Oestrone plus progestin was not effective for long term secondary prevention of coronary heart disease in postmenopausal women


QUESTION: In postmenopausal women with established coronary heart disease (CHD), does oestrone plus progestin reduce the risks of CHD events after 6.8 years of follow up?

Design
Randomised (allocation concealed*), placebo controlled trial. The study was blinded (patients, investigators, and outcome assessors*) for the initial mean 4.1 years of follow up and unblinded* for the subsequent 2.7 years of follow up (the latter 2.7 years was the HERS II study).

Setting
20 US outpatient and community centres.

Patients
2763 postmenopausal women < 80 years of age (mean age 67 y) with established CHD who had not had a hysterectomy. Of those alive at 4.1 years (n=2510), follow up was 84% at 6.8 years.

Intervention
Women were allocated to conjugated oestrone, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day (n=1380), or placebo (n=1383) for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the oestrogen plus progestin group and 1165 women in the placebo group continued follow up, and open label hormone therapy was prescribed at the discretion of the women’s personal physicians.

Main outcome measures
The main outcome was the composite end point of CHD death or nonfatal myocardial infarction (MI). Secondary outcomes included coronary artery bypass graft surgery, percutaneous coronary revascularisation, hospital admission for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischaemic attack, and peripheral arterial disease.

Main results
Analysis was by intention to treat. The composite end point rate of CHD death or nonfatal MI did not differ between groups after mean follow up durations of 4.1 years, between 4.1 and 6.8 years, or at 6.8 years (table). Rates of CHD death, nonfatal MI, and secondary cardiovascular outcomes also did not differ between groups (p ≥ 0.27).

Conclusion
In postmenopausal women with established coronary heart disease, oestrone plus progestin did not reduce the risk of coronary heart disease events after 6.8 years of follow up.

*See glossary.
Long term oestrogen plus progestin increased venous thromboembolism and biliary tract surgery in postmenopausal women


QUESTION: In postmenopausal women with established coronary heart disease (CHD), what is the effect of oestrogen plus progestin on the risks of common noncardiovascular disease outcomes after 6.8 years of follow up?

**Design**
Randomised (allocation concealed*), placebo controlled trial. The study was blinded (patients, investigators, and outcome assessors* for the mean 4.1 years of follow up and unblinded* for the subsequent mean 2.7 years of follow up (the latter 2.7 years was the HERS II study).

**Setting**
20 US outpatient and community centres.

**Patients**
2763 postmenopausal women < 80 years of age (mean age 67 y) with established CHD who had not had a hysterectomy. Exclusion criteria included deep venous thrombosis, pulmonary embolism, breast cancer, endometrial hyperplasia or cancer, abnormal Papanicolaou result, hormone use in the previous 3 months, and life threatening disease. Of those alive at 4.1 years, (n=2510), follow up was 84% at 6.8 years.

**Intervention**
Women were allocated to conjugated oestrogen, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day (n=1383), or placebo (n=1380) for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the oestrogen plus progestin group and 1165 women in the placebo group continued follow up, and open label hormone therapy was prescribed at the discretion of the women’s personal physicians.

**Main outcome measures**
Venous thromboembolism, biliary tract surgery, cancer, fractures, and mortality.

**Main results**
Analysis was by intention to treat. At 6.8 years, women who received oestrogen plus progestin had increased risks of venous thromboembolism and biliary tract surgery (table). Rates of cancer, fractures, and total mortality did not differ between groups (table).

**Conclusion**
In postmenopausal women with established coronary heart disease, treatment for 6.8 years with oestrogen plus progestin increased the risks of venous thromboembolism and biliary tract surgery.

*See glossary.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Events/1000 person y</th>
<th>Adjusted relative hazard (95% CI)†</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>5.9</td>
<td>2.8</td>
<td>2.06 (1.26 to 3.36)</td>
</tr>
<tr>
<td>Biliary tract surgery</td>
<td>19.1</td>
<td>12.9</td>
<td>1.44 (1.10 to 1.90)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>19.7</td>
<td>16.5</td>
<td>1.19 (0.95 to 1.50)</td>
</tr>
<tr>
<td>Any fracture</td>
<td>29.7</td>
<td>28.4</td>
<td>1.07 (0.89 to 1.29)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>30.6</td>
<td>27.6</td>
<td>1.08 (0.91 to 1.29)</td>
</tr>
</tbody>
</table>

†See glossary.

**COMMENTARY—continued from previous page**

A reasonable consensus is now emerging.** Firstly, HRT should not be prescribed to prevent CHD or used for general “prevention” purposes. Secondly, other alternatives for osteoporosis prevention should be considered and clinicians should be cautious about using HRT for the sole purpose of osteoporosis prevention. Finally, women should be advised of the risks and benefits before taking HRT to relieve menopausal symptoms. Although women may decide that the risks are worth relief of troublesome symptoms, they should use the lowest effective dose for the shortest time possible.

David Atkins, MD, MPH
Agency for Healthcare Research and Quality
Rockville, Maryland, USA