Estrogens and SERMS

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Estrogen Preserves Bone Metacarpal Mineral

First Longitudinal data on estrogen as a preventive strategy for bone loss
Hormone Products

- Estrogen
  - Low doses
  - Alternate routes of administration
- Progestins
  - Micronized progesterone
  - Progestin intrauterine device
- Vaginal estrogen
- Bioidentical hormones
- Estrogens plus SERMs
Estrogen + progesterone increases spine bone mass more than alendronate.
Estrogen Reduces the Risk of Non-vertebral Fractures

Women’s Health Initiative: Estrogen Alone in Postmenopausal Women Compared to Placebo: Major Clinical Outcomes

* P < .05 Favoring Treatment

Women’s Health Initiative Estrogen and Progestin Arm: Absolute Excess Risk

- Excess CHD events: 7/10,000 woman-years
- Excess stroke events : 8/10,000 woman-years
- Excess pulmonary emboli: 8/10,000 woman-years
- Excess invasive breast cancer: 8/10,000 woman-years

Estrogen Alone Did Not Effect CHD Events in WHI: After Cessation of Estrogen, Younger Women Who Had Taken CEE‡ Had Fewer CHD Events

Source: Writing Group for the WHI Investigators 2002

CEE: conjugated equine estrogen

Source: Andersen 2004; LaCroix 2011
### Estrogen Dose Equivalents

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Standard</th>
<th>Low Dose</th>
<th>Ultra-Low Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.625 mg</td>
<td>0.3 mg</td>
<td></td>
</tr>
<tr>
<td>Oral E2</td>
<td>1 mg</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>Transdermal E2</td>
<td>0.05 mg</td>
<td>0.025 mg</td>
<td>0.014 mg</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>5 µg</td>
<td>2.5 µg</td>
<td></td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen; E2 = estradiol.
Graphic courtesy of Kathryn A. Martin, MD.

### Summary of Published Studies With Lower-dose ERT/HRT

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Estrogen Dose</th>
<th>+Ca</th>
<th>MPA</th>
<th>Radius</th>
<th>Spine</th>
<th>Hip</th>
<th>Total Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genant 1982</td>
<td>0.15-0.625</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Lindsay 1984</td>
<td>0.15-1.25</td>
<td>N</td>
<td>N</td>
<td>*</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ellinger 1987</td>
<td>0.3</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Gallagher 1991</td>
<td>0.3-0.625</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Ellioter 1992</td>
<td>0.5-2.0</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Webber 1994</td>
<td>0.3-0.625</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Genant 1997</td>
<td>0.3-1.25</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Mizunuma 1997</td>
<td>0.3-0.625</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Recker 1999</td>
<td>0.3</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

*Metacarpal; †micronized 17β estradiol; ‡Ca supplement if needed.

### Impact of Lower-dose CEE + Calcium on Spinal BMC

**HOPE Trial**
- Women’s Health, Osteoporosis, Progestin, Estrogen (HOPE) trial
- 2600+ postmenopausal women with uterus, treated for 2 years
- 8 treatment groups and placebo
  - CEE 0.625 mg/d ± MPA 2.5 mg/d
  - CEE 0.45 mg/d ± MPA 2.5 mg/d
  - CEE 0.45 mg/d + MPA 1.5 mg/d
  - CEE 0.3 mg/d ± MPA 1.5 mg/d
  - Placebo
- Endpoints: vasomotor symptoms, BMD, endometrial safety

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; BMD = bone mineral density.
CEE and Spine BMD

HOPE Trial

- Placebo
- CEE 0.3 mg
- CEE 0.45 mg
- CEE 0.625 mg

-3 -2 -1 0 1 2 3

Change in Spine BMD (%)

Month

-3 -2 -1 0 1 2 3

Change in Spine BMD (%)

Month

CEE and Hot Flashes HOPE Trial

- Placebo
- CEE 0.45 mg/d
- CEE 0.3 mg/d
- CEE 0.625 mg/d

Women's HOPE Study: Bone Substudy Conclusions

- All doses of CEE and CEE/MPA demonstrated a statistically significant improvement in BMD relative to placebo
- All doses except .3 CEE at the femoral neck demonstrate a statistically significant improvement in BMD relative to baseline

Ultra–Low-Dose Estrogen

- ULTRA trial: Ultra–low-dose Transdermal Estradiol Assessment
  - Transdermal E2 (0.014 mg/day) vs placebo x 2 years
  - N = 417 women, mean age 67
  - Asymptomatic population – no effect on hot flashes
- Effective for hot flashes in trials of younger women (N = 425)

References:
Ultra–Low-Dose Estrogen and BMD

ULTRA Trial

- BMD increased more in spine (2%) and hip (1.2%) vs placebo1
- Greater bone effect with lower endogenous E2


Hormone Therapy (HRT/ERT)

- BMD: increased at spine and hip
- Fracture reduction: 34% spine and hip fracture reduction at 5.2 years in older women (baseline status not available)
- Early efficacy: 5 years
- Duration: fracture reduction at 5 yrs
- Discontinuation: significant bone loss in first year, no inc fracture

Discontinuation of ERT and Risk of Osteoporotic Fracture

<table>
<thead>
<tr>
<th>Oral Estrogens</th>
<th>Cutaneous Estrogens</th>
<th>P for Homogeneity</th>
<th>P for Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>HR</td>
<td>95% CI</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Current use</td>
<td>1227</td>
<td>0.69</td>
<td>0.60, 0.77</td>
</tr>
<tr>
<td>Treatment stopped &lt;5 years previously</td>
<td>520</td>
<td>0.86</td>
<td>0.78, 0.94</td>
</tr>
<tr>
<td>Treatment stopped ≥5 years previously</td>
<td>308</td>
<td>1.00</td>
<td>0.89, 1.11</td>
</tr>
</tbody>
</table>

HRT/ERT continued

- Issues: Risks>benefits: WHI data
  - increase in CHD events, strokes, breast cancer
    - May be due to type of HRT or progesterone
    - May be due to dose of HRT
  - menstrual bleeding if no progesterone
    - oral, patch, cream, vaginal suppository/ring
- Future: different types, lower dose, combination
The signal transduction pathways available to estrogen or a selective estrogen receptor modulator (SERM) to initiate gene transcription.

JNCI J Natl Cancer Inst 2001;93:1449-1457
© Oxford University Press

**Functional domains of estrogen receptor (ER)**

- **Helix 12**
- **Full Estrogen**
- **Tamoxifen (Antiestrogen)**
- **Raloxifene (Antiestrogen)**
- **GW 7604 (Antiestrogen)**
- **Carboxy trotz (GW 7604)**
- **Receptor Destroyed** (Pure antiestrogen)

JNCI

**Raloxifene**
- Selective estrogen receptor modulator
- Acts as an estrogen agonist on bone
- Acts as an estrogen antagonist on breast and uterus
- Approved for prevention and treatment of postmenopausal osteoporosis
- Adverse events: Hot flashes, venous thromboembolism, leg cramps

Raloxifene improves BMD but less than alendronate

**Fig. 1.** Lumbar Spine and Femoral Neck BMD in Postmenopausal Women

**Fig. 2.** Raloxifene Reduces Bone Turnover Markers (resorption and formation)
**Effect ofRaloxifene Treatment in Women With or Without Existing Fractures - MORE Trial 36 Months -**

- **RR 0.70*** (95% CI 0.56, 0.86)
- **RR 0.45*** (95% CI 0.29, 0.71)

*rounded off in paper


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**Effect ofRaloxifene on Non-vertebral Fractures - MORE Trial 36 Months -**

- All Non-vertebral Fractures
  - Wrist Fractures: Placebo vs. Raloxifene
  - Ankle Fractures: Placebo vs. Raloxifene

*P<0.05* (Placebo vs. Raloxifene)


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**Raloxifene: Effect on Radiographic Vertebral Fractures (MORE)**

- RR, 0.3 (95% CI, 0.4-0.8)
- RR, 0.7 (95% CI, 0.5-0.9)

*postmenopausal women
MORE = multiple outcomes of raloxifene evaluation; RR = risk ratio

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**Raloxifene: Effect on Nonvertebral and Hip Fracture**

- **Pooled Data (60 mg and 120 mg)**
  - Nonvertebral Fractures
  - Hip Fractures

*P=0.24* (Nonvertebral Fractures)

*P=0.71* (Hip Fractures)

Significant alterations of trabecular bone material-level biomechanical properties with raloxifene.


Raloxifene alters energy to failure and toughness of cortical bone through changes in postyield displacement.


Raloxifene prevents bone loss from baseline to 12 months (N=107) in patients with GC.


Raloxifene prevents bone marker changes from baseline to 12 months (N=107) in GC patients.

Bazedoxifene; A New SERM

Figure 1. Chemical structure of bazedoxifene.

Bazedoxifene Prevents Bone Loss in a Dose Dependent Manner

Figure 2. Effects of bazedoxifene on bone mineral density of the lumbar spine in postmenopausal women at risk for osteoporosis. *P < 0.01 vs. placebo at all time points. Adopted from /Bone Miner Ala 2006;23(3):25–30 with permission of the American Society for Bone and Mineral Research.

Bazedoxifene Increases BMD at All Sites

Bazedoxifene Reduces Markers of Bone Turnover
Bazedoxifene Reduces the Risk of Vert Frx

Summary

- Estrogens are very effective in raising BMD and reducing vert and non-vert fracture risk
- Off-target effects of estrogen limit clinical utility (breast cardiovascular, thrombosis)
- SERMS are protective to the skeleton
- At least one SERM has non-vert fracture risk reduction
- There may be beneficial off-target effects; e.g. protection vs breast cancer
- Duavee- Baso+ Estrogen- fracture risk redx with treatment of hot flashes