Estrogen and SERMs

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A Unitary Model for Age Related Osteoporosis


Pfeilschifter J, et al Endocrine Reviews February 1, 2002 vol. 23 no. 1

Spinal BMD by Age and Menopausal Status

Serum Estradiol and BMD

Estradiol levels of 10-25 pg/mL vs <5 pg/mL
P<0.05 for each comparison

% difference in BMD

0 3 6 9 12

Total hip 6.8% 4.9%
Spine 9.6%
Proximal radius 7.3%
Calcaneus


Serum Estradiol, SHBG and Fracture Risk

Relative risk adjusted for age and weight


Estrogen Therapy

* Treats symptoms of estrogen deficiency
* Increases BMD
* Decreases fracture risk
* Balancing of non-skeletal risks/benefits
* Limited adherence to therapy—short-term and long-term

Conjugated Equine Estrogens Increase BMD in Early Postmenopausal Women

HOPE Study

% Change

Lindsay R, et al. JAMA 2002;287:2668-76
**ULTRA Study: Transdermal Estradiol**

- **Hypothesis**
  - Raising serum $E_2$ in postmenopausal women by ~5 pg/mL will increase BMD without causing endometrial hyperplasia

- **Design**
  - Randomized, double-blind, placebo-controlled, 2-year, multicenter trial
  - Postmenopausal (>5 years) women (n=417) aged 60-80 years, with intact uterus
  - Normal BMD for age (spinal Z-score above -2)
  - Weekly $E_2$ patch (14 mcg/day) or placebo
  - Calcium 800 mg + vitamin D 400 IU daily


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**Effect on Spine BMD**

![Graph showing effect on spine BMD](image)

- Mean % change in BMD
- Placebo vs. Transdermal estradiol 14 mcg
- 12 Months: +0.51%, p<0.001
- 24 Months: +0.54%, p<0.001


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**Effect on Total Hip BMD**

![Graph showing effect on total hip BMD](image)

- Mean % change in BMD
- Placebo vs. Transdermal estradiol 14 mcg
- 12 Months: -0.22%, p<0.001
- 24 Months: -0.71%, p<0.001


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**Relative Risk of Nonvertebral Fractures With HT in Randomized Trials: A Meta-Analysis**

- Relative Risk (95% CI)
- All Nonvertebral Fractures
- All Nonvertebral Fractures (<60 years)
- Hip and Wrist Fractures
- Hip and Wrist Fractures (<60 years)

Torgerson DJ, Bell-Syer SEM. JAMA 2001;285:2691-7
Women’s Health Initiative (WHI)

- 161,809 postmenopausal women (ages 50-79)
- HT sub-study: Prempro (8506) or placebo (8102)
- Mean age 63.3 ± 7.1 years (67% ≥ age 60)
- 74% had never used hormones
- Previous history of fracture at or after age 55 in 13.5%
- Average follow-up: 5.2 years (range: 3.5 to 8.5 years)

JAMA 2002;288:321-33 (July 17, 2002)

<table>
<thead>
<tr>
<th>Women’s Health Initiative (WHI)</th>
<th>HT</th>
<th>Placebo</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>164</td>
<td>122</td>
<td>+29%</td>
</tr>
<tr>
<td>Stroke</td>
<td>127</td>
<td>85</td>
<td>+41%</td>
</tr>
<tr>
<td>Total VTE</td>
<td>151</td>
<td>67</td>
<td>+111%</td>
</tr>
<tr>
<td>PE</td>
<td>70</td>
<td>31</td>
<td>+113%</td>
</tr>
<tr>
<td>Breast Ca</td>
<td>166</td>
<td>124</td>
<td>+26%</td>
</tr>
<tr>
<td>Dementia</td>
<td>40</td>
<td>21</td>
<td>+105%</td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td>45</td>
<td>67</td>
<td>-37%</td>
</tr>
<tr>
<td>Fractures</td>
<td>650</td>
<td>788</td>
<td>-24%</td>
</tr>
</tbody>
</table>

JAMA 2002;288:321-33 (July 17, 2002)

Women’s Health Initiative Fracture Risk Reduction

<table>
<thead>
<tr>
<th>CEE + MPA</th>
<th>CEE Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=8,102)</td>
<td>Placebo (n=5,429)</td>
</tr>
<tr>
<td>CEE + MPA (n=8,506)</td>
<td>CEE (n=5,310)</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>Hip Fracture</td>
</tr>
<tr>
<td>PE</td>
<td>PE</td>
</tr>
<tr>
<td>Vertebral Fracture</td>
<td>Vertebral Fracture</td>
</tr>
</tbody>
</table>

Writing Group for the Women’s Health Initiative Investigators. JAMA 2002;288:321-33
The Women’s Health Steering Committee. JAMA 2004;291:1701-12
**Hormone Therapy: Summary**

- Increases BMD, decreases bone turnover
- Reduces fracture risk—at least with conjugated equine estrogens (with or without MPA) in the WHI population
  - Reduction in clinical vertebral fracture, hip fracture and “total” osteoporotic fractures
- Confers additional health benefits and risks
  - Menopausal symptoms, cognitive effects, cardiovascular risk, breast cancer risk

**HT and Osteoporosis: Unresolved Issues**

- How much of a change in a surrogate such as BMD or a biochemical marker is “enough” to decrease fracture risk? A gradient of benefit seems likely. What are the effects of HT on “bone quality”?
- Is the dose-response curve for the skeleton the same as it is for other risks and benefits?
- Are there meaningful differences among various preparations? “Bioidentical hormones?”

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**The Concept of a SERM**

Selective Estrogen Receptor Modulator

- Binds to the estrogen receptors
- Produces an estrogen agonist effect in some tissues
- Produces an estrogen antagonist effect in others

**SERMs**

Selective Estrogen Receptor Modulators

- tamoxifen
- raloxifene
- lasofoxifene
- bazedoxifene
**MORE**

**Multiple Outcomes of Raloxifene Evaluation**

- 7705 postmenopausal women less than age 80 at 180 sites in 25 countries
- Treatment groups (with calcium + vitamin D)
  - Placebo, raloxifene (60 mg/d), or raloxifene (120 mg/d)
- Osteoporosis
  - Prevalent vertebral fracture and/or hip or spine BMD T score ≤ -2.5

*Cummings SR, et al. JAMA 1999; 281:2189-97*

**Effect of Raloxifene on Spine and Hip BMD**

*C Cummings SR, et al. JAMA 1999; 281:2189-97*

**Effects of Raloxifene on New Vertebral Fractures**

*Delmas PD, et al. J Clin Endocrinol Metab 2002;87:3609-17*

**Raloxifene and Breast Cancer Incidence**

*MORE Trial - 40 Months Median Follow-Up*

*P<.001*
Hot Flash Incidence
Treatment and Prevention Populations

<table>
<thead>
<tr>
<th>N=2576</th>
<th>N=2557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age 67</td>
<td>Mean age 54</td>
</tr>
<tr>
<td>Placebo</td>
<td>Raloxifene 60 mg/d</td>
</tr>
</tbody>
</table>

- Mean age 67, P < 0.001
- Mean age 54, P < 0.001

MORE 4 Year Prevention Studies


Effect of HT and SERMs on Venous Thromboembolic Events (VTE)

- Relative Risk
- HT HERS
- Tamoxifen P-1
- Raloxifene 60 mg MORE

- Grady 2000
- Fisher 1998
- Adapted from Cauley 2001

CORE Study
Continuing Outcomes Relevant to Evista

- Patients having completed MORE
  - Randomized, placebo vs. raloxifene (60 mg)
- Primary endpoint: Breast cancer
- Secondary endpoints: Nonvertebral fracture, uterine safety
- Length of trial: 48 months
- Completion: 10/2003


Five-year incidence of invasive breast cancer, calculated based on observed incidence in CORE, in women with a 5-year predicted risk ≥1.67% (high risk) or <1.67% (low risk) by treatment group.


©2000 by American Association for Cancer Research
### Variables in Final Multivariate Model and Corresponding Hazard Ratios for Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (&lt;65 vs ≥65 y)</td>
<td>1.54 (1.03-2.30)</td>
<td>0.033</td>
</tr>
<tr>
<td>Estradiol level (≥5 vs &lt;5 pmol/L)</td>
<td>1.72 (1.17-2.53)</td>
<td>0.006</td>
</tr>
<tr>
<td>Treatment (raloxifene vs placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With FH of breast cancer</td>
<td>0.16 (0.06-0.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No FH of breast cancer</td>
<td>0.55 (0.36-0.84)</td>
<td>0.005</td>
</tr>
<tr>
<td>Family history of breast cancer (yes vs no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>2.91 (1.64-5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raloxifene group</td>
<td>0.86 (0.37-2.51)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

RUTH (Raloxifene Use for The Heart)
Cases per 10,000 Patient-years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Raloxifene</th>
<th>Placebo</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>206</td>
<td>216</td>
<td>-10</td>
</tr>
<tr>
<td>Stroke</td>
<td>95</td>
<td>86</td>
<td>+9</td>
</tr>
<tr>
<td>VTE</td>
<td>39</td>
<td>27</td>
<td>+9</td>
</tr>
<tr>
<td>Breast Ca</td>
<td>20</td>
<td>27</td>
<td>-9</td>
</tr>
<tr>
<td>Vertebral fx</td>
<td>24</td>
<td>29</td>
<td>-9</td>
</tr>
<tr>
<td>Non-vert fx</td>
<td>167</td>
<td>173</td>
<td>-6</td>
</tr>
</tbody>
</table>


Raloxifene Summary

- **Raloxifene**
  - Modest improvement in BMD of spine/hip
  - Reduction in vertebral fracture risk in MORE/CORE studies—and in STAR/RUTH
  - No documented reduction in non-vertebral fracture risk in entire MORE/CORE studies
  - Other extraskeletal benefits and risks; reduction in breast cancer risk over 8 years; increased risk of VTE

Use of Raloxifene after rhPTH (1-34) Treatment

- Postmenopausal women with osteoporosis were treated with rhPTH (1-34) for 1 yr. then randomized to raloxifene for 2 yrs or placebo (1 yr ) and raloxifene (1 yr.)
- Results
  - After 1 yr. LS BMD loss with raloxifene 1%, placebo 4% (p<0.001)
  - After 2 yrs. ( ral-ra) -2.7% or pbo-ra -2.6%
  - After 1 yr rhPTH (1-34) and 2 yrs ( ral-ra) or pbo-ra) LS and TH
  - LS: 6.1 % vs. 5.1 %; FN: 3.4% vs. 3.0%) from baseline
- Summary: Sequential raloxifene prevented rapid bone loss at the LS and increased FN BMD whether raloxifene was started immediately or after a 1 yr. delay following teriparatide treatment.


Novel SERMs

Bazedoxifene
Lasofoxifene
Bazedoxifene – New SERM (‘Estrogen Agonist/Antagonist’)

Phase III trials – doses ranged from 10 to 60 mg/day
- Spinal BMD increase at 24 months – roughly 1+% 
- New vertebral fracture risk reduction: 42%
- Non-vertebral fracture risk reduction of 52% in a subgroup (FN T-score ≤ -3.0 or ≥1 moderate/multiple vertebral fractures), but not in the entire study group
- Safety and tolerability data presented
  - Numerical increase in venous thromboembolic events at all doses, although not statistically significant

Bazedoxifene vs Raloxifene 3-year Trial


The PEARL Trial
Postmenopausal Evaluation and Risk reduction with Lasofoxifene

- Randomized, placebo-controlled trial
- 8,556 women 59 to 80 years old
- BMD T-score ≤ -2.5 and ≥ -4.5 at the femoral neck or spine
- Two daily doses (0.25 mg or 0.5 mg)

Vertebral Fracture Reduction in PEARL

Summary

- Both Estrogen and SERMS are able to reduce loss of BMD in postmenopausal women.
- However, only estrogen has been shown to reduce non-vertebral fractures.
- Both raloxifene and lasofoxifene are effective in reducing incident breast cancer, especially ER+ subgroups.
- The side effect profile of both estrogen and SERMS limit their use in clinical practice.