Disclosures

- Gilead Research Grant
- NIH (NHLBI)
Why Talk about Women and Heart Disease?

- How big is the problem?
- Is there a gender difference?
- What are some of the road blocks?
- What can we do?
Facts

- Heart Disease is the #1 killer in women.
- In 2007, ≈ 1 death per minute due to CVD in women in U.S.
- This is 421,918 annual deaths - More than cancer, chronic respiratory disease, Alzheimer’s, and accidents combined.
- CHD death rates in women 35 to 54 are increasing.
- >12 million women have diabetes.
- 2 out of 3 women in United States over age 20 have elevated BMI.

Mosca L et al. Circ 2011;123
Heart Disease: leading killer of women at all ages

One in three women dies from heart disease. It’s the #1 killer of women, regardless of race or ethnicity. It also strikes at younger ages than most people think, and the risk rises in middle age. Two-thirds of women who have heart attacks never fully recover.

*Numbers of deaths are rounded to the nearest thousand.
To learn more, visit www.nhlbi.nih.gov/health/hearttruth.
Gender Differences in Heart Attack Symptoms

Typical in both sexes

- Pain, pressure, squeezing, or stabbing pain in the chest
- Pain radiating to neck, shoulder, back, arm, or jaw
- Pounding heart, change in rhythm
- Difficulty breathing
- Heartburn, nausea, vomiting, abdominal pain
- Cold sweats or clammy skin
- Dizziness
Heart Attack Symptoms in Women

- Milder symptoms without accompanying chest pain
- Sudden onset of weakness, shortness of breath, fatigue, body aches, overall feeling of illness
- Burning sensation in the chest, may be mistaken as heartburn
- An “unusual” feeling or mild discomfort in the back, chest, arm, neck, or jaw
Gender Differences in Heart Attack Symptoms

- Women have more symptoms overall
- Women also have more atypical symptoms

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Cigarette Smoking</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>High Blood Cholesterol</td>
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<tr>
<td>High Blood Pressure</td>
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<tr>
<td>Family History</td>
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<tr>
<td>Physical Inactivity</td>
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<tr>
<td>Nutrition</td>
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<tr>
<td>Gestational Diabetes</td>
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<tr>
<td>Pregnancy-Induced Hypertension</td>
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<tr>
<td>Pre-Eclampsia</td>
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<tr>
<td>Autoimmune Dz (lupus, RA)</td>
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</tbody>
</table>
BP Rises After Menopause
Risk of HTN Triples

Changes in SBP From Baseline to Follow-Up (Mean 5.2 y)

Women

Controls

Change From Baseline‡

Change From Baseline‡

SBP (mm Hg)

SBP (mm Hg)

Women

Controls

Pre (n = 166)

Peri (n = 44)

Post (n = 105)

* $P \leq .05$; † $P = .07$. ‡ Baseline SBP: Pre = 121.4 1.3 mm Hg; Peri = 122.0 1.8 mm Hg; Post = 126.5 1.7 mm Hg.

Controls were men matched by age and BMI.

Change in Lipids After Menopause

N=10.
Observation: Alarming Trend

Current Strategies not Working Optimally in Women

CHD Mortality in Younger Women

Women under 65 suffer the highest relative sex-specific MI mortality

Figure 1. Rates of Death during Hospitalization for Myocardial Infarction among Women and Men, According to Age. The interaction between sex and age was significant (P<0.001).

Vaccarino V et al. NEJM 1999;341:217
Women and Heart Disease: Paradox

- There is a significant national gender gap in CHD-MI mortality
- Women, particularly younger women, face a more adverse CHD prognosis
- Adjustment for disease severity, comorbidity, and treatment does not fully account for the gap
Paradox: Pathophysiological Gender Differences: FRISC II

- 749 women and 1,708 men with unstable coronary artery disease
- Entry criteria = symptoms plus ischemia, defined as ECG change or + enzymes
- Randomized to early invasive versus noninvasive strategy
- Women were older, had fewer prior MI, better LVEF and lower troponin T levels

Lagerqvist et al, JACC 2001;38:41
**Women have worse function and outcomes with less obstructive CAD (FRISC II ACS)**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td>EF ≤45%</td>
<td>12%*</td>
<td>14%</td>
</tr>
<tr>
<td>No CAD</td>
<td>25%*</td>
<td>10%</td>
</tr>
<tr>
<td>LM/3 VD/2 VD/2 prox LAD</td>
<td>32%*</td>
<td>43%</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>(Death/MI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>12%</td>
<td>11%**</td>
</tr>
<tr>
<td>(Death/MI)</td>
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</tr>
</tbody>
</table>

*p<0.05 vs men; ** P = 0.001 vs noninvasive

Lagerqvist et al, JACC 2001;38:41
Paradox: Women have a two-fold increase in “normal” coronary arteries in the setting of ACS, NSTEMI and STEMI

<table>
<thead>
<tr>
<th>Table. Prevalence of “Normal” and Nonobstructive Coronary Arteries in Women Compared With Men</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>No./Total (%)</strong></td>
</tr>
<tr>
<td><strong>Acute coronary syndrome</strong></td>
</tr>
<tr>
<td>GUSTO(^2)</td>
</tr>
<tr>
<td>TIMI 18(^3)</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
</tr>
<tr>
<td>TIMI IIIa(^6)</td>
</tr>
<tr>
<td><strong>MI without ST-segment elevation</strong></td>
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<tr>
<td>MI without ST-segment elevation(^2)</td>
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<tr>
<td><strong>MI with ST-segment elevation</strong></td>
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<tr>
<td>MI with ST-segment elevation(^2)</td>
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</tbody>
</table>

**Abbreviations:** GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.
NHLBI-sponsored WISE

- Women’s Ischemia Syndrome Evaluation Study
- Started in 1997 – current
NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation (WISE): 1997-current

- **Clinical Coordinating Center** - Cedars-Sinai Medical Center (PI Bairey Merz)
- **Data Coordinating Center** - University of Pittsburgh (PI Kelsey)
- **Clinical Sites:**
  - Cedars-Sinai Medical Center (Site PI Bairey Merz) and CMRI Core
  - University of Florida, Gainesville, FL (Site PI Pepine CJ)
  - University of Alabama at Birmingham, AL (Site PI Rogers W)
  - University of Pittsburgh, Pittsburgh, PA (Site PI Reis SE)
  - Allegheny General Hospital, Pittsburgh, PA (Site PI Reicheck N)
  - Brown University, Providence, RI (also Angiographic Core Lab) (Core Lab and Site PI Sharaf BL)
  - Mayo Clinic, Rochester, MN (Site PI Lermin A)
  - Emory University, Atlanta, GA (Site PI Quiyumi A)
WISE Phenotype = Microvascular Coronary Dysfunction (MCD)

- Persistent symptoms of angina (typical and atypical)
- Objective evidence of ischemia by stress testing
- No obstructive CAD by angiography
Exertional Angina Evidence of Ischemia

No obstructive CAD Abnormal coronary flow reserve and elevated LVEDP

Diffuse atherosclerosis by IVUS

Obstructive Coronary Disease

More prevalent in men

Microvascular Coronary Dysfunction

More prevalent in women

From the NCDR, we estimate 3 million women have MCD.
Women may have greater \textit{positive remodeling} in response to injury and atherosclerosis with relatively smaller coronary artery size.
Plaque Erosion and Outward (Positive) Remodeling

- Plaque erosion and thrombus formation 2x likely in women (men have more plaque rupture)
- Outward (positive) remodeling - atherosclerotic lesion protrudes outward than impinging on the lumen

Adapted from Bellasi et al, New insights into ischemic heart disease in women. Cleveland clinic journal of medicine; 74: 585-594
Morphology of Intramyocardial Emboli in Epicardial Plaque Thrombosis

Women vs. men:

- Any emboli: 73% vs. 37%, p<.001
- Mean emboli: 12 ± 3 vs. 4 ± 1, p=.02

Acute myocardial necrosis:

- Any emboli: 88% vs. 39%, p<.001
- Mean emboli: 18 ± 5, 4 ± 1, p<.001

Virmani R et al, Circulation 2008
Hypothetical New Understanding of Ischemic Heart Disease in Women

- Post-Menopause
- Hypothalamic Hypoestrogenemic
- PCOS

↓ E2  

↑ Inflammatory milieu  

↑ Autoimmune Diseases

Symptomatic Manifestations

- Subclinical CAD
- Obstructive CAD

Progressive Manifestations of Demand Ischemia

Normal Artery & CFR  

Normal Artery & CFR  

Progenitor Cell Repair,  

Metabolic Δs, ↓ Perfusion

↓ Progenitor Cell Repair,  

↓ Diastolic Function

Bairey Merz, JACC 2009
Classification of Microvascular Coronary Dysfunction (MCD)

1. MCD in the absence of obstructive CAD or structural disease

2. MCD due to the presence of obstructive CAD

3. Iatrogenic MCD
   - Distal embolization during PTCA and vasoconstriction due to recanalization

4. MCD due to myocardial diseases
   - Adverse remodeling of intramural arterioles
   - CM – dilated, hypertensive, valvular, hypertrophic

Interventional No Reflow:

21% MI and 2% elective PCI-stenting

Circulation 2008;117;3152-3156
## Components of CRT in Evaluation of Coronary Vascular Function

<table>
<thead>
<tr>
<th></th>
<th>Macrovascular dysfunction</th>
<th>Microvascular dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial dependent</td>
<td>Abnormal vasoreactivity to Acetylcholine</td>
<td>Reduced coronary blood flow in response to Acetylcholine</td>
</tr>
<tr>
<td>Endothelial Independent</td>
<td>Abnormal vasoreactivity to Nitroglycerin</td>
<td>Reduced coronary flow reserve in response to Adenosine</td>
</tr>
</tbody>
</table>
Coronary Reactivity Testing: Adenosine

APV = Average Peak Velocity
CBF = Cross section area of coronary artery X APV/2
Abnormal Coronary Flow Reserve to Adenosine Predicts Cardiac Events in Women with No Obstructive CAD

Women without CAD

% Event-Free Survival

Years Follow-Up

p=0.004 (Log Rank)

CFR ≥2.32
(n=97)

CFR <2.32
(n=56)

Coronary Reactivity Testing: Acetylcholine

Baseline

Post ACH

Post NTG

Vasoconstriction Of LAD
Abnormal Coronary Vasomotion To Acetylcholine Independently Predicts Cardiac Events In Women with No Obstructive CAD

Log-rank p=0.0037
Multivariate p=0.001

Non-Invasive Evaluation

- Risk factor assessment and noninvasive perfusion stress testing works similarly well in women and men, and should be used for assessment.

- Newer testing techniques, such as magnetic resonance imaging and carotid IMT offer promise for improved test accuracy; research is ongoing.
Cardiac Magnetic Resonance Imaging (CMRI)

- <60 min evaluation
  - Cardiac structure and function
  - Stress and rest cardiac perfusion
  - Scar imaging

- Zero radiation
  - Adenosine stress
  - Gadolinium contrast
Example CMRI: Myocardial Hypoperfusion in Patients with Normal Coronary Angiography

Patient 1.
Coronary angiography: 70% stenosis in left circumflex marginal artery

Patient 2.
Coronary angiography: proximal 95% stenosis in left anterior descending artery

Patient 3.
Coronary angiography: normal coronaries

51/100 female
Therapy for MCD

- **Coronary Endothelial Dysfunction** - Angiotensin Converting Enzyme Inhibitors (ACE-I), HMG CoA Reductase Inhibitors (Statins), L-arginine supplementation, Aerobic Exercise, Enhanced External Counterpulsation (ECP)

- **Abnormal Coronary Flow Reserve** - Beta-blockers/ alpha-beta blockers

- **Coronary Smooth Muscle Dysfunction** - Calcium Channel Blockers

- **Anti-Anginal - Anti-Ischemic** – Ranolazine

- **Abnormal Cardiac Nociception** - Low Dose Tricyclic Medication, Spinal Cord Stimulation (TENS unit), Cognitive Behavioral Therapy

Beta Blockers vs. Calcium Channel Blockers in Cardiac Syndrome X

- Atenolol more effective than Amlodipine or Isosorbide 5-Mononitrate for reduction of angina.¹
- Propranolol more effective than Verapamil.²
- Diltiazem did not improve CFR.³
- Beta-Blockers are endothelium-dependent vasodilators.⁴

Pilot Trial on Ranolazine

- A pilot randomized, double-blinded, placebo-controlled, cross-over trial was conducted in 20 women with angina, no obstructive CAD by angiography, and myocardial ischemia defined as ≥ 10% summed difference score (SDS) on adenosine stress perfusion with CMRI.

- Participants were assigned to ranolazine or placebo first for the two 4-week intervention periods separated by a 2-week washout.
Study Design Flow Diagram

Qualifying CMRI

Baseline SAQ & DASI

Enrollment & Randomization

Treatment Period 1

CMRI, SAQ, & DASI

Washout

2 Weeks

Treatment Period 2

CMRI, SAQ, & DASI

4 Weeks

Upto 24 months

4 Weeks

2 Weeks

4 Weeks

Treatment: Ranolazine vs. Placebo, CMRI: Cardiac Magnetic Resonance Imaging, SAQ: Seattle Angina Questionnaire, DASI: Duke Activity Score Index

Mehta PK et al. JACC: CV Imaging April 2011
<table>
<thead>
<tr>
<th></th>
<th>Ranolazine</th>
<th>Placebo</th>
<th>Treatment effect (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Functioning</strong></td>
<td>91.7 (79.2, 97.9)</td>
<td>83.3 (66.6, 97.2)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Angina Stability</strong></td>
<td>75 (50, 100)</td>
<td>50 (25, 75)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Angina Frequency</strong></td>
<td>80 (50, 100)</td>
<td>75 (60, 87.5)</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>Treatment Satisfaction</strong></td>
<td>87.5 (75, 100)</td>
<td>93.8 (75, 100)</td>
<td>0.058</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>75 (60.4, 83.3)</td>
<td>66.7 (58.3, 75)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
### Visual and Quantitative CMR Defects on Ranolazine vs. Placebo

<table>
<thead>
<tr>
<th>Metric</th>
<th>Ranolazine Median (min, max)</th>
<th>Placebo Median (min, max)</th>
<th>Treatment effect (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ischemic myocardium</td>
<td>11.7 % (8.0, 19.3)</td>
<td>16.0 % (8.6, 22.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Global MPRI</td>
<td>2.1 (2.2, 2.4)</td>
<td>1.9 (1.7, 2.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Mid Ventricular MPRI</td>
<td>2.4 (2.0, 2.8)</td>
<td>2.1 (1.7, 2.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Subendocardial MPRI (whole)</td>
<td>2.0 (1.7, 2.2)</td>
<td>1.8 (1.5, 2.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Subendocardial MPRI (mid ventricular)</td>
<td>2.1 (1.7, 2.5)</td>
<td>1.9 (1.5, 2.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Subepicardial MPRI (whole)</td>
<td>2.3 (2.1, 2.6)</td>
<td>2.0 (1.8, 2.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Subepicardial MPRI (mid ventricular)</td>
<td>2.6 (2.2, 3.0)</td>
<td>2.2 (1.9, 2.5)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Mehta PK et al. *JACC: CV Imaging* April 2011
An example of a representative CMRI from a subject. Mid ventricular images on placebo (rest [A] and stress [B]) showed inferolateral and anterolateral hypoperfusion which improved on ranolazine (rest [C] and stress [D]).
Observation: Alarming Trend

Current Strategies not Working Optimally in Women

Disconnect Remains - Educational Efforts Needed

- AHA National Awareness Survey
  - 1997 – 30% aware heart disease is #1 killer
  - 2000 – 34%
  - 2003 – 46%
  - 2009 – 54%

- Knowledge gap remains – especially in women younger than 45, Hispanic, and African American women

- “Disconnect” remains – only 13% say heart disease is their own greatest health risk

CVD in Women: What can we do?

- Look in your practice for high and intermediate risk women.
- Risk factor assessment and noninvasive perfusion testing works well in women.
- Use guidelines for treatment of risk factor and CVD management.

- Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women – 2011 Update
Ischemic heart disease is a significant, under-recognized contributor to death and disability in women.

Women face an adverse CHD prognosis that is not fully accounted for by age, comorbidity, CAD extent and severity, or treatment gender gaps.

Coronary endothelial and microvascular dysfunction are key players in CHD in women.
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