Women and Cardiovascular Disease: Is there a Sex Difference?

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Martha Gulati, MD, MD, FACC, FAHA
Professor of Medicine in the Division of Cardiology
Chief, Section of Cardiology
University of Arizona-Phoenix
Phoenix, AZ
Hygieia: Goddess of Women’s Health

(With Asclepius, God of Medicine)
The Difference Between Men and Women: The Way We See Ourselves
The Difference Between Men and Women: The Way We Communicate
The Difference Between Men and Women

"Here's all you have to know about men and women: women are crazy, men are stupid.

And the main reason women are crazy is that men are stupid." - George Carlin
Cardiovascular Disease Mortality Trends for Males and Females in USA

Mozaffarian D et al. Circulation. 2015;131:e29-e322
Total Deaths in Women in USA 2011: 1,236,003

- Cardiovascular Disease: 398,035
- Chronic Lung Disease: 75,422
- Lung Cancer: 70,550
- Breast Cancer: 40,931

Prevalence of CVD in US Women: • 42,700,000

Prevalence of Breast Cancer in US Women: • 2,899,726

Mozaffarian D et al. Circulation. 2015;131:e29-e322
<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence in US Women</th>
<th>Number of Deaths in US Women</th>
<th>Cost ($Billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>42,700,000</td>
<td>419,730</td>
<td>$297.7 Billion</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td>267,000</td>
<td>$190.3 Billion</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>73,968</td>
<td>$53.9 Billion</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>• 2,899,726</td>
<td>40,931</td>
<td>$228 Billion</td>
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</table>
# Remaining Lifetime Risk for CVD vs Breast Cancer in Women

<table>
<thead>
<tr>
<th></th>
<th>Lifetime Risk at Age 40 Years</th>
<th>Lifetime Risk at Age 70 Years</th>
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<tbody>
<tr>
<td>Any CVD</td>
<td>1 in 2</td>
<td>1 in 2</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>1 in 3</td>
<td>1 in 4</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1 in 5</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 in 5</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1 in 8</td>
<td>1 in 15</td>
</tr>
</tbody>
</table>

*Go et al Circulation. 2014;129:e28–e292..*
“... The medical community has viewed women’s health almost with a ‘bikini’ approach, looking essentially at the breast and reproductive system, and almost ignoring the rest of the woman as part of women’s health”

_Nanette Wenger, MD_  
_Chief of Cardiology, Grady Hospital_  
_Emory University_
WE HAVE STUDIES OF FRUIT FLIES, MICE, HAMSTERS, FROGS, MONKEYS AND MEN WITH THIS CONDITION – BUT MEDICAL RESEARCH USING WOMEN AS SUBJECTS JUST NEVER OCCURRED TO ANYBODY.
Women Have Poorer Outcomes Compared with Men

- **Angina**: ~2x ↑ morbidity/mortality
- **MI**: ~1.5x ↑ 1-year mortality
- **Heart failure**: ~2x ↑ incidence
- **CABG**: ~2x ↑ morbidity/mortality
Sex Differences in Treatment

Do We Follow the Guidelines Equally in Women vs Men?

Sex Differences in Treatment
Sex Differences in Treatment: Euro Heart Survey of Stable Angina

3779 patients, 42% women, initially diagnosed by cardiologist

**Women vs Men**
- ↓ Exercise ECG testing: 73% vs 78%
- ↓ Coronary Angiography: 31% vs 49%, despite higher angina class
- ↓ Statin, antiplatelet initially, 1 year
- ↓ Revascularization: 13% vs 29%

**Women 2 x ↑ death, nonfatal MI**
- Adjusted for age, DM, LV function, CAD severity, pharmacotherapy, and revascularization

Women ↑ angina at follow up, 57% vs 47%

Daly, Circulation 113:490, 2006
### Get With The Guidelines (GWTG): Clinical Performance after MI

<table>
<thead>
<tr>
<th>Measure/Treatment/Outcome</th>
<th>n</th>
<th>Adjusted OR (95% CI) (Women vs Men)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early medical therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin within 24 h</td>
<td>70 360</td>
<td>0.86 (0.81–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-Blocker within 24 h</td>
<td>64 681</td>
<td>0.90 (0.86–0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Invasive procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>74 769</td>
<td>0.91 (0.88–0.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>67 477</td>
<td>0.78 (0.74–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG</td>
<td>67 477</td>
<td>0.60 (0.55–0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>67 477</td>
<td>0.68 (0.65–0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute reperfusion and timeliness of reperfusion†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTN ≤30 min</td>
<td>2807</td>
<td>0.78 (0.65–0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>DTB ≤90 min</td>
<td>7673</td>
<td>0.87 (0.79–0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td>24 742</td>
<td>0.75 (0.70–0.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>24 742</td>
<td>0.83 (0.78–0.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinolytic therapy</td>
<td>24 742</td>
<td>0.87 (0.81–0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In-hospital death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall AMI cohort</td>
<td>70 105</td>
<td>1.04 (0.99–1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>STEMI subpopulation</td>
<td>23 015</td>
<td>1.12 (1.02–1.23)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Jneid, H. et al. Circulation 2008;118:2803-2810*
Get With The Guidelines (GWTG): Age & Gender Differences in Quality of Care and Outcomes in STEMI

Quality of care was significantly lower and mortality was higher in young women vs. young men
(Similar finding in the very young: ≤35 vs 36-45 years)
Younger and Older Women were
• Less likely to receive ACEI/ARB
• Less likely to receive lipid-lowering therapy
• Less likely to have a BP< 140/90 mm Hg at discharge
• More likely to have longer door-to-balloon times (fewer achieving a door-to-balloon time ≤90min & door-to-thrombolytic time ≤30min)

Bangalore S et al. The American Journal of Medicine 2012;125:2803-2810
Underutilization of Evidence Based Treatments in Women
Canadian Registry of ACS

<table>
<thead>
<tr>
<th></th>
<th>Male (N=4471)</th>
<th>Female (N=2087)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications at Discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>93%</td>
<td>93%</td>
<td>0.49</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>79%</td>
<td>76%</td>
<td>0.0015</td>
</tr>
<tr>
<td>Lipid-Lowering</td>
<td>65%</td>
<td>56%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>60%</td>
<td>56%</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>50%</td>
<td>42%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>23%</td>
<td>18%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG</td>
<td>0.08%</td>
<td>0.04%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2%</td>
<td>3%</td>
<td>0.0078</td>
</tr>
<tr>
<td>Death/MI</td>
<td>8%</td>
<td>8%</td>
<td>0.36</td>
</tr>
<tr>
<td>Death 1 year</td>
<td>8%</td>
<td>11%</td>
<td>0.0017</td>
</tr>
<tr>
<td>Death/MI 1 year</td>
<td>16%</td>
<td>17%</td>
<td>0.095</td>
</tr>
</tbody>
</table>

*Bugiardini et al. ESC 2011;32:1337-1344*
Sex Differences in Inhospital Complications & Mortality after Percutaneous Coronary Intervention

ACC National Cardiovascular Data Registry – CathPCI (n=1,079,751)

Outcomes in Women vs. Men Stratified by Age

- Women, Regardless of Age, Experience More Complications post-PCI
- Young Women Are At Increased Mortality Risk After Elective PCI
- Identifying Strategies to Reduce Adverse Outcomes, Particularly For Women <55 Years, is Important

*Lichtman Am Heart J 2014;167:376-83.*
Sex and Race Differences in ICD Use 2005-2007: Primary Prevention CHF

American Heart Association’s Get with the Guidelines
Heart Failure Quality Improvement Program

Hernandez et al. JAMA 2007;298:1525-1532
Do Women Experience CVD Like Men?

Sex Differences in Diagnosis
Yentl Syndrome

- Term coined by Dr. Bernadine Healy

- Noted discrepancy in inclusion of women in trials, particularly cardiovascular trials

- Most clinical trials at this point excluded women, yet applied the study results to both men AND women

- Assumption that if women (and diseases) present like men, they will be taken seriously
“Typical Angina” definition based on men (exertional)
- Women have less obstructive CAD regardless of symptoms (typical or atypical)
- Women report more angina despite lower rates of obstructive CAD
  - Meta Analysis of 74 reports from 13,311 women 11,511 men
    - Angina prevalence 11-27% greater for women <65 years
- Symptomatic women without obstructive CAD continue to have signs/symptoms of ischemia, repeat hospitalization and coronary angiography, consumption of health-care resources
- WISE: increased rates of mortality in women with chest pain and no obstructive CAD
Underdiagnosis of MI in Women: Sex Differences When We Look For Them

- High-Sensitivity Troponin in Acute Coronary Syndrome
- Sex Specific MI threshold of 16 ng/L in women/34 ng/L in men for troponin I (based on defining levels as the 99th percentiles based on sex) vs conventional assay of 50 ng/L
  - High STEAC Trial: Sex-Specific Thresholds: diagnosis of MI in women INCREASED from 13% to 23%; no effect in men (23% to 24%)
    - Sensitivity of the conventional assay: 77% in men and 47% in women
    - Sensitivity of high-sensitivity assay: 86% in men and 95% in women
    - In comparison to men, women are more likely to be misdiagnosed and undertreated for MI
  - 2015 Study: 1126 patients with suspected ACS: 45% women/55% men
    - High sensitivity troponin I increased diagnosis of MI in women (from 11% to 22%; \( P<0.001 \)) but minimal effect in men (19% to 21%, \( P=0.002 \))

Mills N et al. ESC 2013
Mills N et al. JAMA 2011;305:1210-5
Shah AS et al. BMJ 2015;350:g7873
Is the Disease the Same in Women and Men?

Sex Differences in CVD Pathophysiology
Do the Guidelines Apply to Women?
Overt Focus on Obstructive CAD as pathophysiology for SIHD
Objective of Anti-Anginal Strategies

Reduce Ischemia & Relieve Symptoms

Normal → Fatty streak → Plaque → Increased plaque → Obstructive atherosclerotic plaque → Exertional angina

Noninvasive tests: normal → Noninvasive tests: abnormal

Stable CAD: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials (N = 2,950)

<table>
<thead>
<tr>
<th>Event</th>
<th>Favors PCI</th>
<th>Favors Medical Therapy</th>
<th>p value</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>CAD Death or MI</td>
<td></td>
<td></td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td></td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

SIHD: Paradigm Shift

- The “SIHD = obstructive CAD” paradigm
- Decades of information from pathological studies have established that CAD underlies SIHD
- Reinforced by coronary angiographic data from large trials/registries assuming SIHD = flow-limiting lesion in a major coronary artery (obstructive CAD)
- Link between symptoms and obstructive stenosis is so ingrained that patients and tests are labeled as “Atypical” or “False Positive” if they have symptoms +/- signs of ischemia, if no obstructive CAD
- Patients without obstructive CAD with symptoms and signs of ischemia have increased adverse event rates, poor QOL, consume health care resources compared with those without evidence of ischemia
Percentage of Patients Who Had IHD But No CAD: GUSTO IIb

GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb) study

Symptomatic (WISE) Non Obstructive CAD vs. Asymptomatic (WTH) : Risk Factors

Gulati et al. Archives Internal Medicine 2009;169:843-50
Cumulative CV death/MI for WISE women

Estimating Time to Cardiovascular Death (CVD)

Nonobstructive CAD

1 Vessel CAD
RR=3.6 (p=0.004)

2 Vessel CAD
RR=7.3 (p<0.0001)

3 Vessel CAD
RR=6.5 (p<0.0001)

Estimating Time to Cardiovascular Death (CVD) or Nonfatal Myocardial Infarction

Nonobstructive CAD

1 Vessel CAD
RR=3.2 (p<0.0001)

2-3 Vessel CAD
RR=6.0 (p<0.0001)

Model $\chi^2=33$, p<0.0001

Model $\chi^2=55$, p<0.0001
Cumulative Chest Pain Hospitalizations in WISE

Nonobstructive CAD

3 Vessel CAD
RR=2.1 (p<0.0001)

2 Vessel CAD
RR=2.5 (p<0.0001)

1 Vessel CAD
RR=3.1 (p<0.0001)

Estimated average lifetime costs: $767,288

Compared with average lifetime costs: $1,001,493 to 1,051,302 for those with 1-3 vessel disease

Model $\chi^2=58, p<0.0001$

Shaw, L. J. et al. Circulation 2006;114:894-904
**ACC NCDR CathPCI Registry:**

**Frequency of Significant CAD* by Race**

**SIHD**

(n=375,886)

<table>
<thead>
<tr>
<th>Race</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>24,998</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>3,562</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>1,251</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>7,823</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
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<td></td>
</tr>
<tr>
<td>n=</td>
<td>338,252</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- Rate of significant CAD was 49% for women and 67% for men ($P<0.0001$)

**ACS**

(n=450,329)

<table>
<thead>
<tr>
<th>Race</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
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<tr>
<td>p</td>
<td>&lt;0.0001</td>
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<td>n=</td>
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<tr>
<td>p</td>
<td>&lt;0.0001</td>
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<tr>
<td>Native American</td>
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<td></td>
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<tr>
<td>n=</td>
<td>1,596</td>
<td></td>
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<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>3,725</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>412,918</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- OR=0.47 for Significant CAD in women vs. men ($P<0.0001$)
- Black Women: Lowest Rate

*defined as $\geq$70% stenosis in $\geq$1 coronary arteries

Higher Hospital Mortality for Women of all Races vs. Men: Stable Chest Pain and ACS

**Sex and Heart Disease: Female Specific Ischemic Heart Disease**

**Male-pattern**
Obstructive CAD

**Female-pattern**
Microvascular Coronary Disease
Working Model of Ischemic Heart Disease Pathophysiology in Women

Figure illustration by Rob Flewell.

Epicardial versus Microvascular Disease

FFR

CFR
Functional Angiogram Protocol

[Diagram showing the steps of the protocol, including diagnostic angiography, adenosine IC 24-36 μg, Ach 10^-6, Ach 10^-5, Ach 10^-4, and NTG, with hemodynamic data and Doppler velocity.]
Algorithm for assessment of angina in patients with non-obstructive CAD

Abnormal: An increase in CBF less that 50% or less than a 20% increase in coronary artery diameter

From: Cardiol Clin 23 (2005) 559–568
Summary Relative Risk (RR) for MACE in Women with Coronary or Peripheral Endothelial Dysfunction

**Coronary Circulation**
- Halcox '02: <0.0001
- Schachinger '00: <0.0001
- Suwaidi '00: <0.0001
- Targonski '03: 0.003
- Von Mering '04: <0.0001

Summary RR: 11.1 (6.9-17.8) <0.0001

**Peripheral Circulation**
- Brevetti '03: <0.0001
- Chan '03: <0.0001
- Fichtlscherer '03: <0.0001
- Gokce '02: <0.0001
- Gokce '03: <0.0001
- Heitzer '01: <0.0001
- Hyrniewicz '03: <0.0001
- Murakami '03: 0.043
- Neunteufl '00: <0.0001
- Perticone '01: <0.0001

Summary RR: 9.6 (7.1-12.8) <0.0001

**Combined**
- Summary RR: 10.0 <0.0001

Source: Bairey Merz JACC 2006;47:S21-S29.
Diagnosis of Ischemic Heart Disease Without Obstructive CAD

Control

Peak Myocardial Enhancement during the First Pass of Gadolinium in a Control Subject at Rest (Panel A) and during Stress (Panel B): Uniform Myocardial Signal Enhancement.

Female Specific IHD

IHD/No CAD may have subendocardial ischemia as demonstrated using cardiac MR perfusion

Peak Myocardial Enhancement during the First Pass of Gadolinium in a Patient with Ischemia/No CAD at Rest (Panel A) and during Stress (Panel B): Ring of Delayed Subendocardial Enhancement (Arrows in Panel B).
42 year-old F with exertional chest pain and nonobstructive LAD plaque (confirmed by IVUS)

Adenosine and treadmill stress CMR run on consecutive days

More chest pain similar to symptoms with exercise vs. adenosine
More prominent perfusion defect (arrows)

Slide Courtesy of Dr. Subha Raman
# Proposed Classification for SIHD

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>POTENTIAL MECHANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VASCULAR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>Macrovessels</td>
<td>Flow-limiting stenosis&lt;br&gt;Endothelial dysfunction&lt;br&gt;Spasm&lt;br&gt;Muscle bridge&lt;br&gt;Inflammation&lt;br&gt;Aberrant origin&lt;br&gt;Dissection</td>
</tr>
<tr>
<td>Microvessels</td>
<td></td>
<td>Microvascular dysfunction&lt;br&gt;Endothelial dysfunction&lt;br&gt;Spasm&lt;br&gt;Inflammation&lt;br&gt;Microemboli&lt;br&gt;Capillary insufficiency (LVH)</td>
</tr>
<tr>
<td>Other Vessels</td>
<td>Capacitance vessels</td>
<td>Increased stiffness (aging, calcification, hypertension, CRI)</td>
</tr>
<tr>
<td><strong>NONVASCULAR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>Transcellular&lt;br&gt;Intracellular&lt;br&gt;Mitochondria</td>
<td>O2 Transport (ie. Amyloid)&lt;br&gt;O2 Transport&lt;br&gt;Mitochondrial dysfunction</td>
</tr>
<tr>
<td>Adventitia</td>
<td>Adipocytes</td>
<td></td>
</tr>
<tr>
<td>Matrix</td>
<td>Mast Cells</td>
<td></td>
</tr>
</tbody>
</table>

Understanding the Yentl Syndrome: Sex Differences in Ischemic Heart Disease

- “Normal” coronary angiograms (luminal irregularities <50% stenosis) are seen far more frequently in women with SIHD & ACS vs. men
- For women presenting with ACS, 10-25% women vs 6-10% of men have no obstructive CAD: 1.4 million patients discharged after an ACS/year, 600,000 are women - translates into 60,000-150,000 women with ACS having nonobstructive CAD
- Specific investigation is needed to understand the paradox whereby women have less obstructive CAD and less severe MIs yet worse clinical outcomes compared to men
- Pathophysiology needs to be further understood, as does treatment and impact on symptoms and outcomes
Searching for the Cause of SIHD

"I'm searching for my keys."
Women are Just More Complicated
Women and Cardiovascular Disease: Is there a Sex Difference? Part II

ACC Alaska 2016
Anchorage, AK
February 5, 2016

Martha Gulati, MD, MD, FACC, FAHA
Professor of Medicine in the Division of Cardiology
Chief, Section of Cardiology
University of Arizona-Phoenix
Phoenix, AZ
Do CVD Risk Factors affect Women in the same way as Men?

Sex Differences in Cardiac Risk Factors
Cardiovascular Risk Identification

- Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update
- 2013 ACC/AHA Guidelines on the Assessment of Cardiovascular Risk
- 2014 AHA Stroke Prevention Guidelines in Women
## CVD Risk Factors in Women

<table>
<thead>
<tr>
<th></th>
<th>Prevalence vs Men</th>
<th>Relative Risk vs Men</th>
<th>Sex Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>↓</td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>Diabetes/Metabolic Syndrome</td>
<td>↑</td>
<td>↑↑↑↑</td>
<td>Gestational DM PCOS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑</td>
<td>↑</td>
<td>Preeclampsia Gestational HTN</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Physical Inactivity/ Poor Fitness</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>↑</td>
<td>-/↑</td>
<td>Postpartum Weight Gain</td>
</tr>
<tr>
<td>Depression</td>
<td>↑↑↑↑</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>SLE/RA</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of the Cardiovascular Health in USA: NHANES 2011-2012

Mozaffarian D et al. Circulation. 2015;131:e29-e322
Sitting for Too Long Can Kill You

• Pooled data from 41 international studies
• The amount of time a person sits during the day is associated with a higher risk of heart disease, diabetes, cancer and death, regardless of regular exercise.
• Despite the health-enhancing benefits of physical activity, this alone may not be enough to reduce the risk for disease.
• Prolonged sedentary behaviour was associated with a 15-20% higher risk of death from any cause; a 15-20% higher risk of heart disease, death from heart disease, cancer, death from cancer; and as much as a 90% increased risk of developing diabetes.

Sitting is the 'new' Smoking

Nurses Health Study II: Risk for Coronary Heart Disease based on Optimal Lifestyle Behaviors

- 73% of CHD cases were attributable to poor adherence to a healthy lifestyle
- 46% of clinical CVD risk factors developed were attributable to a poor lifestyle

Sex Differences in Type I Diabetes and Risk of Death

- 26 studies: 214,114 individuals and 15,273 events
- Women with Type 1 DM have ~40% greater excess risk of all-cause mortality, 2X excess risk of fatal and nonfatal vascular events compared with men with Type 1 DM

Risk Women:Men

Huxley RR et al. Lancet Diabetes Endocrinol. 2015;doi:10.1016/s2213-8587(14)70248-
“Baby Weight” and Risk of Heart Disease and Diabetes

- Followed 305 Patients for 1 year post partum
- Women who maintained excess pounds between 3-12 months postpartum had elevated risk factors for diabetes and cardiovascular disease
- Women who didn't lose weight had higher blood pressure, higher levels of LDL, apo B and greater resistance to insulin (25% of cohort)
- Indirect Evidence that women who don’t lose their “baby weight” are at greater risk for heart disease

Kew S et al. Diabetes Care 2014
Cohort (N=47,908): women who delivered preterm (<37 weeks' gestation) [N=5992 (12.5%)] vs. Normal term birth at the same period

During a follow-up period of >10 years, patients with PTD had higher rates of simple and complex cardiovascular events and higher rates of total cardiovascular-related hospitalizations.
Gestational Diabetes Mellitus and Relative Risk of Maternal CVD

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Relative Risk (95% CI)</th>
<th>Mean or Median Years of Follow-up</th>
<th>Caption Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr, 2006 (56)</td>
<td>1.58 (1.00, 2.49)</td>
<td>30</td>
<td>a</td>
</tr>
<tr>
<td>Shah, 2008 (55)</td>
<td>1.71 (1.08, 2.69)</td>
<td>12</td>
<td>b</td>
</tr>
</tbody>
</table>

Hypertensive Disorders of Pregnancy (HDP) and Risk of Maternal CVD

Northern Finland Birth Cohort 1966:
Risk For CVD, MI and MI Deaths in Women with Hypertension during Pregnancy.

Northern Finland Birth Cohort in 1966 (12,055)

Elevated BP during pregnancy, regardless of type, signals high risk of CVD, CKD and DM

Women’s Perception of Future CVD Risk Following Pregnancies With Preeclampsia

Interviews with 12 women with a recent history of preeclampsia who had attended a postnatal follow-up clinic.

- The interviews were held a median of 47 weeks postpartum (24-62 weeks).
- Family history of CVD was associated with a greater awareness of future CVD risk.
- Women without traditional risk factors found it hard to envisage themselves as being at risk (saw less relevance of such information).
- May take several months after delivery for a woman to be able to fully consider her own health as well as the baby’s.
- Situational factors of being a new mother need to be taken into account to successfully engage with this patient group.

Brown MC et al. HTN in Pregnancy 2013, Vol. 32, No. 1, Pages 60-73
Theoretical Timelines of Impairment of Endothelial Function and Development of CVD following Preeclampsia

- In women there is a gradual age-related reduction in endothelial function (exacerbated by the presence of CV risk factors)
- Women who experience preeclampsia have impaired endothelial function during pregnancy and up to 3 years following an affected pregnancy.
  - Theory 1: Begin with normal endothelial function, which is acutely impaired during preeclampsia, followed by ongoing age-related decreases
  - Theory 2: Women who develop preeclampsia may have primary endothelial dysfunction which both puts them at risk of preeclampsia. May be exacerbated by preeclampsia (solid line), or simply persist (dotted line)
Pregnancy Related Disorders and CVD Risk Association

The Evidence to Date:

- GDM: 1a evidence as a risk factor for DM (>7X)
- HDP: 1a evidence as a risk factor for DM (1.8X)
- HDP: 1a evidence as a risk factor for HTN (3.7X)
- Preeclampsia: 1a evidence as a risk factor for CVD/Mortality (2X)
- GDM: 1b evidence as a risk factor for CVD/Mortality (1.7X)

<table>
<thead>
<tr>
<th></th>
<th>Type 2 DM</th>
<th>HTN</th>
<th>CVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM</td>
<td>1a</td>
<td>ND</td>
<td>1b</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1a</td>
<td>1a</td>
<td>1a</td>
</tr>
<tr>
<td>G-HTN</td>
<td>1a</td>
<td>1b</td>
<td>1a</td>
</tr>
</tbody>
</table>

Level of Evidence based on Oxford Classification

Nerenberg N et al. Canadian Journal of Cardiology 2014;1-14
Heart Disease & Breast Cancer: What is the Connection?
**Total Deaths in Women in USA 2011:**

1,236,003

- **Cardiovascular Disease:** 398,035
- **Chronic Lung Disease:** 75,422
- **Lung Cancer:** 70,550
- **Breast Cancer:** 40,931

**Prevalence of CVD in US Women:**
- 42,900,000

**Prevalence of Breast Cancer in US Women:**
- 2,899,726

Mozaffarian D et al. *Circulation.* 2015;131:e29-e322

### Awareness of the Problem In Women

<table>
<thead>
<tr>
<th>Leading Cause of Death?</th>
<th>2009 Overall</th>
<th>1997 Overall</th>
<th>White Woman</th>
<th>Black Woman</th>
<th>Hispanic Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>11%</td>
<td>15%</td>
<td>10</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Cancer</td>
<td>23%</td>
<td>35%</td>
<td>20</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>54%</td>
<td>30%</td>
<td>60</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Greatest Health Problem?</th>
<th>2009 Overall USA</th>
<th>1997 Overall USA</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>28%</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>Cancer</td>
<td>18%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>16%</td>
<td>7%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Mosca et al. Circ Cardiovasc Qual Outcomes. 2010;3:*
Breast Cancer Survival has Improved…

Percent Surviving 5 years - 89.2%

..and are more likely to die from heart disease than breast cancer
WHERE WE DONATE VS. DISEASES THAT KILL US

<table>
<thead>
<tr>
<th>Disease</th>
<th>Money Raised</th>
<th>Deaths (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>$257.85M</td>
<td>506,577</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$147M</td>
<td>73,651</td>
</tr>
<tr>
<td>Motor Neuron Disease (including ALS)</td>
<td>$54.1M</td>
<td>41,374</td>
</tr>
<tr>
<td>HIV / AIDS</td>
<td>$22.9M</td>
<td>39,518</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>$14M</td>
<td>21,176</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>$7M</td>
<td>14,960</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>$4.2M</td>
<td>7,683</td>
</tr>
<tr>
<td></td>
<td>$3.2M</td>
<td>6,849</td>
</tr>
</tbody>
</table>

Source: CDC (2011)
Risk Factors for Breast Cancer

- Tobacco
- Genetics BRCA1/2
- Radiation
- Menarche Onset/End
- Age of Pregnancy
- No Breast Feeding
- Nullparity
- EtOH
- Environment Pollutants
- Age
- Obesity
- HRT
- Decreased Physical Activity
- Inflammation

Risk Factors for Heart Disease

- Tobacco
- Genetics BRCA1/2
- Radiation
- Menarche Onset/End
- Age of Pregnancy
- No Breast Feeding
- Nullparity
- EtOH
- Environment Pollutants
- Age
- Obesity
- HRT
- Metabolic Syndrome
- Diabetes
- Poor Diet
- Decreased Physical Activity
- Inflammation
# Obesity Prevalence in the USA

<table>
<thead>
<tr>
<th></th>
<th>Obesity 2005-2008 Age ≥20 years</th>
<th>Obesity 2007-2008 2-19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>White Women</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Black Women</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Hispanic Women</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Filipino</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Asian-Indian</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Asian-Chinese</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

- 40,100,000 US Women are Obese
- 5,800,000 US Female Children are Obese
- Estimated Cost of Obesity: $147 Billion

Sources: National Health and Nutrition Examination Survey (NHANES) 2005–2008 (National Center for Health Statistics), National Heart, Lung, and Blood Institute
Obesity – Breast Cancer

• Multiple Pathways that Obesity increases risk of Breast Cancer
  • Obesity increases Fat Tissue, increasing estrogen
  • Obesity increases Insulin, IGF-1 ➔ Promotes Tumor Development
  • Obesity increases fat cells ➔ Increased Adopokines (leptin) ➔ Cell Growth Indented Levels
  • Obesity results in Increased Inflammation ➔ ↑Cancer Risk
The Obesity Epidemic & Breast Cancer

- 6300 Postmenopausal Women from 13 studies showed increased Estrogen (50%) and Testosterone (16%) levels if Obese vs Normal BMI
  - Obesity appeared to have a greater effect on Estrogen levels than Alcohol (2.5 Units) or Tobacco Use (15+ cigarettes/day)

- NCI SEER Data attributed 50,500 New Cancer Cases per year to Obesity
  - 2030: Predict Obesity will increased cases by 500,000
  - If every Adult lost 1% of BMI (~1kg) would result in preventing these new cases and avoid an additional 100,000 new cases

British Journal of Cancer 2011;105:709-22
NCI SEER data
## Physical Activity in the USA-2010

<table>
<thead>
<tr>
<th>Meeting Guidelines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25%</td>
</tr>
<tr>
<td>Female</td>
<td>16%</td>
</tr>
<tr>
<td>White Women</td>
<td>19%</td>
</tr>
<tr>
<td>Black Women</td>
<td>11%</td>
</tr>
<tr>
<td>Asian</td>
<td>18%</td>
</tr>
<tr>
<td>American-Indian</td>
<td>13%</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Interviews in 2010
- Based on 2008 Physical Activity Guidelines

Sources: National Health Interview Survey 2010
Fit vs Fat: Metabolic Influence

If Metabolic Syndrome is not present in those who are obese, there is a 38% lower risk of CVD Death vs. Metabolically Abnormal/Obese persons.

No difference in those with Normal Weight/Metabolically Normal vs Obese/Metabolically Normal. After controlling for Fitness, significance disappeared.

Fitness may defend against the effect of Fatness.

Some Genetics May Be Shared for Heart Disease and Breast Cancer

Study of Mice with Breast Cancer showed Genetic Defect in BRCA1/BRCA2 may be not only associated with Breast Cancer but also heart disease.

Shukla P et al. Nature Communications 2011; 2
Heart Disease Secondary to Breast Cancer Treatment

- Heart Disease and Breast Cancer Radiation:
  - Left vs Right Breast: Increased risk of CAD & MI
  - No Increase in cardiac death

- Heart Disease and Anthracyclines:
  - Reported 10-50% with some degree of heart failure in following 10 years

- Heart Disease and Herceptin (Tratuzumab):
  - Increased risk if age >50, use of hypertensive medications or low-normal heart function (3.8% vs 0.9% after 5 years)
  - In elderly (>70 y), much greater risk shown- higher rates in those with heart disease or with diabetes

- Heart Disease with Combination Chemotherapy:
  - 12,500 Women: 7X more likely to develop heart disease or CHF if received both anthracycline and Herceptin
  - 4X more likely to have heart disease or CHF received Herceptin alone

Harris et al. J Clin Oncology 2006:26:1390
Serrano et al. Annals of Oncology 2011
Bowles et al. Journal NCI. 2012;104:1293-1305
Heart Failure and Breast Cancer In Older Women

- SEER-Medicare Data- identified women with Stage I-III breast cancer diagnosed 2000-2009 who received potentially cardiotoxic adjuvant therapy (anthracyclines, trastuzumab) and developed HF/CM

- ~12 percent of older breast cancer patients developed heart failure within three years, often as a result of the cancer drugs and treatments.

- Only a third of older breast cancer patients saw a cardiologist within 90 days of developing heart problems.

- Those who saw a cardiologist were more likely to receive standard drugs for heart failure than those who didn’t.

Chen J et al 2014 Circulation
Risk of IHD after Radiation for Breast Cancer

Rates of Coronary events increased by 7.4% per Gy (P<0.001)
Avg radiation 1-2 Gy to Right Breast, usually higher in Left Breast
Risk of major coronary events began within the first 5 years after exposure

Incidence of IHD

Increase per gray, 7.4% (95% CI, 2.9–14.5)
P<0.001

Cumulative risk of death from ischemic heart disease

Darby et al. NEJM 2013;368:987-998
The Red Dress vs The Pink Ribbon

- Number 1 Publicity (Best PR)
- Number 1 Awareness
- NIH Allocation: NCI received $5.098 billion from the NIH pot, of which $2.168 billion funded research: $705 Million+ to Breast Cancer (+$130 Million Dept of Defense)

- Number 1 Killer
- Number 1 Medical Expenditure
- Number 1 Prevalence
- NIH Allocation: NHLBI received $3.093 billion, of which $1.320 billion went toward cardiovascular research

NIH Research Reporting  Feb 13, 2012
Health Prevention: Reduction in Heart Disease and Breast Cancer

Focus of Cardiovascular Disease in the Future Must Be Prevention

- Common Risk Factors Mean Common Goals of Prevention should be Joined

Focus of Breast Cancer in the Future Must be Prevention
Sex Differences in CVD

- Cardiovascular Disease remains the number one killer of women
- Increased overlap in risk factors for breast cancer and heart disease, including genetic abnormalities
- Goals for prevention of both also overlap
- Screening women with breast cancer for heart disease is a priority and needs to be emphasized in patients after undergoing treatment
Classification of CVD Risk in Women

At risk

1 major risk factors for CVD, including:

Cigarette smoking
Poor diet
Physical inactivity
Obesity, especially central adiposity
Family history of premature CVD (CVD at <55 years of age in male relative and <65 years of age in female relative)
Hypertension
Dyslipidemia
Evidence of subclinical vascular disease (eg, coronary calcification)
Metabolic syndrome
Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise

History of Gestational DM, Pregnancy induced HTN, preeclampsia Lupus, Rheumatoid Arthritis
### Classification of CVD Risk in Women

| High risk | Established coronary heart disease  
|          | Cerebrovascular disease  
|          | Peripheral arterial disease  
|          | Abdominal aortic aneurysm  
|          | End-stage or chronic renal disease  
|          | Diabetes mellitus  
|          | 10-Year Framingham global risk >10%* |

| Optimal risk | Healthy lifestyle, with no risk factors, BP <120/80, Total cholesterol <200, BMI <25 kg/m², 150 min of activity per week, DASH diet |

*Mosca, L. et al. Circulation 2011;123*
Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator

- 10 year risk: 40-79 years
- Lifetime risk: 20-59 risk estimator provides lifetime risk estimate
- Internal/External Validation in diverse populations
- This is intended to drive discussions of greater adherence to heart-healthy lifestyle in addition to determining who would benefit from lipid-lowering therapy
- Sex Specific Risk Factors?

[Interactive Calculator]

http://tools.cardiosource.org/ASCVD-Risk-Estimator/
2014 Stroke Prevention Guidelines in Women (AHA/ASA)

- 55,000 more strokes in women than in men (Risk of Stroke: 1 in 5 women)
- Risk factors for stroke unique to women: pregnancy, use of OC, and HRT
- Migraines with Aura, Cerebral venous thrombosis Associated with Stroke
- Preeclampsia: Doubles risk of stroke, even if BP returns to normal

**Recommendations:**
- Women with HTN before pregnancy should be considered for low-dose ASA and/or calcium supplement therapy to decrease pre-eclampsia risks
- Pregnant women with Moderate HTN(150-159/100-109) may be considered for BP meds, severe HTN (≥160/110) should be treated
- Screening women for HTN before they begin taking OC
- All women >75 should be screened for Afib due to link to higher stroke risk.
- Migraines with auras: Need to quit smoking to lower risk of stroke

*Bushnell C et al. Stroke, Feb 6, 2014*
Comprehensive Guidelines of ASCVD Prevention and Assessment: Future Considerations

- Pregnancy Related Complications (need guidelines for screening/timing/intervention)
- PCOS
- Functional hypothalamic amenorrhea (FHA)
- Prior Chest Radiation
- Prior Chemotherapy
- Prior Breast Cancer

Sex Specific Calculator of CVD Risk?
Sex Differences in CVD

• Risk for women with obstructive CAD is increased compared with men, yet **women are less likely to receive guideline-indicated therapies**
• Sex Specific CVD Risk Factors & Sex differences in traditional risk factors
• “Normal” coronary angiograms (luminal irregularities <50% stenosis) seen more frequently in women vs. men with IHD
• Investigations needed to understand the paradox whereby women have less obstructive CAD and less severe MIs yet worse outcomes compared to men
• Pathophysiology needs to be further understood, as does treatment and impact on symptoms and outcomes
WOMEN ≠ SMALL MEN
SAVING WOMEN’S HEARTS
How You Can Prevent and Reverse Heart Disease With Natural and Conventional Strategies

MARTHA GULATI MD, MS, FACC, FAHA
SHERRY TORKOS BSc PHM

@drmarthagulati

“An extraordinary story that reveals the secrets of the heart and the keys to a heart-healthy life.”
— Robert O. Brown, MD, Past President, American Heart Association