ACC-Talk
The State of Women and CVD: Where do we go from here?

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

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Honorarium*: Practice Point, Pri-Med, VBWG

Stocks: None
Monet or Manet?
Monet or Manet?
The Yentl Syndrome  1991
New female majority
Yentl and Yentl Syndrome

1984-1996: 12 years to recognize / take action
Monet vs Manet?

More men receive treatment

More women die

Bairey Merz EHJ 2011

Obstructive CAD
Male-pattern

Microvascular CAD
Female-pattern

Rx: ASA, BB, ACE, STATIN

Death/MI Followup
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
Years
Deaths in Thousands
Males Females
1997-2007
Source: NCHS and NHLBI
Deaths in Thousands

Males
Females

NHLBI Heart Truth/AHA, WISE and Guideline Campaigns

1997-2007: 43% ↓

Source: NCHS and NHLBI

Is this optimal for women?
Underrepresentation of Women in Cardiovascular Clinical Trials

Remains low compared to disease prevalence and death rates - Perseverates knowledge gaps which adversely impact women

Melloni, et al, Circ Cardiovasc Qual Outcomes 2010
Despite published sex differences, cardiac troponin assays lack sex specific reference value reporting, even for widely used commercial assays that indicate 99\textsuperscript{th} percentile cutoffs or ranges 1.2-2.4 fold higher in males than females\textsuperscript{22}. The same is true for CPK-MB\textsuperscript{16}

- 20\% of women are not diagnosed for AMI using the standard male sex-specific threshold. Reduces female enrollment in AMI trials.
- Women that meet standard AMI troponin criteria have suffered a greater degree of myocardial damage\textsuperscript{26}

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>COMET (Carvedilol vs Metoprolol)</td>
<td>1511</td>
<td>94</td>
<td>6</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>EPHEUS [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 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 (most trials are HFrEF and most women are HFpEF)


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Risk Factor Studies - Sex Differences in Diagnosis Coding

- The VIRGO is a large multi-center observational registry of young (<50 yrs) AMI matched to young men (2:1) to understand the greater mortality in women vs men.
- **JACC manuscript** identifies that women compared to men prior to AMI are:
  - Less dyslipidemic (by Rx of statin)
  - More overweight (by physician Rx to “lose weight”)
  - But less overweight when measured!
- **JACC editorial** discusses and contrasts sex gender differences (young women are higher AMI risk but more “objectified” in society and told to lose weight rather than treat lipids)
- Young women are less likely to qualify for RF trials.

Krumholtz manuscript and Bairey Merz editorial JACC 2016
The State of Women and CVD: Where do we go from here?

Female-pattern CVD - Monet vs Manet (or why women have more adverse IHD outcomes)

1. MI with No Obstructive CAD (MINOCA)

2. Heart Failure with Preserved Ejection Fraction (HFpEF)

3. Adverse pregnancy outcomes (APOs)
MI with no obstructive CAD (MINOCA): Women have a two-fold increase in “normal” coronary arteries in the setting of ACS, NSTEMI and STEMI

<table>
<thead>
<tr>
<th>Acute coronary syndrome</th>
<th>Women</th>
<th>Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO²</td>
<td>343/1768 (19.4)</td>
<td>394/4638 (8.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIMI 18³</td>
<td>95/555 (17)</td>
<td>99/1091 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unstable angina²</td>
<td>252/826 (30.5)</td>
<td>220/1580 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIMI IIla⁶</td>
<td>30/113 (26.5)</td>
<td>27/278 (8.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MI without ST-segment elevation²</td>
<td>41/450 (9.1)</td>
<td>55/1299 (4.2)</td>
<td>.001</td>
</tr>
<tr>
<td>MI with ST-segment elevation²</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.
Plaque rupture/ulceration located in a normal area of the vessel in 45% of cases

Reynolds HR et al Circ 2011
Low use of meds and elevated 1 year MI rate in angiographic non-obstructive CAD

<table>
<thead>
<tr>
<th></th>
<th>Normal Coronaries</th>
<th>1V Non-Obstructive CAD</th>
<th>2V Non-Obstructive CAD</th>
<th>3V Non-Obstructive CAD</th>
<th>1V Obstructive CAD</th>
<th>2V Obstructive CAD</th>
<th>3V/LM Obstructive CAD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>100 (1.2%)</td>
<td>119 (2.3%)</td>
<td>73 (2.4%)</td>
<td>40 (2.9%)</td>
<td>618 (7.2%)</td>
<td>443 (8.5%)</td>
<td>545 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Stable Angina</td>
<td>281 (3.3%)</td>
<td>188 (3.6%)</td>
<td>101 (3.3%)</td>
<td>60 (4.4%)</td>
<td>391 (4.6%)</td>
<td>254 (4.9%)</td>
<td>232 (3.9%)</td>
<td></td>
</tr>
</tbody>
</table>

**Discharge Medications**

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>Beta-blockers</th>
<th>ACE/ARB</th>
<th>Thienopyridines</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>3,758 (44.8%)</td>
<td>3,142 (37.4%)</td>
<td>2,848 (33.9%)</td>
<td>109 (1.3%)</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>3,129 (60.1%)</td>
<td>2,506 (48.2%)</td>
<td>2,341 (45.0%)</td>
<td>258 (5.0%)</td>
</tr>
<tr>
<td></td>
<td>1,920 (63.5%)</td>
<td>1,591 (52.6%)</td>
<td>1,399 (46.3%)</td>
<td>196 (6.5%)</td>
</tr>
<tr>
<td></td>
<td>885 (64.4%)</td>
<td>733 (53.3%)</td>
<td>694 (50.5%)</td>
<td>125 (9.1%)</td>
</tr>
<tr>
<td></td>
<td>6,395 (74.9%)</td>
<td>5,831 (68.3%)</td>
<td>4,414 (51.7%)</td>
<td>4,283 (50.2%)</td>
</tr>
<tr>
<td></td>
<td>3,893 (75.1%)</td>
<td>3,745 (72.3%)</td>
<td>2,747 (53.0%)</td>
<td>2,502 (48.3%)</td>
</tr>
<tr>
<td></td>
<td>4,359 (73.1%)</td>
<td>4,440 (74.4%)</td>
<td>2,928 (49.1%)</td>
<td>1,773 (29.7%)</td>
</tr>
</tbody>
</table>

**HR**

Mild Non-Obstructive 3.26 (1.45, 7.35)
Mod Non-Obstructive 3.91 (1.86, 8.18)
1V Obstructive 9.30 (4.37, 19.81)
2V Obstructive 17.52 (8.51, 36.06)
3V/LM Obstructive 20.28 (10.34, 39.77)
Conclusions - MINOCA

- MINOCA occurs dominantly in women
- MINOCA is not a false positive MI!
- Additional diagnostics should be used (IVUS, MRI, OCT, CTA)
- Differential can include plaque rupture, plaque erosion, coronary dissection, Takotsubo, vasospasm, pro-thrombotic disorder, myocarditis)
- Current US guidelines do not address MINOCA
- DAPT and high intensity statin therapy makes sense
- MINOCA research needed!
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3. Adverse pregnancy outcomes (APOs)
Distribution of EF Among Men and Women With HF: Most HF in Women is HFpEF

Evidence-based Treatment

HFrEF
- ACE/ARB
- Beta Blockers
- Aldo antagonists
- AICD
- CRT

HFpEF
- Diuretics
- Verapamil
- Digoxin
- Beta blockers
- Hydralazine/ISDN
- Ace inhibitors/ ARBs
- Aldo antagonists
- PD5 inhibitors
- Nitrates
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,
Conclusions - HFpEF

- HFpEF has become the dominant form of HF and accounts for the majority of HF hospitalization.
- HFpEF occurs dominantly in older women.
- HFrEF is well understood and effective treatment available in stark contrast to HFpEF which is NOT UNDERSTOOD and a TREATMENT DESERT!
- “Custodial” HFpEF management involves diuretics and BBs and patients remain limited.
- Phenotype characterization, mechanistic factors, and intervention trials (stem cells, anti-fibrosis, anti-inflammatory) for HFpEF needed.
- Would mandatory female-only studies help?
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2. Heart Failure with Preserved Ejection Fraction (HFpEF)

3. Adverse pregnancy outcomes (APOs)
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 Pregnancy Outcomes (APOs) With Increased CVD Risk

- Gestational Diabetes
- Gestational Hypertension
- Preeclampsia/eclampsia
- Preterm delivery
- Fetal growth restriction
- Macrosomia

- >80% of women bear at least 1 child
- ~30% of women have adverse pregnancy outcomes
- ~25% of women carry a predictor of their future CVD risk

Incidence of hypertension up to 42 years after 1st pregnancy by hypertensive disorder in pregnancy, Nurses' Health Study II

Proportion with Hypertension

Years Since First Pregnancy

- Gestational Hypertension (3.0%)
- Preeclampsia (6.4%)
- Normotension (90.6%)

5% are hypertensive at 5 year followup

Preliminary data, not for citation
A true story

- 48 year old internist at her family’s Thanksgiving
- 46 year old brother states he has hypertension
- She says “You can’t have hypertension!” and takes his blood pressure – he has hypertension
- She checks her own blood pressure – she has hypertension
- She looks in her OB-GYN medical records – she had gestational hypertension with both pregnancies (37 and 39 yrs) and has been hypertensive (140/90) in her OB-GYN annual checkups for years without notice or action
Recognition of hypertension in medicine vs ob-gyn clinic
(Hypertension. 2011 Apr; 57(4): 717–722)

Medicine does better than OB-GYN for BP recognition and RX, but both are poor

p < .001 for all comparisons
Conclusions - APOs

- Current guidelines for blood pressure screening should be implemented in OB-GYN practice.
- Existing guidelines appear adequate to identify the 5% who will develop HTN in the first 5 years (but guidelines are not often followed!)
- Referral patterns vs embedding preventive providers (NP, PA) in OB-GYN practices to conduct CV health assessments and/or refer to primary care for ongoing risk assessment and management.
- Research regarding additive value of incorporating APOs into CV risk scores and the utility of early preventive care is ongoing.
- Will specific Pregnancy CVD guidelines help?
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?
The State of Women and CVD:
Where do we go from here?
Female-pattern Ischemic Heart Disease: Monet vs Manet
(or why women have more adverse IHD outcomes)

Policy and our future

a. Science – advocacy, social justice in funding
b. Policy – research equality, publication policy, sex and gender in guidelines
c. Education – disparities, youth and technology opportunity