Update on Estrogen Therapy 2016:
Is the WHI Still the Last Word On The Use of Estrogen?

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Clinical Professor
Department of Ob/Gyn
George Washington University
Washington, DC

Medical Director
Women’s Health & Research Consultants®

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Thank You

- Dr. Howard Hodis
- Dr. Philip Sarrel
- NIH

Learning Objectives:

Upon completion of this lecture, participants will be able to:

- Describe the current status/outcomes of the WHI, KEEPS, ELITE and other current hormone therapy (HT) and estrogen therapy (ET) trials, and have a contextual understanding of their clinical implications to date.
- Understand the tenets of the gap hypothesis and how it applies differentially to cardiovascular disease vs. breast cancer.
- Have a working knowledge of how route of administration could impact the overall risk/benefit ratio for postmenopausal systemic HT or ET
- Appreciate the alternatives to standard progestogens for endometrial protection

Zombie Idea

“An idea that should have been killed by evidence, but refuses to die”

Paul Krugman, Nobel Prize in Economics, 2008 NYT. March 30, 2014

Slide by Voelker EE and Sarrel PM

N.B.: “Zombies” tap into deep-rooted, irrational human fears
Vasomotor Symptoms and Related Psychosocial Impairment During the Menopausal Transition

- Hot flushes
- Night sweats
- Sleep disturbances
  - Insomnia
  - Sleep apnea
- Mood swings
  - Irritability
  - Sadness
  - Tension
- Cognitive deficits
  - Poor concentration
  - Verbal memory
  - Spatial memory

Other Quality-of-Life Impairment
- Social impairment
  - Disruption of family relationships
  - Social isolation
- Work-Related Difficulties
  - Reduced Productivity
- Other Quality-of-Life Impairment
  - Emotional
  - Anxiety
  - Fatigue

Cauley JA, et al. JAMA 2005;350;991


Revised

Simon JA and Reape KZ. Understanding the menopausal experiences of professional women. Menopause 2009; 16 (1): 73

The Woman’s Health Initiative

(July 2002 WHI Press Conference RE: E+P)

Causes of Death Among U.S. Women

The Woman’s Health Initiative

(July 2002 WHI Press Conference RE: E+P)

WHI-E+P: Relative and Absolute Risk

Women 50 to 79 (mean 63.5) Years of Age at Baseline

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall Hazard Ratio</th>
<th>95% Confidence Interval Adjusted</th>
<th>Absolute Risk per 10,000 Women/Year</th>
<th>Absolute Benefit per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.53</td>
<td>0.89-1.62</td>
<td>3.3-3.68</td>
<td>8</td>
</tr>
<tr>
<td>CHD:Revised</td>
<td>1.24</td>
<td>1.01-1.54</td>
<td>0.97-1.60</td>
<td>6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26</td>
<td>1.05-1.50</td>
<td>0.92-1.82</td>
<td>8</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.24</td>
<td>0.81-1.54</td>
<td>0.97-1.59</td>
<td>8</td>
</tr>
<tr>
<td>Strokes</td>
<td>1.31</td>
<td>1.02-1.66</td>
<td>0.93-1.84</td>
<td>7</td>
</tr>
<tr>
<td>VTE</td>
<td>2.11</td>
<td>1.08-2.32</td>
<td>0.98-2.35</td>
<td>18</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.56</td>
<td>0.38-0.81</td>
<td>0.33-0.94</td>
<td>7</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.67</td>
<td>0.47-0.96</td>
<td>0.41-1.10</td>
<td>5</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76</td>
<td>0.69-0.99</td>
<td>0.63-0.92</td>
<td>47</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>0.79</td>
<td>0.67-0.93</td>
<td>0.56-0.97</td>
<td>15</td>
</tr>
</tbody>
</table>


Decline in the Use of Postmenopausal HT
In the US 1999-2010*

<table>
<thead>
<tr>
<th>HT Use in Women &gt; 40 years (%)</th>
<th>1999-2000</th>
<th>2009-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any formulation</td>
<td>22.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Estrogen only</td>
<td>13.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Estrogen + Progestogen</td>
<td>8.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

p < 0.01 for all comparisons 1999-2000 vs 2009-2010


WHI-E: Relative and Absolute Risk

Women 50 to 79 (mean 64) Years of Age at Baseline

<table>
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<th>Event</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.91</td>
<td>0.75-1.12</td>
<td>0.72-1.15</td>
<td>5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.77</td>
<td>0.59-1.01</td>
<td>0.57-1.06</td>
<td>7</td>
</tr>
<tr>
<td>Strokes</td>
<td>1.39</td>
<td>1.10-1.77</td>
<td>0.97-1.99</td>
<td>12</td>
</tr>
<tr>
<td>VTE</td>
<td>1.33</td>
<td>0.99-1.79</td>
<td>0.86-2.08</td>
<td>7</td>
</tr>
<tr>
<td>PE</td>
<td>1.34</td>
<td>0.87-2.06</td>
<td>0.70-2.55</td>
<td>3</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.66</td>
<td>1.05-2.55</td>
<td>0.63-1.08</td>
<td>1</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.61</td>
<td>0.41-0.91</td>
<td>0.25-1.51</td>
<td>6</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.70</td>
<td>0.63-0.97</td>
<td>0.58-0.93</td>
<td>56</td>
</tr>
<tr>
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<td>0.88</td>
<td>0.77-1.01</td>
<td>0.59-1.01</td>
<td>14</td>
</tr>
</tbody>
</table>

Rates for Everyday Life Events and Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Event (United States)</th>
<th>Rate (per 100,000 population)</th>
<th>Same as:</th>
<th>Translates to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traffic Death Rate (2009)</td>
<td>11.0</td>
<td>0.011%</td>
<td>1.1 in 10,000</td>
</tr>
<tr>
<td>Maternal death during pregnancy and childbirth (2010)</td>
<td>21</td>
<td>0.021%</td>
<td>2.1 in 10,000</td>
</tr>
<tr>
<td>Identity Theft (2010)</td>
<td>8.12</td>
<td>0.00612%</td>
<td>8.12 in 10,000</td>
</tr>
<tr>
<td>Total Violent Crime (2009)</td>
<td>1,690</td>
<td>1.69%</td>
<td>169 in 10,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of Adverse Drug Reactions (CIOMS)</th>
<th>Same as:</th>
<th>Translates to:</th>
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<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td></td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Common (≥1/100 and &lt; 1/10)</td>
<td></td>
<td>≥ 1% to &lt; 10%</td>
</tr>
<tr>
<td>Uncommon (≥1/1,000 and &lt; 1/100)</td>
<td></td>
<td>≥ 0.1% to &lt; 1%</td>
</tr>
<tr>
<td>Rare (≥1/10,000 and &lt; 1/1,000)</td>
<td></td>
<td>≥0.01% to &lt; 0.1%</td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000)</td>
<td></td>
<td>&lt; 0.01%</td>
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別の対象イベントと薬物反応の頻度

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<tr>
<td>Rare (≥1/10,000 and &lt; 1/1,000)</td>
<td></td>
<td>≥0.01% to &lt; 0.1%</td>
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<tr>
<td>Very rare (&lt;1/10,000)</td>
<td></td>
<td>&lt; 0.01%</td>
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</table>

WHI E+P Substudy

Risk by Age

<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>0.8</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Number of Events</th>
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<tbody>
<tr>
<td>CHD</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>VTE</td>
</tr>
</tbody>
</table>

WHI E-Alone Substudy

Risk by Age

<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
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<tr>
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<td>VTE</td>
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Results of the WHI After More Than a Decade of Follow-up

<table>
<thead>
<tr>
<th>Exercise (n=828)</th>
<th>Placebo (n=5429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo (Baseline Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>VTE</td>
</tr>
</tbody>
</table>

HRT and CV Risk by Age: WHI Second Arm

(Estrogen Alone after Hysterectomy)

<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.59</td>
<td>1.0</td>
</tr>
<tr>
<td>MI</td>
<td>0.54</td>
<td>1.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.73</td>
<td>1.04</td>
</tr>
<tr>
<td>Breast Ca</td>
<td>0.80</td>
<td>0.73</td>
</tr>
</tbody>
</table>

WHI Post-Intervention Reports:

ET+P 2010 and ET 2011
Kronos Early Estrogen Prevention Study (KEEPS): Design

- N=727 menopausal women aged 42-59 (mean age, 52.7, within 3 years of LMP)
- Trial Duration: 48 months
- Design: Multicenter double blind, placebo controlled RCT
- Treatment Arms:
  - Oral conjugated equine estrogens (o-CEE) given as Premarin®, 0.45 mg/d (lower dose than WHI)
  - Transdermal estradiol (t-E2) given by Climara® patch, 0.05 mg/d
  - Placebo
  
  (active arms received cyclical micronized progesterone [Prometrium®] 200 mg/d x 12 d/mo; placebo arm received placebo Prometrium®)

KEEPS: Directions of Changes in CHD* Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>O-CEE</th>
<th>T-E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>Favorable</td>
<td>Neutral</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Adverse</td>
<td>Neutral</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Favorable</td>
<td>Neutral</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Neutral</td>
<td>Favorable</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>Neutral</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

*CHD: Coronary Heart Disease; HOMA-IR: homeostasis model assessment-estimated insulin resistance

**KEEPS Overall Summary & Conclusions**

- **Similarities:** Both o-CEE and t-E2 had:
  - neutral to favorable effects on CVD biomarkers (differences related to first-pass liver metabolism).
  - neutral effects on CIMT and CAC (ns trend for CAC benefit).
  - neutral effects on cognition; favorable effects on VMS.

- **Differences:**
  - o-CEE improved mood
  - t-E2 improved HOMA-IR and some advantages on sexual function.

- **Conclusions:**
  - KEEPS highlights the need for individualized decision making about HT, by treatment priorities and risk factor status.
  - Additional research on HT in newly menopausal women (i.e. formulations/doses/routes of delivery) is needed.

*Presented by JoAnn E. Manson, MD, Dr.PH, NCMP at NAMS Annual Meeting October 11, 2013*

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**Early vs. Late Intervention Trial with Estradiol (ELITE)**

The “timing hypothesis” posits that there is a differential effect on atherosclerosis and clinical events according to when postmenopausal HRT is initiated in relation to menopause.
**Pathogenic Sequence of Vascular Aging**

No HRT

- Adventitia
- Media
- Internal Elastic Lamina
- Fatty Streak/Plaque
- Internal Elastic Lamina
- Fibrin Cap
- Plaque
- Necrotic Core
- Fibrin Cap
- Plaque

**EPAT = HRT Early & Continued**

- Age 35-45 years
- Age 45-55 years
- Age 55-65 years
- Age >65 years

**WELL-HART = HRT Late**

- HRT
- Mural Thrombus

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**ELITE - Design**

**Study design:** Single-center, randomized, double-blinded, placebo-controlled trial with a 2 x 2 factorial design

**Subjects:** 643 healthy recently postmenopausal (<6 years) and remotely postmenopausal women (>10 years) without preexisting CVD and diabetes mellitus

**Intervention:** Oral micronized 17β-estradiol 1 mg/d (+ 45 mg vaginal micronized progesterone gel x 10 days every month in women with a uterus) or Matching Placebos

**Follow-up:** Every month for the first 6 months and then every 2 months for 5-6 years

**Funding:** NIH – National Institute on Aging (R01AG-024154)

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**ELITE TRIAL RESULTS**

*Table 2: Carotid Artery Intima-Media Thickness (CMT): Progression and Baseline CMT.*

<table>
<thead>
<tr>
<th>Measure and Postmenopausal Status</th>
<th>Placebo (N=239)</th>
<th>Estradiol (N=271)</th>
<th>P Value for Postmenopausal Status Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rate of change in CMT (%)</td>
<td>0.007 (0.006-0.008)</td>
<td>0.064 (0.056-0.076)</td>
<td>0.008</td>
</tr>
<tr>
<td>Early postmenopause</td>
<td>0.008 (0.007-0.010)</td>
<td>0.030 (0.025-0.035)</td>
<td>0.19</td>
</tr>
<tr>
<td>Late postmenopause</td>
<td>0.070 (0.067-0.074)</td>
<td>0.070 (0.067-0.074)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

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

- All Ages
  - >10 years since menopause, >60 years old: 0.49 (0.38-0.64)
  - >10 years since menopause, >60 years old: 1.03 (0.91-1.16)
- All Ages
  - <10 years since menopause, >60 years old: 0.48 (0.38-0.64)
  - <10 years since menopause, >60 years old: 1.03 (0.91-1.16)

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**Mortality**
All-Cause Mortality Associated with HRT in Younger and Older Women: Meta-analysis of 30 Randomized Controlled Trials (119,118 patient-years)

Bayesian Meta-Analysis of HRT and All-Cause Mortality in Younger (mean age 54.5 years) Postmenopausal Women

Cochrane Meta-analysis: All-Cause Mortality from Randomized Controlled Trials of HRT in Younger and Older Postmenopausal Women

Sex-Specificity of Primary Prevention Therapies

Primary vs. Secondary Prevention of CHD with Lipid-Lowering Therapy in Women

Meta-Analysis of Primary Prevention of CHD with Statin Therapy in Women vs. Men
Meta-Analysis of Primary Prevention of CHD with Statin Therapy in Women vs. Men

Women

0.25 0.50 1.0 1.5 2.0
Relative Risk (95% CI)

CHD events
0.95 (0.78 - 1.16)
N=13,346

0.92 (0.82 - 1.04)
N=20,626

Total mortality
0.96 (0.81 - 1.11)
N=13,346

0.93 (0.83 - 1.04)
N=20,626

Men

0.25 0.50 1.0 1.5 2.0
Relative Risk (95% CI)

CHD events
0.52 (0.41 - 0.71)
N=28,346

0.53 (0.42 - 0.67)
N=20,426

Total mortality
0.96 (0.81 - 1.11)
N=13,346

0.93 (0.83 - 1.04)
N=20,626

Meta-Analysis of Primary Prevention of CVD with Aspirin in Women vs. Men

Women

0.25 0.50 1.0 1.5 2.0
Relative Risk (95% CI)

MI
0.91 (0.83 - 1.01)
N=45,155

1.06 (0.97 - 1.15)
N=44,114

Stroke
1.06 (0.97 - 1.15)
N=44,114

1.09 (0.99 - 1.20)
N=44,114

Total mortality
0.91 (0.83 - 1.01)
N=45,155

1.06 (0.97 - 1.15)
N=44,114

Men

0.25 0.50 1.0 1.5 2.0
Relative Risk (95% CI)

MI
0.83 (0.70 - 0.97)
N=51,342

1.13 (0.96 - 1.33)
N=44,114

Stroke
1.01 (0.84 - 1.21)
N=51,342

0.94 (0.74 - 1.19)
N=44,114

Total mortality
0.83 (0.70 - 0.97)
N=51,342

1.13 (0.96 - 1.33)
N=44,114

Are Transdermal Preparations Safer?

CHD
- In a Danish national registry, significantly lower risk of MI was found with the transdermal route than with oral unopposed estrogen (P=0.04).

STROKE
- In a nested case-control study from the UK General Practice Research database (n=15,710), the risk of stroke was not increased with low-dose transdermal estrogen (<50 mcg) but did increase with higher transdermal doses and oral therapies.

VTE
- In a French systematic review and meta-analysis, the risk of first-time VTE was increased in oral estrogen users, but not in transdermal estrogen users (OR 2.5 [1.9 - 3.4] for oral; 1.2 [0.9 - 1.7] for transdermal).

Adjusted Incidence Rate Ratio of CVD Events Transdermal ET vs Oral ET (sensitivity analysis)

Increased Risk of Venous Thrombosis with Conjugated Equine Estrogens (CEE) vs Estradiol

<table>
<thead>
<tr>
<th>Event Type</th>
<th>CEE Use</th>
<th>Estradiol Use</th>
<th>Reference</th>
<th>Estradiol Use</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Case</td>
<td>Control</td>
<td>Case</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>29</td>
<td>114</td>
<td>38</td>
<td>87</td>
<td>2.02 (1.34 - 3.03)</td>
<td>&lt;0.001</td>
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<td>Ischemic event</td>
<td>29</td>
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<td>114</td>
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<td>2.02 (1.34 - 3.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

4.adjusted for: age, race, smoking, body mass index, current statin use, estrogen dose, diabetes, history of diabetes, hypertension, history of stroke, history of heart disease, and the number of VTE events in the year before the intervention, and the number of VTE events in the year before the intervention.
Transdermal estrogen and change in body weight or BMI
• “One crossover study noted greater fat gain with oral vs. transdermal estrogen, results that are supported by clinical data.”

Santen RJ. Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement. JCEM. 2010;95:S1-S66

The Headlines:
The Women’s Health Initiative Results (E + P)

- 41% Increase in Strokes
- 29% Increase in Heart Attacks
- 100% Increase in Venous Thromboembolism
- 22% Increase in Total CV Disease
- 26% Increase in Breast Cancer (3.3/1000 increased to 4.1/1000 for each year)
- 37% Decrease in Colorectal Cancer
- 33% Decrease in Hip Fracture
- 24% Decrease in Total Fractures
- No Difference in All Cause Mortality

WHI Breast Cancer by Years of Prior Use (E + P) [2002]

<table>
<thead>
<tr>
<th>YRS</th>
<th>N</th>
<th>HT vs PBO</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12304</td>
<td>114 vs 102</td>
<td>1.06</td>
<td>0.81-1.38</td>
</tr>
<tr>
<td>&lt;5 yrs</td>
<td>3005</td>
<td>32 vs 15</td>
<td>2.13</td>
<td>1.15-3.94</td>
</tr>
<tr>
<td>5-10 yrs</td>
<td>783</td>
<td>11 vs 2</td>
<td>4.61</td>
<td>1.01-21.02</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>515</td>
<td>9 vs 5</td>
<td>1.81</td>
<td>0.60-5.43</td>
</tr>
</tbody>
</table>

Writing Group for Women’s Health Initiative Investigators. JAMA. 2002; 288

WHI E+P Trial: No Effect of E+P on Risk of In Situ Breast Cancer

Cumulative Hazard for Total, Invasive, and In Situ Breast Cancer Estrogen-Only


Permission to reprint requested from the American Medical Association.
The Gap or Timing Hypothesis (earlier “better”, later “worse”)

This Gap Hypothesis also seems to apply to:
- Mood
- Dementia
- Ischemic Stroke
- Mild cognitive impairment
- Parkinson’s Disease

1 Soares, CN, Maki PM. Menopausal transition, mood, and cognition: an integrated view to close the gaps. Menopause. 2010; 17 (4), 812-814.

WHI-E in Perspective (Not Head-To-Head)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>WHI-E</th>
<th>RUTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age</td>
<td>ns 10,729</td>
<td>ns10,101</td>
</tr>
<tr>
<td>mean follow-up</td>
<td>6.8 years</td>
<td>5.6 years</td>
</tr>
</tbody>
</table>

No. cases/10,000 women/year of treatment

<table>
<thead>
<tr>
<th>CHD</th>
<th>Stroke</th>
<th>VTE</th>
<th>PE</th>
<th>DVT</th>
<th>Breast cancer</th>
<th>Bone fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>12</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>-6</td>
<td>-56</td>
</tr>
<tr>
<td>-7</td>
<td>9</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>-6</td>
<td>-15</td>
</tr>
</tbody>
</table>

Is There a Difference Among Progestogens?

- Comparative data is insufficient
- Current research is ongoing in light of WHI findings that suggested possible harm from progesterone (EPT compared with ET)
- PEPI, a large RCT, suggested micronized progesterone has less negative impact on lipids.
- Small trials suggest VTE with micronized progesterone
- Caveat: formulated in a peanut oil suspension so ask about peanut allergies!

**Progestin Routes of Administration**

- Oral
- Medroxyprogesterone
- Micronized progesterone
- Transdermal progesterin (combined with estrogen)
- IUD with levonorgestrol

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**Cancer Risk in Women Using the Levonorgestrel-Releasing Intrauterine System in Finland**

Tuuli Stait, MD, Rita Hurskainen, MD, Seija Granman, MD, Johanna Mempil, MD, Jorma Pasanen, MD, and Eero Pulkala, MD

CONCLUSION: The levonorgestrel-releasing intrauterine system may have a protective effect against endometrial malignant transformation. Using the levonorgestrel-releasing intrauterine system for treatment of menorrhagia during reproductive years was associated with a lower incidence of endometrial, ovarian, pancreatic, and lung cancers than expected. Levonorgestrel-releasing intrauterine system use was associated with a higher than expected incidence of breast cancer.


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**Tissue Selective Estrogen Complex (TSEC)**

- SERM-Bazedoxifen (BDZ) coupled with CEE
- At 0.45 mg or 0.625 mg CEE with 20mg BDZ found to be effective and safe for treatment of menopausal symptoms, and osteoporosis prevention in women with intact uterus
- BDZ competitively inhibits binding of 17β-estradiol, protecting the endometrium
- No need for progestin
- Current marketed dose: CEE 0.45 with BDZ 20mg daily
- Not currently FDA approved for GMS/VVA

---

**Effects of Bazedoxifene/CEE on menopausal symptoms**

- Reduction in number of hot flashes up 80%
- Reduction in severity up to 54%
- Early onset of action (2/3 weeks)
- Persistence of effect up to 2 years
- Increased superficial cells, reduced parabasal cells, improved vaginal pH* (not FDA approved for VVA/GSM)
- Decreased dyspareunia* (not FDA approved for VVA/GSM)
- Improved sexual domain on MENGOL®
- Improvement of sleep and HR QoL over 1 year

---

**Bazedoxifene/CEE-Overall Safety Profile and other effects**

- No increase in DVTs, MI or strokes
- No difference in cancers from placebo group
- Acceptable endometrial safety (<1% hyperplasia)
- High rates of amenorrhea
- Decreased breast pain
- Neutral effects on breast density at .45 mg/20 mg marketed dose
WHI E+P Evolving Conclusions: 2002

“Results from WHI indicate that the combined postmenopausal hormones CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.”


WHI E+P Evolving Conclusions: 2003

“These conclusions are consistent with those of recently published guidelines. The trial did not address the role of estrogen plus progestin for the short-term treatment of menopausal symptoms, which remains the only clear indication for the use of this regimen…. Women with indications for treatment, such as menopausal symptoms, need to consider with their clinicians the suggestion of a slight overall increase in the risk of CHD and information on the risks of other outcomes in making decisions about the use of estrogen plus progestin therapy.”


WHI E+P Evolving Conclusions: 2007

“These analyses, although not definitive, suggest that the health consequences of hormone therapy may vary by distance from menopause, with an apparent increase in CHD risk for women close to menopause, and particularly high risks in women who are distant from menopause….

We did not identify any subgroup with reduced risk of CHD, although total mortality was reduced among women aged 50 to 59 years.”


Aftermath of WHI – Fracture Data

- Longitudinal observation of 80,955 PM women from 2002 followed for 6.5 years: hip fractures increased in those discontinuing HT versus those staying on HT.
  HR: 1.55 (1.36-1.77) – began within 2 yrs
  Karim R. Menopause 2011; 18: 1172-7

And What if You Stop…?

<table>
<thead>
<tr>
<th>Period</th>
<th>Mortality Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>1.26</td>
<td>1.16-1.37</td>
</tr>
<tr>
<td>Beyond 1 year</td>
<td>0.75</td>
<td>0.72-0.78</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>1.63</td>
<td>1.47-1.79</td>
</tr>
<tr>
<td>Beyond 1 year</td>
<td>0.89</td>
<td>0.85-0.94</td>
</tr>
</tbody>
</table>


So When Your Menopausal Patients Are Get Mixed Signals About Hormone Therapy…

Conclusion

- Compared with placebo, the risks associated with HT in early menopausal women are statistically non-significant; HT risks are rare and even more rare (<1/1,000 women per year of treatment) when initiated in women who are <60 years of age and/or <10 years since menopause.
- The magnitude and type of risks associated with HT are less than or similar to other commonly used medications and therapies.
- HT reduces all-cause mortality, CHD, fractures, and new onset diabetes mellitus and thus the benefits of HT far outweigh the risks.
- HT significantly reduced fractures in an unselected population of women (i.e. without osteoporosis or prior fractures) and is the most effective therapy for significantly reducing menopausal symptoms (vasomotor and vulvovaginal atrophy).

Suggested Reading

- Lobo RA. Wheres Are We 10 Years After the Women’s Health Initiative? J Clin Endocrinol Metab. 2013 May;98(5):1771-80.
- Simon JA. What if the Women’s Health Initiative had used transdermal estradiol and oral progesterone instead? Menopause. 2014 Jul;21(7):769-83.

“We enter the world through the brim of the pelvis and frequently exit by the neck of the femur.”

C.A. Newhall, MD