Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis
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CRD summary
The authors concluded that hormone replacement therapy reduces coronary heart disease events in younger postmenopausal women, and initially increases and then decreases such events in older women. The data appear to support the authors’ conclusion, but poor reporting of the review methods mean it is difficult to assess the reliability of these conclusions.

Authors' objectives
To evaluate the effects of hormone replacement therapy (HRT) on coronary heart disease (CHD) events in younger and older postmenopausal women.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from 1966 to November 2004; the search terms were not reported. In addition, selected journals and reference lists were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 6 months’ duration were eligible for inclusion in the review. The mean duration of the included studies was 4.9 years (range: 0.5 to 10).

Specific interventions included in the review
Studies that compared HRT with placebo or no HRT were eligible for inclusion. The included studies evaluated transdermal and oral oestrogen alone and in combination with various progestins. Details of specific drug treatments were reported.

Participants included in the review
Studies of postmenopausal women were eligible for inclusion. Where reported, in the included studies, the mean number of years from menopause ranged from 0.7 to 24 years in treatment and control groups. The mean age of the participants ranged from 47 to 74 years across treatment and control groups.

Outcomes assessed in the review
The review assessed CHD events, defined as myocardial infarction or death considered to be due to cardiac causes. Studies had to report at least one CHD event.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state how the validity assessment was performed. Studies were assessed for method of randomisation, adequate allocation concealment, blinding of the providers and patients, description of withdrawals and drop-outs, and use of intention-to-treat analysis (see Other Publications of Related Interest). Studies meeting all quality criteria were classified as A, studies that partially met one or more criteria were classified as B, and studies that did not meet one or more criteria were classified as C.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Trial investigators were contacted in order to obtain all available information on CHD events.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for CHD events for women of all ages using meta-analysis.

How were differences between studies investigated?
Studies were classified according to the mean time from menopause at baseline or the mean age as including either younger women (less than 10 years from menopause or younger than 60 years of age) or older women (more than 10 years from menopause or older than 60 years of age). Studies of younger and older women were analysed separately. The results for all ages and younger and older women were compared using the test of interaction. Separate analyses were conducted for studies that included only younger or only older women, and also for events in the first year of treatment and events after 2 years. The influence of study quality was examined by excluding the 5 studies with the lowest quality score on at least one domain.

Results of the review
Twenty-three RCTs (n=39,049) were included.

The drop-out rate was approximately 12% in the treatment groups and 10.8% in the control groups.

For all ages of women (23 RCTs), there was no significant difference between HRT and no HRT in CHD events (OR 0.99, 95% CI: 0.88, 1.11).

In younger women (12 RCTs), HRT was associated with a significant reduction in CHD events compared with the control (OR 0.68, 95% CI: 0.48, 0.96), representing a 32% reduction. The results were similar when studies that included only younger women (number of women not reported) were analysed (OR 0.7, 95% CI: 0.49, 1.0).

In older women (13 RCTs), there was no significant difference between HRT and no HRT in CHD events (OR 1.03, 95% CI: 0.91, 1.16). The results were similar when studies that included only older women (number of women not reported) were analysed (OR 1.08, 95% CI: 0.91, 1.27).

Comparing the results from the two age groups, HRT was associated with a significantly lower CHD event rate in younger women compared with older women (OR 0.66, 95% CI: 0.46, 0.95).

For older women, HRT was associated with a significant increase in CHD events in the first year of treatment (OR 1.47, 95% CI: 1.12, 1.92) and a significant reduction in CHD events after 2 years (OR 0.79, 95% CI: 0.67, 0.93). This time trend was not observed in younger women.

The results were similar after excluding lower quality studies.

There was no evidence of statistical heterogeneity for any of the analyses (p>0.7).

Authors' conclusions
In younger postmenopausal women, HRT reduces CHD events. In older women, HRT initially increases and then decreases CHD events.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched but no attempts to minimise language or publication bias were reported. Validity was assessed using defined criteria, but the results were not reported in full. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Statistical heterogeneity was assessed, studies appear to have been appropriately pooled using meta-analysis, and the influence on the results of various factors was examined. The data appear to support the authors’ conclusion, but lack of reporting of review methods and study quality mean it is difficult to assess the reliability of these conclusions.

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

Practice: The authors stated that decisions about the use of HRT should be made on an individual basis, taking into account the woman's age, menopausal symptoms and risk factors.

Research: The authors stated the need for large RCTs to evaluate clinical CHD measures and other outcomes (including cerebrovascular events and cancer) in younger women.

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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.