Heart Failure in Women: Gender-Based Differences

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Cardiology & Cardiovascular Intervention
Disclosures:
Nothing to disclose
Objectives

• Highlight the prevalence of Heart Failure (HF) in women
• Understand the role that gender plays in recognition, diagnosis, and management
• Discuss gender variations in epidemiology, symptoms, pharmacology, and treatment
• Examine the representation of women in clinical trials
Cardiovascular disease and other major causes of death for all males and females (United States: 2014).

Prevalence of Heart Failure

Hospital Discharges
Prevalence of HFpEF and HFrEF: Effect of Gender
Significant Differences Between Men and Women

- Epidemiology, recognition, diagnosis and treatment
- Women are not referred as often as men for appropriate tests and/or therapeutic procedures by physicians
- Women under-represented in clinical trials
  - Only in the last 15 yrs have women been included
  - They still only represent ~27% of populations in most trials
Barriers to Cardiovascular Care in Women

- Confusion due to mixed messages from the media
- Tendency to underestimate the problem by women themselves
- Lack of awareness on part of patients and healthcare providers
Epidemiology of HF in Women: Framingham Cohort

• 1950s & 1960s, HF incidence rate/10,000 person-years of follow-up:
  – 42 (95% [CI]: 34–50) in women
  – 63 (95% CI: 48–78) in men

• Rate then declined in women but not men, presumably secondary to improved recognition and treatment of rheumatic heart disease
Epidemiology

- 5-year incidence of HF increased:
  - 23% in the 1970s
  - 32% in the 1990s
  - For both men and women who survived first 30 days after MI, rates of incident HF did not change

- 1948 – 1988:
  - Median survival for women was better than men
  - Although both sexes had higher mortality with increasing age

- 1990s, 5-year mortality was >50%
Epidemiology - Current

- ~50% of patients living with HF are women
- 50% of pts hospitalized for HF are women
- Deaths from HF contribute to 35% of total CVD in women
- Lifetime risk of developing HF is 20% for Americans 40 years of age
- Lifetime risk of HF without a prior MI
  - 15% at age 40 years for women
  - 11% for men, risk rising rapidly with age
Preserved ejection fraction

Reduced ejection fraction

P = 0.03

Mortality in Women

- Mortality better for women than men
  - Most likely related to higher incidence of preserved EF
  - Lower prevalence and incidence of ischemic cardiomyopathy
  - Less coexisting PAD, COPD and CAD
- Women less likely than men to die from Sudden Cardiac Death (SCD)
Morbidity in Women

• Women have more frequent and longer hospitalizations
  – Lower quality of life
  – More functional impairment
  – More symptoms of depression
  – Hospitalized women w/ HF have more comorbidities

• Clinical outcomes in women have not improved at the same rate as for men w/ guideline-directed medical therapy (GDMT)
# Risk Factors for HF: Impact Varies by Gender

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age-and Risk Factor-Adjusted Hazard Ratio</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>High blood pressure (≥140/90 mm Hg)</td>
<td>2.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.3</td>
<td>6.0</td>
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<tr>
<td>Angina</td>
<td>1.4</td>
<td>1.7</td>
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<tr>
<td>Diabetes</td>
<td>1.8</td>
<td>3.7</td>
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<tr>
<td>Left ventricular hypertrophy</td>
<td>2.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Subjects aged 40-89 yr; 18-yr follow-up.

Symptoms & Diagnosis

• Women present w/ more symptom burden
• More dyspnea, bronchitis-like symptoms, edema, fatigue, worse quality of life
• Provider perceptions of HF being a “man's syndrome” lead to delay in diagnosis and treatment
  – Treating a presumed URI w/out further evaluation
• Symptoms of HF can often be missed or misinterpreted in women
Presentation

• Older women w/ HF: HFpEF and HTN
• Women more likely to develop HF after MI
• Increased BNP concentrations compared to men:
  – 1.6-fold increase in baseline circulating plasma BNP levels
  – 1.3-fold increase in NT-proBNP levels
• BNP has been validated in nonischemic cardiomyopathy, this test is critical in the assessment of women with HF
Nonischemic Cardiomyopathy

- Peripartum CDM: up to 6 mos post-partum
- Stress CDM: ~90% of cases in women
- Spontaneous Coronary Artery Dissection (SCAD):
  - 80% of pts w/ SCAD are women
  - Consider in perimenopausal pts w/ chest pain
Sex Differences in Pharmacology

- Gender differences in the pharmacokinetics (PK) and pharmacodynamics (PD) exist
- Disparities among drug absorption, distribution, metabolism, and excretion
- Lead to disparities of drug concentration at the site of action and resulting effect of common HF therapies
<table>
<thead>
<tr>
<th>PK Property</th>
<th>Effect in Women</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Less oral drug absorption</td>
<td>Less gastric acid secretion, Slower GI motility and transit time</td>
</tr>
<tr>
<td>Distribution</td>
<td>Larger for lipophilic drugs, Smaller for hydrophilic drugs</td>
<td>Greater body fat, Lower total body water</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Phase I: Increased activity of CYP2B6, CYP2D6, CYP3A4, Decreased activity of CYP1A2, CYP2E1</td>
<td>Variations in enzyme activity due to pregnancy, menopause, OC use and menstruation</td>
</tr>
<tr>
<td></td>
<td>Phase II: Increased activity of xanthine-oxidases, Decreased activity of N-acetyltransferases, sulfotransferases, methyltransferases</td>
<td></td>
</tr>
<tr>
<td>Excretion</td>
<td>Lower but marginal difference when normalized for body weight</td>
<td>Decreased renal blood flow, GFR, and tubular secretion and reabsorption</td>
</tr>
</tbody>
</table>

Abbreviations: CYP, cytochrome P450; GI, gastrointestinal; GFR, glomerular filtration rate; OC, oral contraception; PK, pharmacokinetic.
Clinically Relevant PK & PD
Gender Differences

• Captopril:
  – Better absorbed on an empty stomach
  – Women should wait longer after eating, prolonged GI transit may decrease absorption

• Digoxin:
  – Serum concentrations higher in woman due to reduced volume of distribution (Vd) and lower clearance (Cl)
  – Use lower doses and target serum concentrations to avoid toxicity
Clinically Relevant PK & PD Gender Differences

• Torsemide:
  – Peak plasma concentration and area under the curve of plasma levels significantly higher in women
  – Results in reduced elimination and noted gender differences in the frequency of hospitalizations secondary to diuretic use

• Metoprolol succinate:
  – Reduced Vd and slower Cl via CYP2D6
  – Results in a greater reduction in blood pressure and heart rate at lower doses in women
Adverse Drug Effects (ADEs)

- Incidence 1.5-1.7-fold higher in women than men
- Hospitalizations due to ADEs occur more frequently in women
- Women with HF receiving diuretic therapy are more likely to experience hyponatremia, hypokalemia, subsequent severe arrhythmias
  - Electrolytes should be monitored closely
- Angiotensin-converting enzyme (ACE) inhibitor–induced cough occurs ~1.5-2 times more frequently in women than men
Sex Differences in Treatment of HF
Women in Clinical Trials

- Women have been historically underrepresented in clinical trials
  - 50% of US population
  - There are more women than men over the age of 7
  - 17-20% clinical trials
History of Women’s Health Research

- 1977, US FDA issued a guideline: “General Considerations for the Clinical Evaluation of Drugs”
  Restricted women of childbearing potential from participating in phase 1 and early phase 2 clinical studies until reproductive toxicity studies had been conducted in animals and some evidence of human effectiveness had become available.

- Policy emerged in the aftermath of the discovery of birth defects resulting from fetal exposure to thalidomide and diethylstilbestrol.
1985, The Public Health Service Task Force on Women’s Health Issues:

The “historical lack of research focus on women’s health concerns has compromised the quality of health information available to women as well as the health care they receive.”
Guideline-Directed Therapies in Heart Failure

![Diagram showing the guideline-directed therapies in heart failure.](Image)

(Diagnosis of HF confirmed)

- Assess for fluid retention
  - Fluid retention
    - Diuretic
      - ICD if NYHA Class II or III
  - No Fluid retention
    - ACE inhibitor*
      - Beta blocker
      - NYHA I-IV

* ("ARB if ACE intolerant)

CRT if NYHA Class III-IV and QRS > 120 ms

ARB Aldosterone antagonist
Hydralazine/Isosorbide
Digoxin

Persistent symptoms or special populations}

### Treatment of HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>
Treatment of Systolic Heart Failure

Stage A: High risk with no symptoms
- Risk-factor reduction, patient and family education

Stage B: Structural heart disease, no symptoms
- ACE inhibitors or ARBs in all patients; beta-blockers in selected patients

Stage C: Structural disease, previous or current symptoms
- ACE inhibitors and beta-blockers in all patients
- Dietary sodium restriction, diuretics, and digoxin
- Cardiac resynchronization if bundle-branch block present
- Revascularization, mitral-valve surgery

Stage D: Refractory symptoms requiring special intervention
- Aldosterone antagonist, nesiritide
- Consider multidisciplinary team

Advanced stages:
- VAD, transplantation
- Inotropes
- Hospice

Medical Therapy for HFrEF

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.

Adapted with permission from Fonarow et al. (483).
## Treatment Effect

### Gender Disparities

<table>
<thead>
<tr>
<th>Agent</th>
<th>Treatment Effect</th>
</tr>
</thead>
</table>
| Beta blockers                | Hypothesis: sex hormones affect regulation of Beta receptors  
Pooled data from 3 major trials (MERIT HF, COPERNICUS, CIBIS II) suggest *similar* benefit in mortality reduction for men and women                                                                 |
| ACE Inhibitors               | Combined analysis of 30 trials  
37% reduction of mortality in men vs. 22% in women  
Hypothesis: estrogens downregulate components of RAAS                                                                                                                                                                |
| Digoxin                      | DIG trial subgroup analysis shown **increased risk of death** compared to men  
Benefit in reduction of hospitalizations seen in both genders                                                                                                                                                     |
| Aldosterone antagonists      | **Equal** prognostic benefit in men and women (RALES and EPHESUS)                                                                                                                                                     |
| Device therapies             | 40% less likely than men to receive a device  
25% of CRT recipients were women vs. 75% men  
MADIT-CRT showed **greater degree of reverse remodeling** and better outcomes with CRT in women  
Hypothesis: estrogens affect remodeling/fibrosis pathways                                                                                                                                                            |
## Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B (27,91)</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
Demographics of HFpEF

- 60-70% are women
  - Ventricular and vascular stiffness increased in women more sharply with age than in men
  - Estrogen dependent pathways
  - Less fibrosis with equivalent LV loading conditions
- Hypertension, obesity, atrial fibrillation and diabetes are the most prevalent comorbid conditions
ADHERE Registry

- 52% of admissions for ADHF were women
- Women received less evidence based therapies than men
- Women were less likely to undergo invasive testing or procedures
- Women were more symptomatic on admission
Causes of Death in HFpEF

- Prognosis of HFpEF patients is much worse than those with hypertension and other CVD RFs
- HFpEF is an entity that identifies high risk patients
- 70% of deaths are cardiovascular
  - 26-28% SCD
  - 14-21% heart failure
  - Coronary artery disease most common cause of death (30%)
## HFpEF - Therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG trial</td>
<td>Digoxin did not change the primary endpoint of HF hospitalization or cardiovascular mortality Reduction in HF hospitalizations, but an increase in admissions for unstable angina</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td><strong>Group on candesartan had reduction in combined endpoint of CV death or HF hospitalization</strong></td>
</tr>
<tr>
<td>PEP-CHF trial</td>
<td>No benefit of ACE-Inh in reduction of composite endpoint of all cause death or unplanned hospitalization</td>
</tr>
<tr>
<td>SENIORS trial</td>
<td>No benefit of nebivolol in combined endpoint study was underpowered for patients with preserved LVEF</td>
</tr>
<tr>
<td>IPRESERVE trial</td>
<td>No benefit of irbesartan in heart failure outcomes</td>
</tr>
<tr>
<td>TOPCAT trial</td>
<td>No reduction of combined endpoints with use of spinonolactone</td>
</tr>
</tbody>
</table>
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<em>Level of Evidence: A</em>) (9-14), OR ARBs (<em>Level of Evidence: A</em>) (15-18), OR ARNI (<em>Level of Evidence: B-R</em>) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
</tbody>
</table>
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*

- Double blind RCT
- Valsartan/Sacubitril (ARB/ARNI) vs. Enalapril (ACE Inh)
- N=8442; 22% women
- CHF NYHA Class II – IV with EF ≤ 40%
  - Mean EF 29%
  - Background tx: 80% diuretic, 93% BB1, 54% MRA
- Primary outcome
  - Composite of death from CV causes or hospitalization for HF
  - Designed to detect difference in death rates from CV causes
  - Trial stopped early (27 months) because of overwhelming benefit
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

**Endogenous vasoactive peptides**

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

**Neprilysin**

Inactive metabolites

**Neprilysin inhibition**
Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 no.</th>
<th>Enalapril no.</th>
<th>PRIMARY END POINT</th>
<th>HAZARD RATIO (95% CI)</th>
<th>P VALUE FOR INTERACTION</th>
<th>DEATH FROM CARDIOVASCULAR CAUSES</th>
<th>HAZARD RATIO (95% CI)</th>
<th>P VALUE FOR INTERACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
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<td>4212</td>
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<td>Age</td>
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</tr>
<tr>
<td>&lt;65 yr</td>
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<td>≥65 yr</td>
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<tr>
<td>Sex</td>
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<td>Male</td>
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<td>Other</td>
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<tr>
<td>Region</td>
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<td>Latin America</td>
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<td>Western Europe and other</td>
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<td>Asia–Pacific</td>
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<td>NYHA class</td>
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<td></td>
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<td>I or II</td>
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<td>3130</td>
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<td>0.03</td>
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<td></td>
<td>0.76</td>
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<td>III or IV</td>
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<td>1076</td>
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<td></td>
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<tr>
<td>Estimated GFR</td>
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<td></td>
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<td></td>
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<tr>
<td>&lt;60 ml/min/1.73 m²</td>
<td>1541</td>
<td>1520</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 ml/min/1.73 m²</td>
<td>2646</td>
<td>2692</td>
<td></td>
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</tbody>
</table>
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
</tbody>
</table>
Ivabradine  (Corlanor)

- New therapeutic agent
- Selectively inhibits the If current in the SA node causing heart rate reduction
- Funny channel
- Cardiotonic agent
  - selective decrease in rate without loss of contractility
  - In contrast to Beta Blockers and Calcium Channel Blockers
Resting Heart Rate is an Independent Predictor of Cardiovascular Mortality

### Association of Baseline Resting Heart Rate and Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease (708 events)</td>
<td>1.29 (1.20 to 1.39)</td>
<td>&lt;0.0001</td>
<td>1.15 (1.07 to 1.24)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Heart failure (303 events)</td>
<td>1.46 (1.31 to 1.62)</td>
<td>&lt;0.0001</td>
<td>1.32 (1.18 to 1.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary heart disease (343 events)</td>
<td>1.26 (1.14 to 1.40)</td>
<td>&lt;0.0001</td>
<td>1.08 (0.96 to 1.20)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stroke (216 events)</td>
<td>1.22 (1.07 to 1.39)</td>
<td>0.003</td>
<td>1.10 (0.96 to 1.26)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker (48 events)</td>
<td>0.53 (0.37 to 0.75)</td>
<td>0.0003</td>
<td>0.55 (0.38 to 0.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>Death (1186 events)</td>
<td>1.26 (1.19 to 1.33)</td>
<td>&lt;0.0001</td>
<td>1.17 (1.11 to 1.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular death (252 events)</td>
<td>1.34 (1.19 to 1.51)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.04 to 1.33)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; HR, hazard ratio per 1-SD increase in heart rate.
# Beta Blockers Benefit in Heart Failure

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Drug</th>
<th>Population</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS II (1999)</td>
<td>Bisoprolol</td>
<td>&lt; EF 35%</td>
<td>34% reduction in all cause mortality</td>
</tr>
<tr>
<td>MERIT HF (1999)</td>
<td>Metoprolol CR/XL</td>
<td>EF &lt;40%</td>
<td>34% all cause mortality redxn in 1 y</td>
</tr>
<tr>
<td>COPERNICUS (2002)</td>
<td>Carvedilol</td>
<td>EF &lt;25%</td>
<td>38% redxn of combined death and hospitalization</td>
</tr>
<tr>
<td>COMET</td>
<td>Compare MTP and Carvedilol</td>
<td>EF &lt;35%</td>
<td>All cause mortality redxn: MTP 40%, Coreg 34%</td>
</tr>
</tbody>
</table>
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Prof Karl Swedberg, MD, Prof Michel Komajda, MD, Prof Michael Böhm, MD, Prof Jeffrey S Borer, MD, Prof Ian Ford, PhD, Ariane Dubost-Brama, MD, Guy Lerebours, MD, Prof Luigi Tavazzi, MD, on behalf of the SHIFT Investigators†

- 6558 patients; 24% women
- Randomized to ivabradine vs. placebo
- Median follow-up was 22.9 months
- Class II and IV NYHA HF with LV systolic dysfunction (EF \(\leq 35\%\))
  - Mean EF 29%
- HR\(\geq 70\) bpm
- On background medical therapy
  - BB I 90%, ACE Inh 79%, ARB 14%, Diuretics 84%, MRA 60%
- Primary endpoint
- Composite of cardiovascular death or hospital admission for worsening heart failure
Significant Reduction in Primary Endpoint

- **Primary Endpoint:**
  - 24% vs 29%
  - HR 0.82

- **Driven by:**
  - 26% reduction in hospitalization for worsening HF
  - 26% reduction in death from HF

Ivabradine or placebo on top of guideline-recommended therapy including ACE inhibitor, β-blocker, mineralocorticoid receptor antagonist.
More pronounced effect with HR > 75 bpm

24% $P<0.0001$ REDUCTION in primary end point with ivabradine

17% $P=0.0164$ REDUCTION in cardiovascular death with ivabradine
Benefit in all prespecified subgroups

Figure 5: Effect of treatment on primary composite endpoint in prespecified subgroups

Data are number (%) of patients with first events. HR = hazard ratio. NYHA = New York Heart Association. bpm = beats per min.
A Large Number of Eligible Patients Are Untreated

US Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>63.9</td>
<td></td>
</tr>
<tr>
<td>Hydral/Nitrate</td>
<td>92.7</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>61.2</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>49.4</td>
<td></td>
</tr>
</tbody>
</table>

Number of Eligible Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>2,459,644</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>2,512,560</td>
</tr>
<tr>
<td>MRA</td>
<td>603,014</td>
</tr>
<tr>
<td>Hydral/Nitrate</td>
<td>150,754</td>
</tr>
<tr>
<td>CRT</td>
<td>326,151</td>
</tr>
<tr>
<td>ICD</td>
<td>1,725,732</td>
</tr>
</tbody>
</table>

Conclusions

• Recognize the prevalence of HF in women
• Not to confuse symptoms of HF with those of other disorders, such as COPD or asthma
• Medical therapy should be offered to female patients the same as to male patients using evidence-based care, not preconceived notions
• There needs to be larger numbers of women represented in HF clinical trials so appropriate and statistically sound conclusions can be made in analyses by sex
CC: Chest pain

HPI: 47 yo black woman w/ no significant known PMHx presented with chest pain characterized as dull, pressure and burning, in the epigastric and substernal area, 8/10 a/w nausea and vomiting, started @ 7 PM, it was now past midnight. Her symptoms had been intermittent for the 2-3 days prior. She had presented to UC but was treated for GERD w/ Pepcid.

PMHx:
- HTN
- S/p Gastric Bypass Surgery

Meds: None

All: Iburofen, Avocados

SHx: Smokes 3 cig/day, drinks socially, uses marijuana
ER Course

- Given Aspirin & Heparin IV load
- Pt became unresponsive
- VF arrest -> shocked -> NSR
- Intubated for airway protection
- VF again -> shocked -> NSR
Studies/Course

- H/H 10/33, MCV 76, cre 1.26, LFTs 256/93, BNP 15
- Rapid troponin 0.13
- TC 118, Triglycerides 112, HDL 36, LDL 60
- HgbA1c 5.5
- Echo: EF 36%, Akinesis and thinning of most of the anterior wall, septum and apex c/w large anteroapical infarct. Apical aneurysm w/out obvious thrombus.
- Normal valves, Mild DD, IVC dilated.
- Extubated.
- Transferred to OSH.
Recommendations
2014 Guidelines

• ACC/AHA recommend that women with heart attacks and heart disease be treated in an equal manner to men with the same indications for noninvasive and invasive testing
STEMI: A Paradigm Shift

Mortality ↓↓

Heart Failure ↑↑↑

Adapted from Roger VL et al. Circulation 2011;123:e18-e209
STEMI -> Heart Failure

**Figure 2:** Projected Heart Failure direct medical costs and indirect (lost productivity) costs.

Adapted from Circulation 2011; 123:933–44