Cardiovascular Disease Disparities and Prevention in Women

or

How Gender Bias in Cardiovascular Disease Impacts Women’s Lives and What We Can Do About It

The RightCare Initiative, UC Berkeley Healthcare Education and Outcome Monitoring Program, California
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C. Noel Bairey Merz MD
Medical Director and
Women’s Guild Endowed Chair
Barbra Streisand Women’s Heart Center
Cedars-Sinai Heart Institute
Bairey Merz

DISCLOSURE INFORMATION
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Stocks: None
CVD Disparities and Prevention in Women

1. An epidemic of death in women
2. Gender and secondary prevention
3. Gender and primary prevention
4. Policy and our future
Following a heart attack, women age 50 and younger are:

a. More likely to die than men of the same age

b. Less likely to die than men of the same age

c. Equally likely to die than men of the same age
New female majority
Yentl and Yentl Syndrome

1984-1996: 12 years to recognize /take action

WISE NHLBI AHA Begin
The Yentl Syndrome  1991
Sex and Myocardial Infarction (MI) Mortality: Does Age Explain the Disparity?

Largest Mortality Gaps are Young Women

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Women Hospital Mortality (%)</th>
<th>Men Hospital Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>50-54</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>55-59</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>60-64</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>70-74</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>75-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
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<tr>
<td>85-89</td>
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</tbody>
</table>

Paradox: Women have a two-fold increase in “normal” Coronary arteries in the setting of ACS, NSTEMI and STEMI

| Table. Prevalence of “Normal” and Nonobstructive Coronary Arteries in Women Compared With Men |
|-----------------------------------------|----------------------------------|------------------|
|                                        | No./Total (%)                    |                  |
|                                        | Women                            | Men              | P Value |
| Acute coronary syndrome                |                                  |                  |
| GUSTO²                                 | 343/1768 (19.4)                  | 394/4638 (8.4)   | <.001   |
| TIMI 18³                              | 95/555 (17)                      | 99/1091 (9)      | <.001   |
| Unstable angina²                       | 252/826 (30.5)                   | 220/1580 (13.9)  | <.001   |
| TIMI IIIa⁶                             | 30/113 (26.5)                    | 27/278 (8.3)     | <.001   |
| MI without ST-segment elevation²      | 41/450 (9.1)                     | 55/1299 (4.2)    | .001    |
| MI with ST-segment elevation²         | 50/492 (10.2)                    | 119/1759 (6.8)   | .02     |

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.
More women die

More men receive treatment

Rx: ASA, BB, ACE, STATIN

Death/MI Followup
Summary: An Epidemic of Death in Women

1. There is a significant adverse 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
CVD Disparities and Prevention in Women

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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

Proportional Effects of Treatment Strategies on Mortality

AMI Treatment: women and men have similar risk benefit

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Blocker</td>
<td></td>
<td></td>
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<tr>
<td>Fibrinolytics</td>
<td></td>
<td></td>
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<tr>
<td>Streptokinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tPA vs. SK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR (95% CI)
Women equally likely to receive guideline high intensity but less likely to receive any statin post AMI.

Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women

Vaccarino V, et al
CIRCULATIONAHA.115.015293 Published online before print August 24, 2015, doi: 10.1161/CIRCULATIONAHA.115.015293
Adverse Trends in Ischemic Heart Disease Mortality among Young New Yorkers, Particularly Young Black Women
https://doi.org/10.1371/journal.pone.0149015

Death rates actually rising in non-white young women
Figure  Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.
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.
Summary: Gender and Secondary Prevention

1. AMI guidelines therapy works equally well in women and men
2. Application of AMI guidelines preferentially saves women’s lives
3. Can we routinely deploy guidelines to save women’s lives?
CVD Disparities and Prevention in Women

1. An epidemic of death in women
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4. Policy and our future
The Number Needed to Treat (NNT) magnitude for primary and secondary prevention of CVD for statin therapy is:

a. Similar for women and men

b. Higher for women than men

c. Lower for women than men
Coronary Heart Disease Mortality Among Young Adults in the US: 1980-2002 (Ford et al JACC 2007;50:2128)

- Included women and men aged 35 and older using ICD-9 codes in US Census data
- Mortality from CHD fell 52% in men and 49% in women
- Improved mortality each decade from 1980s, 1990s until the 2000s
- Age analysis demonstrates:
  - Leveling off of mortality decline in men 35-54 yrs in the 2000s
  - Actual *increase* in mortality in women 35-54 yrs, and specifically among women 35-44 yrs (p<0.05)

Results are consistent with a UK study (O’Flahrty et al Heart 2007:10:1136).

Concomitant with increased use of thrombolysis, PCI, statins and antithrombotics (ASA), yet adverse nutrition, physical activity, obesity and smoking trends.
Figure 1. Mean serum total cholesterol levels of adults aged 20 years and older by age and sex, United States, 1999–2006.

Meta-analysis of Exclusively Primary Prevention Statin Trials in Women

13,154 Women, 240 CVD events

AFCAPS/TexCAPS
- 1998
- RR: 0.67, 95% CI: 0.34-1.31
- Placebo: 21/498, Statin: 14/499

MEGA
- 2006
- RR: 0.73, 95% CI: 0.49-1.10
- Placebo: 56/271, Statin: 40/263

JUPITER
- 2008
- RR: 0.54, 95% CI: 0.37-0.80
- Placebo: 70/337, Statin: 39/342

ALL
- P for heterogeneity: 0.56
- RR: 0.63, 95% CI: 0.49-0.82
- Placebo: 21/498 + 56/271 + 70/337 = 147, Statin: 14/499 + 40/263 + 39/342 = 93

Mora S et al Circulation 2010; 1069
## JUPITER

### Primary Trial Endpoint: Number Needed to Treat (5-years)

<table>
<thead>
<tr>
<th></th>
<th>Rosuva</th>
<th>Placebo</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (Rate)</td>
<td>No. (Rate)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>39 (0.56)</td>
<td>70 (1.04)</td>
<td>36</td>
</tr>
<tr>
<td>Men</td>
<td>103 (0.88)</td>
<td>181 (1.54)</td>
<td>22</td>
</tr>
<tr>
<td>All</td>
<td>142 (0.77)</td>
<td>251 (1.36)</td>
<td>25</td>
</tr>
</tbody>
</table>

* Calculated based on the method of Altman and Andersen

Mora S et al Circulation 2010; 1069
The Intersection of Racial and Ethnic Disparities in Risk Factors for CVD

**Figure 2**
Relative Risk of Cardiovascular Events in Men and Women With Diabetes

**Table 1**
Disparities in Outcomes Between Blacks and Whites With Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Blacks</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization rate</td>
<td>26.5 %</td>
<td>16.1 %</td>
</tr>
<tr>
<td>Well-controlled glycemia</td>
<td>37.6 %</td>
<td>44.0 %</td>
</tr>
<tr>
<td>Well-controlled cholesterol</td>
<td>39.5 %</td>
<td>46.8 %</td>
</tr>
<tr>
<td>Well-controlled blood pressure</td>
<td>29.0 %</td>
<td>35.4 %</td>
</tr>
</tbody>
</table>

Sex and Gender Disparities – The VIRGO Registry

- The VIRGO registry matched young (<50 yrs) AMI women to age-matched AMI men (2:1)
- VIRGO paper identifies that women compared to men prior to AMI are:
  - More DM (by Rx of DM meds)
  - Less dyslipidemic (by Rx of statin)
  - More overweight (by physician advisement to “lose weight”), but less overweight!
- VIRGO editorial contrasts sex and gender differences:
  - DM is a more potent AMI RF for women – why are guidelines of statin Rx not followed?
  - Overweight/obesity are not AMI risk factors – why are women “objectified” and given non-evidenced based guidelines therapy to “lose weight”?

Difference between men and women
Almost 400,000 CVD deaths in US Women (2016)

Summary:
- CVD in women remains largely invisible in women and among physicians.
- Weight and breast health rank higher than CVD in women by PCPs.
- Social stigma particularly regarding body weight is a barrier to women not discussing heart health.
- Knowledge gaps for diabetes, autoimmune, pregnancy, early menopause and menstrual irreg.

Campaigns are needed to:
- Make CVD “real” to US women
- De-stigmatize CVD risk
- Counter stereotypes with validated CVD risk assessments.
- Invest in women’s CVD research
- Physician education and guideline use

Summary:
- CVD is not a physician priority for female patients.
- Physicians report limited knowledge and training in assessing women’s CVD risk.
- Physicians report low use of guidelines CVD risk assessment in women.
- A majority support a national action campaign and improved physician education.
A tsunami of chronic health conditions as a result of the SARS-CoV-2 pandemic, especially cardiometabolic disease, will produce an enormous wave of death and disability, particularly in women, that demands immediate, comprehensive strategies.

The COVID-19 pandemic has magnified societal and health care disparities; millions of people lost jobs, particularly women, minority and rural populations; numerous industries and small businesses have been financially decimated; and every aspect of scientific research and medicine has been altered -- education, research and clinical care.
This difference between men and women was the most dramatic in the United States; women from the US were 19.02% more likely to gain weight than men.
A Larger Share of Women Have Gone Without Health Care Services During the Pandemic, Particularly Women in Fair or Poor Health

Since March 1, 2020, have you experienced any of the following because of the COVID-19 pandemic, or not?

<table>
<thead>
<tr>
<th>Service</th>
<th>Men Overall</th>
<th>Women Overall</th>
<th>Women in Fair/Poor Health</th>
<th>Women in Excellent/Very good/Good Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipped preventive health services, such as a yearly check-up or routine test</td>
<td>26%</td>
<td>38%</td>
<td>46%</td>
<td>36%</td>
</tr>
<tr>
<td>Skipped a recommended medical test or treatment</td>
<td>15%</td>
<td>23%</td>
<td>32%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Summary: Gender and Primary Prevention

1. Primary prevention works equally in women and men relative to risk.

2. Calculate ASCVD risk scores for women and men

3. Act on scores not on intuition or physical appearance – avoid the gender disparity gap!

4. Prepare for a post-COVID CVD epidemic in women
CVD Disparities and Prevention in Women

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Women with diabetes or similarly elevated CVD risk are:

a. More likely to be treated with statin than men of the same age

b. Less likely to be treated with a statin than men of the same age

c. Equally likely to be treated with a statin than men of the same age
Clinical Practice Guidelines

- 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

Years

1997-2007

Source: NCHS and NHLBI
Source: NCHS and NHLBI
Trends in Cardiovascular Disease (CVD) Mortality Among Women & Men – 1979-2018

Sex Differences in Presentation, Diagnostic Evaluation, & Management of Women with Ischemic Heart Disease

30% CVD Mortality Decline for Women

Increased Awareness, Focused Clinical Research, & Application of Guideline-Directed Care

However, Declines for Women Are Less Particularly for Younger Women of Diverse Race & Ethnicity

CVD Mortality Trends for Women & Men

Research focus on CVD in women

Women comprise half of CVD but <30% studied and research funded
CVD Disparities and Prevention in Women

Policy and our future:
- Investigate – increase research funding
- Educate – sex and gender in curriculum
- Translate – guidelines and guidelines care
- Advocate – health policy for all
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.
Current Status: 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).

VA CART data now demonstrate that half of men undergoing indicated angiography have nonobstructive CAD.

Source: Anderson Circulation 2007;115:823-826.
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\(^2\). The same is true for CPK MB\(^{16}\)

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\(^{26}\)


Undiagnosed MIs are untreated MIs - 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!

for women

and men!
Table 1. Percentage of women’s population in HF trials

<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)
Central Illustration: Achieving Equity in Quality of Care for Women


https://doi.org/10.1016/j.jacc.2017.05.051
Women’s Cardiovascular Disease – remains a “subpopulation” despite a majority of female CVD morbidity and mortality

• Preliminary data are key to obtaining extra-mural funding, especially for young investigators

• NIH budget spent for the category of “Women’s Health” in the National Heart, Lung and Blood Institute was $477,325,940 on women’s CVD research, which is less than half the $1,156,653,584 budget spent on women’s cancer research in the National Cancer Institute

Following a heart attack, women age 50 and younger are:

a. More likely to die than men of the same age
b. Less likely to die than men of the same age
c. Equally likely to die than men of the same age
Younger women with diabetes or similarly elevated CVD risk are:

a. More likely to be treated with statin than men of the same age

b. Less likely to be treated with a statin than men of the same age

c. Equally likely to be treated with a statin than men of the same age
The Number Needed to Treat (NNT) magnitude for primary and secondary prevention of CVD for statin therapy is:

a. Similar for women and men

b. Higher for women than men

c. Lower for women than men
Thank You

merz@cshs.org

https://www.cedars-sinai.org/programs/heart/clinical/womens-heart.html