Sex Differences in Heart Failure (Function): What We Know...And What We Don’t Know

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DISCLOSURES

• Consulting Fee/Advisory Board
  • Merck, AstraZeneca, Cytokinetics, Novartis

• Speaker Honoraria
  • Merck, AstraZeneca, Cytokinetics, Novartis
OUTLINE

• Defining “Heart Failure”
• Framework for outlining sex differences
  • Predisposition
  • Manifestation
  • Therapeutic Approach
• Call To Action
WHAT DO WE MEAN BY “HEART FAILURE” (IN WOMEN)?
Symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality

corroborated by at least one of the following

- Elevated natriuretic peptide levels
- Objective evidence of cardiogenic pulmonary or systemic congestion

Bozkurt, Coates JCardFail 2021; Artwork courtesy of Vanessa Blumer, JCF FIT Editor
STAGES OF HEART FAILURE

**AT RISK (STAGE A)**
Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease.

**PRE-HF (STAGE B)**
Patients without current or prior symptoms or signs of HF with evidence of one of the following:
- Structural Heart Disease
- Abnormal cardiac function
- Elevated natriuretic peptide or cardiac troponin levels

**HF (STAGE C)**
Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality.

**ADVANCED HF (STAGE D)**
Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advanced therapies transplantation, mechanical circulatory support, or palliative care.

With GDMT & RF modification:

- HF in Remission
- Persistent HF

Gibson/Lala, www.acc.org, Heidenreich, Bozkurt, JCF 2022
MY *OLD* APPROACH TO HEART FAILURE...

Heart Failure with reduced Ejection Fraction (HFrEF) <40%

Heart Failure with preserved Ejection Fraction (HFpEF) >50%

Intermediate EF: 41-49%

Acute Decompensated Heart Failure (ADHF)

S/V, SGLT2i & Decongestion

Decongestion for HFpEF

Chronic Heart Failure

GDMT for HFrEF

SGLT2i, ARNI? MRA Volume/Comorbidities

Advanced Therapies
Universal Definition and Classification of Heart Failure (HF)

**Definition**

HF is a *clinical syndrome* with current or prior
- Symptoms and or signs caused by a structural and/or functional cardiac
And corroborated by at least one of the following:
- Elevated natriuretic peptide levels
- Objective evidence of cardiogenic pulmonary or systemic congestion

**Stages**

**AT RISK (STAGE A)**
Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease

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Patients without current or prior symptoms or signs of HF with evidence of one of the following:
- Structural Heart Disease
- Abnormal cardiac function
- Elevated natriuretic peptide or cardiac troponin levels

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Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality

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Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advanced therapies transplantation, mechanical circulatory support, or palliative care

**Classification By EF**

- **HF with reduced EF (HFrEF)**
  - HF with LVEF < 40%
- **HF with mildly reduced EF (HFmrEF)**
  - HF with LVEF 41-49%
- **HF with preserved EF (HFpEF)**
  - HF with LVEF > 50%
- **HF with improved EF (HFimpEF)**
  - HF with a baseline LVEF of < 40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF of > 40%

Language matters! The new universal definition offers opportunities for *more precise communication* and description with terms including **persistent HF** instead of “stable HF,” and **HF in remission** rather than “recovered HF.”

Gibson/Lala [www.acc.org](http://www.acc.org), Heidenreich, Bozkurt, JCF 2022
HOW DID “STAGES” OF HEART FAILURE EVOLVE?

Stage D
• VO2 < 10 mL/kg/min

Stage C
• VO2 10-15 mL/kg/min

Stage B
• VO2 16-20 mL/kg/min

Stage A
• VO2 > 20 mL/kg/min

EF ≠ Functional Capacity

Weber Circulation 1984; Mancini 1991
ORGANIZATIONAL FRAMEWORK FOR SEX DIFFERENCES IN HF
ORGANIZATIONAL FRAMEWORK: SPECTRUM OF HF IN WOMEN

**Predisposition**
- Traditional risk factors
- Sex-specific risk factors

**Manifestation**
- “Diastolic dysfunction” (HFpEF syndrome)
- Acuity
- Severity

**Therapeutic Approach & Response**
- Pharmacotherapy
- Device therapy
EPIDEMIOLOGY

• 2019: HF-related-CV death:
  • Women: age-adjusted mortality rate (AAMR) of 49.8 (95% CI: 49.5-50.1) per 100,000 population
  • Men: AAMR of 70.4 (95% CI: 70.0-70.8)
  • Black women vs White women AAMR rate ratio: 1.54)
  • Black men vs White men (AAMR rate ratio: 1.43 estimated in 2017)
PREDISPOSITION – TRADITIONAL RISK FACTORS

- HYPERTENSION
  - More potent risk factor for heart failure in women
  - 3x vs 2x

- DIABETES
  - More potent risk factor for heart failure in women
  - 5x vs 2x

- OBESITY
  - Higher risk for heart failure in women
  - Stronger risk factor for HFrEF

- SMOKING
  - More potent risk factor for heart failure in women vs men

Graphics courtesy of C. Hamo/Adv HF Fellow

Lala/Gulati JCardFail 2021
OBESITY

A

Cumulative Incidence of HFpEF

N at risk
Non-obese Men 8424
Obese Men 2221
Non-obese Women 9009
Obese women 3027

Years
0 2 4 6 8 10 12 14

B

Cumulative Incidence of HFrEF

N at risk
Non-obese Men 9009
Obese Men 3027
Non-obese Women 8424
Obese women 2221

Years
0 2 4 6 8 10 12 14

Savji/Ho JACC HF 2018
PREDISPOSITION : SEX-SPECIFIC RISK FACTORS

SEX-SPECIFIC RISK FACTORS in WOMEN

- Anthracycline/tyrosine kinase inhibitor-associated LV dysfunction (potentiated risk if both)
- Radiation

- Gestational HTN, DM,
- Preeclampsia
- Eclampsia
- Peripartum cardiomyopathy

BREAST CANCER THERAPY

PREGNANCY

AUTOIMMUNE DISEASE

Acute Coronary Syndrome w/o CAD

Stress Cardiomyopathy
- Emotional > physical triggers
- Apical ballooning & LV dysfunction
- Spontaneous Coronary Artery Dissection (?)

↑ Prevalence of SLE, RA, scleroderma in women
- ↑ Inflammation
- ↑ Innate immunity

Graphics courtesy of C. Hamo/Adv HF Fellow
MANIFESTATION

- Higher innate immune profiles
- Differential expression of NT-proBNP
- Diastolic dysfunction
- O2 handling
- Cardiometabolic syndrome
- DCM 2:1 men:women
- PPCM - titin
- Penetrance

Goli, Circulation 2021
Predominant endothelial inflammation-coronary microvascular dysfunction

Significant comorbidity burden
Emotional stress
Great vascular stiffness
Systemic inflammation

Phenotypes
HFpEF
Takotsubo CM
PPCM

Prognosis
Greater exercise limitation
Lower QoL
Better survival

Predominant macrovascular disease, myocyte necrosis and scar formation

Myocardial infarction predominates as a HF risk factor
Younger age at presentation
Obesity promotes development of HFrEF rather than HFpEF
Alcohol and illicit drug use more common exposures

Phenotypes
HFrEF

Prognosis
Higher mortality
Better QoL

Lam C, Circulation 2019
MANIFESTATION

- More HFpEF
- Acuity of presentation
  - More cardiogenic shock after STEMI
  - ?More symptomatic at presentation
- Biomarkers
  - Markers of stress/fibrosis higher in women?
  - Prone to natriuretic peptide deficiency?
    - Similar diagnostic and prognostic value
- Ejection fraction
  - Women with smaller cavity size, higher EF
- QRS Duration
  - Shorter in women!

- Is an ejection fraction of 50% the same in a woman as in a man?
- Is QRS of 130ms same in woman as in a man?
BIOMARKERS

- Women with HFpEF lower NP levels (potentiated by obesity)
- Loss of estrogen following menopause ↓ signaling of the cGMP-protein kinase G
  - Sacubitril/valsartan, which increases cGMP-protein kinase G signaling, may uniquely benefit post menopausal women
EF

- **2D ECHO:**
  - normal values: 64% in women vs 62% in men

- **cMR:**
  - Dallas study: (1435 women and 1183 men): Median LVEF ↑ in women than in men (75% [70%, 79%] vs. 70% [65%, 75%] \( P < 0.001 \)).
  - LVEDV and ESV indexed to BSA were ↓ in women than in men (\( P < 0.001 \) for both).

L. Soulant-Dufour, JASE(2021), Chung Circulation 2006
QRS DURATION

• QRS duration is up to 10ms shorter in women compared with men

Table 1. The most relevant sex-based differences in standard ECG.

<table>
<thead>
<tr>
<th>ECG parameters</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>P wave amplitude</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>P wave duration</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>PR interval</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>QRS amplitude</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>QRS duration</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>QT interval</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>JT interval</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>QT dispersion</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>T wave amplitude</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>T wave duration</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>J point amplitude</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>ST amplitude</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
FUNCTIONAL LIMITATION

Arterial stiffness is higher in women vs men with HFrEF.

Arterial stiffness is correlated with abnormal diastolic response to exercise, particularly in women.

Central Illustration: Mechanisms of Impaired Exercise Tolerance in Women

- **Pulmonary mechanisms**
  - ↑ pulmonary vascular resistance (exercise)
  - ↓ pulmonary arterial compliance (rest & exercise)
  - Pulmonary vascular dysfunction

- **Systemic mechanisms**
  - ↓ DMO₂ (rest)
  - ↑ lactate/workload
  - Impaired peripheral oxygen utilization

- **Exercise intolerance in women**
  - Elevated LV filling pressures
  - ↑ E/e' (exercise) (rest & exercise)
  - ↑ Ees, Ed & ↓ Ea/Ees (exercise)

- **Cardiac mechanisms**
  - ↑ PCWP/workload (exercise)
  - ↑ MAP (exercise)
  - ↑ SBP & arterial PP (rest)

FRAILTY

- More common in women
- More symptom oriented?
- In men more physical / body composition related?

Denfeld, Circ HF 2021; Lala JCardFail 2022
THERAPEUTIC RESPONSE
## PHARMACOLOGIC THERAPIES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physiologic Differences</th>
<th>Pharmacokinetic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABSORPTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intestinal Transit Times</td>
<td>&gt;</td>
<td>Slower Intestinal Transit in Women</td>
</tr>
<tr>
<td>• Transdermal Absorption</td>
<td>&gt;</td>
<td>↑Transdermal Absorption in Women</td>
</tr>
<tr>
<td><strong>DISTRIBUTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total Body Water</td>
<td>&gt; &gt;</td>
<td>↑Total Body Water in Pregnant Women &amp; Men</td>
</tr>
<tr>
<td>• Women Greater Adipose Tissue</td>
<td>&gt; &gt;</td>
<td>↑Adiposity in Women</td>
</tr>
<tr>
<td>• Plasma proteins modulated by Estrogen</td>
<td>&gt; &gt;</td>
<td>↑Free Concentrations in Women (modulated by estrogen)</td>
</tr>
<tr>
<td><strong>METABOLISM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Organ Blood Flow</td>
<td>&gt; &gt;</td>
<td>↓Hepatic Blood Flow in Women</td>
</tr>
<tr>
<td>• Cardiac Output</td>
<td>&gt; &gt;</td>
<td>↑Cardiac Output/ Rate of Distribution in Men vs Women</td>
</tr>
<tr>
<td>• Body Fat</td>
<td>&gt; &gt;</td>
<td>↑Body Burden of Lipid Soluble Drugs in Women</td>
</tr>
<tr>
<td><strong>ELIMINATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Renal Excretion</td>
<td>&gt; &gt;</td>
<td>↑Glomerular Filtration Rate, Tubular Secretion &amp; Resorption in Men</td>
</tr>
<tr>
<td>• Liver Metabolism</td>
<td>&gt;</td>
<td>↑Renal Blood Flow in Pregnancy by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓Liver Enzyme Activity in presence of Estrogen: metabolism varies through pregnancy, menstrual cycle, use of contraceptives, after menopause in women</td>
</tr>
<tr>
<td>Drug</td>
<td>Metabolism</td>
<td>Sex-Specific Considerations</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>↑ Plasma concentrations in ♀</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Beta Blockers</strong></td>
<td>↑ Plasma Concentrations in ♀</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>ACEI/ARB</strong></td>
<td>↑ Plasma Concentrations in ♀</td>
<td>HFrEF ♀ benefit from low &amp; high doses; ♂ benefit from high doses; Angioedema / cough 2x ♀ vs ♂, Teratogenic</td>
</tr>
<tr>
<td>Hydralazine / Isosorbide Dinitrate</td>
<td>No established sex differences in pharmacokinetics</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>ARNI</strong></td>
<td>No established sex difference in pharmacokinetics</td>
<td>HFrEF Same ↓ in HFH but &lt; ↓ in CV death HFrEF &gt; benefit ♀ vs ♂ with ↓ CV death/HFH by 27% vs no effect in ♂</td>
</tr>
<tr>
<td><strong>SGLT2i</strong></td>
<td>No established sex difference in pharmacokinetics</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>MRA</strong></td>
<td>No established sex difference in pharmacokinetics</td>
<td>♀ benefit across EF spectrum; ♂ benefit at lower LVEF Possible &gt; ↓ in CV Mortality in ♀ vs ♂</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>Dose based on weight</td>
<td>HFrEF ↑ concentrations in ♀ Benefit in ↓ HFH in ♀ vs ♂ ↑ mortality in ♀ vs ♂</td>
</tr>
</tbody>
</table>
Aldosterone Antagonist - TOPCAT

Sacubitril/Valsartan - PARAGON

Aldosterone antagonist ↓ CV mortality in women

Sacubitril/Valsartan ↓ HF hospitalizations in
### Gender Based Analysis

<table>
<thead>
<tr>
<th>Group by</th>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALE</td>
<td>EMPAREG</td>
<td>0.760</td>
<td>0.481</td>
<td>1.202</td>
<td>-1.174</td>
<td>0.240</td>
</tr>
<tr>
<td>FEMALE</td>
<td>DAPA-HF</td>
<td>0.790</td>
<td>0.599</td>
<td>1.059</td>
<td>-1.577</td>
<td>0.115</td>
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<tr>
<td>FEMALE</td>
<td>EMPEROR-REDUCTION</td>
<td>0.590</td>
<td>0.438</td>
<td>0.796</td>
<td>-3.480</td>
<td>0.001</td>
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<tr>
<td>FEMALE</td>
<td>VERTIS-CV</td>
<td>0.990</td>
<td>0.713</td>
<td>1.375</td>
<td>-0.080</td>
<td>0.932</td>
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<tr>
<td>FEMALE</td>
<td>SCORED</td>
<td>0.770</td>
<td>0.599</td>
<td>0.889</td>
<td>-2.046</td>
<td>0.041</td>
</tr>
<tr>
<td>FEMALE</td>
<td>SOLOIST-WHF</td>
<td>0.800</td>
<td>0.511</td>
<td>1.252</td>
<td>-0.976</td>
<td>0.329</td>
</tr>
<tr>
<td>FEMALE</td>
<td>EMPAREG</td>
<td>0.767</td>
<td>0.672</td>
<td>0.875</td>
<td>-3.953</td>
<td>0.000</td>
</tr>
<tr>
<td>MALE</td>
<td>EMPAREG</td>
<td>0.580</td>
<td>0.449</td>
<td>0.749</td>
<td>-4.180</td>
<td>0.000</td>
</tr>
<tr>
<td>MALE</td>
<td>DAPA-HF</td>
<td>0.730</td>
<td>0.628</td>
<td>0.848</td>
<td>-4.119</td>
<td>0.000</td>
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<tr>
<td>MALE</td>
<td>EMPEROR-REDUCTION</td>
<td>0.800</td>
<td>0.684</td>
<td>0.936</td>
<td>-2.794</td>
<td>0.005</td>
</tr>
<tr>
<td>MALE</td>
<td>VERTIS-CV</td>
<td>0.850</td>
<td>0.713</td>
<td>1.014</td>
<td>-1.808</td>
<td>0.067</td>
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<tr>
<td>MALE</td>
<td>SCORED</td>
<td>0.730</td>
<td>0.591</td>
<td>0.902</td>
<td>-2.921</td>
<td>0.003</td>
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<tr>
<td>MALE</td>
<td>SOLOIST-WHF</td>
<td>0.620</td>
<td>0.469</td>
<td>0.819</td>
<td>-3.367</td>
<td>0.001</td>
</tr>
<tr>
<td>MALE</td>
<td>EMPAREG</td>
<td>0.743</td>
<td>0.688</td>
<td>0.803</td>
<td>-7.548</td>
<td>0.000</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.749</td>
<td>0.701</td>
<td>0.801</td>
<td>-8.510</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Hazard ratio and 95% CI**

- **Favours SGLT2i**
- **Favours Placebo**

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Bhatia, EJHF 2021
Functional Mitral Regurgitation

Women with baseline worse NYHA Class

Worse 6MWD

Worse QOL scores

Benefit derived from MV Clip less than men

ISCHEMIC MITRAL REGURGITATION

Patients with severe ischemic mitral regurgitation (N = 251)

Women (N = 96) vs. Men (N = 155)

- Smaller LV volumes
- Smaller EROA
- Larger EROA / LVEDV ratio

Baseline echocardiographic characteristics

- Surgical mitral valve repair or replacement

- Higher 2-year mortality
- Higher 2-year MACCE
- Worse 2-year QOL
- Worse 2-year functional status

- Similar LV reverse remodeling at 2 years

- Lower 2-year mortality
- Lower 2-year MACCE
- Better 2-year QOL
- Better 2-year functional status

Giustino, Lala, Hung JACC HF 2019
BETTER REMODELING RESPONSE IN WOMEN?

- Sacubitril/valsartan
- Cardiac resynchronization therapy
- LVAD therapy

Greater reduction in LV volumes

Ibrahim NE, EHFJ 2020; Kenigsberg BB JCF 2020; Yin FH, PLoSOne 2017; Chatterjee NA, EHJ 2017
REGARDLESS... THERAPIES IN WOMEN ARE UNDERUTILIZED...

- ICD
- CRT
- MV clip (36% in COAPT)
- 25% LVAD
- 25% heart transplant

Increasing focus on patient reported outcomes, understanding patient preferences by sex/gender

Blumer/VanSpall H EJHF 2021; Lala/Gulati JCardFail 2021
• 26.6% of patients are women
• Nonischemic, restrictive, congenital heart disease is more common
• No difference in reason for referral or referring physician

Table 1. Summary of Comparisons by Sex in Patients Referred for and Completed an Evaluation for Advanced Heart Failure Therapies. *Other, indicates composite of all variables marked with an asterisk.

<table>
<thead>
<tr>
<th>Etiology of Heart Failure</th>
<th>Male (%) (n=378)</th>
<th>Female (%) (n=137)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Cardiomyopathy</td>
<td>37.8%</td>
<td>20.4%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Nonischemic Cardiomyopathy</td>
<td>53.7%</td>
<td>62.0%</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>1.9%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>Restrictive Cardiomyopathy</td>
<td>1.9%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>1.6%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Other Cardiomyopathy*</td>
<td>3.2%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Retransplant*</td>
<td>1.6%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>ARVC*</td>
<td>1.1%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>Valvular Disease*</td>
<td>0.5%</td>
<td>1.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for Referral</th>
<th>Male (%) (n=378)</th>
<th>Female (%) (n=137)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular Arrhythmia / ICD Discharge</td>
<td>5.6%</td>
<td>5.8%</td>
<td>0.89</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>20.4%</td>
<td>16.8%</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>17.5%</td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>Worsening Heart Failure</td>
<td>29.1%</td>
<td>32.8%</td>
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</tr>
<tr>
<td>Inotrope Dependence</td>
<td>20.1%</td>
<td>17.5%</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>7.4%</td>
<td>8.0%</td>
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<tr>
<td>Right Ventricular Failure*</td>
<td>1.6%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>Renal Failure*</td>
<td>2.9%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension*</td>
<td>1.9%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Valvular Disease*</td>
<td>1.1%</td>
<td>17.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Referring Physician</th>
<th>Male (%) (n=378)</th>
<th>Female (%) (n=137)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Surgery</td>
<td>3.4%</td>
<td>3.6%</td>
<td>0.5</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td>5.6%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>General Cardiology</td>
<td>29.6%</td>
<td>36.5%</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>50.3%</td>
<td>46.0%</td>
<td></td>
</tr>
<tr>
<td>Interventional Cardiology</td>
<td>10.8%</td>
<td>10.9%</td>
<td></td>
</tr>
</tbody>
</table>
REFERRAL FOR ADVANCED THERAPIES

- Women deemed “too well” for HT
- Men declined HT more due to psychosocial contraindications
- No difference in LVAD by sex

<table>
<thead>
<tr>
<th>HT Evaluation</th>
<th>Male % (n=378)</th>
<th>Female % (n=137)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accept</td>
<td>32.5%</td>
<td>38.0%</td>
<td>0.3</td>
</tr>
<tr>
<td>Decline/Deferred</td>
<td>44.2%</td>
<td>44.5%</td>
<td></td>
</tr>
<tr>
<td>Not Performed</td>
<td>23.3%</td>
<td>17.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVAD Evaluation</th>
<th>Male % (n=378)</th>
<th>Female % (n=137)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accept</td>
<td>46.3%</td>
<td>38.0%</td>
<td>0.163</td>
</tr>
<tr>
<td>Decline/Deferred</td>
<td>32.0%</td>
<td>33.6%</td>
<td></td>
</tr>
<tr>
<td>Not Performed</td>
<td>21.7%</td>
<td>28.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for HT Decline</th>
<th>Male % (n=167)</th>
<th>Female % (n=61)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too Well</td>
<td>11.1%</td>
<td>26.7%</td>
<td>0.0047</td>
</tr>
<tr>
<td>Too Sick</td>
<td>46.4%</td>
<td>41.7%</td>
<td>0.068</td>
</tr>
<tr>
<td>Patient Declined</td>
<td>6.5%</td>
<td>10.0%</td>
<td>0.388</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>34.0%</td>
<td>15.0%</td>
<td>0.0058</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2.0%</td>
<td>6.7%</td>
<td>0.831</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21.7%</strong></td>
<td><strong>28.5%</strong></td>
<td><strong>0.003</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for LVAD Decline</th>
<th>Male % (n=123)</th>
<th>Female % (n=45)</th>
<th>P-Value (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too Well</td>
<td>16.3%</td>
<td>26.7%</td>
<td></td>
</tr>
<tr>
<td>Too Sick</td>
<td>37.4%</td>
<td>35.6%</td>
<td></td>
</tr>
<tr>
<td>Patient Declined</td>
<td>20.3%</td>
<td>15.6%</td>
<td></td>
</tr>
<tr>
<td>Psychosocial</td>
<td>20.3%</td>
<td>15.6%</td>
<td></td>
</tr>
<tr>
<td>RV Failure</td>
<td>4.9%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.8%</td>
<td>2.2%</td>
<td>0.605</td>
</tr>
</tbody>
</table>
SO WHAT DO WE DO ABOUT IT?

Calls to Action!
Intersection of Biological, Cultural and Environmental Variables

Preclinical studies
Male and female cells and animals
Data reported by sex

Clinical Studies
Male and female participants
Data reported by sex

Medical Practice
Sex-specific guidelines

Tissue source of cells
Sex/Age of donor
Culture condition: substrate media

Species strain
Sex/Age/hormonal or reproductive status
Housing Social factors: single or group housing

Race/ethnicity
Sex/Age/hormonal or reproductive status
Housing conditions (family status, geographic and environmental factors)
Cultural factors (education, occupation, income, access to health care, lifestyle, etc.)
Is it Time for Sex-Specific Guidelines for Cardiovascular Disease?

Ersilia M. DeFilippis, MD, Harriette G.C. Van Spall, MD, MPH

**Figure 1: An Algorithm for the Development of Sex-Specific Guidelines**

1. **Assess for sex-related risk factors or pathophysiologic differences that may influence incidence of disease**
   - Disorders of pregnancy, premature menopause, inflammatory conditions

2. **Assess for sex-related differences that may have implications on treatment of disease**
   - Differences in biology, pharmacokinetics, pharmacodynamics, psychosocial factors

3. **Assess whether there is an adequate body of sex-specific evidence**
   - Is there adequate representation of men and women in the studies?
   - Are sex-disaggregated data reported?
   - YES

4. **Develop sex-specific guidelines for prevention and treatment recommendations**
   - Grade the level of evidence
   - Provide sex-specific recommendations

5. **Reassess as new data emerges**
### WHAT GAPS REMAIN?

| Sex Differences in Risk Factors for Heart Failure  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GAPS IN KNOWLEDGE</td>
<td></td>
</tr>
<tr>
<td>To what extent do social determinants of health influence HF risk in men vs women?</td>
<td></td>
</tr>
<tr>
<td>How can women at risk for heart failure during and after pregnancy be identified early?</td>
<td></td>
</tr>
<tr>
<td>What is the actual rate of “recovery” versus persistent myocardial dysfunction in PPCM &amp; what is the risk of subsequent relapse with subsequent pregnancies?</td>
<td></td>
</tr>
<tr>
<td>Are there sex differences in the risk of chemotherapy-related cardiomyopathy?</td>
<td></td>
</tr>
<tr>
<td>What are the specific effects of autoimmune disease (and its treatment) on the development of heart failure in women?</td>
<td></td>
</tr>
<tr>
<td>Can women who are at risk for stress (Takotsubo) cardiomyopathy be identified and what strategies can mitigate that risk?</td>
<td></td>
</tr>
</tbody>
</table>
CIS- AND TRANS- GENDER WOMEN – EVERYONE MATTERS!

Challenges of the LGBT Community in Healthcare: Focus on Heart Failure

Amin Yehya, MD MS  ⓐ  ⓞ  ⓖ Show footnotes

Published: February 01, 2022  ⋆  DOI: https://doi.org/10.1016/j.cardfail.2021.12.021
MY CURRENT APPROACH TO HEART FAILURE

GDMT for mildly reduced EF

GDMT for preserved EF

LVEF as a continuum

GDMT for HFrEF

40% 50% 60%

57%
HEART FUNCTION CONTINUUM: WORDS MATTER

Language Matters During This 'Exciting Time' in Heart Failure
— A rethinking of what heart failure is and how to communicate with patients

Contemplation from Our Hearts: A Call to Shift From Failure to Function

Age, ejection fraction, symptoms, response

Lala/Mentz JCardFail 2021
SUMMARY

Heart FUNCTION not failure

• Consider across a continuum, not simply by age, EF, QRS

Important HF sex-based differences

• Risk factors (traditional & sex-specific)
• Manifestations - HFpEF
• Implementation of and response to therapies

Calls to Action

• ↑ women in trials, in leadership, in publishing
• Preclinical, clinical studies with more women & sex-based analyses
• Consideration of sex-specific guidelines in HF
“THERE IS NO CHANCE OF THE WELFARE OF THE WORLD UNLESS THE CONDITION OF WOMEN IS IMPROVED. IT IS NOT POSSIBLE FOR A BIRD TO FLY ON ONE WING”
- SWAMI VIVEKANANDA
Thank you!