Hormone replacement therapy and risk of venous thromboembolism
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Authors' objectives
To assess the risk of venous thromboembolism with the use of postmenopausal hormone replacement therapy (HRT).

Searching
The authors searched MEDLINE and HealthSTAR from their inception to December 2000, and performed three searches of the Cochrane Controlled Trials Register; the search terms were reported. The reference lists of relevant studies and reviews were checked. Only articles with English abstracts were considered in the review.

Study selection
Study designs of evaluations included in the review
No specific inclusion criteria were reported with regards to the study designs that were eligible for inclusion. Randomised controlled trials (RCTs), case-control studies and cohort studies were included in the review.

Specific interventions included in the review
Studies of HRT or selective oestrogen receptor modulators (SERMs) were eligible for inclusion. Studies using a variety of HRTs, at a range of dosages, and the SERMs tamoxifen or raloxifene were included in the review.

Participants included in the review
Studies enrolling postmenopausal women were eligible for inclusion in the review. Studies were excluded if the population was selected based on prior thrombotic events or the presence of conditions associated with a higher risk of thrombosis. The women in the studies were aged from 35 to 79 years.

Outcomes assessed in the review
Studies reporting deep venous thrombosis and/or pulmonary embolism as either a primary or secondary outcome, or as a reportable adverse event related to HRT or SERM use, were eligible for inclusion in the review.

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 included studies were assessed for quality using criteria developed by the U.S. Preventive Services Task Force. The studies were rated as good, fair or poor based on criteria specific to study design, such as adequate ascertainment and selection of cases or treatment groups, and the appropriateness of analysis. The agreement between reviewers was calculated. Two reviewers independently assessed the quality of the included studies. Any disagreements were resolved by consensus.

Data extraction
The abstracted data were entered into evidence tables, but the authors did not state how many reviewers performed the data extraction. Data on study details, rate of thrombotic events, confounders controlled for and methods of outcome measurement were extracted. Where studies reported the hazard ratios or odds ratios, the authors regarded these as relative risks (RRs); if raw data were available, the RRs were calculated.

Methods of synthesis
How were the studies combined?
For studies of HRT, pooled RRs with 95% confidence intervals (CIs) were calculated for each type of study design.
using both random-effects and fixed-effect models. The Bayesian data analysis framework was used for the meta-
alysis. The SERM studies were combined in a narrative. Publication and selection bias was assessed visually using
funnel plots and tested using the 'trim-and-fill' method.

How were differences between studies investigated?
Studies using HRT were combined according to study design. The authors stated that they tested for the presence of
statistical heterogeneity, although they did not state what test was used. Differences in the characteristics of studies
using HRT and of those using SERMs were discussed in a narrative synthesis.

Results of the review
Seventeen studies were included in the review. Twelve studies assessed the use of HRTs: 3 RCTs (n=3,947), 8 case-
control studies (171 cases) and 1 cohort study (n=112,593). Five RCTs assessed the use of SERMs (n=29,138).

RCTs of HRT (3 studies).

One of the RCTs was rated as good quality and the remaining two were of fair quality.

The authors stated that the RRs from the fixed-effect and random- effects meta-analyses were highly variable as no
events occurred in the placebo group of one trial; the RRs were 3.15 (95% CI: 1.55, 5.69) and 3.08 (95% CI: 0.21,
45.14), respectively.

Case-control studies of HRT (8 studies).

Three of the case-control studies were rated as good quality, three were of fair quality and two were of poor quality.

There was a significant increase in the risk of venous thromboembolism for women receiving HRT in both the fixed-
effect and random-effects meta-analyses; the RRs were 1.97 (95% CI: 1.54, 2.47) and 2.05 (95% CI: 1.40, 2.95),
respectively.

Cohort studies of HRT (1 study).

This study was of a good quality and only the occurrence of pulmonary embolisms was examined. The RRs for current
and past use of HRT were 2.1 (95% CI: 1.2, 3.8) and 1.3 (95% CI: 0.7, 2.4), respectively. Current users with a duration
of 5 or more years had an RR of 1.9 (95% CI: 0.9, 4.0), while current users of less than 5 years had an RR of 2.6 (95%
CI: 1.2, 5.2).

Combining the 12 studies gave RRs of 2.08 (95% CI: 1.68, 2.54) and 2.14 (95% CI: 1.64, 2.81) for the fixed-effect and
random-effects meta-analyses, respectively. No statistical heterogeneity was identified (P=0.196). No publication bias
was identified, either visually from funnel plots or by testing using the trim-and-fill method.

SERM use (5 studies).

Two of the studies were rated as fair quality and the remaining three were of poor quality.

Two of the RCTs assessed the use of raloxifene. One found that there was a significant increase in the risk of venous
thromboembolism for raloxifene use compared with placebo (RR 3.1, 95% CI: 1.5, 6.2), while the other reported that
no events occurred. Three RCTs assessed the use of tamoxifen for breast cancer prevention; one suggested that
tamoxifen use was associated with a statistically significant increase in pulmonary embolism risk, one suggested a
statistically significant increase in general vascular events compared with placebo, and one did not suggest any
significant differences in terms of general vascular events.

Authors' conclusions
Postmenopausal HRT use is associated with an increase risk of venous thromboembolism, and this risk may be highest
in the first year of use. SERMs are also associated with a similar increased risk.
CRD commentary
The review question was clear in terms of the participants, interventions and outcomes of interest, although a broad range of study designs were included in the review. Three electronic databases were searched but, given the limited search for unpublished material and language restrictions, the presence of language and publication bias cannot be ruled out. The authors did, however, assess the possibility of publication bias. The methods used to select studies for inclusion in the review were not reported, so it is not known whether any efforts were made to reduce bias or reviewer error. The validity of the included studies was assessed using established criteria in an adequate manner to reduce error and bias.

The studies were combined according to study design, although the main conclusion appears to have been based on the combined study design meta-analysis. The authors stated that most of the studies presented results that were adjusted for potential confounders. However, limited details were presented and combining results from various studies that have been adjusted for a number of potentially different confounders may be inappropriate. Given the restrictions on the search it is possible that relevant studies might have been missed, which reduces the reliability of the authors' conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: Further investigation is needed to identify the individuals at highest risk, to determine the utility of screening for coagulopathies prior to starting hormone treatment, and to determine the optimal HRT regimen.

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