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 Be There Project, San Diego, California
Heart Health Summit
June 3, 2019

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Women’s Guild Endowed Chair
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Cedars-Sinai Heart Institute
Bairey Merz

DISCLOSURE INFORMATION
The following relationships exist related to this presentation (*paid to Cedars-Sinai Medical Center):

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Consulting*: Medscape, NIH, iRhythm

Honorarium*: Pri-Med

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

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

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute coronary syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GUSTO(^2)</td>
<td>343/1768 (19.4)</td>
<td>394/4638 (8.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIMI 18(^3)</td>
<td>95/555 (17)</td>
<td>99/1091 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Unstable angina(^2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI IIIa(^6)</td>
<td>30/113 (26.5)</td>
<td>27/278 (8.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>MI without ST-segment elevation(^2)</strong></td>
<td>41/450 (9.1)</td>
<td>55/1299 (4.2)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>MI with ST-segment elevation(^2)</strong></td>
<td>50/492 (10.2)</td>
<td>119/1759 (6.8)</td>
<td>.02</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.
More men receive treatment

More women die

Angina/ACS

Coronary Angiography

Obstructive CAD
Male-pattern

Microvascular CAD
Female-pattern

RX: ASA, BB, ACE, STATIN

DEATH/MI FOLLOWUP

Bairey Merz EHJ 2011
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

AMI Treatment: women and men have similar risk benefit
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
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.

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.

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?
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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
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**

<table>
<thead>
<tr>
<th>Year</th>
<th>AFCAPS/TexCAPS</th>
<th>MEGA</th>
<th>JUPITER</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>Placebo</td>
<td>Statin</td>
</tr>
<tr>
<td>1998</td>
<td>0.67</td>
<td>(0.34-1.31)</td>
<td>21/498</td>
<td>14/499</td>
</tr>
<tr>
<td>2006</td>
<td>0.73</td>
<td>(0.49-1.10)</td>
<td>56/271</td>
<td>40/263</td>
</tr>
<tr>
<td>2008</td>
<td>0.54</td>
<td>(0.37-0.80)</td>
<td>70/337</td>
<td>39/342</td>
</tr>
</tbody>
</table>

**RR for heterogeneity 0.56**

**Favors Statin:**

- **Placebo:** 0.67 (0.34-1.31)
- **Statin:** 0.54 (0.37-0.80)

**Favors Placebo:**

- **Placebo:** 0.73 (0.49-1.10)
- **Statin:** 0.54 (0.37-0.80)

**P for heterogeneity 0.56**

**0.63 (0.49-0.82) P<0.001**

Mora S et al Circulation 2010; 1069
JUPITER
Primary Trial Endpoint: Number Needed to Treat (5-years)

Mora S et al Circulation 2010; 1069

<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
The Effect of Race and Sex on Physicians' Recommendations for Treatment

Despite full risk and history adjustment:

- Men are twice as likely as women to be treated than women
- Caucasians are twice as likely to be treated than non-caucasians

**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
CENTRAL ILLUSTRATION

Women & Physician Knowledge, Attitudes and Beliefs Regarding Heart Disease in Women: Women’s Heart Alliance

Almost 400,000 CVD deaths in US Women (2016)

Community Women (n=1,101)

45% unaware, 89% do not know a women with CVD
75% with personal connection prioritize heart health
40% routine care includes a heart risk check
63% defer doctor visit; 45% to “lose weight”

Barriers

Women and Physicians Agree

Opportunities

PCP and Cardiology Physicians (n=200)

39% prioritize CVD for women after breast and weight
22% PCs and 42% cardiologist well-prepared
44% PCPs and 53% cardiologist use CVD risk assessment
Over 82% support a physician and guideline campaign

Barriers

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 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.

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.
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!
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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
Clinical Practice Guidelines

- This slide set was adapted from the following 2004-6 ACC/AHA guidelines:
  - 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 and www.americanheart.org

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

Years

1997-2007

Source: NCHS and NHLBI
Deaths in Thousands

<table>
<thead>
<tr>
<th>Years</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td></td>
<td></td>
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<tr>
<td>90</td>
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<td></td>
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<tr>
<td>04</td>
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</tbody>
</table>

Source: NCHS and NHLBI

NHLBI Heart Truth/AHA, WISE and Guideline Campaigns

1997-2007: 43%
Is this optimal for women?
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
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.
Changes in Myocardial Infarction Incidence

RESULTS

46,086 hospitalized predominantly male patients with myocardial infarction over 18,691,131 person-years

STEMI-related large plaque ruptures are going away

Due to outpatient meds

Alan S. Go, MD
Kaiser Division of Research
University of California, San Francisco
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.

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

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

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] (Lavbradine)</td>
<td>6558</td>
<td>1171</td>
<td>17</td>
</tr>
<tr>
<td>BEAUTIFUL [77] (Lavbradine)</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)
Status Quo: Male animals used to study female disease

1985 “Task Force” calls for an expansion of research on women’s health
1986 NIH “urges” the inclusion of women in NIH clinical research
1987 NIH “encourages” the inclusion of minorities in NIH clinical research
1990 Congressional Caucus for Women’s Issues action lead to 1990 establishment of ORWH
1993 NIH Reorganization Act established ORWH by statute and require women and minorities in phase III clinical trials
2006 NIH Reform Act calls for a reorganization of the OD and ORWH

Any time there have been major advances in women’s health, it has been due to very purposeful actions and “not by chance.”

2014 Members of Congress call for GAO report on inclusion of women in clinical trials
2015 NIH agrees to include women, female animals and cells in adequate numbers. GAO recommends NIH report more detailed data on women’s enrollment and report on sex differences. Gao criticizes federal agencies for lack of enforcement of Title IX. FDA Drug Trials Snapshots website established.
2016 Congress proposes bill to require NIH to follow GAO recommendations on sex differences data reporting
NEW GRANT GUIDELINES
what you need to know

WHY UPDATE THE GUIDELINES?
The updates focus on four areas deemed important for enhancing rigor and transparency:

1. PREMISE
   The scientific premise forming the basis of the proposed research

2. DESIGN
   Rigorous experimental design for robust and unbiased results

3. VARIABLES
   Consideration of relevant biological variables

4. AUTHENTICATION
   Authentication of key biological and/or chemical resources

Send inquiries to reproducibility@nih.gov
See also NIH Notice NOT-OD-16-011

NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES
From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These include, but are not limited to:
- CELL LINES
- ANTIBODIES
- SPECIALTY CHEMICALS
- OTHER BIOLOGICS

NEW REVIEWER GUIDELINES
Here are the additional criteria the reviewers will be asked to use:

⇒ Is there a strong scientific premise for the project?
⇒ Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
⇒ Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?

Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.

[Red circled annotations on the diagram]

Reviewers will also be asked to comment on that new attachment (see Update 2)!
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