Sex Differences in CVD: Drug and Device Approval and Use in Controversies and Advancement in the Treatment of Cardiovascular Disease
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Presenter Disclosure Information

Bairey Merz

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

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

Consulting*: Medscape, Gilead, NIH, Sanofi

Honorarium*: Practice Point, Pri-Med, VBWG

Stocks: None

What happened to explain this?

Is this optimal for women?

Darlensh Mozaffarian et al. Circulation. 2016;133:e38–e360

American Heart Association.
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.
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 Revitalization Act established ORWH constate and required women and minorities in phase III clinical trials

2006 NIH Reform Act calls for a reorganization of the OD and ORWH

2014 Members of Congress call to 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

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


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

Undiagnosed MIs are untreated MIs with a 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>EMPHASIS [67] (Eplerenone)</td>
<td>2737</td>
<td>610</td>
<td>22</td>
</tr>
<tr>
<td>RALES [68] (Aldactone)</td>
<td>1663</td>
<td>446</td>
<td>27</td>
</tr>
<tr>
<td>EPESUS [69] (Eplerenone)</td>
<td>6632</td>
<td>1918</td>
<td>29</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)</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)

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: 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.)
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

WHAT ARE THE UPDATES?

1. UPDATES TO RESEARCH STRATEGY GUIDANCE
   The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:

   The new research strategy guidelines require that you:
   • State the strengths and weaknesses of published research or preliminary data crucial to the support of your application
   • Describe how your experimental design and methods will achieve robust and unbiased results
   • Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

   Introduction to resubmission and revision applications
   Specific aims
   Research strategy
   Commercialization plan
   Biographical sketch

2. 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

   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.

   • DO NOT put experimental methods or preliminary data in this section
   • DO focus on authentication and validation of key resources

3. 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?

   Reviewers will also be asked to comment on that new attachment (see Update 2)!
Sex Differences in CVD: Drug and Device Approval and Use

1. Example of Sex Differences of Clinical Relevance to Women and Men: CRT – Viviany Taqueti MD, MPH Brigham and Women’s Hospital

2. Considerations of Sex Differences in FDA Device Approval - Terri L Cornelison MD, PhD, FDA

3. Overview of FDA Review, Approval, Post-approval Monitoring and the FDA Snapshot Website – Majorie Jenkins MD, MEd, FDA Office of Women’s Health

4. Panel Q and A