Reproductive Hormone Therapy for Bone & Muscle Health

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• Relationships with commercial interests:
  I have received grants/research support/speakers honoraria and consulting fees from:
  Allergan, Amgen, Merck, Novo Nordisk, Teva Pharmaceuticals, Wyeth/Pfizer, Grants/Research Support:
Reproductive Hormone Therapy for Bone & Muscle Health

OBJECTIVES

1. Review current evidence regarding the role of reproductive hormones notably estrogen on women’s bone and muscle health

2. Summarize the data on the effect of menopausal hormone therapy on bone health

3. Consider the relative risks and benefits of menopausal hormone therapy
Multiple Sites of Estrogen Action

Brain
Helps maintain body temperature
mood, cognition, sexual health

Heart and liver
Regulates production of cholesterol /
decreases plaque in coronary arteries

Ovaries
Stimulates maturation and start of
woman’s menstrual cycle

Vagina
Stimulates maturation and helps
maintain lubricated and thick
vaginal lining

Bones
Helps to preserve bone density

Breast
Stimulates development at puberty and
prepares glands for future milk
production

Uterus
Stimulates maturation and helps to
prepare the uterus to nourish a
developing fetus

Muscles
Improves the intrinsic quality and
strength of skeletal muscle
ESTROGEN & BONES
Pathogenesis of osteoporotic fracture includes low bone mass, bone loss and poor bone quality.

- Low peak bone mass
- Age-related bone loss
- Postmenopausal Bone loss
- Other risk factors

Non-skeletal factors (propensity to fall) → FRACTURE → Poor bone quality (architecture)

LOW BONE MASS

LOW BMD = \downarrow PBM and/or \uparrow Loss

BMD = Bone Mineral Density
PBM = Peak Bone Mass

Adapted from Riggs BL and Melton LJ III. Raven Press. 1988:155-179
Females lose an average of 2% of their bone mass per year. The greatest period of bone loss occurs during the first 5-10 years after menopause.

Adapted from Heaney RP et al. Osteoporos Int. 2000;11:985-1009.
Bone Mineral Density Loss in Relation to the Final Menstrual Period in a Multi-ethnic Cohort: Results from the Study of Women’s Health Across the Nation (SWAN)

Gail A. Greendale.

**TRANSMENOPAUSAL DECLINE LS BMD**

- No measurable decline in either LS or FN BMD between 5 yrs & 1 yr before FMP.
- BMD loss started 1 yr before FMP, cont’d X 2 yrs after FMP then slowed but did not stop.

NB LS loss > FN loss during transmenopause; equal rate of loss after 2 yrs.
Menopausal Transition* (lasts average of 5 yr)

<table>
<thead>
<tr>
<th>Perimenopause</th>
<th>LMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable cycle length</td>
<td>≥2 skipped cycles &amp; interval of amenorrhea</td>
</tr>
<tr>
<td>Amenorrhea x 12 mos</td>
<td>None</td>
</tr>
</tbody>
</table>

Menopause

Postmenopause (recognized 12 months post-FMP)

Premenopausal years

Postmenopausal years

Benefits of Hormonal Contraceptive Use in Perimenopausal Women

Prevent pregnancy

Reduce hormonal fluctuations associated with perimenopause

Provide additional noncontraceptive benefits

- Cancer prevention
- Bone protection
Oral Contraceptives Maintain Bone Mass in Women Aged 41–49 Years

Oral Contraceptives and Hip Fractures: Possible Risk Reduction

Do 20 µg EE OCs Increase Bone Mineral Density?

20 µg EE OCs: significant increases in vertebral bone density (oligomenorrheic, perimenopausal women)

0.625 mg conjugated equine estrogens (HRT) = ~ 5 µg EE

5 µg EE doses: demonstrate bone-sparing properties

20 µg EE OCs: protective benefits are maintained in perimenopausal women
Premature Menopause & OP
Malmo Study 2012

34 year f/u of 390 Swedish ♀:

2 groups

- (Group A) = early menopause (<47yo mean 42yo) - 61 ♀
- (Group B) = N Menopause ( >47yo mean 51yo) -- 329 ♀

RESULTS at age 77 yo:

**Group A**: 56% = OP (cf Group B : 30% = OP)

**Group A**: fragility # 68% > Group B

BJOG Apr 25, 2012
Consequences of Premature (<47 yo) Menopause

OP - 83%

Mortality - 59%
First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women

Based on GRADE A evidence as assessed in the Osteoporosis Canada 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada*

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Bisphosphonates</th>
<th>Denosumab</th>
<th>Raloxifene</th>
<th>Estrogen ** (Hormone Therapy)</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alendronate</td>
<td>Risedronate</td>
<td>Zoledronic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Non-Vertebral</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*For postmenopausal women, ✓ indicates first line therapies and Grade A recommendation.

**Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.

In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

Estrogen plays an essential role in the skeletal growth and bone homeostasis in both men and women.

Kousteni S. et al Cell 2001; 719-730.
Pharmacological Modulation of Osteoclast Differentiation and Activity

Established drugs
- Bisphosphonates
- Estrogens**
- SERMs
- Calcitonins (delisted)
- Strontium (not in NA)
- Denosumab

Other potential inhibitors as future drugs
- Blocking RANKL system
  - RANKL-Ab
  - OPG analogues
- Cathepsin K inhibitors
- Integrin (RGD) ligands
- Chloride channel blockers
- Src inhibitors
- Many others

Osteoclasts
Many Factors Affect Osteoblast Expression of RANK Ligand

Glucocorticoids → PTH → PGE₂ → IL-1, -6, -11 → PTHrP → TNF-α → IFN-γ → IL-4, -12 → Estrogen

Osteoblast

Prefusion Osteoclast → Multinucleated Osteoclast

Activated Osteoclast

PTHrP, Calcitriol, IL-1, -6, -11, PGE₂, IL-4, -12, Estrogen

RANKL, RANK

IL = Interleukin
PGE₂ = prostaglandin E2
PTH = parathyroid hormone
PTHrP = PTH-related peptide

ESTROGEN & BONE: Modes of Action

- Estrogen regulates osteoblast lifespan
- Estrogen induces apoptosis (not complete elimination) of osteoclastic cells
- Estrogen inhibits apoptosis of osteoblasts

HRT (Oral & TD) BOTH INCREASE BMD

HRT: Femoral Bone Density

HRT: Vertebral Bone Density

Menopause Congress 2009
HRT: BMD IN OLDER WOMEN

Lumbar spine (g/cm²):
- HRT
- Placebo

Femoral neck (g/cm²):
- HRT
- Placebo

*p<0.01 vs placebo

Lindsay & Tohme. Obstet Gynecol 1990; 76: 290-95
ESTROGEN & SKELETAL MUSCLE
The “Bone-Muscle Unit”

**Bone**

Gain and Loss of Bone Throughout the Life Span

![Graph showing gain and loss of bone throughout life in women.]

**Muscle**

GF, M, E patterns with Puberty and Menopause.

![Graph showing muscle patterns with life stages.]
Sarcopenia -- the loss of muscle mass, strength and function with ageing

Consequences:
-- increased falls risk,
-- a decreased physical ability
-- a decreased quality of life
-- increase of all-cause mortality

Lang TF. J Osteoporosis; 2011(!!) ;702-735.
Recognized correlation between sarcopenia & osteoporosis

The “bone-muscle unit“ differs in ♂ & ♀

\[ E_2 \text{ (unlike } T) \text{ increases muscle strength (not size)} \]

\[ E_2 \text{ improves the intrinsic quality of skeletal muscle fibres } \rightarrow \text{ increased force (strength)} \]
Postmenopausal women on MHT retain muscle strength better than those not taking MHT

OVERALL: 5-10% greater Strength in ♀ On HT

Baltimore Longitudinal Study on Aging (Hurley)
Meta-analyses of Muscle Strength / Muscle Size: Effect of Estrogen

**Systematic review & meta-analysis of 23 studies: >10,000 PM women**

Studies on women
- Taaffe et al., 2005: -0.02
- Onambele et al., 2006: 0.15
- Sipila & Taaffe, 2001 & 2005: 0.39
- Skelton et al., 1999: 0.54
- Phillips et al., 1993: 1.25

Overall: 0.45

Studies on rodents
- Wohlers et al., 2009: -0.26
- Hubal et al., 2005: -0.26
- Fisher et al., 1998: 0.15
- McCormick et al., 2004: 0.41
- Moran et al., 2007: 0.84
- Moran et al., 2006: 1.39
- Wattanapermpool et al., 1999: 2.43

Overall: 0.66

ESTROGEN & SKELETAL MUSCLE
Modes of Action

- E2 effect is at the molecular level - “myosin”

- Mechanisms include
  -- genomic effects (via α & β ER),
  -- cell signaling events,
  -- possibly also anti-oxidant effects

Lang TF. J Osteoporosis; 2011(!!);702-735.
Effect of Addition of Estrogen post Oophorectomy

The graph illustrates the effect of estrogen addition on various parameters post oophorectomy. The parameters measured include Tension, Strong-binding, Stiffness, ATPase activity, and Ca\(^{2+}\) sensitivity. The graph compares the control group (Control), oophorectomy (OVX), and oophorectomy with estrogen (OVX+E\(_2\)) groups. The y-axis represents the myosin function relative to control (in %), while the x-axis lists the parameters measured.
ESTROGEN & SKELETAL MUSCLE

Muscle weakness increases with age

Decreasing E2 & P production at menopause accelerates this muscle weakness

**Hypothesis** that E effect is on nuclear ERα & ERβ receptors improving “myosin” function at the molecular level

Lang TF. J Osteoporosis; 2011(!!);702-735.
ESTROGEN & SKELETAL MUSCLE

Muscle forces are major determinants of bone structure

And so ----

***Could MHT /ERT be a major determinant of the effects/exercise in peri/post menopausal women ?

Lang TF. J Osteoporosis; 2011(!!) ;702-735.
MENOPAUSAL HORMONE RX:
A REVIEW
MENOPAUSAL HORMONE RX & BONES
HRT: BMD Increases in the PEPI Trial

% Mean BMD Increases*

Spine

Hip

Baseline 12 mo 36 mo

Baseline 12 mo 36 mo

Placebo  CEE Only  CEE-MPA (cyc)  CEE-MPA (con)  CEE-MP (cyc)

Placebo  CEE Only  CEE-MPA (cyc)  CEE-MPA (con)  CEE-MP (cyc)

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; MP = micronized progesterone
cyc = cyclic administration (days 1–12 of each month); and con = continuous administration (daily throughout the month)

Clinical Efficacy of FemHRT ® (norethindrone acetate and ethinyl estradiol tablets)

**Effects on Bone**

Adjusted Mean Change From Baseline in Bone Mineral Density (mg/cm³)

*P<0.05 vs. baseline; †P<0.05 vs. placebo.

EE = ethinyl estradiol; NA = norethindrone acetate.

Speroff L et al. JAMA 1996;276:1397-1403
Treatment of postmenopausal osteoporosis with transdermal estrogen
100 μg 17β-estradiol patch or placebo

1 year, prospective, DB RCT / 75 PM ♀

BMD:
5.1% increase (spine BMD) vs placebo
(p=0.007)

Vertebral Fractures:
placebo: 20 fractures in 12 women
estradiol: 8 fractures in 7 women
RR 0.39 (95% CI: 0.16, 0.95)

No non-vertebral fracture data
Hormone Therapy Prevents Vertebral, Non-vertebral, and Hip Fractures in Postmenopausal Women

RCT: WHI study with postmenopausal women treated with hormone therapy for 5.2 years

Placebo HT

% of Patient with Fracture

Clinical Vertebral Fracture
HR 0.66 (95% CI, 0.44–0.98)

Non-vertebral Fracture
HR 0.77 (95% CI, 0.69–0.86)

Hip Fracture
HR 0.66 (95% CI, 0.45–0.98)

CI = confidence interval, HR = hazard ratio, RRR = relative risk reduction HT = daily combined estrogen and progestin

BMD Lost Rapidly After HT Stopped

**Spine BMD**

- Placebo: Initial rise, followed by a decline.
- ET/HT: Initial rise, but a steeper decline.

**Femoral Neck BMD**

- Placebo: Minimal change.
- ET/HT: Initial rise, followed by a decline.

Gallagher 2002
Effect on Spine BMD of Withdrawing Therapy

Women between ages 45-59
Treated for 4 years; followed for 2 more years

L spine BMD - Change from Baseline

Mean Percent Change ± SE

Years

Hormone Therapy/Placebo
ALN 5 mg/ PBO
Placebo

Healthy Postmenopausal Women
Age 65 Years

HRT Or Placebo For 2-3 Years
Follow-up 5, 11 Or 15 Years
Placebo N=108
HRT N=155

All Fractures OR 0.48 (Ci 0.26-0.88)
Spine Fractures OR 0.47 (0.24-0.93)

**NNT To Prevent Any Fracture = 7

Bagger et al. Bone 2004; 34: 728-35
Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization

Roksana Karim, MBBS, PhD,1,2,3 Richard M. Dell, MD,4 Denise F. Greene, RNP, MS,4 Wendy J. Mack, PhD,2,3 J. Christopher Gallagher, MD,5 and Howard N. Hodis, MD2,3,6

<table>
<thead>
<tr>
<th>Year</th>
<th>Hip fracture (n)</th>
<th>At risk (n)</th>
<th>HT use (n)</th>
<th>Hip Fracture IR (per 1,000 women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>88</td>
<td>80,955</td>
<td>80,955</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>196</td>
<td>80,074</td>
<td>80,074</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>238</td>
<td>78,822</td>
<td>71,625</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>200</td>
<td>77,529</td>
<td>70,377</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>282</td>
<td>76,293</td>
<td>64,719</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>300</td>
<td>75,006</td>
<td>63,482</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>211</td>
<td>64,007</td>
<td>63,988</td>
<td></td>
</tr>
</tbody>
</table>

[Graph showing trends in HT use rate and hip fracture rate from 2002 to 2008]
## WHI: Risk or Benefit of CEE/MPA

### Revised Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall HR</th>
<th>95% Confidence Intervals</th>
<th>Increased Absolute Risk per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95% Nominal</td>
<td>95% Adjusted</td>
</tr>
<tr>
<td>CHD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.24</td>
<td>1.00–1.54</td>
<td>0.97–1.60</td>
</tr>
<tr>
<td>Strokes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.31</td>
<td>1.02–1.68</td>
<td>0.93–1.84</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.24</td>
<td>1.01–1.54</td>
<td>0.97–1.59</td>
</tr>
<tr>
<td>VTE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2.11</td>
<td>1.58–2.82</td>
<td>1.26–3.55</td>
</tr>
<tr>
<td>Colorectal cancer&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.63</td>
<td>0.43–0.92</td>
<td>0.32–1.24</td>
</tr>
<tr>
<td>Hip fractures&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.67</td>
<td>0.47–0.96</td>
<td>0.41–1.10</td>
</tr>
<tr>
<td>Total fractures&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.76</td>
<td>0.69–0.83</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.79</td>
<td>0.67–0.93</td>
<td>—</td>
</tr>
</tbody>
</table>

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## WHI CEE Alone: Overall Relative and Attributable Risk

**Women 50 to 79 Years of Age at Baseline**

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall HR</th>
<th>95% Confidence Intervals</th>
<th>Attributable Risk per 10,000 Women/Year</th>
<th>Benefit per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.91</td>
<td>0.75–1.12 (Nominal)</td>
<td>0.72–1.15 (Adjusted)</td>
<td>* 5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.77</td>
<td>0.59–1.01 (Nominal)</td>
<td>0.57–1.06 (Adjusted)</td>
<td>* 7</td>
</tr>
<tr>
<td>Strokes</td>
<td>1.39</td>
<td>1.10–1.77 (Nominal)</td>
<td>0.97–1.99 (Adjusted)</td>
<td>12</td>
</tr>
<tr>
<td>VTE</td>
<td>1.33</td>
<td>0.99–1.79 (Nominal)</td>
<td>0.86–2.08 (Adjusted)</td>
<td>7</td>
</tr>
<tr>
<td>PE</td>
<td>1.34</td>
<td>0.87–2.06 (Nominal)</td>
<td>0.70–2.55 (Adjusted)</td>
<td>3</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08</td>
<td>0.75–1.55 (Nominal)</td>
<td>0.63–1.86 (Adjusted)</td>
<td>1</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.61</td>
<td>0.41–0.91 (Nominal)</td>
<td>0.33–1.11 (Adjusted)</td>
<td>6</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.70</td>
<td>0.63–0.79 (Nominal)</td>
<td>0.59–0.83 (Adjusted)</td>
<td>56</td>
</tr>
</tbody>
</table>

CARDIOVASCULAR RISKS
Emerging Hypothesis

Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications and plaque vulnerability.
There is increasing evidence that ET/HT initiated during the perimenopausal/early postmenopausal period inhibits the progression of atherosclerosis.

Primary Benefits of HT

Favorable Lipid and Endothelial Effects of Estrogen Predominate

Prothrombotic and Proinflammatory Effects of Estrogen Predominate

Benefits of Endogenous & Exogenous Estrogens

No Benefits of ET/HT Harmful Effects of HT

Clarkson T, at NAMS Annual Meeting Oct 2006

Mikkola, Clarkson, & Notelovitz AnnMed 2004
WHI HT Trials: Absolute Risk of CHD by Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cases /100 person-yrs</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.20 0.22</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.46 0.48</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>0.90 0.72</td>
<td>**</td>
</tr>
</tbody>
</table>

Combined Trials* PBO

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cases /100 person-yrs</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.22 0.17</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.36 0.36</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>0.82 0.58</td>
<td>**</td>
</tr>
</tbody>
</table>

CEE+MPA PBO

WHI MHT Trials: Absolute Risk of CHD*—Years Since Menopause

<table>
<thead>
<tr>
<th>Years Since Menopause</th>
<th>CEE</th>
<th>PBO†</th>
<th>** p &lt; 0.05 vs. 50 to 59 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>0.13</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>10-19 years</td>
<td>0.46</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>0.77</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years Since Menopause</th>
<th>CEE + MPA</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>10-19 years</td>
<td>0.40</td>
<td>0.33</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>0.79</td>
<td>0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years Since Menopause</th>
<th>Combined Trials</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>10-19 years</td>
<td>0.43</td>
<td>0.39</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>0.78</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* CHD: coronary heart disease; † PBO: placebo.

WHI MHT Trials:
Total Mortality by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Unopposed CEE</th>
<th>HR* (95% CI**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 years</td>
<td>0.71</td>
<td>(0.46 to 1.11)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>1.02</td>
<td>(0.80 to 1.30)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.20</td>
<td>(0.93 to 1.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CEE + MPA</th>
<th>HR* (95% CI**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 years</td>
<td>0.69</td>
<td>(0.44 to 1.07)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>1.09</td>
<td>(0.83 to 1.44)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.06</td>
<td>(0.80 to 1.41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Both arms</th>
<th>HR* (95% CI**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 years</td>
<td>0.70</td>
<td>(0.51 to 0.96)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>1.05</td>
<td>(0.87 to 1.26)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.14</td>
<td>(0.94 to 1.37)</td>
</tr>
</tbody>
</table>

* HR: hazard ratio; ** CI: confidence interval.

THROMBOEMBOLIC RISKS

1. VTE
2. CVA
Postmenopausal HT and Risk of VTE: Results of the E3n Trial

Hazard ratios of idiopathic VTE in relation to both estrogens by route of administration and concomitant progestogens

<table>
<thead>
<tr>
<th>Group</th>
<th>Age-adjusted HR [reference]</th>
<th>Multivariate-adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use (n=181)</td>
<td>1</td>
<td>1 [reference]</td>
</tr>
<tr>
<td>Past use (n=66)</td>
<td>1.0 (0.7-1.3)</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>Current use of oral estrogens (n=81)</td>
<td>1.5 (0.9-2.3)</td>
<td>1.7 (1.1-2.8)</td>
</tr>
<tr>
<td>Current use of transdermal estrogens (n=174)</td>
<td>1.1 (0.7-1.6)</td>
<td>1.1 (0.8-1.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, body-mass index, parity, educational level and time-period.
<table>
<thead>
<tr>
<th>Route/progestogen</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>4.2</td>
<td>1.5–11.6</td>
</tr>
<tr>
<td>Transdermal</td>
<td>0.9</td>
<td>0.4–2.1</td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>0.7</td>
<td>0.3–1.9</td>
</tr>
<tr>
<td>Pregnanes</td>
<td>0.9</td>
<td>0.4–2.3</td>
</tr>
<tr>
<td>Norpregnanes</td>
<td>3.9</td>
<td>1.5–10.0</td>
</tr>
</tbody>
</table>

## Duration of HT Use and VTE

<table>
<thead>
<tr>
<th>Year</th>
<th>Risk Ratio (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>4.01</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.97</td>
</tr>
<tr>
<td>Year 3</td>
<td>1.74</td>
</tr>
<tr>
<td>Year 4</td>
<td>1.70</td>
</tr>
<tr>
<td>Year 5</td>
<td>2.90</td>
</tr>
<tr>
<td>Year 6</td>
<td>1.04</td>
</tr>
</tbody>
</table>

HT and Risk of VTE

Menopausal HT very slightly increases the risk of a blood clot (1-2 additional cases per 1,000 users)

The risk decreases over time

Age is greater risk factor:

- 50-59
- 60-69 risk doubles
- 70-79 risk quadruples

Weight

- Overweight  1.96 (1.33-2.88)
- Obese  3.09 (2.13-4.49)

**Risk is reduced with lower doses and transdermal HT**
## Oral and Transdermal Estrogen: Risk of Stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Crude HR</th>
<th>Adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=14,496)</td>
<td>1.00 [reference]</td>
<td>1.00 [reference]</td>
</tr>
<tr>
<td>Transdermal route (n=103)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose ≤50 ug (n=76)</td>
<td>0.92 (0.74-1.14)</td>
<td>0.95 (0.75-1.20)</td>
</tr>
<tr>
<td>High dose &gt;50 ug (n=27)</td>
<td>1.20 (1.09-1.33)</td>
<td>1.28 (1.15-1.42)</td>
</tr>
<tr>
<td>Oral route (n=618)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose† (n=515)</td>
<td>1.16 (1.04-1.29)</td>
<td>1.25 (1.12-1.40)</td>
</tr>
<tr>
<td>High dose† (n=103)</td>
<td>1.51 (1.20-1.90)</td>
<td>1.48 (1.16-1.90)</td>
</tr>
</tbody>
</table>

Adjusted for age, body-mass index, smoking status, alcohol misuse, diabetes, hyperlipidemia, hypertension, atrial fibrillation, CVD, transient ischemic attack, aspirin or other NSAID use, and history of hysterectomy or oophorectomy.

† Lose dose: ≤0.625 mg CEE or ≤2 mg estradiol; high dose: >0.625 mg CEE or >2 mg estradiol.

Mean age of cases and controls at index date was 70 years.
Consider Use of Transdermal Estrogen

1. First line therapy ("by choice")

2. For patients with: Higher risk of DVT or PE
   - High triglycerides
   - Gall bladder disease
   - Obesity
   - Smokers
   - Hypertension

3. Need for "steady state"
   - Depression
   - Migraine headaches
   - Patients on shift work

4. Inability to use oral Rx
   - GERD
   - Malabsorption

5. Sexual Dysfunction
BREAST CANCER

& MENOPAUSAL HORMONE THERAPY
WHI: HT and Breast Cancer Risk

Cont CEE+MPA

INVASIVE BREAST CANCER
Higher risk for CEE+MPA

HR, 1.26
95% nCl, 1.00-1.59
95% aCl, 0.83-1.92

CEE in women with hyst

INVASIVE BREAST CANCER
Lower risk for CEE alone

HR, 0.77
(95% CI, 0.59-1.01)

## Comparison of Risk Factors for Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPT &gt; 5 yrs use</td>
<td>1.3</td>
</tr>
<tr>
<td>Early menarche</td>
<td>1.3</td>
</tr>
<tr>
<td>Late menopause</td>
<td>1.2-1.5</td>
</tr>
<tr>
<td>Late first pregnancy</td>
<td>1.7-1.9</td>
</tr>
<tr>
<td>Chest radiation</td>
<td>1.6-5.2</td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td>1.2</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>1.2</td>
</tr>
<tr>
<td>First degree relative Br Ca &gt;50</td>
<td>1.8</td>
</tr>
<tr>
<td>First degree relative Br Ca &lt;50</td>
<td>3.3</td>
</tr>
<tr>
<td>Increased mammographic density</td>
<td>6.0</td>
</tr>
<tr>
<td>BRCA gene mutation</td>
<td>200</td>
</tr>
</tbody>
</table>

DERZKO

<table>
<thead>
<tr>
<th>HRT use or Risk Factor</th>
<th>Risk of breast cancer*</th>
<th>Extra cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HRT</td>
<td>45 (baseline)</td>
<td></td>
</tr>
<tr>
<td>HRT users:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 y</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>10 y</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>15 y</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Late menopause</td>
<td>58</td>
<td>13</td>
</tr>
<tr>
<td>BMI 10 kg/m²</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>72</td>
<td>27</td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>72</td>
<td>27</td>
</tr>
</tbody>
</table>

* Risk per 1000 women between age 50 and 70
Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy

FIG. 1. Breast cancer death risk in women using HT consisting of ET or EPT at different ages. The data are expressed as SMR with 95% CI. The line on 1.0 denotes the risk in age-matched background population. The observed and expected numbers of deaths are given for a 10-year period. ET, estradiol-only therapy; EPT, estrogen-progestogen therapy; HT, hormone therapy; SMR, standardized mortality ratio.
DOPS: MHT* in Recently Menopausal Women

- Danish Osteoporosis Prevention Study (DOPS)

- Examined risks in newly menopausal women
  - 1,006 women 45-58 randomized to MHT (502) or placebo (504) pre-WHI (1990-1993)
  - Followed for 10 years on treatment until trial stopped in August 2002 and for 6 additional years
  - Examined CVD events and deaths

* MHT: menopausal hormone therapy
Fig 2 Risk of death or admission to hospital due to heart failure or myocardial infarction (primary endpoint) over 16 years of follow-up including 11 years of randomised treatment.

DANISH OSTEOPOROSIS PREVENTION TRIAL (DOPS):

Schierbeck L L et al. BMJ 2012;345:bmj.e6409
HRT in Post Menopausal Women
The Danish Osteoporosis Prevention Study (DOPS)

**OUTCOME:**

*Significant Reduction in the risk of*

*“Combined End Point”*

» Mortality

» MI

» Heart Failure

***No significant Increase in Breast Cancer or Stroke***
OVERVIEW OF WHI RESULTS: Benefits vs Risks of Rx
Importance of the Risk:Benefit Ratio

Use of ET/EPT should be consistent with treatment goals, benefits, and risks for the individual woman, taking into account:

- Route of administration
- Time since menopause
- Duration of treatment
- Risk factors

These factors may affect:

- Quality of life
- Underlying risks for other conditions
  - CHD, stroke, VTE, diabetes, cancer

Key Messages

- MHT is the most effective treatment for VMS.
- MHT is safe in young patients who are in the early postmenopausal phase.
- Dosage and duration of treatment must be individualized.
- Route of administration should generally be based on patient preference however the transdermal route may be dictated by special circumstances.
## Hormone Therapy

<table>
<thead>
<tr>
<th>Contraindications to HT</th>
<th>Non-contraindications to HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unexplained/undiagnosed vaginal bleeding prior to investigation</td>
<td>• Smoking</td>
</tr>
<tr>
<td>• Known or suspected breast carcinoma</td>
<td>• Diabetes</td>
</tr>
<tr>
<td>• Acute liver disease</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Active thromboembolic disease</td>
<td>• Migraine</td>
</tr>
<tr>
<td>• Acute cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>• Recent stroke</td>
<td></td>
</tr>
<tr>
<td>• Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>
Benefits and Risks Chart
For Combined Estrogen and Progestin MHT
Women aged 50-59

Benefits
- Hot flashes: 825
- Vaginal atrophy: 875
- Fractures: 5
- Diabetes: 11
- Colorectal cancer: 1
- CHD: 1
- Endometrial cancer: 1
- Overall mortality: 6

Risks
- Breast cancer: 4
- Stroke: < 1
- VTE*: 6
- GB** disease: 9
- Lung cancer: 1

Numbers show the absolute number of events for 1,000 women using combined MHT for 5 years.

* VTE: venous thromboembolism; ** GB: gallbladder.
Benefits and Risks Chart
For Estrogen-alone MHT
Women aged 50-59

- Hot flashes: 900
- Vaginal atrophy: 800
- Fractures: 6
- Diabetes: 11
- Breast cancer: 7
- CHD: 4
- Overall mortality: 5

Benefits

- Stroke: 1
- VTE: 2
- GB disease: 14

Risks

Numbers show the absolute number of events for 1,000 women using estrogen-only MHT for 5 years.
MHT: CHOOSING AN APPROPRIATE RX

1. Route of Rx
2. Dose
3. How long can MHT be continued?
“New data and re-analyses of older studies by women’s age show that, for most women, the potential benefits of MHT given for a clear indication are many and the risks are few when initiated within a few years of menopause” and “the absolute risks known to date for use of MHT in healthy women ages 50-59 years are low”
Benefits of HRT

Postmenopausal osteoporosis

- HRT is effective in preventing bone loss associated with the menopause and decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in women not at high risk of fracture.

- Based on evidence of effectiveness, cost and safety, HRT can be considered as one of the first-line therapies for the prevention and treatment of osteoporosis in postmenopausal women, younger than 60 years, with an increased risk of fracture.
Benefits of HRT

Postmenopausal osteoporosis

- The initiation of HRT for the sole purpose of the prevention of fractures after the age of 60 years is not recommended.

- Continuation of HRT after the age of 60 years for the sole purpose of the prevention of fractures should take into account the possible long-term effects of the specific dose and method of administration of HRT, compared to other proven non-hormonal therapies.
SUMMARY
Menopause-related changes on muscle mass and its impacts on different characteristics that contribute to quality of life

**MENOPAUSE**

**Changes in Hormonal Milieu**
- ↓Estrogen
- ↓Estrone
- ↓DHEA
- ↓Thyroxine
- ↓Progesterone
- ↑IL-6
- ↑TNF-α
- ↓IGF-1
- ↓GH
- ↓Intramuscular LPL

**Changes in Muscle Mass**
- muscle protein synthesis
- MUSCLE PROTEIN BREAKDOWN
- ↑Intramuscular fat
- ↓Type II fibers
- ↑Type I fibers
- ↓Estrogen receptors

**Changes in Muscle Strength**
- ↓Motor units
- ↓Type II fibers
- ↓Calcium release
- ↓Ability to recruit all motor unit

**SARCOPENIA**
- ↓Power output
- ↓Isometric strength
- ↓Torque at high velocity
- ↓Insulin sensitivity
- ↑Risk of fall
- ↓Functional performance

**QUALITY OF LIFE**

*Mediators*
- HRT
- Animal protein intake
- Physical activity
- Isoflavone supplements
- Vitamin D

**EFFECTS ON BONES/SKELETON**

- Prevents postmenopausal bone loss
- Increases bone mass
- Reduces bone turnover
- Reduces osteoporotic fracture incidence
- Effective at all skeletal sites

**EFFECTS ON MUSCLES**

- E2 increases muscle strength (not size) by improving the intrinsic quality of skeletal muscle fibres → increased force of contraction
- Effect is at the molecular level - “myosin”
- Mechanisms include:
  - Genomic effects (via α & β ER),
  - Cell signaling events,
  - Possibly anti-oxidant effects

**Muscle forces are major determinants of bone structure**

**May be as effective as other current treatments?**