Heart Failure
Update

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Disclosures

• Research Support
  – Federal: NIH, European Union, PCORI
  – Industry: Multiple clinical trials

• Consultant
  – Adrenomed, Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, Relypsa, Roche, Sanofi, Vifor
Objectives

- Outline the epidemiology and economic impact of HF
- Incorporate evidence-based therapies to optimize outcomes in patients with HF, including new guideline-recommended therapies
- Recognize the importance of continuity of care for HF patients transitioning from the inpatient to outpatient setting and implement strategies to prevent readmissions
Scope of Heart Failure

- HF is a major public health problem resulting in substantial morbidity and mortality
- 23 million people with HF worldwide
- 6–12 million office visits
- Costs: ~$31 billion in 2012 (80% due to hospitalizations) and projected to be ~$70 billion by 2030\(^1,2\)

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>5,700,000</td>
<td>870,000</td>
<td>50% at 5 years</td>
<td>1,023,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

## Classification of HF

<table>
<thead>
<tr>
<th>ACCF/AHA Stage</th>
<th>NYHA Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td><strong>B</strong> Structural heart disease but without signs or symptoms of HF</td>
<td>I</td>
</tr>
<tr>
<td><strong>C</strong> Structural heart disease with prior or current symptoms of HF</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>IV</td>
</tr>
<tr>
<td><strong>D</strong> Refractory HF requiring specialized interventions</td>
<td>IV</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association.
# Types of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>≤40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

Which of the following therapies for patients with heart failure with reduced ejection fraction have not been shown to reduce mortality?

A. ACE inhibitor
B. Angiotensin receptor neprilysin inhibitor
C. Aldosterone antagonists
D. Ivabradine
E. Beta-blockers

The correct answer is D. Ivabradine.
Pharmacologic Treatment for Stage C HFrEF

NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LOE = level of evidence.
Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF

32 Trials of ACEI in Heart Failure: ACEI (n=3870) vs. Placebo (n=3235)

- Total Mortality: OR 0.77 (0.67–0.88), p<0.001, -23%
- Death or Hospitalization: OR 0.65 (0.57–0.74), p<0.001, -35%
- CHF Hospitalization: OR 0.69 (0.58–0.83), p<0.001, -31%

OR = odds ratio.
High- vs. Low-Dose ACEI Therapy for HF

<table>
<thead>
<tr>
<th></th>
<th>Low Dose*</th>
<th>High Dose*</th>
<th>OR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or hospitalization</td>
<td>1339/1596</td>
<td>1251/1568</td>
<td>0.88</td>
<td>p=0.002</td>
</tr>
<tr>
<td></td>
<td>83.9%</td>
<td>79.8%</td>
<td>(0.82–0.95)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>717/1596</td>
<td>666/1568</td>
<td>0.92</td>
<td>p=0.128</td>
</tr>
<tr>
<td></td>
<td>44.9%</td>
<td>42.5%</td>
<td>(0.81–1.03)</td>
<td></td>
</tr>
</tbody>
</table>

ATLAS: 8% reduction in death and 14% reduction in death and HF hospitalization
SOLVD: 14% reduction in death and 26% reduction in death and HF hospitalization

3164 patients with class II–IV CHF with f/u 46 months, rare use of beta-blockers

*Low dose = lisinopril 2.5 to 5.0 mg/day, high dose = lisinopril 32.5 to 35.0 mg/day

f/u = follow-up.
Val-HeFT = The Valsartan Heart Failure Trial; CHARM = Candesartan in Heart Failure-Assessment of mortality and Morbidity trials; CV = cardiovascular
ACEI/ARB in Heart Failure

• Indicated for all patients with asymptomatic LV dysfunction and for class I to IV heart failure (contraindications: hyperkalemia, angioedema, pregnancy)

• Titrate to target doses (i.e., enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd, valsartan 160 mg bid, candesartan 32 mg qd)

• Monitor serum potassium and renal function; advise checking chemistry panel 1–2 weeks after first dose

• Use of ACEIs preferred over ARBs

• Use of ACEI together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist

LV = left ventricular; qd = every day.
Aldosterone Antagonists in HF

RALES (Severe HFrEF)
30% Risk reduction

EPHESUS (Post-MI)
15% Risk reduction

EMPHASIS (Mild HFrEF)
22% Risk reduction

Aldosterone Antagonists in Heart Failure

- Indicated for patients with mild, moderate, or severe HF due to LVD (LVEF ≤0.40)
  - Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher-risk patients) or eplerenone 25 mg PO qd (or 12.5 mg in higher-risk patients)
  - Decrease potassium supplementation and loop diuretic dose at time of initiation

- Critical to very closely monitor serum potassium and renal function; advise checking chemistry panel at 72 hours, 1 week, and 4 weeks

- Advance spironolactone dose at 4 weeks to 25 mg PO qd or eplerenone 50 mg, which is the target dose; avoid higher doses due to risk of hyperkalemia

- Contraindicated if hyperkalemia or Cr >2.5 mg/dL in men and >2.0 mg/dL in women

LVEF = left ventricular ejection fraction; PO = by mouth; Cr = creatinine.
Beta-Blockers in Heart Failure

Effect of Beta-Blockade on Hospitalizations

Only carvedilol and metoprolol CR/XL are FDA-approved for HF therapy in the U.S.

FDA = Food and Drug Administration.
Effect of Carvedilol Dose on Mortality in Patients with Heart Failure

Carvedilol Dose-Response Trial (MOCHA)

Dose response of carvedilol in moderate HF patients on all-cause mortality

bid = twice daily.
Beta-Blocker Therapy in Heart Failure

• Indicated for all patients with asymptomatic LV dysfunction and for class I to IV HF with LVEF ≤0.40

• Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd-degree HB

• Use of one of the 3 evidence-based beta-blockers in HF: i.e., carvedilol, metoprolol succinate, bisoprolol

• Start at very low HF doses and up-titrate to target doses at two-week intervals or highest dose short of target dose that is well tolerated

• Monitor HR and BP

HB = heart block; HR = heart rate; BP = blood pressure.
Beta-Blockers Differ in Their Long-Term Effects on Mortality in HF

<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Long-Term Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Bucindolol&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No effect</td>
</tr>
<tr>
<td>Carvedilol&lt;sup&gt;3–5&lt;/sup&gt;</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Metoprolol tartrate&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Not well studied</td>
</tr>
<tr>
<td>Metoprolol succinate&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Nebivolol&lt;sup&gt;8&lt;/sup&gt;</td>
<td>No effect</td>
</tr>
<tr>
<td>Xamoterol&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Harmful</td>
</tr>
</tbody>
</table>

AHeFT: Trial Summary

1050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA

<table>
<thead>
<tr>
<th>All-Cause Mortality (%)</th>
<th>First HF Hospitalization (%)</th>
<th>Patient-Reported Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Standard therapies</td>
<td>Hyd/Nit + Standard therapies</td>
<td>Hyd/Nit + Standard therapies</td>
</tr>
<tr>
<td>6.2 (n=32)</td>
<td>10.2 (n=54)</td>
<td>p=0.012</td>
</tr>
<tr>
<td>16.4 (n=85)</td>
<td>24.4 (n=130)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>n=518</td>
<td>n=532</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

AHeFT = African-American Heart Failure Trial; BB = beta-blocker; AA = aldosterone antagonist; Hyd/Nit = hydralazine/nitrate.
Newer Therapies for HFrEF
Effects of Neprilysin Inhibition in Heart Failure

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

Neprilysin

Inactive metabolites

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

Neprilysin inhibition

PARADIGM-HF Trial: Design

Entry Criteria:
• NYHA class II-IV HF, LVEF ≤40% → amended to ≤35%
• BNP ≥150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or 1/3 lower if hospitalized for HF within 12 months
• On a stable dose of ACEI or ARB equivalent to ≥10 mg of enalapril daily for ≥4 weeks
• Unless contraindicated, on stable dose of beta-blocker for ≥4 weeks
• SBP ≥95 mm Hg, eGFR ≥30 mL/min/1.73 m2 and serum K ≤5.4 mmol/L at randomization

Single-blind run-in period

Enalapril 10 mg BID (n=10,513) → Sac/Val 49/51 mg to 97/103 mg BID (n=9,419) → HF Patients (n=8,442)

Study stopped early after median follow-up of 27 months

Enalapril 10 mg BID (n=4,212)
Sac/Val 97/103 mg BID (n=4,187)

34-month follow-up

Primary endpoint: Death from CV causes or hospitalization for HF

## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class II/III (%)</strong></td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>N-terminal pro-BNP (pg/mL)</strong></td>
<td>1631 (885–3154)</td>
<td>1594 (886–3305)</td>
</tr>
<tr>
<td><strong>B-type natriuretic peptide (pg/mL)</strong></td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>34.7%</td>
<td>34.6%</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td><strong>Mineralocorticoid antagonists</strong></td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td><strong>ICD and/or CRT</strong></td>
<td>21.9%</td>
<td>21.4%</td>
</tr>
</tbody>
</table>

ICD = implantable cardioverter defibrillation; CRT = cardiac resynchronization therapy.
PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Sac/Val</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days since Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

Number needed to treat = 21

HR 0.80 (95% CI, 0.73–0.87), p<0.001

Sac/Val = Sacubitril/Valsartan; HR = hazard ratio.
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>711 (17.0%)</td>
<td>835 (19.8%)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>14.0%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/L</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dL</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation for adverse event</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for hypotension</td>
<td>0.9%</td>
<td>0.7%</td>
<td>0.38</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.56</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>0.7%</td>
<td>1.4%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

## Angioedema (adjudicated)

<table>
<thead>
<tr>
<th></th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications; no hospitalization</td>
<td>6 (0.1%)</td>
<td>4 (0.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3 (0.1%)</td>
<td>1 (&lt;0.1%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Influence of Sacubitril/Valsartan on Readmission Rates after HF Hospitalization


PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction when compared with recommended doses of enalapril:

**Sac/Val was more effective than enalapril in...**

- Reducing the risk of CV death and HF hospitalization by 20%
- Reducing the risk of CV death by 20%
- Reducing the risk of HF hospitalization by 21%
- Reducing all-cause mortality by 16%
- Improving symptoms and physical limitations

**Sac/Val was better tolerated than enalapril...**

- Less likely to cause cough, hyperkalemia, or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema
Angiotensin Neprilysin Inhibition with Sac/Val Doubles Effect on CV Death of Current Inhibitors of the RAS

RAS = renin-angiotensin system

FDA-Approved Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>Sacubitril/Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td><strong>Renal/hepatic impairment</strong></td>
</tr>
<tr>
<td><strong>Switching from an ACE inhibitor</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
</tr>
</tbody>
</table>

## 2016 ACC/AHA/HFSA Heart Failure Guideline Update

### Pharmacological Treatment for Stage C HFrEF

#### Recommendations for RAS Inhibition with ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOR</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>), OR ARBs (<em>Level of Evidence: A</em>), OR ARNI (<em>Level of Evidence: B-R</em>) (19) in conjunction with evidence-based beta-blockers, and aldosterone antagonists in selected patients, 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>I</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.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
</tr>
</tbody>
</table>

COR = class of recommendation; LOR = level of recommendation; ARNI = angiotensin receptor blocker and neprilysin inhibitor. Yancy et al. *Circulation.* 2016;134(13):e282-93 [ePUb ahead of print]
PIONEER-HF

Study Design

Hospitalized Patients with Acute Decompensated HF with Reduced EF

Stabilized

Screening
Day -10 - Day -1

Double-blind Period

Sacubitril/valsartan
97/103 mg twice daily*

Enalapril
10 mg twice daily*

Open-Label Period

Sacubitril/valsartan

Sacubitril/valsartan

Week 8

Week 12

Day 0
Randomization

R

*Target Dose
HF, Heart Failure. EF, Ejection Fraction
Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.
Data on File: PIONEER-HF Protocol, Novartis Pharmaceuticals Corp; October 2018
HR = 0.54; 95% CI 0.37-0.79
NNT= 13

• Serious Clinical Composite endpoint was driven by a reduction in death and HF re-hospitalizations

CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD: Left Ventricular Assist Device
Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018
Resting Heart Rate and CV Outcomes in Patients with HF

Retrospective analysis of 7,599 symptomatic HF* patients from the CHARM studies who were followed for a median of 38 months to determine the relationship between resting heart rate at baseline and all-cause mortality and fatal and nonfatal CV outcomes.

- Tertile 1: Median heart rate 60 bpm
- Tertile 2: Median heart rate 72 bpm
- Tertile 3: Median heart rate 85 bpm

Heart rate is an important predictor of mortality and CV outcomes in patients with HF

WHFH = worsening heart failure hospitalization; *symptomatic HF defined as NYHA functional class II to IV.
Ivabradine

- Specific inhibitor of the $I_f$ current in SA node
- This so-called “funny” current controls the rate of spontaneous activity of SA node myocytes
- Reduces the slope for diastolic depolarization
  - Prolongs diastolic duration $\rightarrow$ slows heart rate
- No action on other cardiac channels
- Does not modify cardiac contractility

SHIFT Study: Design

Inclusion Criteria:
- ≥18 years; symptomatic HF NYHA class II to IV; ischemic/non-ischemic etiology
- LV systolic dysfunction (EF ≤35%); heart rate ≥70 bpm; sinus rhythm
- Documented hospital admission for worsening HF ≤12 months

Ivabradine 5 mg bid; titrate to 7.5 mg bid on D14; adjust dose to 7.5/5/2.5 mg bid according to HR and tolerability

Primary endpoint: CV death or hospitalization for worsening HF

7,411 Screened
HF Patients (n=6,558)

Ivabradine 5 mg bid; titrate to 7.5 mg bid on D14; adjust dose to 7.5/5/2.5 mg bid according to HR and tolerability

n=3264
D 0
D 14
Median follow-up 22.9 months

Placebo bid

n=3241
D 0
D 14

Primary endpoint: CV death or hospitalization for worsening HF

SHIFT = ivabradine and outcomes in chronic heart failure study; D 0 = day 0; D 14 = day 14.
Background Beta-Blocker Treatment


<table>
<thead>
<tr>
<th>Category</th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB at Randomization</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>At Least 50% Target Daily Dose</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Target Daily Dose</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

SHIFT Study: Mean Heart Rate

Mean ivabradine dose was 6.4 mg bid at 1 month and 6.5 mg bid at 1 year

HR reduction: ivabradine ↓ HR 10.9 bpm at day 28, 9.1 bpm at 1 year, and 8.1 at study end vs. placebo.

SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF

Ivabradine (n=3241)
Placebo (n=3264)

Placebo
937 events (29%)
Ivabradine
793 events (24%)

HR 0.82 (95% CI, 0.75–0.90)  p<0.0001
ARR = 5%, NNT = 20

ARR = absolute risk reduction; NNT = number needed to treat.
### SHIFT Study: Effect of Ivabradine on Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>HR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>24%</td>
<td>29%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16%</td>
<td>17%</td>
<td>0.90</td>
<td>0.092</td>
</tr>
<tr>
<td>Death from HF</td>
<td>3%</td>
<td>5%</td>
<td>0.74</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>38%</td>
<td>42%</td>
<td>0.89</td>
<td>0.003</td>
</tr>
<tr>
<td>Any CV hospitalization</td>
<td>30%</td>
<td>34%</td>
<td>0.85</td>
<td>0.0002</td>
</tr>
<tr>
<td>CV death, hospitalization for worsening HF, or hospitalization for non-fatal MI</td>
<td>25%</td>
<td>30%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SHIFT Study: Effect of Ivabradine in Patients at ≥50% BB Target Dose (n=3181)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>330 (11.9 PY)</td>
<td>362 (13.3 PY)</td>
<td>0.90</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>176 (5.9 PY)</td>
<td>175 (5.9 PY)</td>
<td>1.00</td>
<td>ns</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>213 (7.7 PY)</td>
<td>260 (9.6 PY)</td>
<td>0.81</td>
<td>p=0.021</td>
</tr>
</tbody>
</table>

BB = beta blocker; ns = not significant.
## SHIFT Study: Incidence of Selected Adverse Events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>45% (1450)</td>
<td>48% (1553)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>75% (2439)</td>
<td>74% (2423)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25% (804)</td>
<td>29% (937)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>5% (150)</td>
<td>1% (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6% (184)</td>
<td>1% (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9% (306)</td>
<td>8% (251)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>3% (89)</td>
<td>1% (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1% (17)</td>
<td>&lt;1% (7)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Phosphenes are luminous phenomena; bradycardia is defined here as resting heart rate lower than 50 bpm or the patient had signs or symptoms related to bradycardia.

Summary of SHIFT Study

• HFrEF + elevated HR is associated with poor outcomes.
  – Primary composite endpoint with placebo = 18%/yr

• Ivabradine reduced CV death or hospitalization for worsening heart failure by 18%.
  – ARR = 5%; NNT = 20

• This beneficial effect was driven mainly by a favorable effect on HF death/admission (RRR 26%).

• Treatment with ivabradine was safe and well tolerated.

RRR = relative risk reduction.
## FDA-Approved Ivabradine

<table>
<thead>
<tr>
<th><strong>Ivabradine</strong></th>
</tr>
</thead>
</table>

### Indication
To reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤ 35% who are in sinus rhythm with resting HR ≥70 bpm and either are on maximum-tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

### Dosage
Start with 5 mg twice daily. After 2 weeks of treatment, adjust dose based on HR. Max is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, start with 2.5 mg twice daily.

### Contraindications
Acute decompensated HF; BP <90/50 mmHg; sick sinus syndrome or third-degree AV block unless a functioning demand pacemaker is present; resting HR < 60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence. WARNING – fetal toxicity.

### Side effects
Occurring in ≥1% of patients are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).

## Pharmacological Treatment for Stage C HFrEF

### Recommendation for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOR</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</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>

COR = class of recommendation; LOR = level of recommendation; GDEM = guideline-directed evaluation and management.  
Transitions of Care
After hospitalization for decompensated heart failure, the subsequent risk for mortality over the next year is:

A. <5%
B. 5-10%
C. 11-20%
D. 21-30%
E. 31-40%

D. 21-30%
Rehospitalizations in Heart Failure

- Nearly one in four patients (~25%) hospitalized with HF is rehospitalized within 30 days of discharge.

- 30 day rates of rehospitalizations in HF have risen over the past 2 decades.

- Rehospitalizations for HF vary widely by hospital, even after adjusting for case mix and other factors.

- HF rehospitalizations may be preventable, but effective strategies to prevent rehospitalizations were traditionally underutilized due to lack of incentives.

- Most of the cost associated with the care of HF patients is attributable to these rehospitalizations.

Causes of Hospital Readmissions for Heart Failure

- Inappropriate Rx: 16%
- Diet Noncompliance: 24%
- Medication Noncompliance: 24%
- Failure to Seek Care: 19%
- Other: 17%

Role of Hospital-Based Providers

- Ensure patients received guideline recommended therapies
- Champion implementation of guideline-based treatment protocols
- Provide clear and comprehensive discharge instructions
- Provide HF education

Repeat Hospitalizations Predict Mortality

All-Cause Mortality after Each Subsequent Hospitalization for HF

Kaplan-Meier Cumulative Mortality

Time since Admission

Heart Failure

4th Admission (n=417)
3rd Admission (n=1,123)
2nd Admission (n=14,374)
1st Admission (n=14,374)

Continuity of HF Care

Reliable Care: Not Missing the Steps

Hospital ED
- Diagnosis
- Admit
- CCU?
- Acute Rx
- Evaluation

CCU Telemetry
- Intravenous meds
- Oral meds
- LV function
- Echo and/or cath?
- Other evaluation
- Transfer to floor

Discharge
- Oral meds
- Other treatment?
- Other evaluation
- Patient education
- Follow-up
- Disease management

Early Post DC
- Right meds?
- Titration?
- Patient education
- Disease management
- Continuity device?

Outpatient
- On right meds?
- On right dose?
- Volume status
- Re-assess EF
- Device?
- Self-manage?
- Other issues?

Rx = medication(s); CCU = critical care unit.
Hospital Discharge: Transitions of Care

<table>
<thead>
<tr>
<th>COR</th>
<th>LOR</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>Performance improvement systems in the hospital and early post discharge outpatient setting to identify HF for GDMT</td>
</tr>
</tbody>
</table>

Before hospital discharge, at the first post discharge visit, and in subsequent follow-up visits, the following should be addressed:

A. Initiation of GDMT if not done or contraindicated
B. Causes of HF, barriers to care, and limitations in support
C. Assessment of volume status and blood pressure with adjustment of HF therapy
D. Optimization of chronic oral HF therapy
E. Renal function and electrolytes
F. Management of comorbid conditions
G. HF education, self-care, emergency plans, and adherence
H. Palliative or hospice care

GDMT = guideline directed medical therapy.
Hospital Discharge: Transitions of Care (continued)

<table>
<thead>
<tr>
<th>Recommendation or Indication</th>
<th>COR</th>
<th>LOR</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I B</td>
<td>Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I B</td>
<td>Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ila B</td>
<td>A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge is reasonable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ila B</td>
<td>Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GDMT = guideline directed medical therapy.
Evidence-Based Interventions to Reduce Rehospitalization in HF

- Pre-discharge HF education by trained educators
- Discharge medication programs
- Comprehensive discharge planning
- Early post-discharge physician follow-up
- Home visits by RNs and/or physicians
- Comprehensive HF disease management programs
- Implantable hemodynamic sensors

RN = registered nurse.
Risk of Death High in All NYHA Functional Classifications

- “Stable” patients with HFrEF on standard of care therapy still had risk of CV death or HF hospitalization
- 25.4% of NYHA class II patients experienced CV death or HF hospitalization
- 22.5% of patients with no prior history of HF hospitalization experienced CV death or HF hospitalization

MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.
“Stable” Patients with HFrEF on GDMT Remains at Risk of CV Death or HF Hospitalization

Patients with mild symptoms and physical limitations (NYHA class II) were still at risk

- 69% of patients randomized to enalapril were NYHA class II\(^1\) (n=2921/4212)
- 25.4% of these NYHA class II patients experienced CV death or HF hospitalization\(^2\) (n=742/2921)

Patients with no prior history of HF hospitalization were still at risk

- 37% of patients randomized to enalapril had no prior history of HF hospitalization\(^1\) (n=1545/4212)
- 22.5% of these patients experienced CV death or HF hospitalization\(^2\) (n=348/1545)

GDMT = guide-directed medical therapy.

Conclusions

• 5.7 million people in the United States have heart failure.
  – 825,000 new HF cases annually
  – Projected to increase by 46% from 2012 to 2030, resulting in >8 million people with HF

• About half of people who develop heart failure die within 5 years of diagnosis.

• There are multiple medications available for the treatment of HFrEF, including new medications that are guideline-recommended.

• There are few effective therapies for patients with normal ejection fraction HF.

• Re-admissions for HF remain a continuing and costly problem.

• Strategies to reduce readmission include early follow-up, guideline-directed therapy, and improved communication among clinicians.