20), 0.01	0.93

*Odds ratios calculated with random effects model.

Twelve trials studied hormone replacement therapy with oestrogen alone, and 16 studied oestrogen plus progesterone. All trials, apart from five,^{w6 w14-w16 w27} were placebo controlled.

We excluded 12 trials (fig 1), eight because they did not report vascular events,^{w30-w35 w37 w38} two because they did not distinguish between stroke and transient ischaemic attacks (total n=685),^{w36 w39} one because it did not have a control group,^{w40} and one because its data are yet to be published (see table B on bmj.com).^{w29}

Data quality

Trials varied in their quality score¹² from 2 to 5, median 5 (maximum score). All trials included were randomised, and 96% of trials gave adequate details of withdrawals.

Quantitative data synthesis

Stroke occurred in 2% of the participants randomised to no hormone replacement therapy and was significantly increased by a third (number needed to harm 147) in those randomised to hormone replacement therapy (fig 2, table). This increase in stroke resulted from an excess of ischaemic strokes but not primary intracerebral haemorrhage, as was seen in the women's health initiative dual trial.^{w26}

A poor outcome after stroke, judged as combined death and dependency, was increased by half with hormone replacement therapy; we also found a non-significant increase in fatal stroke. This relation between hormone replacement therapy and severe

stroke was present individually in three trials.^{w20 w21 w26} Hormone replacement therapy did not alter the rate of transient ischaemic attack (table). We found no statistical heterogeneity for any of the stroke outcomes.

Discussion

This systematic review supports the results of individual trials and previous reviews finding that hormone replacement therapy does not reduce the risk of stroke in postmenopausal women. Indeed, it was associated with an overall 29% increase in the risk of stroke. This effect was driven by an increase in ischaemic but not haemorrhagic stroke. Importantly, the severity of stroke was increased with hormone replacement therapy, since the frequency of a poor functional outcome, judged as combined death and disability or dependency, was 56% higher in those randomised to therapy. Similarly, fatal stroke was non-significantly increased.

We must therefore conclude that hormone replacement therapy cannot be recommended for the primary or secondary prevention of stroke.

Contributors: See bmj.com

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Completing interests: None declared.

Ethical approval: None required.

What is already known on this topic

Postmenopausal women have a greater risk of stroke than premenopausal women

Hormone replacement therapy has been used widely for vascular prophylaxis and to reduce menopausal symptoms and bone loss

Some randomised controlled trials have shown that hormone replacement therapy may increase the risk of stroke

What this study adds

Hormone replacement therapy is associated with an increased risk of stroke, especially of ischaemic type

Hormone replacement therapy cannot be recommended for the primary or secondary prevention of stroke

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Commentary: Time to review all the evidence for hormone replacement therapy

Fay Crawford, Peter Langhorne

The meta-analysis by Bath and Gray provides evidence that hormone replacement therapy does not confer any protection against stroke in postmenopausal women but increases their risk of stroke.¹ These observations add to a rapidly expanding literature on the potential hazards and benefits of the therapy.²

The women's health initiative trial contributes well over half of the current trial data, and its findings dominate the meta-analysis. The women's health initiative trial sought to assess the risks and benefits of three separate interventions—a low fat diet, hormone replacement therapy, and calcium supplements—in 64 500 women over a 15 year period.³ Two separate types of hormone replacement therapy were tested, monotherapy (oestrogen alone) and dual therapy (oestrogen plus progesterone), in two separate trial arms recruiting a total of 27 000 women.

In the dual therapy arm of the trial (n = 16 608) an increased risk of stroke became apparent by the second year, and the trial was ended three years early. Subgroup analysis indicated an increased risk of ischaemic strokes in women in all risk categories, not just those judged to be at high risk. The monotherapy arm (oestrogen alone, for women without a uterus) of the trial (n = 10 739) was also ended early because of an increase in non-fatal strokes. Full details from the subgroup analysis of this second arm are not yet available, and the evaluations of the low fat diet and calcium supplements are continuing.

What should women and their doctors now conclude about hormone replacement therapy? Although opinions may vary about whether the female menopause is a deficiency disease or a rite of passage, several facts seem clear: hormone replacement therapy can relieve some troublesome menopausal symptoms,⁴ but it does have other important health effects, both bad and good.⁵ The women's health initiative trial found that therapy did not meaningfully improve measures of physical and mental function or quality of life,⁵ but some effects that women might value—namely perceptions on youthfulness, attractiveness, and skin tone—have not been adequately studied. Balancing these factors in individual treatment decisions can be difficult. There is a clear need for an overarching meta-analysis of all relevant individual patient data, which can include key baseline participant characteristics, hormone replacement therapy characteristics, and all relevant outcomes (including time to event analyses).

In the interim, all women who consult for hormone replacement therapy need to understand that it can carry an increased risk of ischaemic stroke, coronary events, venous thrombosis, and possibly breast cancer.² In order to minimise these hazards, doctors should recommend hormone replacement therapy only for severe menopausal symptoms and for the shortest possible time in women who are fully informed of these risks.

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Competing interests: None declared.

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Corrections and clarifications

Mother who drowned her five children is granted a retrial after witness gave false evidence

In the full version (on bmj.com) of this News article by Fred Charatan we wrongly said that Andrea Yates had been granted a new trial because an expert medical witness for the prosecution had lied at her original trial (*BMJ* 2005;330:112, 15 Jan). We should have said that the expert witness gave "false testimony" at her original trial.

Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies

The authors of this paper, Mahyar Etminan and colleagues, alerted us shortly before publication to the fact that some of their results were incorrect, although the conclusions are unaffected (*BMJ* 2005;330:63-5, 8 Jan). We managed to correct the abridged version in the journal but not the full version on the web. To see the corrections relating to the web version, go to <http://bmj.bmjournals.com/cgi/content/full/bmj.38302.504063.8F/DC1>

Effectiveness of helmets in skiers and snowboarders: case-control and case crossover study

The wrong lowest recorded temperature mistakenly slipped through in the electronic version of this paper by Brent E Hagel and colleagues (*BMJ* 2005;330:281-3, 5 Feb). The value given in the text on data collection and in table 3 should have read $< -10^{\circ}\text{C}$ [not $\leq 10^{\circ}\text{C}$]. The version in the printed journal is correct.

Agencies "failed miserably" over COX 2 inhibitor

In this News article by Barbara Kermod-Scott, we inadvertently attributed the opening statement (about the failings of two of North America's regulatory agencies) to the Canadian Medical Association (*BMJ* 2005;330:113, 15 Jan). Later in the article we make it clear that the source of the statement is *CMAJ*. Although *CMAJ* is the journal of the Canadian Medical Association, it is at "arms length" from the association.