**Differential Effect of Plasma Estradiol Levels Achieved with Hormone Therapy on the Progression of Subclinical Atherosclerosis in Early and Late Postmenopausal Women**

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**Disclosure**

- The authors have no financial relationships to disclose.

**Hormone Timing Hypothesis**

- Women who initiate hormone therapy (HT) at younger age or sooner after menopause have reduced risk of coronary heart disease (CHD) and all-cause mortality compared with placebo.

- Early versus Late Intervention Trial with Estradiol (ELITE) was specifically designed to test effect of HT on subclinical atherosclerosis progression relative to HT initiation according to time-since-menopause
  - Single-center, double-blinded randomized controlled trial of HT administered to early and late postmenopausal women.

**ELITE Result**

- **Early postmenopause (≤ 6 yrs)**
  - HT significantly reduced the progression of subclinical atherosclerosis

- **Late postmenopause (≥ 10 yrs)**
  - HT had no effect on the progression of subclinical atherosclerosis


**Objective**

- To evaluate whether there is a differential association between plasma estradiol levels and progression of subclinical atherosclerosis based on when HT was initiated in relation to time-since-menopause using ELITE data.

**ELITE Study**

- **ELITE study methods**
  - July 2005 to February 2013
  - Median follow-up duration 4.8 years
  - Stratified block randomization (1:1 ratio)
    - HT vs. placebo
    - early vs. late postmenopause
  - Oral micronized 17-beta-estradiol 1 mg/day with/without 4% vaginal micronized progesterone gel 45 mg/day for 10 days/month

Study Population

- **Inclusion criteria**
  - Healthy postmenopausal women without coronary heart disease

- **Exclusion criteria**
  - Diabetes, hypertriglyceridemia, uncontrolled hypertension
  - Contraindication for HT
  - Current use of HT

- **In this analysis**
  - Participants in ELITE with baseline and at least one follow up measurement of plasma estradiol level and carotid artery intima-media thickness (CIMT)

Measurements

- **Plasma estradiol**
  - Radioimmunoassay with preceding organic solvent extraction and Celite column partition chromatography
  - Assay sensitivity = 2 pg/ml

- **Carotid artery intima-media thickness (CIMT)**
  - At right distal common carotid artery
  - B-mode ultrasonograms
  - Coefficient of variation = 0.69%

- **Baseline and every 6 months**

Statistical Analysis

- **Baseline characteristics**
  - Two-sample t test or chi-square test

- **Per-participant CIMT progression rate**
  - Mixed-effects linear model
  - A product term between time-since-menopause, estradiol level, and duration from baseline tested if association of estradiol level with CIMT rate differed in early vs. late postmenopause

- **Estimates of CIMT progression rate from plasma estradiol levels**

Results

- **Baseline characteristics**

- **Per-participant CIMT progression rate**

- **Estimates of CIMT progression rate from plasma estradiol levels**

**Table 1 Baseline characteristics of women by time-since-menopause strata**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early Postmenopause</th>
<th>Late Postmenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>54.7 ± 4.2</td>
<td>63.6 ± 6.1</td>
</tr>
<tr>
<td>Plasma estradiol level (pg/ml)</td>
<td>7.9 ± 4.8</td>
<td>8.5 ± 5.7</td>
</tr>
<tr>
<td>Carotid artery intima-media thickness* (µm)</td>
<td>747.1 ± 95.5</td>
<td>786.9 ± 103.2</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>161 (64.9%)</td>
<td>254 (72.9%)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>21 (8.5%)</td>
<td>31 (8.9%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>36 (14.5%)</td>
<td>43 (12.4%)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>30 (12.1%)</td>
<td>20 (5.8%)</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate or less</td>
<td>6 (2.4%)</td>
<td>16 (4.6%)</td>
</tr>
<tr>
<td>Trade/business school/some college</td>
<td>60 (24.2%)</td>
<td>113 (32.5%)</td>
</tr>
<tr>
<td>Bachelor’s degree/Graduate/professional</td>
<td>182 (73.4%)</td>
<td>219 (62.9%)</td>
</tr>
</tbody>
</table>

*p value <0.05
Continuous variables: mean±standard deviation, t-test
Categorical variables: frequency (percent), χ² test / Fisher’s exact test

**Table 2 Mean plasma estradiol level during the trial and change of plasma estradiol level from baseline among total sample and participants in HT group by time-since-menopause strata**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early Postmenopause</th>
<th>Late Postmenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ELITE cohort</td>
<td>N=596</td>
<td></td>
</tr>
<tr>
<td>Mean plasma estradiol level during the trial (pg/ml)</td>
<td>29.7 ± 31.8</td>
<td>25.5 ± 22.5</td>
</tr>
<tr>
<td>Change of plasma estradiol level from baseline* (pg/ml)</td>
<td>21.7 ± 31.6</td>
<td>17.0 ± 22.7</td>
</tr>
<tr>
<td>Participants in HT group</td>
<td>N=297</td>
<td></td>
</tr>
<tr>
<td>Mean plasma estradiol level during the trial (pg/ml)</td>
<td>48.2 ± 35.8</td>
<td>40.2 ± 23.6</td>
</tr>
<tr>
<td>Change of plasma estradiol level from baseline* (pg/ml)</td>
<td>40.4 ± 35.4</td>
<td>31.6 ± 24.0</td>
</tr>
</tbody>
</table>

*p value <0.05
Continuous variables: mean±standard deviation, t-test
Results

- Per-participant CIMT progression rate

  - Early postmenopause
    - Inverse association of plasma estradiol and CIMT rate
      - Beta coefficient = -0.04 (95% CI: -0.09, -0.001)
      - (p=0.04)
  
  - Late postmenopause
    - Positive association of plasma estradiol and CIMT rate
      - Beta coefficient = 0.063 (95% CI: 0.018, 0.107)
      - (p=0.006)

Results

- Per-participant CIMT progression rate

  - The effect of plasma estradiol levels on the CIMT rate was significantly different between time-since-menopause strata.
    - 3 way interaction term: time-since-menopause*mean plasma estradiol level*duration from baseline
    - Total ELITE cohort (p<0.001)
    - Participants in HT group (p=0.004)

Discussion

- These results not only support the HT timing hypothesis tested by ELITE, but also add an explanatory mechanism consistent with the timing hypothesis.

  - The timing of HT initiation could be
    - An indicator of underlying vascular health and responsivity to HT
    - A determinant whether estradiol will reduce or have no effect on the progression of atherosclerosis
Conclusion

- Plasma estradiol levels achieved through oral estradiol therapy had opposite effects on the progression of subclinical atherosclerosis among women when initiated in early (≤ 6 yrs) and late postmenopause (≥ 10 yrs).

- With higher plasma estradiol levels, the CIMT progression rate is decreased when HT is initiated early after menopause (≤ 6 yrs) and has no effect when initiated later after menopause (≥ 10 yrs) as analyzed using the all women in ELITE cohort as well as women receiving HT.