Postmenopausal Hormone Therapy: Where Do We Stand Now?

Baptist Health South Florida
14th Annual International Symposium on Cardiovascular Disease Prevention
February 20, 2016, Miami, Florida

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Speaker Disclosures

Dr. Brinton has received:

• Grants/Research Support: Amarin, Aurora Foundation, National Institutes of Health
• Honoraria as Consultant: Alexion, Amarin, Amgen, Aralez, AstraZeneca, Kowa, Merck, PTDiagnostics, Regeneron, Sanofi-Aventis
• Honoraria as Speaker: Amarin, Amgen, AstraZeneca, Janssen, Kowa, Merck, Regeneron, Sanofi-Aventis, Takeda

Dr. Brinton will reference unlabeled/unapproved uses of drugs in his presentation.

Learning Objectives

• Discuss new data regarding early initiation of Menopausal Hormone Therapy (MHT) on protection against atherosclerosis and cardiovascular disease (CVD).
• Explain the mechanisms for the discrepancies between observational studies and randomized clinical trials on the effects of MHT on CVD risk
• Implement appropriate risk/benefit analysis in initiation and continuation of early-start MHT.
CVD Higher Postmenopause vs. Premenopause

Hypothesis:
Estrogen Deficiency is Atherogenic (and otherwise harmful) in Postmenopausal Women

AND therefore
Estrogen Replacement is Anti-atherogenic!
Observational Studies Show ↓ CVD Events with Estrogen Replacement in Postmenopausal Women

Petitt DB, et al, 1987
van der Giezen AM, et al, 1990
Falkeborn MI, et al, 1992
Psaty BM, et al, 1994
Folsom AR, et al, 1995

Observational Studies: ERT/HRT Associate w/ ↓ CHD

Nurses Health Study: HRT Reduces Death (prior D/C ~erases benefits)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Hormone Use</th>
<th>Never</th>
<th>Current</th>
<th>Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td></td>
<td>2051</td>
<td>274</td>
<td>1012</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td></td>
<td>1.0</td>
<td>1.03</td>
<td>1.13</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td>289</td>
<td>43</td>
<td>129</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td></td>
<td>1.0</td>
<td>1.67</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>91</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td></td>
<td>1.0</td>
<td>5.48</td>
<td>1.07</td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td>1103</td>
<td>125</td>
<td>129</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td></td>
<td>1.0</td>
<td>0.71</td>
<td>1.04</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td>246</td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td></td>
<td>1.0</td>
<td>3.77</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*CI = Confidence Interval. Values are adjusted for age, age at menopause, type of menopause, BMI, DM, high BP, high cholesterol, smoking, OC use, family H/O MI or breast Ca, parity


0 0.5 1.0 2.0 5.0

Relative Risk

1.0 0.63 (0.56-0.70)
0.47 (0.32-0.69)
0.71 (0.62-0.81)
0.77 (0.59-1.00)
0.83 (0.63-1.09)
1.03 (0.94-1.12)
0.99 (0.75-1.30)
1.07 (0.66-1.49)
1.04 (0.50-1.77)
0.94 (0.63-1.49)
Mechanisms of HRT in Atherogenesis

**Anti-**-atherosclerotic effects: **Early** stages

HRT Alone vs Statin Alone vs Both: **Additive** Lipid Benefits

Anti-Atherosclerotic HRT Mechanisms: Summary

- Lipid benefits (↓ LDL-C, Apo B & Lp(a), ↑ HDL-C & Apo A-I)
- Anti-inflammatory (↓ cell-adhesion, etc.)
- Anti-oxidant (paraoxonase, etc.)
- Anti-diabetic (insulin ↑ secr. vs ↓ resist?)
- ↑ Endothelial function
Hypothesis:
Estrogen Deficiency is Atherogenic (and otherwise harmful) in Postmenopausal Women

**AND therefore**
Estrogen Replacement is Anti-atherogenic!

If so, what is the optimal:
- Age of initiation of Rx?
- Duration of Rx?
- Route?
- Agent?
- Dose?

Mechanisms of HRT in Atherogenesis

*Pro*-atherosclerotic effects:

*Late* stages

HRT and Plaque Rupture Susceptible Substrate

Incitant | Catalyst | Substrate | Reaction
--- | --- | --- | ---
HRT | MMP | Nothing | early
HRT | MMP | Plaque rupture | late-complex
HRT Increases Venous Thromboembolism

(esp. first 1-2 years)

The Pro-atherogenic “One-two Punch” Hypothesis of HRT in Late Atherosclerosis

Cardiovascular events occur when a vulnerable atherosclerotic plaque undergoes both:
1. Plaque Rupture, followed by
2. Thrombosis

HRT/ERT stimulates both:
1. Plaque Rupture (via ↑ MMP-9+?), and
2. Thrombosis (pro-thrombotic state)


ERT/HRT Effects by Age at Rx Initiation
HRT Reduces CHD When Started Before 60 years old

ERT/HRT vs. CHD:
Late Start ≠ Early Start

<table>
<thead>
<tr>
<th>Research Type</th>
<th>Peri menopausal/Early</th>
<th>Postmenopausal/Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Observational</td>
<td>Good</td>
<td>No data</td>
</tr>
<tr>
<td>Animal</td>
<td>Good</td>
<td>Neutral</td>
</tr>
<tr>
<td>Basic Mechanisms</td>
<td>Good</td>
<td>Bad</td>
</tr>
<tr>
<td>Clinical Randomized</td>
<td>No data*</td>
<td>Bad**</td>
</tr>
</tbody>
</table>

* Suggestion of benefit in post-hoc analyses
** May be beneficial if Lp (a) elevated

Endocrine Society Scientific Statement re: MHT (WHI, etc.)
Selected Conclusions

Overall mortality
• MHT was associated with a 40% reduction in mortality in participants... below 60 yr or... within 10 yr of menopause onset.

Coronary heart disease (CHD)
• Basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events.
• [Lack of benefit or increase in CHD risk...[may have] resulted from harmful effects of MHT in older women starting therapy many years after onset of menopause.

Post-WHI Data:
Early-Start HRT
May → ↓ CVD

WISE—Prospective Observational Study of HRT Onset Timing

KEEPS: Changes in Risk Factors, CIMT


Harman, SM; NAMS Meeting Plenary Presentation, Orlando, FL; Oct 2012.
KEEPS: Percent of Subjects with Increases in CAC Score ≥ 5 Agatston Units

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline ≤ 4</th>
<th>Baseline &gt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-CEE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-E2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
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Harman, SM. AANM Meeting Plenary Presentation, Orlando, FL; Oct 2012.

KEEPS Results & Discussion

HRT Effects on athero:
• No effect on CIMT progression
• NS trend to benefit on CAC progression
Why no effect?
• Pts too healthy at baseline?
• F/U too short?
Other HRT Effects (generally beneficial):
• ↑HDL-C (oral)
• ↓Insulin resistance (patch)
• ↑QoL: cognitive & sexual
• ↑Bone density and structure
• No significant ↑AEs
Conclusions: suggestive (only) of benefit & safety


Danish Osteoporosis Prevention Study

• N=1006 randomized to placebo or HRT:
  – E2 2mg/d (if w/o uterus), or
  – E2 2mg x 12d, E2 2mg + 1mg NETA x 10d, E2 1mg x 6d (if w/ uterus)
• Age 45-58 y/o—avg 50—(45-52 y/o if s/p hysterectomy + FSH >2xULN)
• 3-24 mos postmenopausal (avg 7m), OR Sx w/ FSH >2xULN
• Exclusions: “bone dis” (fx etc.), h/o TE, glucocort >6m, HRT past 3m, h/o Ca
• Rx stopped ~ 11y due to WHI

Testing the Menopausal Hormone Therapy Timing Hypothesis: ELITE

- N=643 healthy postmenopausal women
- 2 x 2 design:
  - <6 yr vs >10 yr postmenop. (55 vs 65 y/o; 4 vs 14 yrs postmenop)
  - Rx Estradiol 1 mg/d po vs pbo, x 6-7 y
- ↓CIMT progression w/ E2, but only in early-start arm (interaction p=0.007)
- Caveat: results ms. not yet published
**ERT/HRT Effects by Rx Dose**

**Effect of Estrogen Dose on Risk for CHD**
*Nurses’ Health Study, 1980-1996*

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<th>Cases (n)</th>
<th>Multivariate-adjusted RR (95% CI)</th>
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<tr>
<td>Never</td>
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<td>699</td>
<td>1.0</td>
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<tr>
<td>0.3 mg*</td>
<td>19,964</td>
<td>19</td>
<td>0.58 (0.37-0.92)</td>
</tr>
<tr>
<td>0.625 mg*</td>
<td>116,150</td>
<td>99</td>
<td>0.54 (0.44-0.67)</td>
</tr>
<tr>
<td>≥1.25 mg</td>
<td>39,026</td>
<td>41</td>
<td>0.70 (0.51-0.97)</td>
</tr>
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CHD: Low-dose = Std. dose

**Effect of Estrogen Dose on Risk for Stroke**
*Nurses’ Health Study, 1980-1996*

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Stroke: Low-dose beats Std. dose

RR = relative risk for current vs. never users.

Postmenopausal ERT/HRT Risk:Benefit Analysis

Subgroup Analyses in Clinical Trials

Standard Statistical Rules
• No subgroup analyses allowed when 1° endpoint is negative in total study population
• In positive trials, any subgroup results are hypothesis generating only!
  But, since RCTs are few and patients are many

My Suggested Amendments
• Subgroup analyses may be considered for clinical application when:
  – Biologically plausible and
  – Consistent between ~comparable trials

HRT and the WHI
• Observational studies show HRT benefits:
  – ↓CHD
  – ↓stroke (low-dose)
  – ↓total mortality, even
  – ↓breast-cancer mortality
• RCTs of HRT (WHI E+P, WHI E only, HERS) all showed net harm (CVD, etc.)
• Standard interpretation: **HRT is “a classic example” that RCTs are always right** and observational data can’t be trusted
**HRT and the WHI**

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- Alternative approach: careful review of discrepancies may → different conclusion!

**HRT and the WHI (cont.)**

- Traditional explanation: observational data are misleading due to “healthy-user” bias
- Alternative explanation: RCT data are misleading due to effects of age at HRT start
- Observational studies: HRT started <=60 y/o
- WHI found:
  - HRT **harmful** when started >60 y/o*
  - HRT **beneficial** when started <60 y/o*
  - Most WHI subjects >60 y/o, so WHI showed net harm

*However
- Since ~99% of HRT starts are <=60 y/o:
  - WHI (as a whole) is irrelevant to clinical practice!
  - Only the <60 y/o subgroup is relevant but since “subgroup analyses aren’t good” → Catch 22.

Similar findings in DOPS study <=60 y/o: Schienbeck LJ BMJ 2012 appd 3Oct

**WHI Interpretation and Misinterpretation**

Correct Interpretations:
- HRT is generally harmful when started (for the 1st time) **AFTER age 60(!)**
- HRT → breast cancer (if w/ MPA)

Misinterpretation:
- “HRT always → breast cancer” (but jw/ E-only)
- “HRT generally dangerous” (but global benefit seen when started < 60 y/o=clinically relevant)
- Adverse effects if started >60 y/o => adverse effects when continued >60 y/o? (#biol. plaus.)
- “Stop HRT ASAP”, but
  - benefit w/ longer use in WHI,
  - [Benefit w/ stopping (in obs studies), effects of stopping never studied in RCT!}
Benefits of Estrogen Deficiency in Women (Complete List)

- May decrease migraines
- May reduce fibrocystic breast disease
- Helps treat estrogen-dependent cancer!

Estrogen Replacement Suggested and Proven Harms

Cardiovascular
- Pro-thrombotic (↑ DVT & PE)
- Pro-inflammatory (↑ MMP-9, other?)
- ↑ CHD—1st yr and late-start Rx only?
- ↑ CVA—full-dose ERT/HRT only?

Malignancy
- ↑ breast ca (E+P only?)
- ↑ endometrial ca (prevent w/ progest. IUD)

Other
- ↑ Dementia (late-start only?)
- ↑ Fibrocystic disease of breasts

Estrogen Replacement Suggested and Proven Benefits

Cardiovascular
- ↓ CHD early-start, longer duration
- ↑ healing venous-stasis and decubitus ulcers

Malignancy
- ↓ colon cancer
- ↓ breast cancer mortality

CNS & Eye
- ↓ Alzheimer’s, Parkinson’s, etc.
- ↓ macular degeneration

General/Misc.
- ↓ hot flashes
- ↓ osteoporosis
- ↓ osteoarthritis?
- DM prevention
- ↑ sleep & mood

Sexual/GU
- ↑ sexual funct.
- ↓ dyspareunia
- ↓ incontinence
- ↓ vaginitis
ERT/HRT: Official Guidelines vs. Preventive Use

Official Guidelines: for short duration only
- "Good company" (FDA, AHA, etc.)
- Standard analyses of WHI, etc. say this, but
- Requires leap of faith: late start = late contin? (seems unlikely)

Early-start Low-dose for CHD Prevention?
- Few favor this (maverick scientists and clinical Gyns), but
- Observational & relevant RDB data say it may work

Clinicians and Patients have had to choose between:
- Solid but likely irrelevant RDB trial data and
- Relevant but "iffy" observational/RDB data
But emerging RDB & cohort data now more strongly & consistently suggest HRT may → ↓ Athero & ASCVD

Dr Brinton’s Conclusion

Emerging Data Suggest:
- Estrogen Deficiency after menop. is Atherogenic AND
- Estrogen Replacement may be anti-atherogenic
And can be optimized:
- Age of initiation of Rx?—<60 y/o
- Duration of Rx?—long-term (lifelong?)
- Route?—oral (transderm to ↓ thromb & HTG)
- Agent?—unclear (CEE vs Estradiol?)
- Dose?—low (CEE 0.3/E2 0.5 mg/d)
- Progestin?—IUD/vag cream if has uterus
- Concurrent use of std. prev Rx (statin, etc.)

Remember
- HRT use is off-label and against official guidelines if:
  - Longer than a few years for menopausal Sx.
  - For intent of CHD prevention
--So, must have “informed assent” & good f/u--
- Dr. Brinton is an Endocrinologist whose job is to replace missing hormones, so feel free to ignore his “crazy” conclusion
- HRT use must always be individualized and patient must understand and agree
- OK to d/c whenever needed/desired