Time Since Menopause Influences the Acute and Chronic Effect of Estrogens on Endothelial Function

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Royal Brompton Hospital & Imperial College
London, UK

Cali Colombia Thurs 20 May 2010
Arterial Sites of Action of Estrogen

Adapted from Sarrel PM, Maturitas 590:287-298, 1990.
Estrogen vascular effects

- Lipids (atheroma)
- Antioxidant
- Fibrinolysis + coagulation
- ACE inhibition
- Inhibition of constrictor agents
- Nitric oxide
- Prostacyclin
- Ion channels
Estrogen hits the surface

P Collins & C Webb

Nature Med 1999;5:1130-1131
Endothelial cell Vasorelaxation
Neuron Neuroprotection
Breast cancer cell Cell cycle stimulation
Osteoblast Cell proliferation/differentiation Bone conservation
Estrogen-intact animal

Coronary flow

- Endothelium-dependent
  - Monkey
- Endothelium-independent
  - Human
  - Dog

Peripheral blood flow (Forearm Carotid)

- Endothelium-dependent
- Endothelium-independent
Left anterior descending coronary artery

Doppler infusion catheter

Quantitative angiography

Cross-sectional area to convert velocity to flow

- Acetylcholine responses before 17β-estradiol
- i.c. estradiol (2.5 µg) given
- Acetylcholine responses 20 min after estradiol
- Isosorbide dinitrate

Collins et al., Circulation, 1995;92:24-30
Mean change in coronary diameter (%) vs. Pre vs. Post estrogen for Females and Males.

- Females:
  - Pre estrogen: Mean change in coronary diameter
  - Post estrogen: Mean change in coronary diameter

- Males:
  - Pre estrogen: Mean change in coronary diameter
  - Post estrogen: Mean change in coronary diameter

* p < 0.01

Collins et al., Circulation, 1995;92:24-30
Flow Mediated Dilatation (FMD)
Flow-mediated dilatation: endothelium-dependent
Time Since Menopause Influences the Acute and Chronic Effect of Estrogens on Endothelial Function

Cristiana Vitale, Giuseppe Mercuro, Elena Cerquetani, Giuseppe Marazzi, Roberto Patrizi, Francesco Pelliccia, Maurizio Volterrani, Massimo Fini, Peter Collins and Giuseppe M.C. Rosano

Methods

- Flow-mediated dilatation (FMD) in 134 postmenopausal women (PMW) before and after acute and chronic E administration
Study Design

- After baseline evaluation, endothelial function - FMD of the brachial artery and blood sampling.
- Assessment of endothelial function repeated within 1 hour (≥40≤60 minutes)
- After acute administration of E (1 mg s.l.) and after 3 months of oral ERT (estradiol valerate 1 mg/d).
Table 1. Baseline Clinical Characteristics of Study Participants (n=134)

<table>
<thead>
<tr>
<th></th>
<th>All (n=134)</th>
<th>Exogenous estrogen naïve (n=53)</th>
<th>Past users (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±6</td>
<td>56.5±4.5</td>
<td>66±3*</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>13.8±2.5</td>
<td>5±2</td>
<td>16±4*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.2±1.7</td>
<td>25.6±1.4</td>
<td>27.1±22</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Hypercholesterolemics</td>
<td>26</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Diabetics</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Baseline clinical features of study subjects. Exogenous estrogen naïve were older and had a longer time since menopause. *P<0.05.
Results

- E administration improved FMD more in women within 5 years since menopause than in those with more than 5 years since menopause (76% and 74% versus 45% and 48%, acute and chronic E, respectively; \( P<0.05 \)).
Results

• Among women with more than 5 years since menopause acute and chronic E increased FMD more in previous E users than in nonusers (59% and 63% versus 31% and 38%, acute and chronic E, respectively; $P<0.01$).
Results

- Baseline FMD was inversely associated to time from menopause ($r = -0.67$, $P<0.001$)
- and age ($r = -0.43$, $P<0.05$), in exogenous estrogen naive but not in previous users.
- Acute and chronic E improved endothelial function in all women.
Conclusions

• Time from menopause influences FMD in PMW. The acute and chronic effect of E on FMD is time dependent and is reduced by a longer time since menopause.

Potential Mechanisms
Early atherogenesis

Established atherosclerosis

Beneficial effects of HRT

- Vasodilation
- Nitric oxide
- Endothelin
- Cox-2
- Lesion progression
- Nitric oxide adhesion
- Platelet activation
- Inflammatory cell adhesion
- LDL oxidation/binding

- Inflammatory activation
- Nitric oxide
- CAMs
- MCP-1, TNF-α

Altered biology of HRT

- ER expression, function
- Vasodilation
- Inflammatory activation
- Plaque instability
- MMP
- Neovascularization

Mendelsohn and Karas, *Science*, June, 2005
Hormone Therapy for CVD in Perspective
Why is Hormone Therapy prescribed?

To treat postmenopausal symptoms

- Hot flushes
- Night sweats
- Tiredness, irritability, depression
- Vaginal dryness (topical estrogen very effective)

Postmenopausal bone loss (other therapies available)

Largely in women aged less than 60 years
TIMING OF HRT INTERVENTION

Effect of Estrogens on Atherogenesis in Nonhuman Primates

Premenopausal Years

1. Healthy diet

2. Atherogenic diet

Postmenopausal Years

Ovariectomy

3. Healthy diet

CEE + atherogenic diet

4. Atherogenic diet

Healthy diet + CEE

Plaque Area (% of Placebo)

70%\(^1,2\)

50%\(^3\)

0%\(^4\)

~ 6 Year Human Equivalent

Time

\(^1\) Clarkson et al. *J Clin Endocrinol Metab* 1998;83:721.  
Atherosclerosis: When does it begin?

Data from 262 heart transplant donors. Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic.

Available Hormone Preparations

- **Women with uterus**
  - Premarin + MPA (oral)
  - Estradiol valerate + norethisterone (oral)
  - Estradiol valerate + levonorgestrel (oral)
  - Estradiol 17β + norethisterone (transdermal)
  - Estradiol 17β (transdermal) + norethisterone (oral)
  - Estradiol 17β + dydrogesterone (oral)
  - Estradiol 17β + norethisterone (oral)
  - Estradiol valerate + MPA (oral)
  - Estradiol 17β + drosperinone

- **Women without uterus**
  - Premarin – conjugated equine estrogens (oral)
  - Estradiol 17β (implant)
  - Estradiol 17β (oral)
  - Estradiol 17β (transdermal patch)
  - Estradiol 17β (transdermal gel)
  - Estriol (oral)
  - Estropipate (oral)
### Differences between Clinical Trials and Observational Studies

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trials</th>
<th>Observational</th>
</tr>
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<tbody>
<tr>
<td>Mean age or age range</td>
<td>&gt;63</td>
<td>30-55</td>
</tr>
<tr>
<td>at enrollment (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal symptoms</td>
<td>excluded</td>
<td>predominant</td>
</tr>
<tr>
<td>(flushing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since menopause</td>
<td>&gt;10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>&lt;7</td>
<td>&gt;10-40</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (BMI;</td>
<td>28.5 kg/m²*</td>
<td>25.1 kg/m²</td>
</tr>
<tr>
<td>mean)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For example, WHI: 34.1% had BMI $\geq$ 30 kg/m²
The WHI Hormone Therapy Trials

• Two main questions were posed:
  – Does a standard regimen of the hormones usually used to treat menopausal symptoms reduce cardiovascular risk in women who are predominantly asymptomatic and many years postmenopausal?
  – Does the treatment increase breast cancer risk significantly?
Conclusion from 2002

“Results from WHI indicate that the combined postmenopausal hormones CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.”

U.S. halts study on hormone therapy

Wednesday: July 10, 2002

In a rare move, the government has halted a study of hormone therapy planned because of a slight increase in breast cancer. Researchers had warned that the hormones might increase the risk of cancer and heart disease. The study, involving more than 16,000 women, was the latest in a series of controversial investigations of hormone therapy.

Women who had been taking the hormones by far the largest amount of estrogen for more than 10 years had a 23 percent increase in breast cancer. Patients had been eagerly awaiting the results of the study, which was designed to evaluate the long-term effects of hormone therapy on heart disease. Its impact is expected to be significant, according to health experts, who say that U.S. women are now on hormone therapy.

Women who have been taking the hormones for more than 10 years should not panic, says the director of the Women's Health Initiative, which was designed to evaluate the long-term effects of hormone therapy on heart disease. Although those on the hormone therapy were matched only eight months after the hormone therapy was stopped, those who continued to take the hormones were matched eight months after the hormone therapy was stopped.

By GINA KOLATA with MELODY PETERSEN

The announcement yesterday that the hormone therapy regimen had been stopped came as doctors across the country were preparing to start taking the drugs when they reached menopause and to take them for years, even for life. Now the growing consensus seems to be that women should consider whether they want to start the drugs at all. Those who

Hormone Replacement Study
A Shock to the Medical System

Wednesday: July 10, 2002

HRT heart benefit disproved

Increased Risks Prompt
Researchers to Halt Study; A Big Dilemma for Women

By THOMAS M. BOYCE

The announcement yesterday that the hormone therapy regimen had been stopped came as doctors across the country were preparing to start taking the drugs when they reached menopause and to take them for years, even for life. Now the growing consensus seems to be that women should consider whether they want to start the drugs at all. Those who

Hormone Replacement Study
A Shock to the Medical System

Wednesday: July 10, 2002

HRT heart benefit disproved
Conclusion from 2003

“In the interim, women with indications for treatment, such as menopausal symptoms, need to consider with their clinicians the suggestion of a slight overall increase in the risk of CHD and information on the risks of other outcomes in making decisions about the use of estrogen-plus-progestin therapy.”

“The numbers of events increased with increasing age but there was no statistically significant additional effect of hormone therapy for any outcome in the combined trials.”
Hazard Ratios for Clinical Outcomes

Hazard Ratio

- Global index
- CHD
- Stroke
- Venous Thromboembolism
- Breast Cancer
- Colorectal cancer
- Hip fracture

Hazard Ratios for Clinical Outcomes

Hazard Ratio

Global index
CHD
Stroke
Venous Thromboembolism
Breast Cancer
Colorectal cancer
Hip fracture

# WHI: CHD-Relative and Absolute Risk

**Average age = 64; Average time since menopause >10 years**

<table>
<thead>
<tr>
<th>Health Event</th>
<th>Overall Hazard Ratio</th>
<th>Confidence Interval</th>
<th>Absolute Risk per 10,000 Women/Year</th>
<th>Absolute Benefit per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nominal 95%</td>
<td>Adjusted 95%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHI – CEE + MPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD 2002</td>
<td>1.29</td>
<td>1.02–1.63</td>
<td>0.85–1.97</td>
<td>7</td>
</tr>
<tr>
<td>CHD 2003</td>
<td>1.24</td>
<td>1.00–1.54</td>
<td>0.97–1.60</td>
<td>6</td>
</tr>
<tr>
<td>CHD 2007</td>
<td>1.23</td>
<td>0.99–1.53</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>CHD 2008</td>
<td>1.22</td>
<td>0.99–1.51</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>WHI – CEE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD 2004</td>
<td>0.91</td>
<td>0.75–1.12</td>
<td>0.72–1.15</td>
<td>5</td>
</tr>
<tr>
<td>CHD 2006</td>
<td>0.95</td>
<td>0.79–1.12</td>
<td>0.76–1.19</td>
<td>5</td>
</tr>
<tr>
<td>CHD 2007</td>
<td>0.95</td>
<td>0.78–1.16</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Misperception

HRT has the same risk-benefit profile across all women
Effect of HT on CHD: Timing of Initiation

### Years Since Menopause

<table>
<thead>
<tr>
<th></th>
<th>WHI-E+P</th>
<th>WHI-E</th>
<th>WHI-Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.88</td>
<td>0.48</td>
<td>0.76</td>
</tr>
<tr>
<td>10-19</td>
<td>1.23</td>
<td>0.96</td>
<td>1.10</td>
</tr>
<tr>
<td>≥20</td>
<td>1.66</td>
<td>1.12</td>
<td>1.28</td>
</tr>
</tbody>
</table>

**P for trend**

- WHI-E+P: 0.05
- WHI-E: 0.15
- WHI-Combined: 0.02

**Absolute Risk per 10,000 Women per Year of HT Use**

- WHI-E+P: -4
- WHI-E: -14
- WHI-Combined: -6

CHD Events Associated with HRT in Younger and Older Women: Meta-analysis of 23 Randomized Controlled Trials (191,340 patient-years)

<table>
<thead>
<tr>
<th>HRT vs. Control</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>&gt;10 years menopause, &gt;60 years old</td>
<td>1.03 (0.91-1.16)</td>
</tr>
<tr>
<td>&lt;10 years menopause, &lt;60 years old</td>
<td>0.68 (0.48-0.96)</td>
</tr>
<tr>
<td>Younger vs. Older women</td>
<td>0.66 (0.46-0.95)</td>
</tr>
</tbody>
</table>

Relative Risk of CHD: Observational Studies and Randomized Controlled Trials

**Epidemiologic Studies**
- Age = 30-55 y
- Time Since Menopause < 6 y
  - Risk Estimate: 0.64

**Randomized Trials**
- Age < 60 y
- Time Since Menopause < 10 y
  - Risk Estimate: 0.68

HRT - coronary heart disease - IMS Scientific Statement 2008

Perception

- HRT increases coronary heart disease (CHD) risk throughout the whole postmenopausal period.

The evidence

- HRT in women aged 50–59 years does not increase CHD risk in healthy women and may even decrease the risk in this age group. [A]

- Early harm (more coronary events during the first 2 years of HRT) was not observed in the early postmenopausal period. The number of CHD events decreased with duration of HRT in both WHI clinical trials. [A]
Estrogen Therapy and Coronary-Artery Calcification

JoAnn E. Manson, M.D., Dr.P.H., Matthew A. Allison, M.D., M.P.H.,
Subjects

• 1064 postmenopausal women aged 50-59
• Imaging mean 7.4 years
• Estrogen CEE 0.625 mg vs placebo
• Coronary artery scores Agastion score central reading centre blinded to treatment

Background

- Coronary artery calcification is pathognomonic of coronary disease (Wexler, Circulation 1996)
- Total area of coronary calcification is strongly correlated with total area of coronary plaque on histo-pathological studies ($r=0.9$, Rumberger, Circulation 1995)
- Approximately 20% of coronary plaque is calcified
Calcium score
Hazard Ratios for Coronary Calcium

Conclusion

• Women aged 50-59 taking estrogen had less calcified plaque burden than women taking placebo

• This may translate into a potential cardioprotective action

• This study cannot be used to recommend that hormone therapy should be used solely for cardioprotection

• Reassurance that younger women who take hormone therapy for menopausal symptoms may benefit from a decrease in coronary risk
Effects of the Selective Estrogen Receptor Modulator Raloxifene on Coronary Outcomes in the RUTH Trial
Results of Subgroup Analyses by Age and Other Factors


For the Raloxifene Use for The Heart (RUTH) Trial Investigators
RUTH: Cumulative Incidence Rate for Invasive Breast Cancer for All Randomized Women (N=10,101)

Cumulative incidence, per 1000 women

HR 0.56 (95% CI 0.38 - 0.83)
p=0.003
RUTH: Primary Coronary Outcome

Cumulative incidence, per 1000

- Placebo
- Raloxifene 60 mg/d

HR 0.95 (95% CI 0.84-1.07)
Log-rank test P-Value = 0.40
### RUTH: Subgroup Analyses of Coronary Primary Endpoint

<table>
<thead>
<tr>
<th>Subgroup (8/22)</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1670</td>
<td>0.59</td>
<td>0.41-0.83</td>
</tr>
<tr>
<td>≥60 and &lt;70</td>
<td>4534</td>
<td>1.06</td>
<td>0.88-1.28</td>
</tr>
<tr>
<td>≥70</td>
<td>3897</td>
<td>0.98</td>
<td>0.82-1.17</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8481</td>
<td>0.94</td>
<td>0.83-1.08</td>
</tr>
<tr>
<td>Other</td>
<td>1620</td>
<td>0.98</td>
<td>0.74-1.31</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>2416</td>
<td>1.01</td>
<td>0.80-1.29</td>
</tr>
<tr>
<td>&gt;25 and ≤30</td>
<td>4052</td>
<td>0.93</td>
<td>0.76-1.12</td>
</tr>
<tr>
<td>&gt;30</td>
<td>3603</td>
<td>0.93</td>
<td>0.76-1.13</td>
</tr>
<tr>
<td>CV risk score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>3671</td>
<td>1.01</td>
<td>0.78-1.31</td>
</tr>
<tr>
<td>&gt;5 and ≤9</td>
<td>3469</td>
<td>1.04</td>
<td>0.86-1.25</td>
</tr>
<tr>
<td>&gt;9</td>
<td>2961</td>
<td>0.83</td>
<td>0.68-1.01</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1256</td>
<td>0.87</td>
<td>0.60-1.26</td>
</tr>
<tr>
<td>No</td>
<td>8845</td>
<td>0.96</td>
<td>0.85-1.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4607</td>
<td>0.89</td>
<td>0.76-1.06</td>
</tr>
<tr>
<td>No</td>
<td>5470</td>
<td>1.01</td>
<td>0.85-1.20</td>
</tr>
</tbody>
</table>

- *Treatment by subgroup interaction P-Value, 0.118*
< 60

>= 60 and < 70

>= 70

P < 0.0118 for interaction
RUTH: Effect of Raloxifene on the Incidence of the Primary Coronary Endpoint by Age

P < 0.0118 for interaction

+++ 95 percent confidence interval
Misperception

HRT risks outweigh benefits
Total Mortality Associated with HRT in Younger and Older Women: Meta-analysis of 30 Randomized Controlled Trials (119,118 patient-years)

<table>
<thead>
<tr>
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<td>All ages</td>
<td>0.98 (0.87-1.18)</td>
</tr>
<tr>
<td>&gt;60 years old; Mean age = 66 years</td>
<td>1.03 (0.91-1.16)</td>
</tr>
<tr>
<td>&lt;60 years old; Mean age = 54 years</td>
<td>0.61 (0.39-0.95)</td>
</tr>
</tbody>
</table>

Misperception

HRT risks are large in magnitude and greater than other commonly used therapies
**Primary Prevention of CHD with HRT in Clinical Perspective**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hormone Therapy&lt;sup&gt;1,2*&lt;/sup&gt;</th>
<th>Lipid Lowering&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Aspirin&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.68 (0.48-0.96)</td>
<td>0.89 (0.69-1.09)</td>
<td>0.91 (0.80-1.03)</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>0.61 (0.39-0.95)</td>
<td>0.95 (0.62-1.46)</td>
<td>0.95 (0.85-1.06)</td>
</tr>
</tbody>
</table>

*Women <60 years old and/or <10 years since menopause when randomized

---

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<td>predominant</td>
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<td>&gt;10</td>
<td>&lt;5</td>
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<td>&gt;10-40</td>
</tr>
<tr>
<td>Body mass index (BMI; mean)</td>
<td>28.5 kg/m³*</td>
<td>25.1 kg/m²</td>
</tr>
</tbody>
</table>

*For example, WHI: 34.1% had BMI ≥30 kg/m²

CONCLUSIONS

• benefits of HRT established
  • symptoms, osteoporosis/fracture

• risks of HRT established
  • VTE (with oral therapy, transient)

• CVD benefits/risks *not* established
  • CHD, stroke, breast cancer (E+P), large bowel Ca, dementia
  • start with low oestrogen doses
  • use appropriate progestin

• if used correctly, HRT is a benefit
• The Effect of HRT on Coronary Risk – Good or Bad!

• It's starting to look pretty good!! Especially for younger women who need it
Assessment and Management of Cardiovascular Risks in Women

A Short Guide for Menopause Physicians

Thank You!
Misperception

WHI enrolled `healthy’ women
WOMEN’S HEALTH INITIATIVE

no = 98705, aged 50-79 years

HYPERTENSION

37.8%

TREATED

64.3%

CONTROLLED

36.1%

NON TREATED

35.7%

Wasserheil-Smoller et al., Hypertension, 2000, 36, 780
Epidemiology

“Truth is ascertained only when sufficient numbers of appropriate studies are conducted and no one study or one study design has a monopoly on the truth”

Trudy Bush Int. J. Fert. 2001:46:56
Conclusions

• The Effect of HRT on Coronary Risk – Good or Bad?
• It is becoming much clearer!
• Evidence is highly supportive of a beneficial effect in younger women who actually need it for treatment of menopausal symptoms
• The ideal HRT is not known and other progestins such as the anti-aldosterone activity of drosperinone may result in enhanced cardiovascular benefits
Raloxifene

L-arginine → NOS → NO

Endothelial cell

Ca²⁺ antagonism

Smooth muscle cell

NO → Relaxation
HRT & MI SURVIVAL

- 114,724 women with confirmed MI
- Age >55 years
- 7,353 (6.4%) on HRT
- Adjusted OR 0.65 (CI 0.59-0.72)

Schlipak et al. Circulation 2001; 104: 2300-09
100 postmenopausal women followed up to 12 months mean age 68 yrs
- acute coronary syndrome (majority MI)
- randomised to placebo or HRT 2 - 28 days post-event
- oestradiol $17\beta$ 1 mg/NETA 0.5 mg daily
- efficacy
  - lipid parameters
  - (clinical events)
- safety
  - haemostatic parameters

RH 0.68
(CI 0.32 - 1.46)

Collins et al. Eur Heart J 2006; 27: 2046-53
PROSPER – The HERS equivalent for Statins in women

- Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

Shepherd et al Lancet 2002;360: 1623-30
PROSPER

- 3000 women aged 70-82 years
- History or at risk vascular disease
- Pravastatin 40mg/day or placebo
- N = Prav 1495, Plac 1505
- treatment for 3.2 years
- Coronary death, NF MI

*Lancet* 2002; 360:1623
PROSPER - Major Cardiovascular Outcomes According to Sex

<table>
<thead>
<tr>
<th></th>
<th>Pravasatin (n=1369)</th>
<th>Placebo (n=1408)</th>
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<tbody>
<tr>
<td>CHD death, non-fatal and fatal non-fatal stroke</td>
<td>222</td>
<td>279</td>
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<tr>
<td>CHD death, non-fatal MI</td>
<td>167</td>
<td>219</td>
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<tr>
<td>Fatal and non-fatal stroke</td>
<td>65</td>
<td>70</td>
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<tr>
<td>TIA</td>
<td>38</td>
<td>53</td>
</tr>
</tbody>
</table>

Women: (n=1495)  (n=1505)

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Shepherd et al Lancet 2002;360:1623-30

Hazard ratio

Statin better

Statin worse
WHI (E): CHD & STARTING AGE

- 10,739 “healthy” postmenopausal women
- age 50 - 79 years
- CEE 0.625 mg
- duration 6.8 years (planned 8.5 years)
- primary benefit: CHD events
- primary adverse event: breast cancer
- overall benefits exceeded risks

The Women’s Health Initiative Steering Committee. JAMA 2004; 291: 1701-12