Coronary heart disease in women: Challenges in diagnosis and management

Loryn S. Feinberg, MD, FACC
Beth Israel Deaconess Medical Center
Women’s Cardiovascular Health Program
No disclosures
CAD unusual premenopause
Once women reach 60s, prevalence = men
Identified less often, at more advanced stages
Treatment advances have not decreased women’s fatality rate
More likely to die
More likely to have recurrent myocardial infarctions

Prevalence of CVD in adults by age and sex, 2007-10

Cardiovascular disease mortality:
U.S. men and women 1979-2006

Challenges in identifying CHD in women

- Women, physicians underestimate risk
- Substantial delays in seeking health care
- Symptoms differ: atypical, silent
- Diagnostic testing has more variability

Many cases of MI go unrecognized, especially in young or diabetic

Mosca L, Circ 2000; Heart Disease and Stroke Statistics Update, AHA 2004
Risk factors

Culture, Race, Socioeconomics

Diet

Obesity

Hypertension

Lipids

Physical inactivity

Ischemic heart disease

Smoking

Diabetes

Family history

Radiation to chest

Preeclampsia
Gestational hypertension

Premature menopause

Stress, work hours

Rheumatoid arthritis, Lupus
Coronary disease mortality in diabetic women

- Risk of CHD 2.5 fold
- Risk of CHD death 2.2 fold
- Lower success rates with PCI/CABG

Risk of fatal and non-fatal CHD >6 fold that of non-diabetics

Cardiovascular mortality relates to severity of obesity

Nurses’ Health Study: >115,000 women followed 16 years
- Relative risk of death from CHD was 4.1 if BMI ≥32 vs. BMI < 20

Relative Risk of CHD Mortality Compared to BMI<19

P for trend < 0.001

Vaccarino V, NEJM 99; Lissner L. NEJM 91, Manson JE NEJM 95
Relative risk of coronary events for smokers vs. non-smokers

- Over 40% of events attributable to smoking
- Meta-analysis (Lancet): Women have 25% higher CHD rate from smoking
- Female smokers had 2-6 times the risk of sudden cardiac death

Nurses’ Health Study
84,129 U.S. female RNs

Triglycerides are a strong independent risk factor in women

- Framingham data suggest low HDL/elevated triglycerides levels as stronger cardiovascular risk predictors in women
- Small, dense LDL particles increase with menopause

Castelli WP. Can J Cardiol 88'; Mosca L; JACC 99'; Ridker PM. JAMA 05; Rich-Edwards JW NEJM 95; Mosca L. JACC 99; Orth-Gomer K. Circ 97
Light/moderate drinking associated with decreased risk of CHD/sudden death

490,000 subjects
50% women

At >2 drinks/day, mortality increased

Moderate intake = 5 oz wine, 12 oz beer, 1.5 oz shot

Thun MJ, NEJM 1997
Coronary disease prevention through lifestyle: The Nurses’ Health Study

Women can reduce risk of cardiovascular event rate by 80%

NEJM 2000; 343

* Diet score, nonsmoker, moderate-vigorous exercise 30+min/day
√ Above + BMI <25
# Above +≥ 0.5 drinks per day
Hormone replacement therapy

- Pre-menopause, estrogen may help protect against CHD
- Previously thought that HRT may maintain CV protection
- Two trials (HERS, WHI): showed ↑ risk of heart attack, stroke, blood clots, if estrogen + progesterone
- Follow-up trial suggested protective effect in younger women (50-59) if estrogen alone
- Bottom line: no evidence to prescribe HRT to prevent CAD
- When used to symptoms of menopause, use at lowest dose, for shortest period of time

Risk stratification for CAD

Limitations in women:

1. Short term risk
2. Excludes family history
3. Looks at hard endpoints
4. Underestimates risk in young

Reynolds Risk Score:
http://www.reynoldsriskscore.org

√ Adds CRP, family history
√ Global CVD: MI, CVD death, stroke, revascularization

Mosca L JACC 2004, Wilson P. JACC 03; Akosah et al JACC 03; Sibley J Women’s Health 2006; D’Agostino Circ 2006
New ACC/AHA risk calculator 2013

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Enter patient values in this column</th>
<th>Acceptable range of values</th>
<th>Default values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans), or WH (American Indians or others)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment for High Blood Pressure (if SBP = 130)</td>
<td>Y (for yes) or N (for no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**10-Year ASCVD Risk (%)**

1.3

**10-Year ASCVD Risk (%) for Someone of Your Age with Optimal Risk Factor Levels (shown above in column E)**

0.9

**Your Lifetime ASCVD Risk (%)**

27.0

**Lifetime ASCVD Risk (%) for Someone at Age 80 with Optimal Risk Factor Levels (shown above in column E)**

8.0

*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches.*
Present ~10 years later
More comorbidities at diagnosis
>60% women present with acute MI or sudden death
Almost 2/3 of women who die suddenly of CHD have had no previous symptoms
Clinical presentation: angina

- Pain description often differs
- Atypical symptoms more common
- Often induced by daily activities, emotional stress

WISE* substudy (n=936) women with CP referred for angiography, classification “typical” angina missed 65% cases

*Women’s Ischemia Syndrome Evaluation

Alexander KP, JACC 98, D’Antono B. Am Ht J 06’, Stangl V. Eur Ht J 08
Myocardial infarction (MI)

- **NSTEMI > STEMI**
- **Silent MI is frequent**
  - 9.3% in HERS trial: MI on ECG, not clinically recognized in 46%
- **Symptoms differ**
  - Acute CP absent in ~40%
- **Prognosis poorer**
  - Higher short term death rate
  - Higher chance of repeat MI

Inpatient mortality by MI type
n >78,000 ; 39% women

Treatment delays in STEMI lead to adverse outcomes in women

N = 23,353 STEMI patients, 2001-06
“Get With the Guidelines” database
34% female

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2N (min)</td>
<td>39</td>
<td>47</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D2B (min)</td>
<td>95</td>
<td>103</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

D2N = door to needle time
D2B = door to balloon time

- Lower rate of evidence based therapies
- Excess rate death, 24h
Age and Gender Differences in Quality of Care and Outcomes for Patients with ST-segment Elevation Myocardial Infarction

Sripal Bangalore, MD, MHA,^a^ Gregg C. Fonarow, MD,^b^ Eric D. Peterson, MD, MPH,^c^ Anne S. Hellkamp, MS,^c^ Adrian F. Hernandez, MD,^c^ Warren Laskey, MD,^g^ W. Frank Peacock, MD,^g^ Christopher P. Cannon, MD,^f^ Lee H. Schwamm, MD,^g^ Deepak L. Bhatt, MD, MPH,^g^ for the Get with the Guidelines Steering Committee and Investigators
Heart failure, sudden death

- Women with CHD more frequently develop heart failure
  - HFpEF

- Risk of sudden death \( \frac{1}{2} \) that of men
- Women more likely to die of cardiac arrest before hospital
- Higher proportion of sudden deaths in absence of known CHD

Bibbins-Domingo K. Circ 04; Kannel WB. Am Ht J 98
Risk of sudden cardiac death in women reduced by four lifestyle measures

If four lifestyle factors followed, 92% lower risk!

1. No current smoking
2. BMI < 25
3. Exercise ≥ 30 minutes daily
4. Adherence to Mediterranean diet

82,000 women followed 26 years → 321 had SCD
Age 32-55 at baseline

Chiuve, et al. JAMA 2011; 306
## Methods to detect coronary heart disease

<table>
<thead>
<tr>
<th>Technique</th>
<th>Assessment</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>Coronary anatomy</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure, contrast,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diffuse disease, microvascular disease.</td>
</tr>
<tr>
<td>Coronary CT</td>
<td>Coronary calcification</td>
<td>Less well-validated</td>
</tr>
<tr>
<td></td>
<td>Coronary anatomy</td>
<td>Higher false + rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less Ca+ in young women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>Nuclear imaging</td>
<td>Regional perfusion</td>
<td>Attenuation issues (breast, obesity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smaller hearts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>Regional wall motion</td>
<td>Reader expertise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasonographer expertise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Body habitus/lung disease</td>
</tr>
<tr>
<td>Cardiac MR</td>
<td>Subendocardial and epicardial perfusion</td>
<td>Not validated, newer</td>
</tr>
<tr>
<td></td>
<td>Coronary anatomy</td>
<td>Claustrophobia, metal implants</td>
</tr>
</tbody>
</table>
Lower accuracy of stress testing in women

- Lower prevalence in young
- Less multivessel CAD
- Functional impairment
- Hormonal influences

Shaw et al. JACC 2006 Vol 47
American Heart Association evaluation: symptomatic, intermediate risk

Adding imaging:
- Increases specificity/accuracy
- Provides important prognostic information
- Possibly cost-effective
Women have higher rates of non-obstructive CAD when presenting with angina or ACS (acute coronary syndrome).

Possible mechanisms: rapid clot lysis, vasospasm, microvascular disease, non-coronary causes of chest pain/ACS.

Anderson RD. Circ 2007; Merz CN. JACC 99; Sullivan AK. BMJ 94; Roe MT. Circ 00’
Lessons from WISE: Women’s Ischemia Syndrome Evaluation

- 1996 NIH/NHLBI trials
- Pathophysiology differs
  - Plaque erosion vs. rupture
  - Inflammatory component
  - Loss of estrogen
- Common findings: non-obstructive disease, microvascular, endothelial dysfunction
  - Have prognostic significance
  - Treat aggressively

a. and b.: Plaque erosion

c. and d.: Plaque rupture

Noel Bairey Merz, C et al. JACC 2006; 47; Burke A P et al. Circulation 1998;97:2110-2116
Women may develop spontaneous coronary dissection as a cause of acute coronary syndrome

- ~75% cases occur in women
- Mean age 42 years
- Connective tissue disorders, arteritis
- Altered hormonal milieu:
  - OCPs, menstruation, cirrhosis
- 30% cases occur peripartum

Sabatine MS, NEJM 2010; 363
Stress-induced/”Takotsubo” cardiomyopathy

- Transient, severe cardiomyopathy triggered by emotional stress
- >80% cases in women
- Acute coronary syndrome-like presentation
- Absence of obstructive coronary disease
- Aberrant adrenergic stimulation of heart

Management, prognosis of CAD in women

- Unadjusted outcomes worse
- Disparity due to age, confounding risk factors
- Success rate of therapies are similar to men
- Complication rates are higher
Underrepresentation in randomized controlled clinical trials

Melloni C et al, Circ CV Qual Outcomes 2010; 3
Management: medical therapy

- **Aspirin:**
  - Equally effective in acute coronary syndromes, 2° prevention
  - Similar risk reduction for 1° prevention if risk score >10%
  - Similar risk reduction for 1° prevention (Women’s Health Study) if >65

- **Beta-blockers, ace-inhibitors, nitrates, thrombolytics:**
  - Well-demonstrated benefit equal to men

- **Glycoprotein IIbIIIa inhibitors:**
  - Troponin negative women with UA/NSTEMI do NOT appear to benefit
Coronary heart disease events in women: Significant secondary prevention benefit from statins

<table>
<thead>
<tr>
<th>Trials</th>
<th>Placebo number</th>
<th>Intervention number</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events:</td>
<td>Women:</td>
<td>Events:</td>
</tr>
<tr>
<td>4S</td>
<td>91</td>
<td>420</td>
<td>60</td>
</tr>
<tr>
<td>CARE</td>
<td>80</td>
<td>290</td>
<td>46</td>
</tr>
<tr>
<td>LIPID</td>
<td>104</td>
<td>760</td>
<td>90</td>
</tr>
<tr>
<td>HPS</td>
<td>282</td>
<td>1638</td>
<td>237</td>
</tr>
<tr>
<td>Total, summary</td>
<td>557</td>
<td>3108</td>
<td>433</td>
</tr>
</tbody>
</table>

*CHD events defined: 4S: CHD mortality, non-fatal MI, resuscitated cardiac arrest. CARE and LIPID: CHD mortality, nonfatal MI; HPS: CHD mortality, non-fatal MI, stroke, revascularization.
Management: invasive approach

- Increased risk of death after catheterization
  - 5.6% vs. 4.6% in >37,000 women, 1995-2000

- Percutaneous coronary intervention +/- MI:
  - Early periprocedural mortality higher
    - Coronary diameter, rate of bleeding, vascular complications

- STEMI:
  - Better outcomes with primary PCI vs. thrombolysis
  - BUT, cardiogenic shock more likely
Women in TACTICS-TIMI 18 trial

Death, MI, rehospitalization with ACS

- Troponin +
- Troponin -
- ST segment deviation +
- ST segment deviation -
- TIMI Risk Score 5-7
- TIMI Risk Score 3-4
- TIMI Risk Score 0-2

Favors Invasive

Favors Conservative

Glaser et al, JAMA 2002
Management: CABG

- Society of Thoracic Surgery (STS) database, n=>416,000
  - Higher 30 day mortality
- But, mortality similar to men if adjusted for:
  - Bypass duration, anemia, surgery urgency, comorbidities
- Female sex = marker of a more complex risk profile
- More advanced disease: involvement of distal circulation
- Smaller targets, conduits, aortic root/annulus
- Overall, improved 5-year survival compared to men

Hogue CW, Circ 01; Jacobs AK, BARI Circ 98; Guru V, Circ 06; Bassaran EJTCVS 2007
In summary

- Mortality for women with coronary heart disease is higher:
  - Presentation may differ
  - Delays
  - Older, risk factor burden ...Younger, not recognized
  - Smaller vessels, grafts, cardiac structures
  - ↑short-term complication rates

- Remember unique risk factors

- Assess lifetime CV risk of global cardiovascular disease

- Pathophysiology: non-obstructive, microvascular/endothelial disease have prognostic significance

- Unusual conditions: coronary dissection, stress-cardiomyopathy
Resources - women & cardiovascular disease

- www.womenshealth.gov/heart-health-stroke/index
- www.cardiosmart.org/Heart-Conditions/Women-and-Coronary-Artery-Disease
- www.goredforwomen.org
- www.nhlbi.nih.gov/whi
Thank you