Looking into the Heart of Women: Insights into the Future of Ischemic Heart Disease (IHD)

(How to Recognize Female-Pattern IHD)

C. Noel Bairey Merz MD
Medical Director and
Barbra Streisand Women’s Heart Center
Preventive Cardiac Center
Cedars-Sinai Heart Institute
Los Angeles, California USA
merz@cshs.org
The following relationships exist related to this presentation (*paid to Cedars-Sinai Medical Center):

Grant support*: NHLBI, FAMRI, Gilead, Louis B Mayer Foundation, CTSI

Consulting*: Medscape, Gilead, NIH

Honorarium*: Practice Point, Pri-Med, VBWG

Stocks: None
Monet or Manet?
Monet or Manet?
Female-pattern Ischemic Heart Disease:  
(or why women have more adverse IHD outcomes)

1. An epidemic of death in women  
2. Low hanging fruit - gender  
3. Critical investigation - sex  
4. Results of our labor  
5. Policy and our future
The Yentl Syndrome  1991
Women and Heart Disease Deaths

An Alarming Trend...

Cardiovascular Disease Mortality Trends for Males and Females
United States: 1979–97

DEATHS IN THOUSANDS

'79  '81  '83  '85  '87  '89  '91  '93  '95  '97

CADENDAR YEARS

Females  Males

New female majority
Yentl and Yentl Syndrome

1984-1996: 12 years to recognize /take action

WISE
NHLBI
AHA
Begin

Source: CDC/NCHS and the American Heart Association
Compliments of Womenheart: the National Coalition for Women with Heart Disease
1718 M Street, NW - #330 • Washington, DC 20036
(www.womenheart.org)
Sex and Myocardial Infarction (MI) Mortality: Does Age Explain the Disparity?

Largest Mortality Gaps are Young Women

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>GUSTO²</td>
</tr>
<tr>
<td>TIMI 18³</td>
</tr>
<tr>
<td>Unstable angina²</td>
</tr>
<tr>
<td>TIMI IIIα⁶</td>
</tr>
<tr>
<td>MI without ST-segment elevation²</td>
</tr>
<tr>
<td>MI with ST-segment elevation²</td>
</tr>
</tbody>
</table>

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.
Summary: An Epidemic of Death in Women

1. There is a significant national gender gap in CHD-MI mortality

2. Women, particularly younger women, face a more adverse CHD prognosis

3. Adjustment for disease severity, comorbidity and treatment does not fully account for the gap
Female-pattern Ischemic Heart Disease:
(or why women have more adverse IHD outcomes)

1. An epidemic of death in women
2. Low hanging fruit - gender
3. Critical investigation - sex
4. Results of our labor
5. Policy and our future
Sex and Gender Differences in CVD

Terminology:

• *Sex* = biological sexual differentiation, (e.g. women have ovaries, men have testes)
• *Gender* = socio-cultural attributes of the biological sex, e.g. women have complex social networks, men have wives
Gender Differences in CVD

• *Gender differences in reporting* = women are more comfortable discussing feelings with friends and reporting symptoms to physicians\(^1\), possibly due to gender-related acculturation

• *Gender differences in physician response to symptoms* = physicians are more likely to evaluate men compared to women and minorities\(^2\), possibly due to gender-related presentation styles, and/or cultural sexism/racism biases

\(^1\) Stoverink J Fam Pract 1996;43:567; \(^2\) Schulman NEJM 1999;340:618-626
Disparities in ACS Treatment for Women

- 35,835 pts with NSTEMI: 41% women
- Women had:
  - ↑ DM, HTN, age; ↓ CAD events
  - ↓ Early ASA, heparin, GPIIb-IIIa, ACE-I
  - ↓ Revascularizations: CABG ↓41%
  - ↓ Discharge ASA, beta blocker, ACE-I, statins (Four Magic Pills)*
  - ↑ Death, MI, CHF

* Associated with a 90% reduction in recurrent major adverse cardiac events, AMI Guidelines Therapy

MI Treatment: Women and Men have similar risk benefit
Guideline Implementation and ACS and the Sex Survival Gap

Figure  Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602
Guideline Implementation and ACS and the Sex Survival Gap

Following guideline implementation, mortality for women improves and the sex gap narrows (RED).

**Figure** Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602
Guideline Implementation and ACS and the Sex Survival Gap

Following guideline implementation, mortality for women improves and the sex gap narrows (RED).

Persistent sex gap (BLUE) suggests more work still needed to understand sex-specific pathophysiology to improve outcomes for women and men.

Figure  Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602
Summary: Low hanging fruit - gender

1. AMI guidelines therapy works equally well in women and men
2. Application of AMI guidelines preferentially saves women’s lives
3. Lack of AMI guidelines management (gender) is insufficient to fully explain the adverse outcomes
Female-pattern Ischemic Heart Disease: (or why women have more adverse IHD outcomes)

1. An epidemic of death in women
2. Low hanging fruit - gender
3. Critical investigation - sex
4. Results of our labor
5. Policy and our future
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.
Sex Differences in CVD

• *Sex differences in perception* = women have greater perception (high frequency non-auditory brain testing). Gay men are intermediate between women (higher perception) and men (lower perception), suggesting that this may be genotypic¹

• *Sex differences in pain* = women have lower thermal pain thresholds compared to men. Thresholds appear mediated by estrogen levels, with higher E2 levels associated with enhanced pain, suggesting that this may be phenotypic²

Clinical Translational Research

1. A systematic approach to an identified problem
2. T1 (bench ↔ bed), T2 (bed ↔ clinic), T3 (clinic ↔ community)
3. Four steps –
   1. Observation
   2. Mechanisms
   3. Intervention
   4. Translation
Observation:
Phenotype -
Microvascular Coronary Disease
Exertional angina
Abnormal SPECT
No obstructive CAD
Abnormal coronary flow reserve and elevated LVEDP
Diffuse atherosclerosis by IVUS
NCDR estimate 3 million women in the US – a larger problem than breast cancer.

_Circulation_. 1999;99:1774
WISE Patients with signs and symptoms of ischemia have elevated MACE compared to asymptomatic Women Take Heart (WTH) with no ischemia by ETT

All comparisons adjusted for age, race, BMI, history of hypertension, diabetes, education, employment, family history of CAD, menopausal status, smoking history and metabolic syndrome.

Gulati et al Arch Int Med 2010
Clinical Translational Research

1. Observation
2. Mechanisms
3. Intervention
4. Translation
Hypothetical New Understanding of Ischemic Heart Disease in Women (Bairey Merz and Shaw JACC 2009)

- Post-Menopause
  - Hypothalamic Hypoestrogenemic
  - PCOS

- Inflammatory Milieu
  - E2
  - HTN
  - Obesity
  - Lipids

- Autoimmune Diseases
  - Symptomatic Manifestations

- Vascular Dysfunction
  - Abnormal coronary vasomotion
  - Metabolic Δs, ↓Perfusion

- Myocardial Dysfunction
  - ↓Progenitor Cell Repair, Microvascular Obliteration
  - ↑Fibrosis, ↓Diastolic Dysfxn

- Normal Artery & CFR

- Obstructive CAD

Progressive Manifestations of Demand Ischemia

Exposure Time of Mismatch in Myocardial Oxygen Supply / Demand

Near Term ------------------------------- Prolonged
Coronary Reactivity Testing

• Interventional cardiologist
• PTCA setup
• FloMed Doppler
• 1/600 SAE

Intracoronary:
  Adenosine
  Acetylcholine
  NTG

1. CFR (micro fxn)
2. Endo fxn
3. Non-endo fxn
4. Micro-endo fxn
OBESE, HYPERTENSIVE, NIDDM, BLACK, 57 yo, FEMALE
with HYSTERECTOMY at AGE 21
Mechanisms: MACE by CFR with adenosine: *Women without CAD* (Death, MI, Stroke, CHF)

- CFR $\geq 2.32$ (n=97)
- CFR < 2.32 (n=56)

$p=0.009$ (Log-Rank)
Clinical Translational Research

1. Observation
2. Mechanisms
3. Intervention
4. Translation
## WISE CMD pharmacologic probe trial results

<table>
<thead>
<tr>
<th>Trial (n)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>QWISE(^1) (n=78)</td>
<td>quinipril</td>
<td>↑ CFR; ↓ angina</td>
</tr>
<tr>
<td>FemHRT-WISE (^2)(n=35)</td>
<td>ethinyl estradiol and norethindrone acetate</td>
<td>→ MRS; ↓ angina</td>
</tr>
<tr>
<td>EWISE(^3) (n=41)</td>
<td>eplerenone</td>
<td>→ CFR; → angina</td>
</tr>
<tr>
<td>SWISE(^4) (n=23)</td>
<td>sildenafil</td>
<td>→ CFR; → angina</td>
</tr>
<tr>
<td>RWISE Pilot(^5) (n=20)</td>
<td>ranolazine</td>
<td>→ MPRI; ↓ angina</td>
</tr>
<tr>
<td>RWISE(^6) (n=128)</td>
<td>ranolazine</td>
<td>→ MPRI; → angina</td>
</tr>
</tbody>
</table>

Clinical Translational Research

1. Observation
2. Mechanisms
3. Intervention
4. Translation
   2. ESC Guidelines
Summary: Critical investigation - sex

1. Ischemia in the absence of obstructive coronary disease is prevalent, and has an adverse prognosis and cost.

2. Mechanistic pathways include atherosclerosis, and coronary endothelial and microvascular dysfunction.

3. Existing guidelines focus on symptom management and current clinical practice is reassurance.

4. A practical therapeutic clinical trial is needed.
Female-pattern Ischemic Heart Disease: 
(or why women have more adverse IHD outcomes)

1. An epidemic of death in women
2. Low hanging fruit - gender
3. Critical investigation - sex
4. Results of our labor
5. Policy and our future
Monet vs Manet?

More men receive treatment

More women die

Bairey Merz EHJ 2011
This slide set was adapted from the following 2004-6 ACC/AHA guidelines:

- *Cardiovascular Disease Prevention in Women 2004, 2007, 2010*
- *Management of Patients With ST-Elevation Myocardial Infarction*
- *Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction*
- *Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease*
- *Management of Patients with Chronic Stable Angina*
- *Update for Coronary Artery Bypass Graft Surgery*
- *Evaluation and Management of Chronic Heart Failure in the Adult*

The full-text guidelines and executive summaries are also available on the ACC and AHA websites at [www.acc.org](http://www.acc.org) and [www.americanheart.org](http://www.americanheart.org)

ACC=American College of Cardiology, AHA=American Heart Association
Deaths in Thousands

NHLBI Heart Truth, and AHA Go Red Awareness, and Guidelines Campaigns

1997-2007

Source: NCHS and NHLBI
NHLBI Heart Truth/AHA, WISE and Guideline Campaigns

1997-2007: 43%
Summary: Results of our labor

1. CAD/CHD renamed to IHD to improve recognition of women (and small men)

2. Guidelines campaigns are effective for improving quality of care and outcomes

3. Female mortality has substantially fallen
Female-pattern Ischemic Heart Disease: (or why women have more adverse IHD outcomes)

1. An epidemic of death in women
2. Low hanging fruit - gender
3. Critical investigation - sex
4. Results of our labor
5. Policy and our future
Under-representation of Women in Cardiovascular Clinical Trials

Remains low compared to disease prevalence and death rates -
Largest gaps in CAD and HF due to phenotype inclusion criteria
(e.g. obstructive CAD, troponin, and reduced ejection fraction)

Melloni, et al, Circ Cardiovasc Qual Outcomes 2010
Non-obstructive CAD Rates in ACS Trials

Women comprise only 25% of CAD trial participants (most trials are obstructive CAD)

Source: Anderson Circulation 2007;115:823-826.
Sex Differences in Cardiovascular Disease Biomarkers
(Van Eyk, Bairey Merz, submitted)

Despite their current widespread use, cardiac troponin assays lack sex specific reference value reporting, even for widely used commercial assays that indicate 99th percentile cutoffs or ranges 1.2-2.4 fold higher in males than females. The same is true for CPK-MB.

Overall, these data suggest that at-risk women can be missed using the standard male sex-specific threshold, and that those women that meet standard AMI troponin criteria have suffered a greater degree of myocardial damage.

---


Undiagnosed MIs are untreated MIs with a 25-35% 1 yr death/MI rate

Fig 4 Survival free from death or recurrent myocardial infarction in women and men with suspected acute coronary syndrome.

Back to 1970s AMI mortality!
<table>
<thead>
<tr>
<th>Trial</th>
<th>Total population</th>
<th>Female population</th>
<th>Percentage of females</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS [58] (Enalapril)</td>
<td>253</td>
<td>75</td>
<td>30</td>
</tr>
<tr>
<td>SOLVD [59] (Ramipril)</td>
<td>4228</td>
<td>486</td>
<td>11.5</td>
</tr>
<tr>
<td>ATLAS [60] (Lisinopril)</td>
<td>3164</td>
<td>648</td>
<td>20</td>
</tr>
<tr>
<td>COPERNICUS [61] (Carvedilol)</td>
<td>2289</td>
<td>469</td>
<td>20</td>
</tr>
<tr>
<td>MERIT HF [62] (Metoprolol)</td>
<td>3991</td>
<td>898</td>
<td>22.5</td>
</tr>
<tr>
<td>CIBIS II [63] (Bisoprolol)</td>
<td>2647</td>
<td>515</td>
<td>19</td>
</tr>
<tr>
<td>SENIORS [64] (Nebivolol)</td>
<td>2061</td>
<td>785</td>
<td>38</td>
</tr>
<tr>
<td>VAL-HeFT [70] (Valsartan)</td>
<td>5010</td>
<td>1003</td>
<td>20</td>
</tr>
<tr>
<td>CHARM Added [71] (Valsartan vs Candesartan vs placebo)</td>
<td>2548</td>
<td>542</td>
<td>21.3</td>
</tr>
<tr>
<td>ELITE II [72] (Losartan vs Captopril)</td>
<td>3152</td>
<td>966</td>
<td>31</td>
</tr>
<tr>
<td>HEEAL [73] (Losartan vs Lisinopril)</td>
<td>3846</td>
<td>1155</td>
<td>29.5</td>
</tr>
<tr>
<td>VALIANT [74] (Valsartan)</td>
<td>14703</td>
<td>4570</td>
<td>31.1</td>
</tr>
<tr>
<td>OPTIMAAL [75] (Losartan vs Captopril)</td>
<td>20573</td>
<td>5925</td>
<td>28.8</td>
</tr>
<tr>
<td>SHIFT [76] (Ivabradine)</td>
<td>6558</td>
<td>1171</td>
<td>17</td>
</tr>
<tr>
<td>BEAUTIFUL [77] (Ivabradine)</td>
<td>10917</td>
<td>1870</td>
<td>17</td>
</tr>
<tr>
<td>MADIT II [78] (ICD)</td>
<td>720</td>
<td>192</td>
<td>26</td>
</tr>
<tr>
<td>SCD-HeFT [79] (ICD)</td>
<td>2521</td>
<td>588</td>
<td>23</td>
</tr>
<tr>
<td>COMPANION [80] (CRT)</td>
<td>1520</td>
<td>493</td>
<td>32</td>
</tr>
<tr>
<td>CARE HF [81] (CRT)</td>
<td>813</td>
<td>215</td>
<td>26</td>
</tr>
</tbody>
</table>

Women comprise only 6-38% of HF trial participants (because most trials are HFrEF)

© The Author(s) 2013. Published by Science and Education Publishing.
Historical Policy Actions

- Clinical studies and trials must include both men and women when the condition being studied affects both sexes (NIH Healy)
- Women’s Health Initiative (WHI) (Healy)
- Women’s Health Centers of Excellence (WH CoE) – 20 centers funded (Clinton)
- WH CoE centers defunded (GW Bush)
- National Institute of Minority Health, and Precision Medicine (but no plans for a Women’s or Gender Institute) (Obama)
- Basic science studies must include male and female cells, animals when the condition being studied affects both sexes (NIH Collins)
Status Quo: Male animals used to study female disease

Gender gap. The percentage of women in the total population presenting with a disease (purple; see ref. 1) outstrips the percentage of females in rat and mouse models of that disease (green; data from Web of Science). Only studies with ‘female’ or ‘male’ as keywords were captured, so the chart underestimates male bias relative to a survey of individual articles by field.
Female cells and animals are important for drug and device development

- **Sex-specific response to therapy**
  - Pharmacokinetics:
    - GFR in women is 10% below those of men after correction for BMI; increased difference with age (40%)
    - Cytochrom P450 system is sex-specific
  - Pharmacodynamics:
    - Digitalis; ACEI, antiarrhythmic drugs, anticoagulants
    - SSRI (Selective Serotonin re-uptake inhibitors), ambien
  - Sex-specific adverse effects: effects 15-17% higher in women
  - 7/10 medications withdrawn by the FDA are due to unanticipated adverse events in women

Sex and Gender Differences in Pharmacology, Editors: Regitz-Zagrosek, Vera (Ed.)
Monet or Manet?

Okay maybe Monet and Manet are kind of similar. They use the same kind of brushstrokes, use a mix of en plein air and alla prime, and both love color. But the subjects are usually different and Manet is more realistic. But we won’t forgive anyone who confuses who made what masterpiece.

WHAT CAN THIS TEACH US ABOUT CVD SEX AND GENDER DIFFERENCES?
Conclusions and Clinical Pearls

Female-pattern Ischemic Heart Disease: Monet vs Manet
(or why women have more adverse IHD outcomes)

Policy and our future
a. Science – advocacy, philanthropy
b. Policy – research, publication, guidelines
c. Education – disparities, technology