HRT and Heart

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1976

Data from the Framingham Heart Study and the National Health and Nutrition Examination Survey-I suggest that at least 70% of women with HF are over age 50 years

JACC Vol. 42, No. 7, 2003 Lindenfeld et al. 1245
October 1, 2003:1238–45 HRT and Heart Failure
Framingham study: 1976

2.6 fold higher CVS events in post menopausal women

2.7 fold increase in surgical menopause

The risk seemed to be prevented with estrogen therapy
As the years rolled by, it was evident that the participants had an increased risk of cardiac events. Participants were informed about increased incidence of MI, DVT, PE, Stroke.

Risk of increased MI, Stroke, DVT, Evidence of breast cancer

The harm caused by not taking Drugs seemingly was less than The harm caused by taking The drug.
HERS: a Secondary Prevention Trial

There were more CAD events within the first year of HRT, and fewer events in years 4 and beyond.

There was absence of protection overall, and the increased CVD risk within 1 year

In the earlier years of menopause, due to improvement of lipid profile with estrogen, MHT is beneficial to heart. But after 10 years, clots have already formed in the vessels. At this point of time, the prothrombotic action of estrogen will worsen the clot.
These observations underscore the potential importance of the mode of administration on the overall effects of HT on CHD risk.

(J Am Coll Cardiol 2006;47:1741–53)
Danish Osteoporosis prevention study

1006 recently menopausal women followed for 12-16 years

There were significantly favorable hazard ratios in the estrogen only (posthysterectomy) and estrogen plus progestin groups, supporting a cardiovascular primary prevention benefit for HRT when started in recently menopausal women.

Co-administration of progestin, however, blunts the benefits seen in serum lipids due to oral estrogen and also similar amount of benefits are not seen with transdermal estrogen preparations.

Based on WHI: number of less events on estrogen vs. placebo per 10,000 women per year of HT use between the age group of 50-59 years (R: Grade A)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of less events with estrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8</td>
</tr>
</tbody>
</table>

Number of less events with E/E+P

<table>
<thead>
<tr>
<th>Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>10</td>
</tr>
<tr>
<td>Adverse events</td>
<td>18</td>
</tr>
<tr>
<td>Fractures</td>
<td>5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>6</td>
</tr>
</tbody>
</table>
Based on WHI: number of excess events on HT vs. placebo per 10,000 women per year of HT use between the age group of 50–59 years (R: Grade A)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estrogen</th>
<th>WHO/CIOMS definition of risk</th>
<th>Estrogen+ progesterone</th>
<th>WHO/CIOMS definition of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>4</td>
<td>Rare &lt;1/10,000 and &lt;1/1,000</td>
<td>11</td>
<td>Rare &gt;1/10,000 and &lt;1/1,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>Rare &gt;1/10,000 and &lt;1/1,000</td>
<td>4</td>
<td>Rare &gt;1/10,000 and &lt;1/1,000</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td>Rare &gt;1/10,000 and &lt;1/1,000</td>
<td>5</td>
<td>Rare &gt;1/10,000 and &lt;1/1,000</td>
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<tr>
<td>CVD</td>
<td></td>
<td></td>
<td>5</td>
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</table>
Type of progestin may help

16 post menopausal women

Estradiol 2mg-28 days

Forearm blood flow increased

Estradiol + dydrogesterone last 14 days

Forearm blood flow increased

i.e. Vasodilatory effect of estrogen was not reversed.

Dydrogesterone does not reverse the effects of estradiol on endothelium-dependent vasodilation in postmenopausal women: a randomised clinical trial. Marco Gambacciani b, Patrizia Monteleone b et al... M.C. Rosano a, Maturitas 43 (2002) 117/123
Dydrogesterone vs Norethisterone in HRT

115 non-hysterectomised women on oestrogen and progesterone

6 cycles of estrogen + dydrogesterone

The HDL-C levels were increased
Sharp increase in SHBG

Dydrogesterone is a lipid friendly molecule

6 cycles of estrogen + Norethisterone

The HDL-C levels were decreased
IGF-I levels increased

C. Campagnoli et al. / Maturitas 41 (2002) 299–311
(HT) Hormone Therapy given to women below the age of 60 or within 10 years of menopause, the risks are rare.
Peripheral vascular resistance

Volume regulatory mechanism

Interplay

HRT and hypertension
Women with HRT had reduced left ventricular cavity dimensions, diminished resting aortic blood flow velocity, and lower resting-mean and post-exercise blood pressures.

HRT would be expected to leave blood pressure unchanged or to actually promote a blood-pressure reduction in post-menopausal normotensive and hypertensive women.
Effects of hormonal replacement therapy in postmenopausal hypertensive patients

60 women with hypertension. 24 hour BP recorded. (Age around 50)

Transdermal continuous HRT in a sequential regimen

Placebo

Followed up at 3,6, months

No significant variations of systolic and diastolic BP measured with standard sphygmanometer were detected in both groups

24 hour BP was less in the treatment group. Decrease in daytime BP was significant for both systolic and diastolic BP.

Maturitas 40 (2001) 75–83

19 such studies have been performed

- 5 found no effect on BP
- 14 studies demonstrated BP reductions.

- BP was lowered by treatment with transdermal estradiol in 11 of 13 studies
- by oral estrogen in 4 of 11 studies.

- The effects were not consistent with regard to systolic or diastolic BP nor to action on day- and night-time BP.
So far......

- HRT given in perimenopausal period can be good for the heart
- HRT is safe and may be beneficial in hypertension
- HRT started for the first time in a woman who is more than 10 years post menopausal can be detrimental...
- In hysterectomised women more than 55 years of age......
- Lipid friendly progesterones are better to use.
Beta-Blocker Evaluation of Survival Trial (BEST)

Heart failure patients with NYHA functional class III or IV

<table>
<thead>
<tr>
<th>Bucindol, a beta blocker</th>
<th>Placebo</th>
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Presence of the 435 women age 50 years or older

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<tr>
<th>102 were using HRT</th>
<th>333 No HRT</th>
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<tr>
<td>21(21%) died.</td>
<td>113(34%) died</td>
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There was a significant difference in survival favoring HRT users

HRT and Heart Failure October 1, 2003:1238–45
When these factors are accounted for in a multivariate analysis, HRT remains a significant predictor of mortality with a relative risk of 0.60 (p 0.039).

Was it affected by better baseline features?

Younger age of patients in the group
Less hypertension and diabetes
Higher frequency of non ischaemic etiology
HRT evaluated with direct cardiac functions and not in relation to atherosclerotic disease

In conclusion, postmenopausal HRT leads to a progressive improvement on left ventricular function parameters, and in parallel, in exercise performance.

Maturitas 47 (2004) 107–113
Nurses study

70,000 women studied

Lower incidence of CHD events in HT users compared with nonusers

Women in the study started taking HT in perimenopausal period and were free of Known CHD.
Pulse wave velocity (PWV) determines Aortic stiffness.

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<th>56 postmenopausal women studied using brachial to ankle PWV</th>
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<tr>
<td>26 on HRT</td>
</tr>
<tr>
<td>29 not on HRT</td>
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BaPWV decreased significantly after ERT

Conclusion: Estrogen appears to improve arterial compliance independently of BP within 4 weeks

Maturitas 45 (2003) 293/298
Raloxifene in hypertensive patients

Women with HT on hydrochlorothiazide.

Given HT or Raloxifene in addition

Significant reduction in BP and PWV

Am J Cardiol 2004;94:1453–1456
The Estrogen Replacement and Atherosclerosis (ERA) trial

- Unopposed oral CEE
- CEE plus MPA
- Placebo

No difference in mean minimum artery diameter was found among the 3 groups.
No progression of atherosclerosis

Improvement in lipids and lipoproteins
Papworth HRT Atherosclerosis Study Enquiry (PHASE) trial

255 PM women with CAD studied

Followed up till

Angina, MI, or death (4 year)

Women with HRT

Women without HRT

Event rates were higher in the HRT
Difference was not statistically significant
The Estrogen and Prevention of Atherosclerosis Trial (EPAT)

199 women with high LDL on oral estradiol vs placebo

Carotid artery thickness studied

After 2 years Carotid thickness decreased with estradiol

This happened only in women who were not taking lipid lowering agents

Conclusion

- HRT is not currently recommended solely to prevent future heart attacks in perimenopausal or postmenopausal women.

- For perimenopausal, recently perimenopausal, or even more than a decade postmenopausal women with life-disrupting vasomotor and urogenital symptoms, topical estrogens should be first considered, followed by hormone patches with the lowest effective estrogen dose possible.

- Treatment should be maintained for the shortest duration possible.

- For women who are a decade or the more after the menopause and are no longer troubled by symptoms, HRT should be discontinued.
THANK YOU!