The Kronos Early Estrogen Prevention Study (KEEPS): Do the Findings Inform Clinical Practice?

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**Absolute Risks of Health Outcomes by 10-Year Age Groups in the WHI Hormone Therapy Trials during the Intervention Phase**


**Women's Health Initiative Estrogen-Alone Trial: MI and CABG/PCI Results According to Age at Randomization**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total MI HR (95% CI)</th>
<th>CABG/PCI HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.55 (0.31-1.00)</td>
<td>0.56 (0.35-0.88)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.95 (0.69-1.30)</td>
<td>1.13 (0.88-1.46)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.24 (0.88-1.75)</td>
<td>1.07 (0.79-1.43)</td>
</tr>
</tbody>
</table>

*P, interaction = 0.02*, † *P, interaction = 0.06*.

*MI = myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, † *p, trend by age group.*


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**KEEPS Study Design**

N = 727 women aged 42-59 (mean age, 52.7, within 3 yrs of FMP)

Trial Duration = 48 months

Multi-center double-blinded 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, 50 µg/d
- Placebo (active arms received cyclical micronized progesterone [Prometrium®], 200 mg/d x 12 days/month; placebo arm received placebo Prometrium)

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**Summary: Direction of Changes in Risk Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>O-CEE Effect</th>
<th>T-E2 Effect</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>Neutral</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>
Changes in Imaging Endpoints, CIMT

CAC Agatston Scores at Baseline

Percent of Subjects with Increases in CAC Score ≥ 5 Agatston Units

Cognition: Change from Baseline on 3MSE

No statistically significant differences.

Results: Tests of Mood and Affect

Profile of Mood States (POMS)
- Total Score
- Depression-Dejection
- Tension-Anxiety

Change from Baseline on Total POMS

Better
Female Sexual Function Index (FSFI)

- The FSFI, a well validated 19-item questionnaire, is a brief self-report instrument for assessing the key dimensions of sexual function in women.

  Domain Scoring:
  - Desire 1–5
  - Arousal 0–5
  - Lubrication 0–5
  - Orgasm 0–5
  - Pain 0–5

Female Sexual Function Index, Lubrication

Female Sexual Function Index, Pain

Female Sexual Function Index, Desire
Both o-CEE and t-E2 had generally favorable or neutral effects on CVD biomarkers (but differences related to first-pass liver metabolism).

Both had neutral effects on CIMT and CAC (but ns trend for latter).

Both had neutral effects on cognition; favorable effects on VMS.

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

KEEPS highlights the need for individualized decision making about HT, given different treatment priorities and risk factor status of women.

Additional research on HT in newly menopausal women, including different formulations/doses/routes of delivery, is needed.

**Overall Summary and Conclusions**

* Both o-CEE and t-E2 had generally favorable or neutral effects on CVD biomarkers (but differences related to first-pass liver metabolism).
* Both had neutral effects on CIMT and CAC (but ns trend for latter).
* Both had neutral effects on cognition; favorable effects on VMS.
* Differences: o-CEE improved mood, t-E2 improved HOMA-IR and some advantages for sexual function.
* KEEPS highlights the need for individualized decision making about HT, given different treatment priorities and risk factor status of women.
* Additional research on HT in newly menopausal women, including different formulations/doses/routes of delivery, is needed.