Gender Based Differences and HF Therapies: Drugs, Devices and Surgery

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Vice President Canadian Heart Failure Society
Disclosures

Consulting/Advisory Board:
Amgen, Astra Zeneca, Boehringer Ingelheim, Medtronic, Novartis, Servier

Speaker:
Boehringer Ingelheim, Medtronic, Novartis, Servier, St. Jude Medical (Abbot)

Clinical Trials:
Amgen, Bayer, Boehringer Ingelheim, Medtronic, Merck, Novartis, Servier, Tenax

Research Grants:
Novartis

Educational Grants:
Servier
Audience Question

What’s your favorite hockey team?
Objectives

- Discuss what differences are involved in how women and men respond to treatments for heart failure
- Employ gender-specific strategies for medication, devices and surgical procedures for heart failure
Are Women More Likely to Get HF or Not?

- Within 6 years of acute MI,
  - 46% of women are disabled because of HF, as compared to a 22% rate of disability in men

- Framingham Heart Study (FHS) mostly white cohort:
  - Over the past 20 years the incidence of HF was rising faster in women than in men (9% vs 6%)

Nahid J. Geriatr Cardiol. 2011 Mar; 8(1): 15–23
Who Gets Heart Failure?

- Affects men and women equally
- Mortality risk between men and women is similar

What are the differences?

- Men with HF are more likely to have HFrEF and CAD

Nahid J. Geriatr Cardiol. 2011 Mar; 8(1): 15–23
Who Gets Heart Failure?

- Women with HF are more likely to be older with HFpEF and hypertension
- When women do develop coronary artery disease, they are more likely than men to also develop HF

“We found convergence of findings between prospective, retrospective and cross sectional analysis; demonstrating there is positive correlation between female gender and preserved LV function and non-ischemic etiologies”

Nahid J. Geriatr Cardiol. 2011 Mar; 8(1): 15–23
Who Gets Heart Failure?

- Survival among women with heart failure is better than for men with the disease. The reasons for this remain unclear.
- Women with heart failure are more likely to be sicker than men and have more hospital stays.
- They are also more likely to suffer from depression than men.

Other Phenotypical Differences for Females with HF

- Peripartum cardiomyopathy
- Takotsubo’s
- MI without epicardial coronary thrombosis
- Low flow Low gradient AS
- Differences in cutpoint for Tn?

Pacheco, Asgar, CJC, 34 (2018) 422-428
Humphries, Pilote, CJC, 34 (2018) 349-353
Implications for Gender Differences in HF

- Impacts risk factor screening and targeting gender-specific intervention
- Clinical guidelines should reflect on these gender-based data and provide needed evidence and recommendations regarding appropriate approach and management
- Researchers need to acknowledge the importance of balanced recruitment of both men and women in clinical trials
Clinical Trial Design
Enrollment in cardiovascular clinical trials

- NHLBI enrollment figures between 1965 – 1998:
  - Males 183 005
  - Females 215 796

- The overall enrollment of women (54%) exceeded the prevalence of CAD in women (49%) and increased over time (p.002)

- Excluded Women-only trials WHI and WHS women = 108 011 = 38%

(Harris, NEJM 343, 2000)
CAD

Hypertension

(Harris, NEJM 343, 2000)
Heart Failure

Arrhythmia

(Harris, NEJM 343, 2000)
Study Designs

- Representation of women is not sufficient
- Require large number of women to ensure study has statistical power to evaluate the effect of the intervention in each sex
- Underpowered trials can do great harm
- They can also result in inappropriate assumptions as to no benefit in women

(Buring, NEJM 343, 2000)
Blame it on an “epiphenomenon”

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1040</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1232</td>
<td></td>
</tr>
</tbody>
</table>

MADIT – II
Subgroup analysis
Back in the Day: Ace Inhibitor Trials

- SOLVD original publication (1991) did not specify sex based differences
- SAVE trial (1992):

Table 3. Effect of Captopril on Major Clinical End Points in Subgroups Defined by Characteristics Known to Have an Important Influence on Survival after Myocardial Infarction.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DEATH FROM ALL CAUSES</th>
<th>CARDIOVASCULAR DEATH AND MORBIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLACEBO</td>
<td>Captopril</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>54/365 (14.8)</td>
<td>52/375 (13.9)</td>
</tr>
<tr>
<td>56–64</td>
<td>77/352 (21.9)</td>
<td>69/356 (19.4)</td>
</tr>
<tr>
<td>&gt;64</td>
<td>144/399 (36.1)</td>
<td>107/384 (27.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>234/912 (25.7)</td>
<td>191/929 (20.6)</td>
</tr>
<tr>
<td>Female</td>
<td>41/204 (20.1)</td>
<td>37/186 (19.9)</td>
</tr>
</tbody>
</table>

Who Was in Charge of the SOLVD Trial?

- Executive Committee — Bertram Pitt (chairman), Jay N. Cohn, Clarence E. Davis, William B. Hood, Jeffrey Probstfield, and Salim Yusuf (project officer).

- Data and Safety Monitoring Board — Elliot Rapaport (chairman), Byron W. Brown, Lawrence S. Cohen, Max Halperin (deceased), Milton Packer, Leroy Walters, Rolf Gunnar, and William Friedewald.
Paradigm-HF: Sac-Val

Table 1. Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>63.8±11.5</td>
<td>63.8±11.3</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2763 (66.0)</td>
<td>2781 (66.0)</td>
</tr>
<tr>
<td>Black</td>
<td>213 (5.1)</td>
<td>215 (5.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>759 (18.1)</td>
<td>750 (17.8)</td>
</tr>
<tr>
<td>Other</td>
<td>452 (10.8)</td>
<td>466 (11.1)</td>
</tr>
</tbody>
</table>

McMurray *NEJM* 2014
Paradigm-HF: Sac-Val
Females Didn’t Cross the Line!!!!

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 no.</th>
<th>Enalapril no.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value for interaction</th>
<th>Hazard ratio (95% CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>2111</td>
<td>2168</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>≥65 yr</td>
<td>2076</td>
<td>2044</td>
<td>—</td>
<td>0.47</td>
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<td>0.70</td>
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<td>&lt;75 yr</td>
<td>3403</td>
<td>3433</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>784</td>
<td>779</td>
<td>—</td>
<td>0.32</td>
<td>—</td>
<td>0.62</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3308</td>
<td>3259</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>879</td>
<td>953</td>
<td>—</td>
<td>0.63</td>
<td>—</td>
<td>0.92</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2763</td>
<td>2781</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Black</td>
<td>213</td>
<td>215</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Asian</td>
<td>759</td>
<td>750</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Native American</td>
<td>84</td>
<td>88</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>368</td>
<td>378</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

McMurray *NEJM* 2014
SHIFT: Ivabradine

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.7 (11.2)</td>
<td>60.1 (11.5)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>2462 (76%)</td>
<td>2508 (77%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2879 (89%)</td>
<td>2892 (89%)</td>
</tr>
<tr>
<td>Asian</td>
<td>268 (8%)</td>
<td>264 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>94 (3%)</td>
<td>108 (3%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>541 (17%)</td>
<td>577 (18%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0 (5.1)</td>
<td>28.0 (5.0)</td>
</tr>
</tbody>
</table>

Swedberg K et al, Eur J Heart Fail, 2010, 12:75-81
SHIFT: Ivabradine
Females Didn’t Cross the Line!!

<table>
<thead>
<tr>
<th>Age</th>
<th>Ivabradine group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>407 (20.6%)</td>
<td>527 (25.6%)</td>
<td>0.76 (0.67:0.87)</td>
<td>p=0.099</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>386 (30.5%)</td>
<td>410 (33.9%)</td>
<td>0.89 (0.77:1.02)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Ivabradine group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>624 (25.4%)</td>
<td>725 (28.9%)</td>
<td>0.84 (0.76:0.94)</td>
<td>p=0.260</td>
</tr>
<tr>
<td>Female</td>
<td>169 (21.7%)</td>
<td>212 (28.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Swedberg K et al, Eur J Heart Fail, 2010, 12:75-81
HFpEF: PEP-CHF

Finally lots of females however a negative trial!!!

Cleland JG European Heart Journal (2006) 27, 2338–2345
GATAD1
Neurohumoral stimulation

SLC2A12
Glucose metabolism

PDE6B
Cyclic nucleotide metabolism

\[ \text{Differential gene expression in pathophysiology of heart failure} \]

\[ \text{Clinical phenotype} \]

Hypertension/valvular disease
Preserved
Following acute decompensation
Worse treated by male physicians
Better compliance
More easily affected
Better

Aetiology
Ischaemic coronary disease
Limited

LV-function
BNP levels more predictive
More thorough diagnostics

Diagnosis
Worse medication adherence
Less psychological problems

Management

Therapy

Quality of life

Outcome
Worse

KCNK1
Arrhythmogenesis

CD24
Autoimmunity

PLEKHA8
Cellular homeostasis

Age and Gender Distribution of Patients in Heart Failure Clinic
Male patients with CHF are more likely to receive evidence-based drug treatment than females.

This result was significant for prescription of ACE-Ils and beta-blockers.

Baumhäkel, Eur J Heart Fail, 2009, vol. 11 299-303
Baumhäkel, Eur J Heart Fail, 2009, vol. 11 299-303
1/11 Associate Editors is Female
7(±/-2)/111 Editors are Female
“Ignorance is Bliss”

- A HSF Survey reported that 60% of women polled regarded breast cancer as the leading cause of death among women in Canada while only 17% recognized heart disease as the major cause of mortality in Canada (CJC 17D, Nov 2001)
What Needs to Change?

- Research and clinical trials
- Policy
- Awareness
- Health Equity
If you are female....how are you feeling now?

- Relieved that the emerging HF therapies seem to have benefit in women?
- Frustrated about the lack of females participating in clinical trials?
- Empowered to make a change?
Questions or comments?