ACC Latin America Conference 2017
MEXICO CITY
JUNE 22 - 24, 2017
GLOBAL EXPERTS, LOCAL LEARNING
Women’s Heart Health: Holistic Approaches Throughout the Lifetime - Key Differences in Heart Failure in Women

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
Presenter Disclosure Information

Key Differences in Heart Failure in Women (Bairey Merz)

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation (*paid to CSMC):
Grant support*: NHLBI, FAMRI, SWHR, Gilead, NIH-CTSI
Consulting*: Abbott-Diagnostics, Sanofi
Honorarium*: Gilead, Pri-Med
Stocks: None
55 year old woman with history of hypertension, angina, abnormal exercise treadmill test, invasive coronary angiogram with “normal” coronary arteries, abnormal microvascular blood flow to acetylcholine treated with carvedilol, lisinopril, eplerenone, pravastatin and aspirin. At 10 year followup, she presents to the emergency department for heart failure, after her antihypertensive medications were temporarily discontinued by her surgeon post-shoulder surgery.

EXAM: BP 184/85, lower extremity edema.
LABS: BNP 343 mg/dL. ECHO: LVEF 68%
She was treated medically with lasix, lisinopril, eplerenone, carvedilol, pravastatin, and aspirin. Her BP, SOB improved and BNP fell to 40 mg/dL.

How should she be chronically treated?

1. Current treatment is fine
2. Intensify hypertension therapy
3. Start digoxin
Key Differences in Heart Failure in Women

1. Prevalence – Heart Failure in Women
2. Diastolic Heart Failure (Heart Failure with Preserved Ejection Fraction – HFpEF)
3. Management and Knowledge Gaps
Heart Failure and Gender
Equal HF Prevalence but Higher Mortality in Women

Prevalence of and Mortality From Heart Failure by Gender

A

Prevalence

Percent of population

Men Women

-1 1 3 5 7 9 11

6.2 6.8 9.8 9.7

3.4 6.6

55–64 65–74 ≥75

B

Total Mortality

Men Women

89.9% 90.6%

8.7% 8.5%

Total × 10^3

Distribution of EF Among Men and Women With HF: Most HF in Women is HFP EF

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.
### HF Studies - Sex Differences in Heart Failure

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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total population</th>
<th>Female population</th>
<th>Percentage of females</th>
</tr>
</thead>
<tbody>
<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>


© The Author(s) 2013. Published by Science and Education Publishing.
Underrepresentation of Women in Cardiovascular Clinical Trials

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

Less ectopy?

Concentric LVH

Myocardial Insult

↓ LV performance

↑ Wall stress

 Activation of RAS and SNS

ACE/ARB, aldo blockade

Beta Blocker

Dig, diuretics

Eccentric hypertrophy, chamber dilatation

Is CMD ischemia a Mechanistic pathway for HFpEF?

Women

↓ Apoptosis and cell death

Later onset of cardiac decompensation

Men

↑ Apoptosis and cell death

Earlyonset of cardiac decompensation

Possible pathophysiologic mechanisms

LVH = left ventricular hypertrophy; RAS = renin-angiotensin system; SNS = sympathetic nervous system.

WISE Patients with and without documented ischemia have elevated MACE compared to asymptomatic Women Take Heart (WTH) with no ischemia by Stress Testing.

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
Scheme of the potential causes and consequences of coronary microvascular dysfunction – Ischemia, Diastolic Dysfunction and Takosubo Cardiomyopathy?

- Subendocardial or Epicardial Ischemia
- Diastolic Dysfunction
- Takosubo Cardiomyopathy

Coronary atherosclerosis

Risk Factor Conditions
- Hypertension, Dyslipidemia, Dysglycemia

Inflammatory and pro-oxidative stress

Accelerating Factors
- Early Menopause
- Obesity

Sympathetic nervous system activation, endothelial dysfunction, changes in vascular smooth muscle activation, spasm

Crea, Camici, Bairey Merz EHJ 12/13
55 year old woman with history of hypertension, angina, abnormal exercise treadmill test, invasive coronary angiogram with “normal” coronary arteries, abnormal microvascular blood flow to acetylcholine treated with carvedilol, lisinopril, eplerenone, pravastatin and aspirin. At 10 year followup, she presents to the emergency department for heart failure, after her antihypertensive medications were temporarily discontinued by her surgeon post-shoulder surgery. EXAM: BP 184/85, lower extremity edema. LABS: BNP 343 mg/dL. ECHO: LVEF 68%. She was treated medically with lasix, lisinopril, eplerenone, carvedilol, pravastatin, and aspirin. Her BP, SOB improved and BNP fell to 40 mg/DL.

How should she be chronically treated?

1. Current treatment is fine
2. Intensify hypertension therapy
3. Start digoxin
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?