HT: Where do we stand after WHI?
Hormone therapy and cardiovascular disease risk

• Experimental and clinical evidence indicate that hormone therapy (HT) reduces the risk of cardiovascular disease (CVD)

• Women’s Health Initiative (WHI) trial failed to support observational data
  • “window of opportunity hypothesis”?
  • due to medroxyprogesterone acetate (MPA)?
WHI – OS Results

cases per 10 000 during the first 5 years follow-up

Shufelt et al. Menopause 2014
Secondary analysis of WHI – "window hypothesis"

CEE+MPA and CEE

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>Hazard ratio for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.76 (CI 0.50–1.16)</td>
</tr>
<tr>
<td>10–19</td>
<td>1.10 (CI 0.84–1.45)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1.28 (CI 1.03–1.58)</td>
</tr>
</tbody>
</table>

*P for trend = 0.02*

Rossouw JE et al. JAMA 2007;297:1465-77
Cochrane meta-analysis 2015 (Boardman et al.):

• 19 RCT trials, 40,410 women

• CHD events in relation to the use of HT (death from cardiovascular causes and non-fatal myocardial infarction)

  • Time from menopause
    < 10 v RR 0.52 (95% CI 0.29-0.96)
    > 10 v RR 1.07 (95% CI 0.96-1.20)

• Total mortality: RR 0.70, 95% CI 0.52 to 0.95
Timing hypothesis

15–25 years  25–35 years  35–45 years  45–55 years  55–65 years  >65 years

Benefits of Endogenous $E_2$  Primary benefits of ET/HT  No benefits of ET/HT

ELITE – estradiol vs. placebo

- E2 1 mg + progest. vs. placebo
- <6 or >10 years from menopause
- Progression of subclinical atheroclerosis (CIMT)

Hormone therapy and cardiovascular mortality in Finland

- **Medicine Reimbursement Register**: Identification of different HT regimens and purchases between January 1st, 1994 and December 31st, 2009
  - cover entire country and all HT purchases
  - only partial reimbursement
  - HT regimens can be bought only for 3 months use at one visit
  - Classification – E-alone (estradiol), EPT: NETA (48%), MPA (35%), dydrogesterone (17%), and other progestins (levonorgestrel, progesterone, megestrol acetate, lynesterol, drospirenone, and trimegeston). Sequential 70%.

- **Causes of Death Register**: all deaths due to CHD in women aged ≥ 40 during 1994-2009
  - mandatory in the entire country, diagnoses from the hospital physician or autopsy (30%)
Hormone therapy and cardiovascular mortality in Finland

- The number of **CHD deaths in HT users** was compared to the expected number of deaths due to CHD in the age- and year-matched background population by a standardised mortality ratio (SMR with 95% CI)

- 489 105 women
- 3.3 million HT (estradiol based) exposure yrs
- 3 843 cardiac deaths
- Mean HT exposure 6.7 years

Mikkola et al. Menopause 2015;22:976-83
Risk of cardiac death and the use of postmenopausal HT

<table>
<thead>
<tr>
<th>Years of use</th>
<th>Hormone Therapy</th>
<th>Coronary heart disease</th>
<th>Observed/expected deaths</th>
<th>Difference in deaths per follow-up years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>Any</td>
<td>1 022/1 247</td>
<td>-2/10 000</td>
<td></td>
</tr>
<tr>
<td>&gt;1 to ≤3</td>
<td>Any</td>
<td>464/691</td>
<td>-2/10 000</td>
<td></td>
</tr>
<tr>
<td>&gt;3 to ≤5</td>
<td>Any</td>
<td>318/510</td>
<td>-2/10 000</td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤10</td>
<td>Any</td>
<td>461/1 021</td>
<td>-4/10 000</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>Any</td>
<td>1 578/3 435</td>
<td>-19/10 000</td>
<td></td>
</tr>
</tbody>
</table>

Risk of cardiac death and the use of HT – “timing hypothesis”

Savolainen-Peltonen et al. JCEM 2016;101:2794-801
Not all progestins are alike

- Progestins similar to progesterone show lower impact than the more androgenic progestins on the beneficial estrogen mediated cardiovascular effects

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate (MPA)</td>
<td>-</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Norethisterone acetate (NETA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Stanczyk et al. Endocr Rev 2013;34:171
MPA inferior to other progestins?

• WHI – CEE+MPA HR 1.24 (1.00-1.54) vs. CEE-alone HR 0.95 (0.79-1.16)


• Danish National register
  • MI risk increased with continuous NETA RR 1.35 (1.18-1.53), but not with cyclic NETA or MPA


• DOPS-study HR 0.48 (0.26-0.87)
  • results similar with E2-alone vs. E2+NETA (death, MI, heart failure)

  Schierbeck et al. *BMJ*. 2012;345
### Details on the exposure and follow-up with different regimens

<table>
<thead>
<tr>
<th></th>
<th>Age at Initiation</th>
<th>Exposure years</th>
<th>Cumulative Exposure years</th>
<th>Follow-up years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>52.3</td>
<td>6.1</td>
<td>1 670 971</td>
<td>11.3</td>
</tr>
<tr>
<td>+NETA</td>
<td>52.8</td>
<td>3.4</td>
<td>789 090</td>
<td>10.4</td>
</tr>
<tr>
<td>+MPA</td>
<td>51.9</td>
<td>4.0</td>
<td>686 383</td>
<td>11.8</td>
</tr>
<tr>
<td>+Dydrogest</td>
<td>50.9</td>
<td>1.8</td>
<td>155 673</td>
<td>8.8</td>
</tr>
<tr>
<td>Other</td>
<td>51.0</td>
<td>2.7</td>
<td>230 992</td>
<td>11.4</td>
</tr>
<tr>
<td>Tibolone</td>
<td>57.2</td>
<td>3.8</td>
<td>181 422</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Other progestins include levonorgestrel, progesterone, megestrol acetate, lynesterol, drospirenone, and trimegeston.

Savolainen-Peltonen et al. JCEM 2016;101:2794-801
Risk of cardiac death and progestins

<table>
<thead>
<tr>
<th>Age at hormone therapy initiation</th>
<th>&lt;60 years</th>
<th>≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs deaths</td>
<td>Exp deaths</td>
</tr>
<tr>
<td>Estradiol only</td>
<td>306</td>
<td>580</td>
</tr>
<tr>
<td>NETA</td>
<td>475</td>
<td>1 064</td>
</tr>
<tr>
<td>MPA</td>
<td>369</td>
<td>736</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>102</td>
<td>259</td>
</tr>
<tr>
<td>Other progestins</td>
<td>145</td>
<td>362</td>
</tr>
<tr>
<td>Tibolone</td>
<td>49</td>
<td>139</td>
</tr>
</tbody>
</table>

Other progestins include levonorgestrel, progesterone, megestrol acetate, lynesterol, drospirenone, and trimegeston. Exposure ≤5 years

Savolainen-Peltonen et al. JCEM 2016;101:2794-801
## Risk of all-cause death and progestins

### Age at hormone therapy initiation

<table>
<thead>
<tr>
<th></th>
<th>&lt;60 years</th>
<th></th>
<th></th>
<th>≥60 years</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs deaths</td>
<td>Exp deaths</td>
<td>SMR (95% CI)</td>
<td>Obs deaths</td>
<td>Exp deaths</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td>Estradiol only</td>
<td>5 002</td>
<td>6 594</td>
<td>0.76 (0.74-0.78)</td>
<td>3 049</td>
<td>3 993</td>
<td>0.76 (0.74-0.79)</td>
</tr>
<tr>
<td>NETA</td>
<td>6 116</td>
<td>9 122</td>
<td>0.67 (0.65-0.69)</td>
<td>1 956</td>
<td>2 549</td>
<td>0.77 (0.73-0.80)</td>
</tr>
<tr>
<td>MPA</td>
<td>4 882</td>
<td>6 712</td>
<td>0.73 (0.71-0.75)</td>
<td>672</td>
<td>1 001</td>
<td>0.67 (0.62-0.72)</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>1 565</td>
<td>2 743</td>
<td>0.57 (0.54-0.60)</td>
<td>116</td>
<td>182</td>
<td>0.64 (0.53-0.76)</td>
</tr>
<tr>
<td>Other progestins</td>
<td>2 245</td>
<td>3 466</td>
<td>0.65 (0.62-0.68)</td>
<td>159</td>
<td>276</td>
<td>0.58 (0.49-0.67)</td>
</tr>
<tr>
<td>Tibolone</td>
<td>839</td>
<td>1 178</td>
<td>0.71 (0.66-0.76)</td>
<td>143</td>
<td>125</td>
<td>1.14 (0.96-1.35)</td>
</tr>
</tbody>
</table>

Other progestins include levonorgestrel, progesterone, megestrol acetate, lynesterol, drospirenone, and trimegeston. Exposure ≤5 years

Savolainen-Peltonen et al. JCEM 2016;101:2794-801
Conclusions

• Estradiol based HT is associated with reduced CVD mortality risk in our nationwide study

• Estradiol-based HTs are accompanied with larger CVD mortality risk reductions, the earlier the therapy is initiated

• The various progestins as complements to estradiol do not modify this “timing effect”
  • dydrogesterone appears superior to MPA or NETA
Fig. 1. WHI E+P trial: absolute risk by age.

Fig. 2. WHI ET trial: absolute risk by age.

When to stop using HT?

- Median total VMS duration 7.4 years
- The earlier VMS start, the longer they last

Avis NE JAMA Intern Med. 2015;175:531-9
Hormone therapy discontinuation

• Many women need symptom relief for several years after menopause

• “The lowest effective estrogen dose should be used during the shortest possible time”
  • Annual/biannual review and HT pause
  • Is this safe in symptomatic women?
Long-term CHD risk in WHI trial after HT discontinuation

• Median post-intervention follow-up 6.6 years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE+MPA</td>
<td>1.04 (0.89-1.23)</td>
</tr>
<tr>
<td>CEE</td>
<td>0.96 (0.77-1.19)</td>
</tr>
</tbody>
</table>

Manson et al. JAMA 2013;310;1353-68
Cardiac mortality risk in women discontinuing HT

• 332 202 women
• Follow-up 1.97 million years
• 3 117 cardiac deaths
• Mean HT exposure 6.2 ± 6.0 years
• Mean follow-up 5.5 ± 3.8 years
  • Acute (≤1 year) and long-term (>1 year) HT discontinuation analyzed separately

# Cardiac mortality risk in women discontinuing HT

<table>
<thead>
<tr>
<th>Time since last HT</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
<th>Difference/10 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 year</td>
<td>568</td>
<td>448</td>
<td>1.27 (1.17-1.37)</td>
<td>+4</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2609</td>
<td>3492</td>
<td>0.75 (0.72-0.78)</td>
<td>-5</td>
</tr>
</tbody>
</table>

SMR, standardised mortality ratio

# Cardiovascular mortality risk during the first post-HT year

<table>
<thead>
<tr>
<th>HT exposure</th>
<th>≤5 years</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMR (95% CI)</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td><strong>HT initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1.74 (1.37-2.19)</td>
<td>1.27 (1.14-1.41)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>1.12 (0.95-1.31)</td>
<td>1.30 (0.90-1.82)</td>
</tr>
<tr>
<td><strong>HT discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1.94 (1.51-2.48)</td>
<td>2.54 (1.84-3.44)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>1.11 (0.94-1.29)</td>
<td>1.19 (1.07-1.33)</td>
</tr>
</tbody>
</table>

SMR, standardised mortality ratio

Cardiac mortality risk in women discontinuing HT

- Results due to myocardial infarction (MI) among HT users who discontinue before MI related death??
  - MI fatal within 1-6 months in 30-50% of female patients
    (Lehto et al. Eur J Epidemiol 2011)

- From our data set we discarded all women with MI diagnosis within 1 year before HT discontinuation

Venetkoski M, et al. unpublished data
Vascular effects of estrogen

Discontinuation – possible adverse mechanisms:

- vasoconstriction
- inflammatory activation – plaque rupture
- arrhythmias

Mendelsohn ME et al. Science 2005;308:1583-7
Cardiac events and long-QT

• Congenital long-QT syndrome (LQTS) is most common inherited arrhythmogenic disorder predisposing to sudden cardiac death – particularly LQT2 genotype

• 282 women (LQT1; n=151, LQT2; n=131)
• Risk for recurrent cardiac events 5 years before and after menopause

Buber et al. Circulation 2011;123:2784-91
Cardiac events and long-QT

Rate of Cardiac Events by Menopausal Stages in LQT1 and LQT2 women

Event rate (per 100 patient-years)

LQT1

Reproductive
Transition
Post

LQT2

Reproductive
Transition
Post

HR 7.7

Buber et al. Circulation 2011;123:2784-91
Conclusions

• During the first year after HT discontinuation cardiovascular mortality risk is increased
  • particularly in women <60 years of age

• Our findings question the cardiovascular safety of annual/biannual HT pause practice to evaluate whether young (symptomatic) postmenopausal woman could manage without HT
HT in 2017

• WHI contributed significantly to our knowledge on the risks and benefits of HT

• HT is appropriate for symptomatic women near menopause who have no major contraindication
  • Management of vasomotor symptoms
  • Prevention of osteoporosis

• Vaginal estrogen is almost never contraindicated
Women’s perceptions of their greatest health problems

- Breast cancer 34%
- Cancer 27%
- Other problems 16%
- Don’t know/ No Answer 16%
- CVD 7%


Cardiovascular disease mortality in Europe 2014, Eur Heart J 2014
• Evidence from observational studies and clinical trials suggests *benefits outweigh risks* for most women when started early - 10 yrs from menopause?

![Diagram showing risks and benefits of HT](image)

**Fig. 5.** Risks and benefits of HT: cases per 100 women per 5 years of use. Derived from Ref. [50].

HT in 2017

• Individualizing HT
  • Life style
  • Screen breast cancer and CVD risks
  • Treat CVD risks
  • Dose, formulation, progestin

• Fewer adverse effects with transdermal E2 and progesterone
  • VTE, stroke, obesity, cardiovascular risks
I'M STILL HOT, IT JUST COMES IN FLASHES NOW