SERMS, Hormone Therapy and Calcitonin

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I have nothing to disclose

Thanks to Clifford Rosen and Steven Cummings for use of hormone therapy and SERMS slides
Hormone Therapy

Khosla, Trends Endocrinol Metab 2012
Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial

Prempro:
CEE 0.625mg
MPA 2.5 mg

Primary outcome: coronary heart disease
Primary adverse outcome: invasive breast cancer
WHI: Fracture Outcomes

Reduced hip fracture, clinical vertebral fracture, other osteoporotic fractures and total fractures

Coronary Heart Disease

- HR: 1.23
- 95% CI: 1.02-1.46
- Estimated relative risk compared to placebo

Stroke

- HR: 1.41
- 95% CI: 1.07-1.85
- Estimated relative risk compared to placebo

Pulmonary Embolism

- HR: 2.13
- 95% CI: 1.39-3.25
- Estimated relative risk compared to placebo

Invasive Breast Cancer

- HR: 1.29
- 95% CI: 1.05-1.59
- Estimated relative risk compared to placebo
WHI: Estrogen Alone in Postmenopausal Women Compared to Placebo - Major Clinical Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Source: Adapted from WHI Steering Committee 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.30*</td>
<td></td>
</tr>
</tbody>
</table>

- Favors Treatment
- Favors Placebo

* P < .05

After Cessation of Estrogen, Younger Women Who Had Taken CEE‡ Had Fewer CHD Events

Source: Anderson, JAMA 2004; LaCroix, JAMA 2011

† CEE: conjugated equine estrogen
Hormone Therapy: Current Use

FDA approval:
• Treatment of moderate to severe vasomotor or vulvar and vaginal atrophy due to menopause
• When prescribed solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate

• Special clinical circumstances
  – If a woman on hormone therapy also has osteoporosis, does she need bisphosphonates as well?

Combination therapy may improve lumbar spine BMD more than HRT alone

Potential concern: 2 anti-resorptives, over suppression of bone turnover?
Hormone Therapy Summary

• BMD: increases at the spine and hip
• Fracture reduction: 34% spine and hip fracture reduction at 5.2 years in older women (baseline status not available)
• WHI data: concern that risks > benefits
  – Increase in CHD events, stroke, breast cancer
  – May be due to type of estrogen, progesterone, dose
• Low dose therapy: could carefully consider adding alendronate

Selective Estrogen Receptor Modulators
**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


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**Raloxifene: Effect on Lumbar Spine and Femoral Neck BMD in Postmenopausal Women**

- **Lumbar Spine**
  - Mean percent change in bone mineral density
  - $P<0.001$
  - 2.6% increase

- **Femoral Neck**
  - Mean percent change in bone mineral density
  - $P<0.001$
  - 2.1% increase

Raloxifene: Effect on Radiographic Vertebral Fractures (MORE)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidents of Patients with ( \geq 4 ) Vertebral Fractures</th>
<th>RR (95% CI)</th>
<th>Preexisting Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50%</td>
<td>0.5 (0.4-0.8)</td>
<td>(BMD ( \leq 2.5 ) and no preexisting vertebral fractures) (n=3012)</td>
</tr>
<tr>
<td>Raloxifene 60 mg/d</td>
<td></td>
<td>RR, 0.7 (0.6-0.9)</td>
<td>(BMD ( \leq 2.5 ) and preexisting vertebral fractures) (n=1539)</td>
</tr>
<tr>
<td>n=1522</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=1490</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Raloxifene: Effect on Nonvertebral and Hip Fracture

Pooled Data (60 mg and 120 mg*)

- Nonvertebral Fractures:
  - *P=0.24

- Hip Fractures:
  - *P=0.71

n= placebo = 2576 women; Raloxifene (60 mg and 120 mg) = 5129

*Not FDA-approved dose
Raloxifene has less effect on BMD than alendronate

Recker, Bone 2007

SERMs and breast cancer

- SERMs block estrogen receptors
- Decrease the risk of estrogen sensitive (ER+) breast cancer

USPSTF: assess the risk of breast cancer in women ≥ age 50 and consider chemoprevention in those with >3% 5-year risk of breast cancer
MORE: Raloxifene reduces the risk of invasive breast cancer

![Graph showing the reduction in invasive breast cancer with Raloxifene compared to Placebo.]


Bazedoxifene + CEE (Duavee)

- An option for hot flushes in a postmenopausal women with a uterus
- 25-40% decrease in hot flushes vs. placebo
- Improves BMD a little more than SERM, a little less than the comparable dose of CEE
- Absence of fracture data, long-term safety
  - Unknown effect on breast cancer risk
Summary

- **Raloxifene:**
  - There are more effective drugs for reducing risk of fracture
  - Consider in women with osteoporosis and at increased risk of breast cancer
  - Contraindicated in women with history of venous thromboembolism

- BZA + CEE is an alternative for hot flushes in postmenopausal women with a uterus

2017 ACP Recommendations

**Recommendation 5:** *ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women.* (Grade: strong recommendation; moderate-quality evidence)

**Arguments for:**
- Estrogen: no evidence of fracture reduction in PM women with osteoporosis
- Raloxifene: no reduction in hip or non-vertebral fracture
- Concern for serious harms

**Arguments against:**
- Estrogen: reduces fractures in PM women overall, likely similar in osteoporotic women
- Raloxifene: vertebral fracture reduction
- These may be useful in specific situations
Calcitonin

Calcitonin: Background

Fernandez-Santos, Thyroid Hormone, InTech 2012
Takahashi, BoneKEy Reports 2014
Calcitonin: Fracture Efficacy

- Minimal increase in spine BMD (1%)
- Unknown effects on non-vertebral fractures
- Caveats: high drop out rate, no dose-dependent response


Calcitonin: Analgesia and Side Effects

- Placebo-controlled trials: reduces acute pain in vertebral fractures
- FDA advisory panel: concern for malignancy with long-term use

Summary:
- Benefits may not outweigh risks of long-term osteoporosis treatment, other effective therapies available
- Consider short-term use for significant acute pain from vertebral fracture

Ensrud, NEJM 2011
### Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fracture Efficacy</th>
<th>Side Effects</th>
<th>Special Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>Hip, spine</td>
<td>E+P: MI, stroke, PE, DVT, breast CA E: stroke, DVT</td>
<td>Women who are already on estrogen for severe menopausal symptoms</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Spine</td>
<td>Venous thromboembolism</td>
<td>Women who would also benefit from breast CA chemoprevention</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Spine</td>
<td>Rhinitis Long term: malignancy?</td>
<td>Short term use for acute pain from vertebral fracture</td>
</tr>
</tbody>
</table>

*Use more effective drugs for patients with severe osteoporosis!*