Hormone therapy and cardiovascular disease: a systematic review and meta-analysis

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CRD summary
This review investigated the effects of hormone replacement therapy on cardiovascular disease in postmenopausal women. The authors found no effect on death or heart attack rates, but risk of stroke was significantly increased in women taking hormone therapy, particularly those aged under 65 years. The conclusions appear reliable for Caucasian populations, however, generalisability of the conclusions to other populations is uncertain.

Authors' objectives
To determine the effects of hormone therapy on cardiovascular disease (CVD) in postmenopausal women.

Searching
MEDLINE, the Cochrane CENTRAL Register, CINAHL and EMBASE were searched up to August 2004; the search terms were reported. Reference lists, letters, editorials and clinical trials databases were also reviewed to identify further studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) lasting over 1 year were eligible for inclusion. The average follow-up in the included trials ranged from 2 to 6.8 years.

Specific interventions included in the review
Studies of hormone therapy (hormone replacement therapy) compared with placebo were eligible for inclusion. Studies of combination therapy (oestrogen and progesterone) and oestrogen-only therapy were included. The most common therapy evaluated was 0.625 mg conjugated equine oestrogen combined with 2.5 mg medroxyprogesterone acetate.

Participants included in the review
The participants were required to be non-hospitalised postmenopausal women. Most of the included studies recruited women with a history of CVD, but in the two largest studies most participants (96%) did not have known CVD. The mean age of the participants in the included studies ranged from 62 to 71 years. The majority were Caucasian women living in the USA.

Outcomes assessed in the review
Studies were required to report 'hard' cardiovascular outcomes, defined as nonfatal acute myocardial infarction (AMI), stroke, death caused by coronary heart disease (CHD) and all-cause mortality. Studies evaluating the progression of atherosclerosis, composite CVD, risk sources, or CVD risk factor profiles were excluded.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review; final decisions on inclusion were made by consensus.

Assessment of study quality
The studies were assessed using the Jadad scale, which assesses the adequacy of randomisation, blinding, intention-to-treat analysis and follow-up rates. A quality score (maximum 5) was awarded, based on these criteria. Studies scoring 4 or 5 were considered high quality. Two reviewers independently assessed study quality.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Data on the numbers of events in each group were obtained from the investigators if not reported in the published studies. These data were used to calculate the relative risks (RRs) and associated 95% confidence intervals (CIs) for each outcome.

**Methods of synthesis**

*How were the studies combined?*

Pooled RRs and 95% CIs were calculated using the random-effects model of DerSimonian and Laird.

*How were differences between studies investigated?*

Statistical heterogeneity was assessed using the Mantel-Haenszel chi-squared test. In the meta-analysis, studies were stratified by type of hormone therapy (combination or oestrogen-only) and participant age at baseline (less than 65 years or 65 years and older).

**Results of the review**

Seven RCTs (n=32,523) were included.

All of the included studies were rated as high quality (quality score of 5).

There was no significant difference between hormone therapy and control groups for all-cause mortality (RR 1.02, 95% CI: 0.92, 1.13; 7 RCTs), CHD mortality (RR 0.99, 95% CI: 0.82, 1.21; 7 RCTs) or nonfatal AMI (RR 1.0, 95% CI: 0.88, 1.14; 7 RCTs). The risk of stroke was significantly higher in the hormone therapy group than in the placebo group (RR 1.29, 95% CI: 1.13, 1.48; 6 RCTs). Statistical heterogeneity was not significant for any outcome. There were no differences between combination therapy and oestrogen-only trials. There was an increased risk of stroke associated with hormone therapy in women aged under 65 years compared with older women (RR 1.35, 95% CI: 1.14, 1.60 and RR 1.20, 95% CI: 0.95, 1.51, respectively). All other outcomes did not vary with age.

**Authors' conclusions**

Hormone therapy, given for 3 to 7 years, increases the risk of stroke but has no effect on risk of AMI or death from CHD or any cause in postmenopausal women.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria. The authors searched a range of sources, although they did not search for unpublished material. It was unclear whether language restrictions were applied, so the risk of language bias cannot be ruled out. Publication bias was not assessed. Validity was assessed using a standard method, which indicated that all the included studies were of a high quality. Measures were taken to reduce bias and errors in the study selection and validity assessment processes, but the methods used during the data extraction were not reported.

Relevant details of the included studies were presented in the text and tables. The studies were combined by meta-analysis and the authors showed that significant statistical heterogeneity was not present. Sources of clinical heterogeneity were also investigated. The authors conclusions are based on high-quality RCTs involving a large number of participants and are likely to be reliable for similar populations to those studied (mainly Caucasian Americans). However, the generalisability of the conclusions to other populations is uncertain.

**Implications of the review for practice and research**

Practice: The authors stated that the balance of risks and benefits of hormone therapy should be assessed for each individual patient, and that the use of hormone therapy for reducing the risk or preventing CVD is not supported by the
results of the review.

Research: The authors stated that research may be required to confirm the review's findings in non-Caucasian populations. They also recommended research on the risks of hormone therapy in women at particularly high risk of CVD. In addition, the authors highlighted that there are gaps in the knowledge of relationships between CVD and different hormone combinations, doses and preparations, potential interactions with homocysteine, and potential modification of effects by aspirin.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.