Heart disease in women: new insights into the differences

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On behalf of the UCLA Women’s Cardiovascular Center

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Speaker’s Bureau: Boehringer Ingelheim

1964 – AHA held the first conference on women and heart disease
Featuring the leading cardiologist Paul Dudley White
“Hearts and Husbands”
It was basically about How to Care for Your Man
• “This session has vital importance for the wives of men suffering from any heart disease”
• No discussion about self-care

1995 – Reader’s Digest warned women to protect their husband’s from heart attack

2015 – The Atlantic wonders why doctors still misunderstand heart disease in women

Heart Disease in Women
• Scope of the Problem
• Prevention
  – Differential impact of risk factors
  – Differential response to preventive medications
• Coronary Artery Disease
  – Myocardial Ischemia
  – Difference in pathophysiology and outcomes
• Research from our Center
  – Stress in women
• Hormone Replacement Therapy
Cardiovascular disease mortality trends for males and females (US 1979-2013)

Heart Disease in Women: Scope of the Problem

- Heart disease is the #1 killer of women in the United States, taking more lives than all forms of cancer combined.
- Heart disease affects women of all ages, in fact while rates are decreasing in most segments of the population, in young women, age-adjusted rates are increasing.
- Many cardiovascular approaches have been developed predominately in men and extrapolated to women.
- There are many similarities between heart disease in women and men, yet important differences do exist.
- Defining these differences is imperative.

INTERHEART: Focus on 9 risk or protective factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td>46.2(43.4,48.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td>44.0(41.6,46.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.5(33.0,39.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32.9(30.3,34.5)</td>
</tr>
</tbody>
</table>

Heart Disease in Women

- Scope of the Problem
- Prevention
  - Differential impact of risk factors
  - Differential response to preventive medications
- Coronary Artery Disease
  - Difference in pathophysiology and outcomes in CAD
  - Emerging technologies in the modern era of SHD
- Research from our Center
  - Stress in women
- Hormone Replacement Therapy

Comparison of PAR for AMI in Men vs Women in Interheart

Prevalence of High Blood Pressure in Adults by Age and Sex: NHANES 2005-2006

Definition: Glycemic Index (GI)
a measure of the effects of 50 g of a given carbohydrate on blood glucose levels, as compared to the effects of 50 g of a standard carbohydrate (glucose or white bread)

Carbohydrates that break down quickly and release glucose rapidly into the bloodstream have a high GI

Carbohydrates that break down slowly, releasing glucose gradually, have a low GI

Comparison of PAR for AMI in Men vs Women in Interheart

Risk of CHD by Carbohydrate Intake (low and high GI foods) — women and men

There is a J-shaped relationship between alcohol intake and mortality

Meta-analysis of 34 studies (1,015,835 people)

Most of the mortality reduction is due to a reduction in cardiovascular death
Pregnancy – a Stress Test for the heart

- Preeclampsia with preterm delivery
  - 8 x ↑ risk of future death CVD
  - 5 x ↑ risk of future stroke
- Preeclampsia with full term delivery
  - 3 x ↑ risk of future death CVD
- Gestational diabetes
  - ~30% ↑ risk of future death CVD
  - 20-60% will develop type 2 DM within 5-16 yrs


Gender Differences of Aspirin Affects

Myocardial Infarction

- Aspirin Better
- No Difference
- Aspirin Worse?

Stroke

- Aspirin Better
- Aspirin Worse

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Women are Unique: Symptoms are different!
What are the Symptoms of Heart Attack in Women? Different than Men

- Chest pain or discomfort
- Unusual upper body discomfort
- Shortness of breath
- Breaking out in a cold sweat
- Unusual or unexplained fatigue (tiredness)
- Light-headedness or sudden dizziness
- Nausea (feeling sick to the stomach)

Less obstructive CAD in women undergoing angiography vs. men

Women's Ischemia Syndrome Evaluation (WISE): Chest pain even in absence of CAD predicts cardiovascular events

Women with ACS more likely to have "normal" coronary arteries than men

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Total (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUISTO</td>
<td></td>
<td>30.5%</td>
<td>01</td>
</tr>
<tr>
<td>TIMI 18</td>
<td></td>
<td>10.2%</td>
<td>01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td>6.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI II</td>
<td></td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td></td>
<td>10.2%</td>
<td>01</td>
</tr>
</tbody>
</table>

Abbreviations: QUISTO, Global Utilization of Strategies for Early revascularization; TIMI, Thrombolysis In Myocardial Infarction; STEMI, ST-segment Elevation Myocardial Infarction.

The microvasculature is important

Epicardial coronary arteries (>500 µm) are where we focus

Microvessels (<500 µm) are much more abundant

Image from Prof. F. Canizares
Epicardial CAD vs Microvascular Disease

The microvasculature supplies about 60% of myocardial blood


329 patients (43% women) with abnormal stress tests were referred for coronary angiography and Coronary Flow Reserve testing


Low Coronary Flow Reserve is a poor prognostic factor for women

CAD in women

- Women with “non-obstructive” CAD and stress test abnormalities are at increased cardiovascular risk
- CAD may be more difficult to spot in women
  - Symptoms are atypical and often associated with different triggers (mental or emotional stress vs. physical exertion).
- Evaluation for IHD in symptomatic women must consider coronary obstruction as well as coronary dysfunction.

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Stress and Heart Disease

Cardiac Deaths and Stress: The Northridge earthquake

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Increase in Heart Attacks in Germany during soccer world cup matches

- Daily cardiovascular events in from May 1 to July 31 in 2003, 2005, and 2006 in Germany.
- The FIFA World Cup 2006 started on June 9, and ended on July 9. The 2006 World Cup matches

"Stress" is an Important Component of Cardiovascular Disease Risk in women

- Tako-tsubo Syndrome
  - Non-atherosclerotic form of acute myocardial infarction
  - 90% post-menopausal females
  - Preceding emotional stressor, "lifetime crisis"

Stress Hormones and CVD

- When it comes to the effects of stress on the heart, women appear to be at greater risk
- Heart attacks in young women may be precipitated by stress more often than in men and women also appear to be more vulnerable to heart damage from stress
- To understand potential sex differences in stress hormone levels (as an indicator of amount of stress)
- We measured stress hormone levels in the urine of men and women and compared results

Baseline Characteristics of the Women and Men

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Female N=348</th>
<th>Male N=306</th>
<th>Female vs. Male P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never / former / current smoker</td>
<td>59/34/7</td>
<td>38/49/13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>67.4 ± 9.62</td>
<td>73.5 ± 9.52</td>
<td>0.00001</td>
</tr>
<tr>
<td>Blood pressure medications, %</td>
<td>41</td>
<td>36</td>
<td>0.0134</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.6 ± 5.9</td>
<td>28.0 ± 4.5</td>
<td>0.0014</td>
</tr>
<tr>
<td>HDL, cholesterol, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56.6 ± 15.80</td>
<td>46.3 ± 14.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary Catecholamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE, (ln ng/ creatinine mg/dl)</td>
<td>29.1(23.1-40.6)</td>
<td>24.2(17.9-32.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EPI, (ln ng/ creatinine mg/dl)</td>
<td>2.3(1.4-3.0)</td>
<td>2.4 (1.5-3.3)</td>
<td>0.4200</td>
</tr>
<tr>
<td>DA, (ln ng/ creatinine mg/dl)</td>
<td>242.9 (198.4(158.5-250.5)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Despite having a lower risk factor burden than men. Women had higher stress hormone levels

- Epinephrine levels were comparable between men and women...

- Norepinephrine levels were **higher** in females

- Dopamine levels were also **higher** in females

- The higher stress hormone levels in both men and women were associated with greater coronary calcification

Stress Hormones in Women
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Hormone Replacement Therapy: State of Understanding prior to the 1990s

<table>
<thead>
<tr>
<th>Risks</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Vasomotor Symptoms</td>
<td>GU Symptoms</td>
</tr>
<tr>
<td></td>
<td>Skin Preservation</td>
</tr>
</tbody>
</table>

The HERS Study

- Randomized, double-blind, placebo-controlled trial designed to study cardioprotective effects of HRT in secondary prevention of CHD

  - Postmenopausal women with CHD and intact uterus randomized to receive daily either
    - CEE (0.625 mg) + MPA (2.5 mg) or placebo
  - Primary end point: nonfatal MI or CHD death

HERS: Combined HT Does Not Decrease All-Cause Mortality

Women's Health Initiative (WHI) Hormone Therapy (HT) Trial

The HERS Study

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  - Postmenopausal women with CHD and intact uterus randomized to receive daily either
    - CEE (0.625 mg) + MPA (2.5 mg) or placebo
  - Primary end point: nonfatal MI or CHD death

Women's Health Initiative CV risk factors at enrollment

- Mean age: 63.3 years (range: 50-79)
  - Current smoker: 10.5%
  - Diabetic: 4.4%
  - Hypertension: 35.7%
  - Hyperlipidemia: 12.5%
  - Statin Use: 6.9%
  - ASA Use: 19.1%
  - Prior CVD History: 6.2%
WHI E+P Results

WHI E+P Trial Findings, July 2002 (avg. 5.2 y)

WHI E Alone Trial Findings, 2004 (avg 6.8 y)

WHI Attributable Risk Summary

Hormone Replacement Therapy Risk Benefit Balance: Today
First Pass Hepatic Effects of Estrogens Taken by Mouth

Oral Estrogen → Intestine → Liver → Steroid Metabolites → Inflammatory Factors (CRP) → Oral

KEEPS (Kronos Early Estrogen Prevention Study)
- 727 women in early menopause
- Oral CEE vs transdermal E2 with micronized progesterone
- Outcome: Carotid IMT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated Change in CIMT, mm/year</th>
<th>Participants with Increased CAC Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0072</td>
<td>217 (21.0%)</td>
</tr>
<tr>
<td>Oral conjugated equine estrogens</td>
<td>0.0080</td>
<td>161 (17.4%)</td>
</tr>
<tr>
<td>Transdermal 17β-estradiol</td>
<td>0.0077</td>
<td>172 (10.9%)</td>
</tr>
</tbody>
</table>

No difference | No difference

KEEPS (Kronos Early Estrogen Prevention Study)

“**The Timing Hypothesis**” of hormone therapy

- This timing hypothesis posits that the effects of hormone therapy on atherosclerosis and coronary heart disease depend on the timing of the initiation of hormone therapy relative to menopause, age, or both
- Perhaps early physiological sex hormone replacement can improve or reverse early endothelial dysfunction
- Perhaps HT given in advanced atherosclerotic lesions predisposes the lesion to inflammatory and prothrombotic abnormalities

Effect of hormone therapy on heart disease

Timing of initiation of hormone therapy

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10y</td>
<td>0.92</td>
</tr>
<tr>
<td>10–19y</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt; 20y</td>
<td>1.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estrogen + Progesterone</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10y</td>
<td>1.04</td>
</tr>
<tr>
<td>10–19y</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt; 20y</td>
<td>1.71</td>
</tr>
</tbody>
</table>

Decreased risk | Increased risk

WHI: coronary events by age

Heart attack or cardiac death

- 50–59
- 60–69
- 70–79

Bypass surgery or angioplasty

Decreased risk | Increased risk

ELITE Trial

- 643 healthy women randomized to oral 17β-estradiol (plus progesterone vaginal gel) or placebo

Results: Among women who were less than 6 years past menopause, estradiol was associated with slower cIMT increased vs. placebo (P=0.008)
Among women who were 10 or more years past menopause, there was no difference
Assess Your Patient’s Risk Before Starting HT

ASSESS CARDIOVASCULAR RISK FACTORS

ASSESS Time Since Menopause

Consider preventive therapies

COUNSEL PATIENT

Conclusion

• Heart disease is the leading cause of death for women
• Much of our knowledge about heart disease has been derived from studies in men
• Despite many similarities, there are also differences between heart disease in men and women and these differences may have important implications
• Use of Hormone Therapy in postmenopausal women is NOT recommended for the prevention of CHD but research is ongoing

Factors favoring LOWER risk from HT

• Breast cancer
  – less than 4 years of use
  – absence of breast tenderness
• Cardiovascular disease
  – less than 10 years of use
  – age <60 years of age
  – recent onset of menopause (<10 years)
  – C-reactive protein < 2
  – absence of metabolic syndrome
  – absence of prothrombotic genetic risk
  – Elevated Lp(a)
  – Statin therapy
  – ? transdermal rather than oral route