Postmenopausal hormone replacement therapy and cardiovascular disease

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Authors' objectives
The objective was to evaluate the association between hormone replacement therapy (HRT) and the primary prevention of cardiovascular disease (CVD).

Searching
MEDLINE was searched from 1966 to 2000 and the Cochrane Library was reviewed. The bibliographies of identified studies and reviews were checked. The search was confined to studies published in English or papers in 'key non-English language journals'. The search terms were given in the report. Letters and editorials were also checked.

Study selection
Study designs of evaluations included in the review
Meta-analyses, randomised controlled trials (RCTs), observational cohort and case-control studies were sought. The studies included in the review were limited to population-based case-control studies or cohort studies with adequate internal control, with at least 3 years' follow-up.

Specific interventions included in the review
The inclusion criteria specified HRT for the primary prevention of CVD. The included studies also incorporated studies of secondary prevention. Treatment was either oestrogen alone (unopposed oestrogen) or combined oestrogen and progesterone. When the type of therapy was unclear, the exposure was classified as HRT. In the included studies, HRT use was described as 'ever', 'never', or 'non-use' of HRT; some studies reported 'current' or 'recent' use, or a specific duration of use. Evidence for HRT use was collected by interview or record reviews.

Participants included in the review
The inclusion criteria stated that the participants had to be healthy postmenopausal women without any evidence of CVD. Although this was the main focus of the review, information from three randomised studies of postmenopausal women with CVD were included.

Outcomes assessed in the review
The inclusion criteria stated that the studies had to report on CVD, stroke, or coronary artery disease (CAD) incidence or mortality. Definitions of CVD were taken from the studies and included stroke, sudden cardiac death, congestive heart failure, peripheral vascular disease, coronary artery bypass and percutaneous transluminal coronary angioplasty.

How were decisions on the relevance of primary studies made?
Two investigators reviewed all the papers for inclusion.

Assessment of study quality
The quality of the studies was evaluated using criteria created by the third U.S. Preventive Services Task Force; the criteria were described in full in the report. The studies were scored as good, fair or poor quality. Only studies that were rated good or fair were included in the analyses. Two reviewers independently rated the quality of each study. Any discrepancies were discussed with a third reviewer.

Data extraction
The data were abstracted onto predesigned forms and evidence tables were compiled. Data were extracted on the study design, methods of assessing HRT use, methods of assessing the outcomes, and results. The tables were presented in full.
Methods of synthesis
How were the studies combined?
The results were discussed in a narrative summary and, where appropriate, meta-analyses were performed using a random-effects model. The mean relative risks (RRs) and confidence intervals (CIs) were calculated for each HRT type and for each outcome. Where possible, summary risks were determined by exposure type (past, current, ever) as well as the combined ‘ever’ used category. A Bayesian framework, using non-informative prior probability distributions, was used. The statistical methods were described in full in the report.

How were differences between studies investigated?
The authors did not describe a method for assessing any differences between the studies.

Results of the review
Sixty-five studies were identified, of which there were 34 cohort studies (over 125,000 participants) and 24 case-control studies (over 8,000 cases) on primary prevention. In addition, there were 4 angiographic studies and 3 RCTs of secondary prevention, one of which reported the preliminary findings from the Women's Health Initiative study.

CVD mortality (8 studies): only current HRT use was associated with a reduced risk of CVD mortality. The summary RR was 0.64 (95% CI: 0.44, 0.93) for current HRT use and non significant (RR 0.75, 95% CI: 0.42, 1.23) for any HRT use.

CAD mortality (5 studies): only current HRT use was associated with a reduced risk of CAD mortality (RR 0.62, 95% CI: 0.40, 0.91). There was no association between past, ever or any use of HRT and CAD mortality (‘any use’ RR 0.74, 95% CI: 0.36, 1.45).

Stroke death (8 cohort studies): the summary RR for stroke death was 0.79 (95% CI: 0.60, 1.01) with any HRT use.

Incidence of CVD (4 studies): all measures of HRT use were associated with an increased risk of CVD incidence, although this was not statistically significant (‘any use’ RR 1.28, 95% CI: 0.86, 2.00).

Incidence of CAD: there was no association between ‘any use’ of HRT and the incidence of CAD (RR 0.87, 95% CI: 0.62, 1.21). There was also no association between HRT use and CAD events in those studies that adjusted for socioeconomic status or educational levels, but the summary RRs were reduced in those studies that did not adjust. The authors suggested that this indicates that socioeconomic status may significantly confound observations of reduced CAD amongst women using HRT.

Stroke: the summary RR showed an increased risk of stroke associated with ‘ever use’ of HRT (RR 1.12, 95% CI: 1.01, 1.23). There was an increased risk of ischaemic stroke with any HRT use (RR 1.20, 95% CI: 1.05, 1.40), but no significant effect on haemorrhagic stroke (RR 0.71, 95% CI: 0.25, 1.29). The preliminary results of the Women's Health Initiative trial indicated that HRT is associated with increased rates of stroke, myocardial infarction and blood clots.

Full details of all narrative discussions and other results were given in report.

Authors' conclusions
The association between HRT and CVD is uncertain because the evidence is limited by the lack of RCTs and possible selection bias in the other studies.

CRD commentary
This was a long and detailed report in which the authors summarised information from a large number of studies. Some of the results were also published elsewhere (see Other Publications of Related Interest nos.1-2). The aims and methods were well described and the search appears to have been good. The organisation of such a large amount of information, summarised in extensive tables, means that it was rather difficult to determine how many participants contributed in total to the results of the review, and to the individual outcomes. The authors acknowledged that there
was little information available from good-quality RCTs and, therefore, the results were based on information from lower quality studies that may have been subject to bias. The conclusions were, therefore, suitably conservative.

The authors noted in an addendum that, since the preparation of the report, the Women's Health Initiative RCT was stopped on safety grounds. The preliminary results indicated that HRT showed no benefit in preventing CHD events, but did show an increased rate of stroke (see Other Publications of Related Interest no.3).

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that results from large RCTs are needed. In addition, further research should investigate whether particular subgroups or women are at particular risk, and look at the effects of HRT on non-Caucasian women.

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