Risks and Benefits Related to Cardiovascular and Metabolic Outcomes

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Faculty/Presenter Disclosure

I have no financial conflicts of interest related to this presentation.

Risk Stratification is Important!
(One Size Does Not Fit All)

“things should be as simple as possible, but not any simpler.”
A. Einstein

Objectives

- Review recent findings related to cardiovascular disease (CVD) and metabolic outcomes from the WHI and other recent trials.
- Describe patient characteristics, including age, time since menopause, underlying CVD risk factor status, and biomarker levels, that modify health outcomes on hormone therapy.
- Address the role of recent results from WHI and other studies in improving clinical decision making for hormonal vs non-hormonal therapy.
Key Differences Between the WHI and Observational Studies of Hormone Therapy (HT)

<table>
<thead>
<tr>
<th></th>
<th>WHI</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HT initiation (mean)</td>
<td>63 yrs</td>
<td>52 yrs</td>
</tr>
<tr>
<td>Time since menopause (mean)</td>
<td>&gt;12 yrs</td>
<td>1-3 yrs</td>
</tr>
</tbody>
</table>

Randomized Trials of HT and CVD

Secondary Prevention:
- Heart and Estrogen/Progestin Replacement Study (HERS)
- Estrogen Replacement and Atherosclerosis Trial (ERA)
- Papworth HRT Atherosclerosis Study*
- Women’s Estrogen for Stroke Trial (WEST)?
- Estrogen in the Prevention of ReInfarction Trial (ESPRIT)?
- Women’s Angiographic Vitamin and Estrogen (WAVE) Trial

Primary Prevention:
- Women’s Health Initiative (WHI) Estrogen+Progestin Trial
- Estrogen-Alone Trial

Women’s Health Initiative (WHI), Ages 50-79 (mean age 63)

Hormone Program Design

- Conjugated equine estrogen (CEE) 0.625 mg/d
- Medroxyprogesterone acetate (MPA) 2.5 mg/d

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CEEA/MPA except: *transdermal estradiol/NETA, †oral estradiol
WHI Estrogen-Alone Trial: Myocardial Infarction Results According to Age at Randomization

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CHD: MI (95% CI)</th>
<th>Total MI: MI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.55 (0.31-1.00)</td>
<td>0.55 (0.31-1.00)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.95 (0.69-1.30)</td>
<td>0.95 (0.69-1.30)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.24 (0.88-1.75)</td>
<td>1.24 (0.88-1.75)</td>
</tr>
</tbody>
</table>

*Similar results for CABG/PCI*  
P, trend by age = 0.02*

MI = myocardial infarction  
† p, trend by age group

Estrogen+Progestin Therapy and Risk of MI in WHI: Results According to Age and Time Since Menopause

<table>
<thead>
<tr>
<th>Age</th>
<th>Time since Menopause</th>
<th>HR</th>
<th>P, trend 0.05</th>
<th>P, trend 0.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>&lt;10 yrs</td>
<td>1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>10-19 yrs</td>
<td>1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>&gt;20 yrs</td>
<td>1.46*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† P-value <0.05
† P for trend by age group


Danish Osteoporosis Study (DOPS) (N=1006 women, mean 7 mos since LMP, mean age 50 [45-58 yrs])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR (95% CI)</th>
<th>Composite</th>
<th>CHD/HF Death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>0.48 (0.26-0.87)</td>
<td>0.77 (0.35-1.70)</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
<td>0.61 (0.39-0.94)</td>
<td>0.89 (0.48-1.65)</td>
<td></td>
</tr>
</tbody>
</table>

Participants: 643 healthy recently postmenopausal women without preexisting CVD or diabetes.

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

Participants: 643 healthy recently postmenopausal women without preexisting CVD or diabetes.

Study design: Randomized treatment (estradiol, placebo) x time since menopause (<6 years, >10 years).

Intervention: Oral micronized 17β-estradiol 1 mg/d (+ vaginal micronized progesterone gel x 12 days/mo in women with a uterus). Placebos

Outcomes: Primary: rate of change in Carotid IMT, up to 6 yrs. Other: CAC, contrast CT angiography (low power and not reported in detail).

• HRs similar by age for stroke, venous thrombosis/pulmonary embolism, diabetes, breast cancer, and most other outcomes.

*BUT*

• Much lower absolute risks in younger, compared to older, women.
Transdermal Therapy and Low-Dose Regimens: Advantages over Oral/Conventional?

- Less effect on:
  - Clotting factors
  - Triglycerides
  - C-reactive protein
  - Blood pressure

* But no large-scale randomized trials assessing relative safety (predominately observational data)*

Conclusions

- CEE+MPA and CEE-alone are associated with neutral risk of CHD, increased risk of stroke and VTE, and reduced risk of type 2 diabetes in the overall cohorts.
- When examined by age, significant differences emerge in the overall cohort for CHD/MI in the CEE-alone trial.
- When examined by time since menopause, CHD risk is neutral for women <10 yrs since menopause onset and increased for women ≥20 yrs past menopause.
- Hormone therapy continues to have an important clinical role in the management of menopausal symptoms, but evidence does not support its use for prevention of CVD due to other risks.
- Additional studies of different HT formulations, doses, routes of delivery, and of non-hormonal options are needed.

Thank you!