Hormone Treatment of Menopausal Women: What Are the Data Telling Us (and Not Telling Us)?

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Financial Conflicts of Interest

The author has no conflicts to declare (but wishes he did).
History of the Research

• Evidence that menopause is related to CVD
• Epidemiologic/observational studies
• The Heart and Estrogen/Progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) Hormone Trials, initial interpretations
• The WHI Hormone Trials, revisited: Revisionist views and follow-up studies
• New RCT data since the WHI

Mortality Rates in Women for Different Diseases by Age in Five Year Groups


Incidence of Cardiovascular Events in Women Before and After the Menopause


Incidence of Cardiovascular Disease: Relation to Menopause Status

Observational Data

Before the year 2000, research on estrogens, the menopause, and cardiovascular disease (CVD) was mainly limited to retrospective epidemiologic and prospective observational studies comparing rates of CVD in women for whom estrogen was or was not prescribed. Rates of cardiovascular events and all-cause mortality were the usual outcomes reported.

Circumstantial Evidence for Cardioprotection by Estrogen?

• There are multiple plausible mechanisms by which estrogens could help prevent or delay CVD:
  – Lipid effects- lower LDL and Lpa, higher HDL
  – Antioxidant effects- decreased lipid oxidation
  – Vascular effects- ENOS upregulation, vasodilation
  – Inhibition of platelet aggregation
  – Increased prostacyclin (COX-2 activity)
  – Decreases in cell adhesion molecules (CAMs)
  – Impaired CAM tethering of leucocytes
  – Decreases in inflammatory factors (TNF-α, IL-6, MCP-1, fibrinogen)

• Epidemiologic/Observational Studies suggested 40-50% reduction in CHD rates in women taking estrogen
Observational Studies of ERT/HRT and CHD

Adjusted* Relative Risk of Death Among All Postmenopausal Women in the Nurses Health Study

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>NEVER</th>
<th>CURRENT</th>
<th>PAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>2051</td>
<td>574</td>
<td>1012</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>0.63 (0.56-0.70)</td>
<td>1.03 (0.94-1.12)</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>289</td>
<td>43</td>
<td>129</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>0.47 (0.32-0.69)</td>
<td>0.99 (0.75-1.30)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>91</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>0.68 (0.39-1.16)</td>
<td>1.07 (0.68-1.69)</td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>1103</td>
<td>353</td>
<td>529</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>0.71 (0.62-0.81)</td>
<td>1.04 (0.92-1.17)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>246</td>
<td>85</td>
<td>94</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>0.77 (0.59-1.00)</td>
<td>0.83 (0.63-1.09)</td>
</tr>
</tbody>
</table>

*CI = Confidence Interval. Values are adjusted for age, age at menopause, type of menopause, BMI, DM, high BP, high cholesterol, smoking, OC use, family H/O MI or breast Ca, parity

Inherent Biases in Observational Studies

- **Selection bias**
  - Healthier women prescribed HT

- **Prevention bias**
  - Monitoring and treatment of CVD risk factors more intensive in women prescribed HT

- **Compliance bias**
  - Patients with greater adherence (even to placebo) may have better outcomes

- **Survivor bias**
  - HT may be stopped due to illness and those women counted as non-treated

- **Prevalence-incidence bias**
  - Early adverse effects of HT not observed if user dies before becoming eligible for inclusion in cohort

Prospective Trials: HERS and the WHI

• The need for randomized prospective trials of estrogen effect on CVD risk in menopausal women was widely appreciated, but the magnitude of the effort required to reach acceptable power was daunting
• Heart and Estrogen/Progestin Replacement Study (HERS) - A trial of secondary prevention
• Womens’ Health Initiative (WHI) Hormone Studies- A trial of primary prevention

HERS: A Secondary Prevention Trial

• Goal: Determine CHD event risk in women with documented CHD
  – MI, CABG, cutaneous angioplasty, or 50% narrowing of coronary artery
• 2763 postmenopausal women (average age 67) randomized to receive either CEE 0.625, CEE with MPA 2.5 mg daily, or placebo
• During the average follow-up of 6.8 yrs, the incidence of myocardial infarctions and coronary deaths were about the same in both groups
# HERS Trial: Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>1.08</td>
<td>(0.84-1.38)</td>
</tr>
<tr>
<td>Nonfatal and fatal MI</td>
<td>0.99</td>
<td>(0.80-1.22)</td>
</tr>
<tr>
<td>CABG</td>
<td>0.87</td>
<td>(0.66-1.16)</td>
</tr>
<tr>
<td>Percutaneous revascularization</td>
<td>0.95</td>
<td>(0.77-1.17)</td>
</tr>
<tr>
<td>Stroke / TIA</td>
<td>1.13</td>
<td>(0.85-1.48)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.89</td>
<td>(1.50-5.58)</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>1.38</td>
<td>(1.00-1.92)</td>
</tr>
<tr>
<td>All cancers</td>
<td>1.12</td>
<td>(0.84-1.50)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.30</td>
<td>(0.77-2.19)</td>
</tr>
</tbody>
</table>

*JAMA. 1998;280(7):605-613.*

# HERS: Conclusion

- Estrogen treatment should not be used to reduce the risk of CVD events in older postmenopausal women with established coronary heart disease.
Women’s Heath Initiative (WHI) Hormone Trials

- Randomized, double-blinded placebo-controlled trials intended as test of primary prevention in women ages 50-79, planned for 8.5 years
- Estrogen + Progestin (uterus intact); stopped at 5.2 years
  - PremPro® 0.625 CEE/2.5 MPA daily; n=8506
  - Placebo; n=8102
- Estrogen alone (hysterectomized); stopped at 6.8 years
  - Premarin® 0.625 CEE daily; n=5310
  - Placebo; n=5429
- Endpoints
  - Cardiovascular events (new heart attack, cardiac death,)
  - Other clinical events (fractures, cancers, VTE, stroke)

WHI E+P Trial: Subject Characteristics

Mean age 63
BMI 28.5 kg/m²

Hormone Use Prior to Study Entry

- Never User 74%
- Past User 20%
- Current User 6%
Clinical Event Incidences in the WHI Estrogen + Progestin Arm vs. Placebo

- **Deaths**: 218 (0.98 (0.82-1.18)) vs. 231 (0.76 (0.69-0.85))
- **All Fractures**: 650 (0.63 (0.43-0.92)) vs. 788
- **Colon Cancer**: 46 vs. 46 (1.24 (1.00–1.54))
- **DVT/PE**: 67 vs. 218 (2.1 (1.58-2.82))
- **CHD Events**: 127 vs. 164 (1.40 (1.07–1.85))
- **Strokes**: 151 vs. 86 (1.54 (1.00–1.54))
- **Breast Cancer**: 293 vs. 385 (1.25 (1.07–1.46))

Outcomes

- **Colon Cancer**: 67 vs. 46 (1.24 (1.00–1.54))
- **DVT/PE**: 67 vs. 218 (2.1 (1.58-2.82))
- **CHD Events**: 127 vs. 164 (1.40 (1.07–1.85))
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Clinical Outcomes in the E-only Arm of the WHI HT Trial

- **Fractures**: 724 vs. 503 (0.70 (0.63-0.79))
- **Breast Cancer**: 124 vs. 94 (0.75 (0.51-1.09))
- **Thromboembolic Disease**: 78 vs. 101 (1.33 (0.99-1.79))
- **Stroke**: 118 vs. 58 (1.39 (1.10-1.77))
- **Coronary Heart Disease**: 199 vs. 177 (0.91 (0.75-1.12))

**References**

- Chlebowski RT, et al. JAMA 2010;304:1684 (12 y follow-up data)
- LaCroix, JAMA 2011:305:1305-1314 (10.7 year f/u)
Differences Between Prior MHT Studies and the WHI E and E+ P Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prior Studies</th>
<th>E+P Trial</th>
<th>E Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Observational Cohort</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case Control</td>
<td>Randomized</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blinded</td>
<td></td>
</tr>
<tr>
<td>Age at Onset of Therapy</td>
<td>40-55 years (mean 51.1)</td>
<td>55-79 years (mean 62.7)</td>
<td>55-79 years (mean 63.6)</td>
</tr>
<tr>
<td>Treatment Modality</td>
<td>Mainly CE</td>
<td>PremPro®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some + MPA</td>
<td>CE 0.625 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+MPA 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>Duration Rx</td>
<td>10-15 years</td>
<td>5 years</td>
<td>7 years</td>
</tr>
</tbody>
</table>

The WHI Hormone Trials, Revisited: Follow-up Studies and Revisionist Analyses

- WHI investigators analyzed outcomes by subgroups of age and time since menopause
- WHI investigators conducted a follow-up study measuring CAC in women in the E-alone trial
- WHI critics examined distribution of CVD events by time of occurrence in the study
- New interpretations of WHI data
  - Effects of HRT on CVD are dependent upon time HRT is initiated relative to menopause and/or age (the “timing hypothesis”)
  - Longer duration of treatment may be required for CVD benefit to become apparent
Estrogen plus Progestin and the Risk of CHD in Various Subgroups of WHI Women*

*From Manson, et al. New Engl J Med, 2003;349:530 (Fig. 3)

Assume mean postmenopausal durations of 5, 15, and 25 years for the <10, 10-20, and ≥20 year groups, respectively (actual means not provided).

Draw best fit regression line

Extrapolate the best fit regression line to a value of 0 postmenopausal years.

Event Hazard Ratios by Age Subgroups in WHI Estrogen-only Arm

In 50-59 Group

Coronary Heart Disease
- 50-59: HR=0.56
- 60-69: HR=1.08
- 70-79: HR=1.22

Stroke
- 50-59: HR=0.72
- 60-69: HR=1.08
- 70-79: HR=1.22

Thromboembolism
- 50-59: HR=0.72
- 60-69: HR=1.08
- 70-79: HR=1.22

Breast Cancer
- 50-59: HR=0.72
- 60-69: HR=1.08
- 70-79: HR=1.22

JAMA 2004:291;1701-1712
Multivariate Odds Ratios for a Coronary-Artery Calcium Score of More Than 100, According to Randomized-Group Assignment and Coronary-Risk-Factor Status


CHD Events Associated with HRT in Younger and Older Women: Meta-analysis of 23 Randomized Controlled Trials (191,340 patient-years)

Primary Prevention of Atherosclerotic Disease

**VASCULAR BIOLOGIST’S DEFINITION OF PRIMARY PREVENTION**
- Gradual, Progressive Years
- Estrogen Effects
- Fibrous Cap
- Plaque

**CARDIOLOGIST’S DEFINITION OF PRIMARY PREVENTION**
- Sudden, Rapid, Hours
- Estrogen Effects
- Thrombus
- Event

After Clarkson T, unpublished

Rates of Coronary Heart Disease Outcomes and Absolute Numbers of Events (numerals in bars) in the E+P and Placebo Groups by Year in the WHI Hormone Trial.

Data from JAMA 288:321-333, 2002
First Pass Hepatic Effects of Estrogens Taken by Mouth

Differential Effects of Oral vs. Transdermal Estrogen Therapy on Thromboembolic Complications

Odds Ratios and (Confidence Intervals)

<table>
<thead>
<tr>
<th>Study Publication</th>
<th>Oral Estrogen</th>
<th>Transdermal Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarabin, et al. <em>Lancet</em>, 2003, 362(9382): p. 428-32.</td>
<td>3.5 (1.8-6.8)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td>Canonico, et al. <em>Circulation</em>, 2007,115: 840-845</td>
<td>4.2 (1.5-11.6)</td>
<td>0.9 (0.4-2.1)</td>
</tr>
</tbody>
</table>
Might Duration of Trial Be an Important Factor?

- Observational Studies followed subjects for 10-15 Years
- CHD event rates appear to accelerate 5-10 years after the age of menopause
- New areas of plaque probably do not cause clinical events for 5 or more years
- If HRT only prevents new plaque formation, then more than 5 years may be required before protection against events becomes apparent

Kaplan-Meier Estimates of Cumulative Hazards for CHD Events by Follow-up Year in the WHI E-Only Arm vs. Placebo

Coronary Heart Disease

HR 0.91
(95% CI 0.75 - 1.12)

<table>
<thead>
<tr>
<th>Events</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>5310</td>
</tr>
<tr>
<td></td>
<td>5210</td>
</tr>
<tr>
<td></td>
<td>5147</td>
</tr>
<tr>
<td></td>
<td>5067</td>
</tr>
<tr>
<td></td>
<td>4978</td>
</tr>
<tr>
<td></td>
<td>4874</td>
</tr>
<tr>
<td></td>
<td>4804</td>
</tr>
<tr>
<td></td>
<td>4015</td>
</tr>
<tr>
<td></td>
<td>2331</td>
</tr>
<tr>
<td>Placebo</td>
<td>5429</td>
</tr>
<tr>
<td></td>
<td>5336</td>
</tr>
<tr>
<td></td>
<td>5254</td>
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<td>5171</td>
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<td>5072</td>
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<td></td>
<td>4950</td>
</tr>
<tr>
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<td>4015</td>
</tr>
<tr>
<td></td>
<td>2331</td>
</tr>
<tr>
<td></td>
<td>1106</td>
</tr>
</tbody>
</table>

JAMA 2004:291;1701-1712
**Coronary Heart Disease Event Rates per Thousand Women Active by Follow-up Year in the WHI E-Only Arm vs. Placebo**

Data from *JAMA* 2004:291;1701-1712

**New Data Since the WHI**

- Danish Osteoporosis Prevention Study (DOPS)
- Kronos Early Estrogen Prevention Study (KEEPS)
- Early versus Late Intervention Trial with Estradiol (ELITE)
Danish Osteoporosis Prevention Study (DOPS) CVD Outcome

Various CVD and Mortality Outcomes
Danish Osteoporosis Prevention Study

16 Years Randomized Treatment Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control</th>
<th>Treated</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>53</td>
<td>33</td>
<td>0.61</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>40</td>
<td>27</td>
<td>0.66</td>
<td>0.10</td>
</tr>
<tr>
<td>CVD death</td>
<td>23</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other death</td>
<td>17</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>8</td>
<td>3</td>
<td>0.37</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>11</td>
<td>5</td>
<td>0.45</td>
<td>0.14</td>
</tr>
</tbody>
</table>


# Adverse Outcomes in the Danish Osteoporosis Prevention Study

## 16 Years Randomized Treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>Control</th>
<th>Treated</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>21</td>
<td>19</td>
<td>0.89</td>
<td>0.71</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>5</td>
<td>4</td>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>3</td>
<td>1</td>
<td>0.33</td>
<td>0.34</td>
</tr>
<tr>
<td>All Cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>26</td>
<td>24</td>
<td>0.90</td>
<td>0.72</td>
</tr>
<tr>
<td>Other cancer</td>
<td>43</td>
<td>52</td>
<td>1.21</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*3 women with both breast and other cancer


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## Carotid Artery Wall Imaging

**Carotid Artery Intima-media Thickness (CIMT)**

![Carotid Artery Intima-media Thickness (CIMT)](image)

- MI, Coronary Death
- All CVD Events

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>p trend &lt; 0.01</th>
<th>p trend &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>MI, Coronary Death</td>
<td>All CVD Events</td>
</tr>
<tr>
<td>0.011 - 0.018 mm/yr</td>
<td>0.011 - 0.018 mm/yr</td>
<td>0.011 - 0.018 mm/yr</td>
</tr>
<tr>
<td>0.018 - 0.034 mm/yr</td>
<td>0.018 - 0.034 mm/yr</td>
<td>0.018 - 0.034 mm/yr</td>
</tr>
<tr>
<td>&gt; 0.034 mm/yr</td>
<td>&gt; 0.034 mm/yr</td>
<td>&gt; 0.034 mm/yr</td>
</tr>
</tbody>
</table>

KEEPS Subjects Study Flow

4532 screened by telephone

2811 Screened Out

994 No Showed or Declined

727 Randomized

230 o-CEE

- 150 (65%) completed on protocol
- 37 (16%) completed off medications
- 43 (19%) discontinued

222 t-E2

- 132 (59%) completed on protocol
- 47 (21%) completed off medications
- 43 (19%) discontinued

275 Placebo

- 184 (67%) completed on protocol
- 34 (12%) completed study off medications
- 57 (21%) discontinued

KEEPS Serum Estradiol and Estrone Levels by Treatment and Time
**KEEPS: Effects of Treatment on Imaging Endpoints**

![Graph A](image1)

- o-CEE vs. Pbo: p = 0.51
- T-E2 vs. Pbo: p = 0.27

![Graph B](image2)

- o-CEE vs. Pbo: p = 0.44
- T-E2 vs. Pbo: p = 0.70

**KEEPS Subgroup Analysis of CAC Increase in Women with and without Baseline CAC**

![Graph A](image3)

- Baseline CAC = 0
  - N = 503
  - O-CEE: 12.3% (20/162)
  - T-E2: 12.7% (19/150)
  - Placebo: 13.6% (20/191)

![Graph B](image4)

- Baseline CAC > 0
  - N = 67
  - O-CEE: 63.2% (12/19)
  - T-E2: 63.6% (14/22)
  - Placebo: 73.1% (19/26)
Early versus Late Intervention Trial with Estradiol (ELITE); Enrollment, Randomization, and Follow-up.


ELITE: CIMT Progression According to Study Group and Postmenopause Stratum.

FDA Black Box Warning for HT

Endometrial Cancer Risk
- Unopposed estrogen use increases risk in women with intact uteri; adding progestin may decrease risk of endometrial hyperplasia (possible precursor to endometrial CA); use adequate diagnostic measures such as endometrial sampling to rule out malignancy if undiagnosed persistent or recurrent abnormal genital bleeding occurs

Cardiovascular and Other Risks
- Estrogens +/- progestins are not indicated for cardiovascular disease or dementia prevention; increased risk of stroke and DVT (from WHI estrogen-alone substudy) and MI, stroke, PE/DVT, and invasive breast CA (from WHI estrogen/progestin substudy) in postmenopausal women; increased risk of probable dementia in postmenopausal women >65 yo on a WHI regimen x 4-5 years; WHI regimens = conjugated estrogens 0.625 mg/day with or w/o medroxyprogesterone 2.5 mg/day, other doses or estrogen/progestin combos were not studied, but assume similar risk; use lowest effective estrogen dose and shortest duration based on individual therapeutic goals and risks

Summary I
- Most large observational studies suggested net benefit of HT administration in menopausal women
  - Reduction in CVD events
  - Reduction in vasomotor symptoms
  - Reduction in fractures
- The largest randomized controlled trials to date (HERS and WHI) did not show cardiovascular benefits
  - HERS – Secondary prevention trial in elderly women
  - Limitations of the WHI included:
    - Inclusion of older women, likely with subclinical CVD
    - Short duration compared to observational studies
    - Use of single dose and type of estrogen (oral 0.625 mg CEE)
    - Administration of medroxyprogesterone acetate with possible effect to increase breast cancer rate
Summary II

- Secondary analyses of WHI data and WHI follow-up studies suggest:
  - No excess breast cancer risk in E-alone group
  - Lower rates of appearance of CAC in E-alone group
  - Lower rates of CVD events after 5 years of treatment in E-alone group
- More recent randomized prospective trials show:
  - Lower rates of combined CVD endpoint in estrogen treated women vs. non-treated women after 16 years of observation (DOPS)
  - No difference in CVD progression rates with estrogen treatment vs. placebo in recently menopausal women (KEEPS)
  - Less progression of CIMT with estrogen vs. placebo when initiated within 6 years after menopause but not when initiated 10 or more years after menopause (ELITE)

Conclusions

- Results of the WHI parsed and reanalyzed do not justify the current black box warning* and suggest no harm, or even protection, in younger, more recently menopausal women
- Newer data, consistent with long term observational studies, show no harm (KEEPS) or protection against subclinical CVD progression (ELITE) and CVD events (DOPS) when estrogen treatment is initiated early in the menopause
- Further research on menopausal HT should be pursued to clarify effects of:
  - Doses and agents (especially progestogens)
  - Route of administration
  - Timing/Age

*Opinion of the author and not the Phoenix VAHCS or the U.S. Veterans Administration