Coronary Artery Disease in Women: Clinical Perspectives

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)

Prevalence of CVD by Age and Sex

Cardiovascular Disease Mortality Trends for Males and Females

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Nurses’ Health Study: Preventability of Heart Disease, Stroke, and Type 2 Diabetes

With lifestyle modifications:

- CHD: -63%
- Stroke: -81%
- Diabetes: -90%

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

Nurses’ Health Study: Preventability of Heart Disease, Stroke, and Type 2 Diabetes

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

- Men
- Women


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

- Men
- Women

* 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: 70%
Risk Factors: 50%
Unexplained: 20%


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

#### Risk Factor | Gender | Odds Ratio (99% CI)
--- | --- | ---
Current smoking | F | 0.25
Diabetes | M | 0.5
Hypertension | F | 1
Abdominal obesity | M | 2
Psychosocial index | F | 4
Fruits/Vegetables | M | 8
Exercise | F | 0.1
Alcohol | M | 0.2
ApoB-ApoA1 ratio | F | 0.5

Adjusted for age, sex, geographic region
Note: odds ratio plotted on a doubling scale

**Source:** Yusuf S et al. *Lancet*. 2004;364:937-52

### Lifetime Risk for CVD by Risk Factors at Age 50

#### Men
- 2 Major RFs: 69%
- 1 Major RF: 50%
- 1 Elevated RF: 46%
- 1 Not Optimal RF: 36%

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

**Source:** J. Am. Board. Internal Med. 1998.

### 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**

**Source:** Matthews JACC 2009; 54:2366.

### SWAN Shows A Rise In Fat Mass With The FMP

**Source:** Sowers et al. JCEM 2007; 92: 895–901.

### SWAN: Progression of Subclinical CVD During Late Perimenopause

**Source:** El Khoudary SR, Wildman RP, Matthews KA, Thurston RC, Bromberger JT, Sutton-Tyrrell K. *Menopause In Press*
**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 non-diabetic 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. JAMA 2000; 323:1001-12

**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 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**

Source: Cholesterol Treatment Trialists’ Collaborators. Lancet 2012; 380(9841) supplementary appendix.
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**Relative Risk Estimate**

<table>
<thead>
<tr>
<th>Years Since Quitting</th>
<th>Current Smokers</th>
<th>Ex-smokers</th>
</tr>
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<tbody>
<tr>
<td>1-2</td>
<td></td>
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<tr>
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<tr>
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* 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
- Absence 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
- Stroke
- Pulmonary Embolism
- Breast Cancer

**Benefits**

- Hip Fracture
- Colorectal Cancer

STOPPED Early, Clear Harm

Threshold Level

Stopped 3.3 years early


**WHI Estrogen-Alone and Health Outcomes**

(N=10,739; mean age 63.6 yrs; mean follow-up 6.8 yrs)

**Risks**

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

**Benefits**

- Null

STOPPED Early

Threshold Level

Stopped 1 year early

Source: JAMA 2006;295:1750-1 C1

**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
- Pulm Emb
- Breast Cancer
- Colorectal Cancer
- Total Mortality
- Global Index

* 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 HT  Yes

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

No HT  Yes

Low HBOC

No HT  Yes

CHD Risk Over 10 Years

Assess CHD risk and years since last menstrual period

Years Since Last Menstrual Period

<5  6 to 10  >10

Very low (<5%) HT OK HT OK No HT

Low (5% to <10%) HT OK HT OK No HT

Moderate (10% to 20%) HT OK (Choose transdermal) HT OK (Choose transdermal) No HT

High (more than 20%) No HT No HT No HT

CHD Risk Over 10 Years

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

Low-Dose Aspirin in CVD Primary Prevention Meta-Analysis

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<th>Infarction</th>
<th>Myocardial Stroke</th>
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Calcium and Vitamin D Supplements: Cardiovascular Events by Treatment Group Assignment

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CABG indicates coronary artery bypass grafting. PCI indicates percutaneous coronary intervention. Number of events do not add up to the totals for categories because some women had >1 event.


Antiplatelet Therapy in Secondary Prevention of CVD

Overview of 25 randomized trials (N=29,000)

- 32% reduction in nonfatal MI
- 27% reduction in nonfatal stroke
- 15% reduction in CVD mortality
- 25% reduction in total important vascular events

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Acknowledgments

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

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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