The Economic Return from the Women’s Health Initiative Estrogen Plus Progestin Clinical Trial

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Women’s Health Initiative Annual Investigator Meeting
5/2/2014
Background: Women’s Health Initiative (WHI) Estrogen+Progestin (E+P) Clinical Trial

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
Principal Results From the Women’s Health Initiative Randomized Controlled Trial

Context: Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective: To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design: Estrogen plus progestin component of the Women’s Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 U.S. clinical centers in 1993-1998.

Interventions: Participants received conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8,566) or placebo (n = 8,112).

Main Outcomes Measures: The primary outcome was coronary heart disease (CHD) (myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results: On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the data statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (95% confidence intervals [CI]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.58) with 290 cases; stroke, 1.41 (1.07-1.86) with 212 cases; PE, 2.13 (1.39-3.26) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 12 cases; endometrial cancer, 0.82 (0.47-1.43) with 7 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CI) for composite outcomes were 1.32 (1.06-1.63) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.95 (0.82-1.18) for total mortality, and 1.15 (1.03-1.29) for the global index. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 6 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10,000 person-years.

Conclusions: Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should be terminated or continued for primary prevention of CHD.
# Unexpected Harms and Benefits with Postmenopausal Estrogen+Progestin

## Table 2. Clinical Outcomes by Randomization Assignment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Patients (Annualized %)</th>
<th>Hazard Ratio</th>
<th>Nominal 95% CI</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estrogen + Progestin (n = 8506)</td>
<td>Placebo (n = 8102)</td>
<td></td>
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</tr>
<tr>
<td>Follow-up time, mean (SD), mo</td>
<td>62.2 (16.1)</td>
<td>61.2 (15.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiovascular disease†</td>
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<tr>
<td>CHD</td>
<td>164 (0.37)</td>
<td>122 (0.30)</td>
<td>1.29</td>
<td><strong>1.02-1.63</strong></td>
</tr>
<tr>
<td>CHD death</td>
<td>33 (0.07)</td>
<td>26 (0.06)</td>
<td>1.18</td>
<td><strong>0.70-1.97</strong></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>133 (0.30)</td>
<td>96 (0.23)</td>
<td>1.32</td>
<td><strong>1.02-1.72</strong></td>
</tr>
<tr>
<td>CABG/PTCA</td>
<td>183 (0.42)</td>
<td>171 (0.41)</td>
<td>1.04</td>
<td><strong>0.84-1.28</strong></td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (0.29)</td>
<td>85 (0.21)</td>
<td>1.41</td>
<td><strong>1.07-1.85</strong></td>
</tr>
<tr>
<td>Fatal</td>
<td>16 (0.04)</td>
<td>13 (0.03)</td>
<td>1.20</td>
<td><strong>0.58-2.50</strong></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>94 (0.21)</td>
<td>59 (0.14)</td>
<td>1.50</td>
<td><strong>1.08-2.08</strong></td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td>151 (0.34)</td>
<td>67 (0.16)</td>
<td>2.11</td>
<td><strong>1.58-2.82</strong></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>115 (0.26)</td>
<td>52 (0.13)</td>
<td>2.07</td>
<td><strong>1.49-2.87</strong></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>70 (0.16)</td>
<td>31 (0.08)</td>
<td>2.13</td>
<td><strong>1.39-3.25</strong></td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>694 (1.57)</td>
<td>546 (1.32)</td>
<td>1.22</td>
<td><strong>1.09-1.36</strong></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive breast</td>
<td>166 (0.38)</td>
<td>124 (0.30)</td>
<td>1.26</td>
<td><strong>1.00-1.59</strong></td>
</tr>
<tr>
<td>Endometrial</td>
<td>22 (0.05)</td>
<td>25 (0.06)</td>
<td>0.83</td>
<td><strong>0.27-1.94</strong></td>
</tr>
<tr>
<td>Colorectal</td>
<td>45 (0.10)</td>
<td>67 (0.16)</td>
<td>0.63</td>
<td><strong>0.43-0.92</strong></td>
</tr>
<tr>
<td>Total</td>
<td>502 (1.14)</td>
<td>458 (1.11)</td>
<td>1.03</td>
<td><strong>0.90-1.17</strong></td>
</tr>
<tr>
<td>Fractures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hip</td>
<td>44 (0.10)</td>
<td>62 (0.15)</td>
<td>0.66</td>
<td><strong>0.45-0.98</strong></td>
</tr>
<tr>
<td>Vertebral</td>
<td>41 (0.09)</td>
<td>60 (0.15)</td>
<td>0.66</td>
<td><strong>0.44-0.98</strong></td>
</tr>
<tr>
<td>Other osteoporotic†</td>
<td>579 (1.31)</td>
<td>701 (1.70)</td>
<td>0.77</td>
<td><strong>0.69-0.86</strong></td>
</tr>
<tr>
<td>Total</td>
<td>650 (1.47)</td>
<td>788 (1.91)</td>
<td>0.76</td>
<td><strong>0.69-0.85</strong></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to other causes</td>
<td>165 (0.37)</td>
<td>166 (0.40)</td>
<td>0.92</td>
<td><strong>0.74-1.14</strong></td>
</tr>
<tr>
<td>Total</td>
<td>231 (0.52)</td>
<td>218 (0.53)</td>
<td>0.98</td>
<td><strong>0.82-1.18</strong></td>
</tr>
<tr>
<td>Global index§</td>
<td>751 (1.70)</td>
<td>623 (1.51)</td>
<td>1.15</td>
<td><strong>1.03-1.28</strong></td>
</tr>
</tbody>
</table>

*WHI, JAMA, 2002*
Combined Hormone Therapy (cHT) Use Fell Sharply Following Publication of WHI E+P Trial Results (July, 2002)
Study Rationale & Objective

• Given the substantial investment in the WHI E+P trial ($260 million, 2012 USD), we asked: What was the clinical and economic return on investment?

• The trial’s return (benefit) can be characterized by changes in:
  – Disease incidence
  – Mortality
  – Health-related quality of life
  – Medical expenditure

• We estimated the net economic return of the E+P trial by comparing observed cHT use and outcomes with a “no WHI” scenario where 1998-2002 cHT use trends continue through 2012
Methods: cHT Eligible Population

- Women Age 50-79, post-menopausal, no hysterectomy
Methods: Simulation Model Overview

– Estimate overall outcomes for cHT ever and never users with Markov state transition models

– Weighted averages based on WHI cHT ever and never user outcomes to calculate outcomes in WHI and No WHI scenarios

Diseases of Interest:

– Cardiovascular
  • Coronary Heart Disease
  • CABG/PCTA
  • Stroke

– Venous Thromboembolism
  • Deep Vein Thrombosis
  • Pulmonary Embolism

– Cancer
  • Breast Cancer
  • Endometrial Cancer
  • Colorectal Cancer

– Fracture
  • Hip Fracture
  • Vertebral Fracture
  • Other Osteoporotic Fracture
Methods: Data Sources

• Baseline Disease Risk (never users): WHI observational study
• Relative Disease Risk (cHT ever users): Prentice, Am J Epi, 2009
• Disease and Background Mortality: Literature & U.S. life tables
• cHT Use Patterns: Literature
• Health State Utility Values: WHI clinical trial SF-36 & literature
• Disease-attributable expenditure: Literature
Methods: Primary Model Outcomes

• Quality-Adjusted Life Years (QALYs)
  – A measure that reflects the quantity and quality of life
  – Product of life expectancy and quality of life over that life expectancy (e.g. 10 years @ 0.5 utility = 5 QALYs)

• Direct Medical Expenditure (DME)
  – cHT prescription costs
  – Costs of managing the diseases of interest
  – End of life costs specific to deaths from each disease of interest
Methods: Calculating Net Economic Return

1. Net benefit (NB) for the WHI and No WHI scenarios
   - $NB = [\text{QALYs} \times \text{WTP}] - \text{DME}$
   - Tells us the value of health gains (QALYs) from healthcare spending (DME)
   - We used a range of willingness to pay (WTP) per QALY values ($50,000-$200,000)

2. Incremental net benefit (iNB):
   - $iNB = NB_{\text{WHI}} - NB_{\text{NoWHI}}$
   - Tells us how much more net benefit the WHI scenario generated versus the No WHI scenario

3. Calculate the net economic return (NER) as:
   - $\text{NER} = iNB - \text{Trial Cost}_{\text{WHI}}$
   - This tells us the economic value the E+P trial generated in excess of trial cost
### Results: Clinical and Economic Outcomes in the WHI and No WHI Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>cHT Ever Users</th>
<th>QALYs</th>
<th>Direct Medical Expenditure</th>
<th>Net Economic Benefit</th>
<th>Net Economic Return</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHI</td>
<td>5.2 m</td>
<td>242.7 m</td>
<td>$711.0 b</td>
<td>$23.56 t</td>
<td>+$37.1 b</td>
</tr>
<tr>
<td>No WHI</td>
<td>9.5 m</td>
<td>242.6 m</td>
<td>$746.3 b</td>
<td>$23.51 t</td>
<td>-</td>
</tr>
<tr>
<td>Difference</td>
<td>-4.2 m</td>
<td>+0.1 m</td>
<td>-$35.2 b</td>
<td>+$49.5 b</td>
<td>-</td>
</tr>
</tbody>
</table>

cht=combined hormone therapy, QALY=quality-adjusted life year, m=million, b=billion, t=trillion

- WHI scenario: 4.2 million fewer cHT ever users, which led to:
  - 145,000 more QALYs
  - $35.2 billion in direct medical expenditure savings
  - $49.5 billion in net economic benefit

- At a WTP=$100,000 per QALY, and assuming 75% of the decline in cHT use is attributable to the WHI E+P trial, net economic return is $37.1 billion
Change in 10-year Disease Incidence Resulting from Changes in Prescribing After Publication of WHI E+P Trial Findings

- Coronary heart disease
- CABG/PTCA
- Stroke
- Deep vein thrombosis
- Pulmonary embolism
- Breast cancer
- Endometrial cancer
- Colorectal cancer
- Hip fracture
- Vertebral fracture
- Other osteoporotic fracture
- Death

Absolute Incidence Difference (Thousands of Women), n
Annual Net Economic Return After Publication of WHI E+P Trial Findings
Discussion: Key Findings

- The net economic return of the WHI E+P trial is substantial and robust to uncertainty

<table>
<thead>
<tr>
<th>WHI Scenario Key Impacts</th>
<th>No WHI Scenario Key Impacts</th>
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</thead>
<tbody>
<tr>
<td>Prescription cost savings due to decreased cHT use</td>
<td>Lower Incidence of fractures</td>
</tr>
<tr>
<td>Lower incidence of diseases with relatively major morbidity and mortality impacts (breast cancer, cardiovascular disease, VTE)</td>
<td>Lower Incidence of colorectal cancer</td>
</tr>
</tbody>
</table>

- In base case, net economic return is driven by expenditure savings (72% of NER), rather than monetized QALY gains (28% of NER)

- Trial cost has little impact on NER because NB difference is so much larger
  - Recall, $\text{NER} = [\text{NB}_{\text{WHI}} - \text{NB}_{\text{NoWHI}}] - \text{Trial Cost}_{\text{WHI}}$
Study Implications

• Investment in the WHI provided a very high return on investment in public research funds
  – Approximately $140 return for every dollar spent on the trial

• Returns will continue to accrue over time due to durability of change in E+P prescribing
Study Limitations

• Models are simplified representation of complex and interrelated biologic, clinical, and economic factors
  • Only considered oral combined hormone therapy with conjugated equine estrogens (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d)
  • Focus only on major clinical outcomes that were observed to differ by cHT use in the WHI E+P trial

• Only one disease of interest → We do not consider comorbidity impacts

• cHT utilization trend in the No WHI scenario was an estimate
  • Trend was increasing use of cHT prior to publication of WHI

• Findings to not apply to unopposed estrogen HT in women without a uterus (separate WHI study cohort)
Conclusion

• The WHI E+P trial fundamentally changed understanding about the benefit-risk tradeoffs of long-term cHT use
  – Substantial and sustained decline in cHT utilization

• For an investment of $260 million (2012 $USD), the net economic return of the WHI E+P trial was $37 billion over 10 years

• Our findings demonstrate that large public research investments can yield considerable clinical and economic value when targeted to address research questions with high clinical relevance and public health impact
Thanks to Co-Authors

• Fred Hutchinson Cancer Research Center
  – Scott Ramsey, MD, PhD
  – Ruth Etzioni, PhD
  – Garnet Anderson, PhD
  – Mary Pettinger, MS

• National Lung, Heart, and Blood Institute
  – Jacques Rossouw, MD

• Harvard University Medical School
  – JoAnn Manson, MD, DrPh

• Stanford University Medical School
  – Mark Hlatky, MD

• Harbor-University of California Los Angeles Medical Center
  – Rowan Chlebowski, MD, PhD

• University of Tennessee Health Science Center
  – Karen Johnson, MD, MPH
  – Teresa Waters, PhD
Supplemental Slides
cHT Use 2002-2012

Proportion of cHT Users Among All Women Age 55-79

Proportion of cHT Users Among All Women Age 55-79
Change in 10-year Disease Expenditure Resulting from Changes in Prescribing After Publication of WHI E+P Trial Findings
Considering Alternative Data Sources

- At a willingness to pay of $100,000 per quality-adjusted life year:
  - Net economic return based on combined disease incidence estimates (N=40,845): $37.1 billion (95% CI=$23.1-$51.2 billion)
  - Net economic return with trial only disease incidence estimates (N=16,608): $35.9 billion (95% CI=$14.8-$57.1 billion)
## Disease Incidence Validation

<table>
<thead>
<tr>
<th>Disease of Interest</th>
<th>Annualized Incidence Rate</th>
<th>WHI Scenario Estimate</th>
<th>No WHI Scenario Estimate</th>
<th>Comparator Study Estimate</th>
</tr>
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<tbody>
<tr>
<td>CHD (1)</td>
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<tr>
<td>CABG/PTCA (2)</td>
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<td>Stroke (3)</td>
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<td>DVT (4)</td>
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<tr>
<td>PE (5)</td>
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<tr>
<td>Breast Cancer (6)</td>
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<tr>
<td>Endometrial Cancer (6)</td>
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<tr>
<td>Colorectal Cancer (6)</td>
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<tr>
<td>Hip Fracture (7)</td>
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<tr>
<td>Vertebral Fracture (8)</td>
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<tr>
<td>Other Osteoporotic Fracture (8)</td>
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<tr>
<td>All Cause Death (9)</td>
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</table>

CHD=Coronary Heart Disease, CABG/PTCA=Coronary Artery Bypass Graft/Percutaneous Transluminal Coronary Angioplasty, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism. Data Sources: (1) Canoy, BMC Medicine, 2012; (2) Nollamathu, American Journal of Cardiology, 2007; (3) Carangdang, JAMA, 2006; (4) Mahan, Thrombosis and Haemostasis, 2011; (5) Silverstein, Archives of Internal Medicine, 1998; (6) SEER, 2009; (7) Islam, Menopause, 2009; (8) Burge, Journal of Bone and Mineral Research, 2007; (9) U.S. Life Table, 2000