Coronary Artery Disease in Women: Clinical Perspectives

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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 deaths (1,000)
- Cerebrovascular disease: 42.6 deaths (1,000)
- Lung cancer: 40.0 deaths (1,000)
- COPD: 35.9 deaths (1,000)
- Unintentional Injuries: 25.5 deaths (1,000)
- Breast Cancer: 23.5 deaths (1,000)
- Diabetes: 20.1 deaths (1,000)
- Influenza/Pneumonia: 15.5 deaths (1,000)
- Motor vehicle Accidents: 8.8 deaths (1,000)

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

Deaths in Thousands

Years

1979 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 00

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

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>
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<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>
<td></td>
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<td></td>
<td>M</td>
<td></td>
</tr>
<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

Lifetime Risk for CVD by Risk Factors at Age 50

Men
- ≥2 Major RFs
- 1 Major RF
- ≥1 Elevated RF
- ≥1 Not Optimal RF
- Optimal RFs

Women
- ≥2 Major RFs
- 1 Major RF
- ≥1 Elevated RF
- ≥1 Not Optimal RF
- Optimal RFs

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

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*

- Rate of change in late peri- significantly differs from that in premenopausal stage, \( P<0.05 \)
- Rate of change in late peri- significantly differs from that in early peri-menopausal stage, \( P\leq0.05 \)

Diabetes and Risk of CHD Mortality

Diabetic Men - 2-3 fold ↑ risk
Diabetic Women - 3-7 fold ↑ risk
Lipid Lowering and CHD Risk Reduction in Diabetes

Scandinavian Simvastatin Survival Study (4S): 54% reduction in CHD events in DM subjects randomized to simvastatin vs. controls (32% risk reduction in nondiabetic subjects). All cause mortality: reduction of 43% for DM subjects and 28% for non-DM.

CARE Study (Pravastatin after MI in subjects with average cholesterol levels): 25% reduction in CHD among DM subjects and 23% reduction in non-DM.

Helsinki Heart Study (Gemfibrozil) 

AFCAPS/TexCAPS (Lovastatin) 

Similar risk reductions in DM and non-DM
United Kingdom Prospective Diabetes Study (UKPDS) Predictors of First Coronary Events

1) LDL cholesterol <0.0001
2) HDL cholesterol <0.0001
3) HbA1c 0.002
4) Systolic BP 0.006
5) Smoking 0.056

Source: Stratton et al. BMJ 2000; 321:405-12
Pregnancy: A Stress Test for the Cardiovascular System

- Pregnancy: metabolic syndrome-like state.
- Women predisposed to MetSyn develop gestational hypertension or gestational diabetes.
- Pregnancy induced risk factors often re-emerge later in life.
- Mortality from CVD in later life is increased by these conditions.

2.71-fold higher mortality in women who had a preterm delivery and pre-eclampsia.
Lipids and Coronary Heat 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>
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<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)</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)</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)</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)</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.

AHA Guidelines

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

Mosca L, Benjamin EJ, Berra K, et al. 
*J Am Coll Cardiol* 2011;57:1404-23 and 
*Circulation* 2011;123:1243-1262
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!
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

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

- Stroke 39% ↑

Benefits

- Hip Fracture 39% ↓

Null

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

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)

By years since menopause:

CHD
- <10 y: 0.76 (p=0.02†)
- 10-19 y: 1.10
- 20+ y: 1.28

Total mortality
- <10 y: 0.76 (p=ns)
- 10-19 y: 0.98
- 20+ y: 1.14

Global index‡
- <10 y: 1.05 (p=ns)
- 10-19 y: 1.12
- 20+ y: 1.09

* 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)?

No

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

Assess CHD risk and years since last menstrual period

CHD Risk Over 10 Years (Framingham CHD Risk Score) | Years Since Last Menstrual Period
--- | --- | --- | ---
Very low (<5%) | <5 | 6 to 10 | >10
Low (5% to <10%) | HT OK | HT OK | No HT
Moderate (10% to 20%) | HT OK | HT OK (Choose transdermal) | No HT
High (more than 20%) | No HT | No HT | No HT

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>Infarction</th>
<th>Myocardial 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+


+ p for interaction not significant for Framingham CHD Risk Score or Number of CHD Risk Factors
<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Stroke</td>
<td>362</td>
<td>377</td>
<td>0.95 (0.82-1.10)</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
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