Oestrogen plus progestin increased venous thromboembolic disease in postmenopausal women with coronary artery disease


**QUESTION:** Does oestrogen plus progestin increase the risk of venous thromboembolic events in postmenopausal women with established coronary artery disease (CAD)?

**Design**
Randomised [allocation concealed]*, blinded (investigators, patients, outcome assessors), placebo controlled trial with mean follow up of 4.1 years (Heart and Estrogen/progestin Replacement Study [HERS]).

**Setting**
20 clinical centres in the US.

**Patients**
2763 postmenopausal women < 80 years of age (mean age 67 y, 89% white) with established CAD but no previous venous thromboembolism and who had not had a hysterectomy. Exclusion criteria were CAD event ≤ 6 months or hormone use ≤ 3 months before entry, venous thromboembolism, breast cancer, endometrial cancer, uncontrolled hypertension, diabetes, or other fatal disease. Follow up was 98%.

**Intervention**
1380 women were allocated to hormone replacement therapy (HRT) of conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg once/day; 1383 women were allocated to placebo.

**Main outcome measures**
Deep venous thrombosis or pulmonary embolism.

**Main results**
Analysis was by intention to treat. 34 women (2.5%) who received HRT and 13 (0.9%) who received placebo had a venous thromboembolic event (relative hazard 2.7, 95% CI 1.4 to 5.0, p = 0.003) (table). Women who received HRT had higher rates of deep venous thrombosis (p = 0.008) and non-idiopathic venous thromboembolic events (p = 0.01) than women who received placebo (table); no differences existed between groups for pulmonary embolism (p = 0.08) or idiopathic thromboembolic events (p = 0.09) (table).

**Conclusion**
Oestrogen plus progestin increased the risk of venous thromboembolic disease in postmenopausal women with established coronary artery disease.

*Information provided by author.

**COMMENTARY**
Controversy continues over the nature and extent of the risks of hormone therapy in women, whether used as an oral contraceptive or HRT. The differences of scientific opinion, however, as to the risks and benefits of hormone therapies, arise largely from the difficulty in interpreting studies that are limited by methodological problems.

This well designed, randomised, triple blind, placebo controlled trial by Grady et al provides convincing evidence that women with established CAD who take HRT (specifically oestrogen plus progestin) after menopause have an increased risk of venous thromboembolic disease. At a mean follow up of 3.3 years, the investigators notified participants to discontinue study medications in situations associated with increased risk for venous thromboembolism, such as surgery, admission to hospital, fracture, and cancer. Among women in the study, treating 66 women with CAD for 1 year would result in 1 additional venous thromboembolic event. The findings confirm those of previous studies, concluding that the increased risk was most likely related to the oestrogen component of hormone therapy.

This study supports women’s health advocates who, over the past 50 years, have cautioned women of all ages against indiscriminate use of hormone therapy. Health practitioners are therefore challenged to weigh the benefits and risks when advising postmenopausal women with CAD about the use of HRT. It is clear from this study that women with any risk factors (eg, cancer, cardiovascular disease, lower extremity fracture, or immobilisation for any reason) should not take HRT. If a woman decides that the benefits outweigh the risks, then she needs to be advised on how to prevent thromboembolic disease (eg, increasing mobility). Health practitioners and women also need to be informed of nutritional alternatives to HRT, which are currently still under investigation, and other related current issues.

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**Outcomes at mean 4.1 years v placebo in postmenopausal women with established coronary artery disease†**

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>Placebo</th>
<th>RRI (95% CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any venous thromboembolic event</td>
<td>2.5%</td>
<td>0.9%</td>
<td>162% (40 to 390)</td>
<td>66 (39 to 172)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1.8%</td>
<td>0.7%</td>
<td>176% (33 to 484)</td>
<td>86 (48 to 279)</td>
</tr>
<tr>
<td>Non-idiopathic venous thromboembolic event</td>
<td>1.8%</td>
<td>0.7%</td>
<td>151% (23 to 412)</td>
<td>92 (50 to 372)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.8%</td>
<td>0.3%</td>
<td>176% (7 to 718)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Idiopathic venous thromboembolic event</td>
<td>0.7%</td>
<td>0.2%</td>
<td>201% (12 to 925)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

†Abbreviations defined in glossary: RRI, NNH, and CI calculated from data in article.