Cardiovascular Disease Risk:
Pre-, Peri-, and Post-Menopausal

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*National Lipid Association*
*New Orleans, LA*
*February 23, 2013*
Conflict of Interest Disclosure

JoAnn E. Manson, MD, DrPH, has no real or apparent conflicts of interest to report.
Objectives

• To describe the major risk factors for CVD in women.
• To review key gender differences in risk factors.
• To summarize changes in risk factors during the life cycle, especially at the menopause transition.
• To review (briefly) clinical trial findings on menopausal hormone therapy, aspirin, and calcium/vitamin D.
Cardiovascular Disease: The Leading Cause of Death in US Women (2006 data)

- Heart disease: 162.2
- Cerebrovascular disease: 42.6
- Lung cancer: 40.0
- COPD: 35.9
- Unintentional Injuries: 25.5
- Breast Cancer: 23.5
- Diabetes: 20.1
- Influenza/Pneumonia: 15.5
- Motor vehicle Accidents: 8.8

Deaths (1,000)

Prevalence of CVD by Age and Sex

Cardiovascular Disease Mortality Trends for Males and Females
United States: 1979-2000

Source: CDC/NCHS.
Nurses' Health Study: Preventability of Heart Disease, Stroke, and Type 2 Diabetes

With lifestyle modifications*:

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th>Stroke</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Reduction (%)</td>
<td>-83%</td>
<td>-81%</td>
<td>-90%</td>
</tr>
</tbody>
</table>

* Physical activity, not smoking, weight control, healthy diet (high in whole grains, fiber, fruit/veg, fish, low in saturated fat)

Percentage of US Adults Classified as Obese (BMI ≥30) in Health Surveys from 1963-2010

NHES indicates National Health Examination Survey; NHANES, National Health and Nutrition Examination Survey.

Percent of U.S. adults Engaging in Regular Leisure-time Physical Activity,* by Gender and Age

* Regular activity = light-to-moderate activity ≥5 times/week for 30 minutes each time, or vigorous activity ≥3 times/week for ≥20 minutes each time.

Percentage of the Decrease in U.S. Deaths from CHD Attributed to Treatments and Risk-Factor Changes

- Treatment
- Risk Factors
- Unexplained

The Interheart Study

• Case-control study of 15,000 patients with first MI compared to 15,000 age, sex matched healthy controls.

### INTERHEART: Association of Risk Factors with Acute MI in Women And Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Gender</th>
<th>Odds Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>F</td>
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<td></td>
<td>M</td>
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<tr>
<td>Hypertension</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Psychosocial index</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Fruits/Vegetables</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>ApoB-ApoA1 ratio</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, geographic region

Note: odds ratio plotted on a doubling scale

SWAN Allows Us to Anchor Our Observations to the Final Menstrual Period (FMP).

A Steep Rise In LDL Occurs within One Year of the FMP

Change in Lipids After Menopause

- **Total-C**
- **HDL-C**
- **LDL-C**
- **Triglycerides**

% of Mean Level During Premenopause

- **N=10**

SWAN Shows A Rise In Fat Mass With The FMP

SWAN: Progression of Subclinical CVD During Late Perimenopause

Annual Rates of Change in Carotid IMT in Pre-, Early peri-, Late peri-, and Postmenopausal stages*

* Adjusted for age at baseline and race
  a Rate of change in late peri- significantly differs from that in premenopausal stage, P<0.05
  b Rate of change in late peri- significantly differs from that in early peri-menopausal stage, P≤0.05

Diabetes and Risk of CHD Mortality

Diabetic Men - 2-3 fold ↑ risk
Diabetic Women - 3-7 fold ↑ risk
Lipids and Coronary Heart Disease (CHD): Gender Differences

- LDL cholesterol: Stronger predictor of CHD risk in men than women
- HDL cholesterol: Stronger predictor of CHD risk in women than men
- Triglycerides: Stronger predictor of CHD risk in women than men
## Effects on major Vascular Events per 1.0 mmol/L Reduction in LDL Cholesterol at Different Levels of Risk, by Gender

<table>
<thead>
<tr>
<th>5-year MVE Risk at Baseline</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1.0 mmol/L reduction in LDL cholesterol</th>
<th>Trend Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>78 (0.31)</td>
<td>119 (0.48)</td>
<td>0.57 (0.38 - 0.86)</td>
</tr>
<tr>
<td>≥ 5%,&lt;10%</td>
<td>196 (1.25)</td>
<td>232 (1.48)</td>
<td>0.84 (0.64 - 1.10)</td>
</tr>
<tr>
<td>≥ 10%,&lt;20%</td>
<td>956 (3.04)</td>
<td>1071 (3.36)</td>
<td>0.88 (0.77 - 1.00) (\chi^2=0.23) (p=0.6)</td>
</tr>
<tr>
<td>≥ 20%,&lt;30%</td>
<td>680 (4.94)</td>
<td>750 (5.68)</td>
<td>0.88 (0.76 - 1.02)</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>429 (8.33)</td>
<td>522 (10.41)</td>
<td>0.79 (0.67 - 0.94)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>2339 (2.57)</td>
<td>2694 (2.98)</td>
<td>0.84 (0.79 - 0.89) (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>89 (0.46)</td>
<td>135 (0.67)</td>
<td>0.66 (0.46 - 0.95)</td>
</tr>
<tr>
<td>≥ 5%,&lt;10%</td>
<td>408 (1.04)</td>
<td>615 (1.60)</td>
<td>0.64 (0.55 - 0.75)</td>
</tr>
<tr>
<td>≥ 10%,&lt;20%</td>
<td>2658 (2.94)</td>
<td>3124 (3.55)</td>
<td>0.76 (0.70 - 0.83) (\chi^2=6.73) (p=0.009)</td>
</tr>
<tr>
<td>≥ 20%,&lt;30%</td>
<td>3428 (4.70)</td>
<td>4169 (5.83)</td>
<td>0.80 (0.75 - 0.85)</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>2358 (7.53)</td>
<td>2936 (9.72)</td>
<td>0.79 (0.74 - 0.84)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>8941 (3.53)</td>
<td>10979 (4.42)</td>
<td>0.78 (0.76 - 0.80) (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Difference in overall effect between men and women: \(\chi^2= 5.23\) (p=0.02)

Source: Cholesterol Treatment Trialists’ Collaborators. *Lancet* 2012; 380(9841) supplementary appendix.
Risk of Heart Attack: Smokers vs Ex-smokers
Relative Risk Estimate*

* 1.0 represents no increased risk compared with lifetime nonsmokers.

Rosenberg *NEJM*; 1985 & 1990.
AHA Guidelines

• Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women – 2011 Update: A guideline from the American Heart Association

Ideal Cardiovascular Health
(all are required!)

- Total cholesterol < 200 mg/dL (untreated)
- BP < 120/80 mmHg (untreated)
- Fasting blood glucose < 100 mg/dL (untreated)
- Body mass index < 25 kg/m2
- Abstinence from smoking
- Physical activity at goal for adults > 20 years of age
  >150 min/week moderate intensity
  >75 min/week vigorous activity or combination
- Healthy diet (DASH or similar)

But fewer than 4% of women meet these criteria!
Lifetime Risk for CVD by Risk Factors at Age 50

Men

- ≥2 Major RFs: 69%
- ≥1 Elevated RF: 50%
- ≥1 Not Optimal RF: 46%
- Optimal RFs: 36%
- 5%

Women

- ≥2 Major RFs: 50%
- ≥1 Elevated RF: 39%
- ≥1 Not Optimal RF: 27%
- Optimal RFs: 8%

WHI Estrogen+Progestin Trial Findings, July 2002
(mean follow-up 5.2 yrs)

Risks

- Coronary Heart Disease 29%
- Stroke 41%
- Pulmonary Embolism 113%
- Breast Cancer 26%

Benefits

- Hip Fracture 34%
- Colorectal Cancer 34%

STOPPED Early, Clear Harm

Threshold Level

Stopped 3.3 years early

Adapted from: Writing Group for the Women’s Health Initiative. JAMA 2002;288:321-333.
WHI Estrogen-Alone and Health Outcomes (N=10,739; mean age 63.6 yrs; mean follow-up 6.8 yrs)

Risks

Null

Benefits

CHD (0.91)
Pulm Emb (1.34)
Breast Cancer (0.77)
Colorectal Cancer (1.08)
Total Mortality (1.04)
Global Index (1.01)

Stroke 39%↑

Hip Fracture 39%↓

STOPPED Early

Threshold Level

Stopped 1 year early

Relative Risks and 95% CI* for Selected Health Outcomes by Years Since Menopause in the WHI Trials of Hormone Therapy (E+P and E-Alone)

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10 y</td>
<td>10-19 y</td>
<td>20+ y</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0.76</td>
<td>1.10</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>p=0.02†</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>Total mortality</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10 y</td>
<td>10-19 y</td>
<td>20+ y</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0.76</td>
<td>0.98</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>p=ns</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Global index‡</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10 y</td>
<td>10-19 y</td>
<td>20+ y</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>1.05</td>
<td>1.12</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>p=ns</td>
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</table>

* Confidence intervals plotted as error bars.
† p values for trend.
‡ The global index is a composite outcome of CHD, stroke, PE, breast cancer, colorectal cancer, endometrial cancer (estrogen+progestin trial only), hip fracture, and mortality.

Hormone Therapy (HT) Decision-Making Flowchart

Significant symptoms of menopause (moderate-to-severe hot flashes, night sweats)?

Yes

Free of contraindications to HT and no h/o CHD, stroke, or TIA? AND No increased risk of stroke (<10% by Framingham Stroke Score)?

Yes

No HT

No

No HT

Assess CHD risk and years since last menstrual period

<table>
<thead>
<tr>
<th>CHD Risk Over 10 Years (Framingham CHD Risk Score)</th>
<th>Years Since Last Menstrual Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (&lt;5%)</td>
<td>≤5</td>
</tr>
<tr>
<td>Low (5% to &lt;10%)</td>
<td>HT OK</td>
</tr>
<tr>
<td>Moderate (10% to 20%)</td>
<td>HT OK (Choose transdermal)</td>
</tr>
<tr>
<td>High (more than 20%)</td>
<td>No HT</td>
</tr>
</tbody>
</table>

DECISION ABOUT DURATION OF USE: continued moderate-to-severe symptoms; patient preference; weigh baseline risks of breast cancer vs osteoporosis

Adapted from: J Manson and S Bassuk. In: Harrison’s Principles of Internal Medicine 2008
Antiplatelet Therapy in Secondary Prevention of CVD

Overview of 25 randomized trials (N=29,000)
Aspirin and/or dipyridamole or sulfinpyrazone

• 32% reduction in nonfatal MI
• 27% reduction in nonfatal stroke
• 15% reduction in CVD mortality
• 25% reduction in total important vascular events
## Low-Dose Aspirin in CVD Primary Prevention Meta-Analysis


<table>
<thead>
<tr>
<th></th>
<th>Myocardial Infarction</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Participants</strong></td>
<td>0.76 (0.62–0.95)</td>
<td>0.97 (0.83–1.13)</td>
</tr>
<tr>
<td>(N=95,456)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>0.68 (0.54–0.86)</td>
<td>1.13 (0.96–1.33)</td>
</tr>
<tr>
<td>(N=44,114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>0.99 (0.83–1.19)</td>
<td>0.81 (0.69–0.96)</td>
</tr>
<tr>
<td>(N=51,342)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aspirin and Primary Prevention of CVD in the WHS According to Age Group+

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Total CVD</th>
<th>Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>1.01</td>
<td>0.85</td>
<td>1.23</td>
</tr>
<tr>
<td>55-64</td>
<td>0.98</td>
<td>0.84</td>
<td>1.17</td>
</tr>
<tr>
<td>≥65</td>
<td>0.74</td>
<td>0.78</td>
<td>0.66</td>
</tr>
</tbody>
</table>

P for interaction by age = 0.05 for total CVD and 0.03 for MI

+ p for interaction not significant for Framingham CHD Risk Score or Number of CHD Risk Factors

Calcium and Vitamin D Supplements: Cardiovascular Events by Treatment Group Assignment

<table>
<thead>
<tr>
<th></th>
<th>Calcium/Vitamin D (N=18,176)</th>
<th>Placebo (N=18,106)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction or CHD death</td>
<td>499</td>
<td>475</td>
<td>1.04 (0.92-1.18)</td>
<td>0.50</td>
</tr>
<tr>
<td>Stroke</td>
<td>362</td>
<td>377</td>
<td>0.95 (0.82-1.10)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting. PCI, percutaneous coronary intervention. Number of events do no add up to the totals for categories because some women had >1 event.

Acknowledgments

Colleagues in the Women’s Health Initiative, Women’s Health Study, Nurses’ Health Study and other research studies.

Women volunteers in research studies.

Rebecca Thurston, ScD
Mirian Limacher, MD
Puja Mehta, MD
Karol Watson, MD
Conclusions

There is the potential for greater progress in decreasing risk of cardiovascular disease in women.

More attention must be given to:

- Prevention (incl. behavioral changes)
- Early detection
- Aggressive risk factor modification and treatment