A Review of Chronic Heart Failure and Updates in Pharmacotherapy

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Cardiology Clinical Pharmacist
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Disclosure

• The speaker has no actual or potential conflict of interest in relation to this presentation.
Pharmacist Learning Objectives

• Describe patient outcomes and financial burden associated with heart failure

• Demonstrate understanding of recommended pharmacotherapy for heart failure with reduced and preserved ejection fraction

• Given a patient case, develop an evidence-based patient-specific pharmacotherapy plan for heart failure

• Given a patient case, analyze the appropriateness of utilizing sacubitril/valsartan (Entresto®) and ivabradine (Corlanor®)
Technician Learning Objectives

• Describe patient outcomes and financial burden associated with heart failure

• Recognize evidence-based classes of medications used for management of heart failure with reduced ejection fraction

• Identify medications that are not appropriate for patients with chronic heart failure

• Discuss the appropriate transition from an angiotensin converting enzyme inhibitor (ACE inhibitor) to sacubitril/valsartan
Background

- **Definition:**
  - Progressive clinical syndrome characterized by reduction in systemic perfusion due to ↓ CO caused by cardiac pump impairment
  - May be systolic or diastolic dysfunction or a combination
Review of Cardiovascular Hemodynamics

\[ \text{CO} = \text{SV} \times \text{HR} \]

- **Preload**
  - Venous Return
  - Venous Pressure

- **Contractility**

- **Afterload**
  - Systemic Vascular Resistance

**Edema Detection:**

- **PCWP**
  - Normal: 6-12 mmHg
  - HF: 16-18 mmHg

**Normal EF:**

- 50-70%
Heart Failure: Etiology

Left ventricular systolic dysfunction:

- Myocardial infarction
- Severe CAD
- Hypertensive heart disease
- Toxin-induced cardiomyopathy (drugs, alcohol)
- Congenital heart disease

- Incidence: 60% of all HF patients
- Dilated cardiomyopathy (balloon shape heart with reduced muscle mass)
- Associated with in ↓ EF (≤40%)
Heart Failure: Etiology

- Diastolic dysfunction (impaired LV relaxations)
  - Chronic HTN
  - Ischemic heart disease
  - AV valve stenosis
  - Pericardial disease

- Hypertrophic cardiomyopathy
  - Large heart, small ventricles
  - Associated with preserved EF (≥50%)
Heart Failure: Epidemiology

- 6 million American have HF
  - > 600,000 new cases are diagnosed each year
- > 1 million hospital discharge annually (most common discharge DX is patients > 65 yo)
- Tremendous economic impact!
  - Annual expenditure: $39 billion
- Poor prognosis (despite ↓ in mortality rate): overall 5-year survival: 50%
  - 40% of patients will die from sudden death (d/t ventricular arrhythmia)
Pathophysiology of Heart Failure

Myocardial Damage: ↓ LV function, ↓ CO, ↓ renal perfusion

Neuro-Hormonal Activation

SNS Activation
↑ NE

RAAS Activation
↑ Angiotensin II
↑ Aldosterone

↑ Vasopressin (ADH)
↑ Endothelin
Neuro-Hormonal Compensatory Responses

**SNS Activation**

\[ \uparrow \text{NE} \]

**Beneficial Effect:**
- Tachycardia, \( \uparrow \) contractility
- Ventricular hypertrophy and remodeling to maintain CO

**Detrimental Effect:**
- Diastolic and systolic dysfunction
- Precipitate ventricular arrhythmia
- Cardiac fibrosis
- Sudden cardiac death

**RAAS Activation**

\[ \uparrow \text{Angiotensin II} \]
\[ \uparrow \text{Aldosterone} \]

**Beneficial Effect:**
- \( \uparrow \) preload through Na & H2O retention to optimize SV and CO
- Vasoconstriction to maintain BP

**Detrimental Effect:**
- Pulmonary congestion and edema
- \( \uparrow \) SVR (after load) which can reduce SV
- Myocardial fibrosis, myocardial apoptosis, death
# Heart Failure Stages & Corresponding NYHA Functional Class

<table>
<thead>
<tr>
<th>Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>At risk for HF without structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Structural heart disease without sign and symptoms of HF</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Structural heart disease with prior or current symptoms of HF</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Refractory HF requiring specialist interventions</td>
</tr>
</tbody>
</table>
Management of Chronic Heart Failure
Goals of Therapy

• Modify risk factors
  – **HTN:** goal BP < 130/80 mmHg *
    • COR I, LOE B-R: stage A HF
    • COR I, LOE C-EO: HFrEF
    • COR I, LOE C-LD: HFpEF

• Reduce morbidity and mortality

• Minimize Na\(^+\) and H2O retention (COR IIa, LOE C)

• Minimize HF symptoms

• Block compensatory neuro-hormonal activation

• Slow progression of worsening cardiac function

Drugs to Avoid in Patients with HFrEF

• Class III Harm (LOE B)
  – NDHP calcium channel blockers
  – NSAIDs (including COX2 inhibitors)
  – Antiarrhythmic agents: class I and III (except for amiodarone and doxifitide)
  – Systemic corticosteroids
  – Mioxidil
  – Metformin
  – Cilostazol
  – Thiazolidinediones

• Class III Harm (LOE C)
  – Long-term use of infused positive inotropes
2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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### Applying Classification of Recommendation and Level of Evidence

<table>
<thead>
<tr>
<th>CLASS I</th>
<th>Benefit &gt;&gt; Risk</th>
<th>Procedure/Treatment SHOULD be performed/administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Additional studies with focused objectives needed; IT IS REASONABLE to perform procedure/administer treatment</td>
</tr>
<tr>
<td>CLASS IIb</td>
<td>Benefit ≥ Risk</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful; Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td>CLASS III</td>
<td>No Benefit or CLASS III Harm</td>
<td>Procedure/Test</td>
</tr>
<tr>
<td>COR III: No benefit</td>
<td>Not Helpful</td>
<td>No Proven Benefit</td>
</tr>
<tr>
<td>COR III: Harm</td>
<td>Excess Cost w/o Benefit or Harmful</td>
<td>Harmful to Patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>Multiple populations evaluated*</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL B</td>
<td>Limited populations evaluated*</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td>LEVEL C</td>
<td>Very limited populations evaluated*</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses
- Recommendation in favor of treatment or procedure being useful/effective
- Some conflicting evidence from multiple randomized trials or meta-analyses
- Recommendation’s usefulness/efficacy less well established
- Greater conflicting evidence from multiple randomized trials or meta-analyses
- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses
- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Evidence from single randomized trial or nonrandomized studies
- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Only expert opinion, case studies, or standard of care
- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Only expert opinion, case studies, or standard of care

Yancy CW et al. JACC. 2013;62(16):e147-e239
HF Stage A Recommendations

Treat hypertension and dyslipidemia per contemporary guidelines

Other conditions that may lead to or contribute to HF, such as obesity, DM, tobacco use, should be controlled or avoided

Yancy CW et al. JACC. 2013;62(16):e147-e239
## Recommendations for Treatment of Stage B HF

<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>C</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 $\leq$ 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>
SOLVD Prevention Trial

Studies of Left Ventricular Dysfunction

4,228 patients with EF ≤ 35% randomized to enalapril vs. placebo

Relative Risk Reduction 29%

Captopril vs. Valsartan
Post MI with Low LVEF (N= 14,703)

Hazard Ratio 1.0

Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)

All-Cause Mortality

1,959 patients with LVEF <40% randomized to carvedilol vs. placebo for 24 months

Pharmacologic Therapy for Stage C HFrEF: 2013 ACC/AHA Guidelines

HFrEF Stage C NYHA Class I – IV Treatment:

Class I, LOE A
ACEI or ARB AND Beta Blocker

For all volume overload, NYHA class II-IV patients
Add
Class I, LOE C Loop Diuretics

For persistently symptomatic African Americans, NYHA class III-IV
Add
Class I, LOE A Hydral-Nitrates

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL
Add
Class I, LOE A Aldosterone Antagonist
# Loop Diuretic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Daily Dose</strong></td>
<td>20-40 mg once or BID</td>
<td>0.5-1 mg once or BID</td>
<td>10-20 mg once</td>
</tr>
<tr>
<td><strong>Ceiling Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ClCr</td>
<td>80-160 mg</td>
<td>1-2 mg</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>20-50 mL/min</td>
<td>160 mg</td>
<td>2 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>400 mg</td>
<td>8-10 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>~ 50%</td>
<td>80-90%</td>
<td>80-100%</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>affected by food?</td>
<td>Yes (decreased by food)</td>
<td>Yes (decreased by food)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Duration of Effect</strong></td>
<td>6-8 h</td>
<td>4-6 h</td>
<td>12-16 h</td>
</tr>
</tbody>
</table>

**Conversion**: furosemide 20-40 mg = torsemide 10 mg = bumetanide 1 mg
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
<th>Mean Doses Achieved in Clinical Trials</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>122.7 mg/d</td>
<td>ELITE 2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10-20 mg BID</td>
<td>16.6 mg/d</td>
<td>CONSENSUS 3, SOLVD Treatment 4</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5-10 mg daily</td>
<td>40 mg daily</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg daily</td>
<td>40 mg daily</td>
<td>35 mg/d</td>
<td>ATLAS 5</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8-16 mg daily</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 -2.5 mg daily</td>
<td>10 mg daily</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Effect of ACE Inhibitors in HF

CONSENSUS and SOLVD

CONSENSUS*
NYHA Class IV

SOLVD Treatment†
NYHA Class II–III

Placebo
(n = 126)

Enalapril
(n = 126)

Placebo
(n = 1284)

Enalapril
(n = 1285)

Mortality, %

0
10
20
30
40
50
60
70
80

0 6 12 18 24 30 36 42 48

Months

*Risk reduction 40% (P = 0.003).
†Risk reduction 16% (P = 0.0036).

# Angiotensin II Receptor Blockers (ARBs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
<th>Mean Doses Achieved in Clinical Trials</th>
<th>Clinical Trials</th>
</tr>
</thead>
</table>
| Candesartan| 4-8 mg daily       | 32 mg daily  | 24 mg/d                                | CHARM-Overall ^2  
CHARM-Alternative ^3  
CHARM-Added ^4 |
| Losartan   | 25-50 mg daily     | 150 mg daily | 129 mg/d                               | HEAAL ^5               |
| Valsartan  | 20-40 mg BID       | 160 mg BID   | 254 mg/d                               | Val-HeFT ^6  
VALIANT ^7 |

# Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
<th>Maximum Dose Achieved in Clinical Trials</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>50 mg BID (if &gt; 85 kg) 25 mg BID (if &lt; 85 kg)</td>
<td>37 mg/d</td>
<td>COPERNICUS ²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COMET ⁵</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg once</td>
<td>80 mg once</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Metoprolol XL</td>
<td>12.5 mg once</td>
<td>200 mg once</td>
<td>159 mg/d</td>
<td>MERIT-HF ³</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
<td>8.6 mg/d</td>
<td>CIBIS II ⁴</td>
</tr>
</tbody>
</table>

### Survival studies of β-blockade in HF

<table>
<thead>
<tr>
<th>Study</th>
<th>β-blocker</th>
<th>Patients (N)</th>
<th>Total mortality</th>
<th>NYHA class</th>
<th>EF mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-II</td>
<td>Bisoprolol</td>
<td>2647</td>
<td>228/156</td>
<td>III/IV</td>
<td>28%</td>
<td>0.0001</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol succinate CR/XL</td>
<td>3991</td>
<td>217/145</td>
<td>II-IV</td>
<td>28%</td>
<td>0.00009</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>2289</td>
<td>190/130</td>
<td>III/IV*</td>
<td>20%</td>
<td>0.00013</td>
</tr>
<tr>
<td>All pooled</td>
<td></td>
<td>8927</td>
<td>635/431</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk and 95% CI

---


*not recorded in COPERNICUS, but placebo mortality indicates III/IV
### Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
<th>Maximum Dose Achieved in Clinical Trials</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg once</td>
<td>25 mg once to BID</td>
<td>26 mg/d</td>
<td>RALES. 2</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
<td>42.6 mg/d</td>
<td>EMPHASIS-HF 3</td>
</tr>
</tbody>
</table>

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New Pharmacologic Therapies
Sacubitril/Valsartan (Entresto®)

• FDA Approval: 2015

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.
• When pregnancy is detected, discontinue ENTRESTO as soon as possible.
• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

• **Indication:** ↓ CV death and hospitalization for HF in patient with NYHA Class II-IV HFrEF in place of an ACEI or ARB
Sacubitril/Valsartan (Entresto®)

The diagram illustrates the effects of Sacubitril/Valsartan (Entresto®) on the Renin Angiotensin System (RAS) and the Natriuretic Peptide System (NPS) in the context of heart failure.

**Renin Angiotensin System (liver secretion):**
- Angiotensinogen
  - Angiotensin I
  - Angiotensin II
  - AT₁ receptor

**Valsartan:**
- Blocks the AT₁ receptor

**Sacubitril (AHU377):**
- Increases neprilysin activity
  - ANP
  - BNP
  - CNP
  - Adrenomedullin
  - Substance P
  - Bradykinin

**LBQ657:**
- Inhibits neprilysin

**Heart Failure:**
- Vasoconstriction
- Elevated blood pressure
- Increased sympathetic tone
- Aldosterone elevation
- Increased fibrosis
- Ventricular hypertrophy

**Natriuretic Peptide System (pro-BNP):**
- ANP
- BNP
- CNP
- Adrenomedullin
- Substance P
- Bradykinin
- Angiotensin II
- Others

**Neprilysin:**
- Inactive fragments
- NT-pro BNP (not a substrate for neprilysin)

**Benefits:**
- Vasodilation
- Lower blood pressure
- Reduced sympathetic tone
- Reduced aldosterone levels
- Natriuresis/Diuresis
### Sacubitril/Valsartan (Entresto®)

**Dosing and Titration**

<table>
<thead>
<tr>
<th>Patients receiving a <strong>total daily dose of &gt;10 mg of enalapril</strong> or therapeutically equivalent doses of another ACEi, for example:&lt;br&gt;• Lisinopril &gt;10 mg&lt;br&gt;• Ramipril &gt;5 mg</th>
<th><strong>Stop ACEi 36 hours before starting ENTRESTO</strong></th>
<th><strong>Start ENTRESTO at the recommended dose of 49/51 mg twice daily</strong></th>
<th><strong>Double the dose of ENTRESTO after 2 to 4 weeks, as tolerated by the patient, to reach the target maintenance dose of 97/103 mg twice daily</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving a <strong>total daily dose of ≤10 mg of enalapril</strong> or therapeutically equivalent doses of another ACEi, for example:&lt;br&gt;• Lisinopril ≤10 mg&lt;br&gt;• Ramipril ≤5 mg</td>
<td><strong>Stop ACEi 36 hours before starting ENTRESTO</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
</tr>
</tbody>
</table>

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12/23/2017
Relevant History

- OVERTURE Trial
  - Omapatrilat vs. enalapril in patients with chronic HF
  - Treatment Arms: enalapril 10 mg BID vs. omapatrilat 40 mg daily
  - Subjects: NYHA II-IV HF
  - Primary Endpoint: combined risk of death or hospitalization for HF requiring IV treatment
  - Results:
    - Primary endpoint: HR 0.94; 95% CI: 0.86-1.03, P=0.187 (omapatrilat was non-inferior to enalapril, but not superior)

*Circulation. 2002;106(8):920-6*
Relevant History

- OCTAVE Trial
  - Omapatrilat vs. enalapril in patients with HTN
  - Treatment Arms: enalapril 40 mg daily vs. omapatrilat 80 mg daily
  - Subjects: untreated or uncontrolled HTN
  - Results: ↓ BP by > 3.6 mmHg with omapatrilat
  - Angioedema more frequent with omapatrilat (2.17% vs 0.68%) = 3.2 x higher than ACEI
    - Angioedema requiring hospitalization: 9.5x higher than ACEI
PRADIGM HF Trial

• Angiotensin-Nephrilysin inhibition vs. enalapril in chronic HFrEF
  – Subjects: NYHA Class II-IV (EF ≤ 35%)
    • BNP ≥ 150 pg/mL
    • BNP ≥ 100 pg/mL + HF hospitalization w/in previous 12 months
    • On BB + enalapril ≥ 10 mg daily
  – Exclusion Criteria
    • GFR < 30 mL/min
    • SBP < 95 mmHg
    • K > 5.4 mmol/L
    • H/O angioedema
PARADIGM-HF Trial

**SINGLE-BLIND RUN-IN PERIOD**
(6 to 8 weeks)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>15 days</td>
<td>10,513</td>
</tr>
<tr>
<td>Entresto</td>
<td>29 days</td>
<td>9,419</td>
</tr>
</tbody>
</table>

**DOUBLE-BLIND PERIOD**
(Duration was event-driven; median follow-up duration was 27 months)

- **Entresto**
  - 97/103 mg twice daily
  - N = 4,209

- **(1:1 RANDOMIZATION)**

  **Entresto**
  - 97/103 mg twice daily
  - N = 4,233

- **Enalapril**
  - 10 mg twice daily
  - N = 4,233
PRADIGM HF Trial

• **Primary Outcome**
  – Composite of CV death or first hospitalization for HF

• **Safety Outcome**
  – Hypotension
  – Hyperkalemia
  – Renal impairment
  – Angioedema
# PRADIGM HF Trial

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age - yr</strong></td>
<td>63.8±11.5</td>
<td>63.8±11.3</td>
</tr>
<tr>
<td><strong>White Race – no. (%)</strong></td>
<td>2763 (66)</td>
<td>2781 (66)</td>
</tr>
<tr>
<td><strong>SCr – mg/dL</strong></td>
<td>1.13±0.3</td>
<td>1.12±0.3</td>
</tr>
<tr>
<td><strong>LVEF - %</strong></td>
<td>29.6±6.1</td>
<td>29.4±6.3</td>
</tr>
<tr>
<td><strong>NYHA Functional Class – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>180 (4.3)</td>
<td>209 (5)</td>
</tr>
<tr>
<td>II</td>
<td>2998 (71.6)</td>
<td>2921 (69.3)</td>
</tr>
<tr>
<td>III</td>
<td>269 (23.1)</td>
<td>1049 (24.9)</td>
</tr>
<tr>
<td>IV</td>
<td>33 (0.8)</td>
<td>27 (0.6)</td>
</tr>
<tr>
<td><strong>Pretrial Use of ACEI – no. (%)</strong></td>
<td>3266 (78)</td>
<td>3266 (77.5)</td>
</tr>
<tr>
<td><strong>Diuretics – no. (%)</strong></td>
<td>3363 (80.3)</td>
<td>3375 (80.1)</td>
</tr>
<tr>
<td><strong>Beta Blockers – no. (%)</strong></td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
</tbody>
</table>
PRADIGM HF Trial

- **Results: Primary Outcome**

![Graph showing cumulative probability over days since randomization for Enalapril and LCZ696.](image)

Hazard ratio, 0.80 (95% CI, 0.73–0.87)  
P<0.001

RRR: 20%  
NNT: 21
PRADIGM HF Trial

- Results: Primary Outcome

**Hospitalization for Heart Failure**

- Hazard ratio, 0.79 (95% CI, 0.71–0.89)
- P<0.001

- 21% RRR
- NNT: 36

**Death from Cardiovascular Causes**

- Hazard ratio, 0.80 (95% CI, 0.71–0.89)
- P<0.001

- 20% RRR
- NNT: 32
## Table 3. Adverse Events during Randomized Treatment.*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without 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>

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P = 0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P = 0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P = 0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.
PARAMOUNT Trial

- Phase 2, randomized, parallel-group, double-blind
- Subjects: NYHA II–III HF, EF ≥ 45% , and NT-proBNP > 400 pg/mL
- Arms: LCZ696 titrated to 200 mg BID (N:149) vs. valsartan titrated to 160 mg BID (N: 152)
- Duration: 9 months
- Primary Endpoint: change in NT-proBNP
PARAMOUNT Trial

• Results: Primary Endpoint

[Graph showing changes in NT-proBNP levels over weeks after randomisation for LCZ696 and Valsartan, with p-values indicated for each comparison.]
Ivabradine (Corlanor®)

• FDA Approval: 2015

• **Indication:** to reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic heart failure with LVEF ≤ 35%, who are in sinus rhythm with resting HR ≥ 70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Ivabradine (Corlanor®): Mechanism of Action
Ivabradine (Corlanor®)

• Dosing and Administration

| 5 mg PO BID with meals | 2.5 mg, 5 mg, 7.5 mg PO BID w/ food |

According to heart rate and tolerability

14 days

Recommended titration

• HR > 60 bpm: ↑ dose to 7.5 mg BID
• HR 50-60 bpm: maintain 5 mg BID
• HR < 50 bpm, sign and symptoms of bradycardia: ↓ dose to 2.5 mg BID (if current dose 2.5 mg BID, then D/C)
Ivabradine (Corlanor®)

• Special Populations
  – Renal impairment: no dosage adjustment is needed if ClCr 15-60 mL/min. No data available for ClCr< 15 mL/min
  – Child-Pugh A and B hepatic impairment: no dosage adjustment needed
  – Child-Pugh C hepatic impairment: Contraindicated

• Kinetics
  – Metabolism: hepatic CYP3A4
  – T1/2: 6 hrs
Ivabradine (Corlanor®)

• Contraindications
  • Acute decompensated HF
  • BP < 90/50 mmHg
  • Sick Sinus Syndrome, sinoatrial block, 3rd degree AV block
  • Resting HR < 60 bpm prior to treatment
  • Severe hepatic impairment
  • Concurrent use of potent CYP3A4 inhibitors

• Warning & precautions
  – Fetal toxicity: use effective contraception
  – Increased risk of atrial fibrillation with ivabradine
    • D/C if Atrial fibrillation develops
Ivabradine (Corlanor®)

• Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

• Drug Interactions

  – Concurrent potent CYP3A4 inhibitors: contraindicated
  – Concurrent potent CYP3A4 inducers: avoid
  – Concurrent diltiazem, verapamil, digoxin, amiodarone: caution
Phase III randomized, multinational, double-blind, placebo-controlled trial:

- **Ivabradden (n = 3268)**
  - 5 mg BID x14 days then titration based on HR and tolerability (max dose 7.5 mg BID)

- **Placebo (n = 3,290)**

Primary endpoints: composite of cardiovascular death or hospital admissions for worsening HF

**Exclusion criteria:** MI within past 2 month, afib, aflutter, AV pacing > 40% of the day, symptomatic hypotension

6,558 patients with symptomatic HF and LVEF ≤35% with NSR with HR ≥ 70, hospital admission for HF within previous year, on stable background treatment

**Median Follow-Up:** 22.9 month

Swedberg K et al. *Lancet.* 2010;376(9744): 875-85
Systolic Heart failure treatment with the Hf inhibitor ivabradine Trial

- Placebo (937 events)
- Ivabradine (793 events)

HR 0.82 (95% CI 0.75-0.90), p<0.0001

18% RRR

Swedberg K et al. Lancet. 2010;376(9744): 875-85
Ivabradine Placebo HR (95% CI) P value

Death from HF 3% 5% 0.74 (0.66-0.83) 0.014

# 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

## CLASS (STRENGTH) OF RECOMMENDATION

<table>
<thead>
<tr>
<th>CLASS I (STRONG)</th>
<th>Benefit &gt;&gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ Is recommended</td>
<td></td>
</tr>
<tr>
<td>▪ Is indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>▪ Should be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td>▪ Comparative-Effectiveness Phrases‡:</td>
<td></td>
</tr>
<tr>
<td>  ▪ Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>  ▪ Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IIa (MODERATE)</th>
<th>Benefit &gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ Is reasonable</td>
<td></td>
</tr>
<tr>
<td>▪ Can be useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>▪ Comparative-Effectiveness Phrases‡:</td>
<td></td>
</tr>
<tr>
<td>  ▪ Treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>  ▪ It is reasonable to choose treatment A over treatment B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IIb (WEAK)</th>
<th>Benefit &gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ May/might be reasonable</td>
<td></td>
</tr>
<tr>
<td>▪ May/might be considered</td>
<td></td>
</tr>
<tr>
<td>▪ Usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS III: No Benefit (MODERATE)</th>
<th>Benefit = Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Generally, LOE A or B use only)</td>
<td></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ Is not recommended</td>
<td></td>
</tr>
<tr>
<td>▪ Is not indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>▪ Should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS III: Harm (STRONG)</th>
<th>Risk &gt; Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ Potentially harmful</td>
<td></td>
</tr>
<tr>
<td>▪ Causes harm</td>
<td></td>
</tr>
<tr>
<td>▪ Associated with excess morbidity/mortality</td>
<td></td>
</tr>
<tr>
<td>▪ Should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

## LEVEL (QUALITY) OF EVIDENCE‡:

<table>
<thead>
<tr>
<th>LEVEL A</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ High-quality evidence‡ from more than 1 RCT</td>
</tr>
<tr>
<td>▪ Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>▪ One or more RCTs corroborated by high-quality registry studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL B-R (Randomized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Moderate-quality evidence‡ from 1 or more RCTs</td>
</tr>
<tr>
<td>▪ Meta-analyses of moderate-quality RCTs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL B-NR (Nonrandomized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td>▪ Meta-analyses of such studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL C-LD (Limited Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td>▪ Meta-analyses of such studies</td>
</tr>
<tr>
<td>▪ Physiological or mechanistic studies in human subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL C-EO (Expert Opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Consensus of expert opinion based on clinical experience</td>
</tr>
</tbody>
</table>

---

55
### Pharmacologic Treatments for Stage C HFrEF: Recommendations

#### Renin-Angiotensin System Inhibition With ACE Inhibitor, ARB, or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACEI: A</td>
<td>The clinical strategy of inhibition of renin-angiotensin system with <strong>ACEI, OR ARB, OR ARNI</strong> 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>
</tbody>
</table>

*Circulation. 2016;134:1-46*
Pharmacologic Treatments for Stage C HFrEF: Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for Stage C HFrEF: Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACEI or within 36 hours of the last dose of an ACEI</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-E0</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for Stage C HFrEF: Recommendations

<table>
<thead>
<tr>
<th>Ivabradine</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td></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</td>
</tr>
</tbody>
</table>

Pharmacologic Management of Stage C HFpEF
Clinical Trials of Pharmacologic Treatment of Patients with HFpEF

• Drugs that improved clinical outcomes:
  – Candesartan?

• Drugs that failed to improve clinical outcomes:
  – Digoxin
  – Spironolactone (significant ↓ in HF hospital admission)
  – Irbesartan
  – Isosorbide mononitrate
  – Sildenafil
CHARM-Preserved

Hazard ratio 0.89
(95% CI 0.77–1.03), p=0.118

adjusted hazard ratio 0.86, p=0.051

Number at risk
Candesartan 1514 1458 1377 833 182
Placebo 1509 1441 1359 824 195

TOPCAT Trial

Hazard ratio, 0.89 (95% CI, 0.77–1.04)
P = 0.14 by log-rank test

No. at Risk
Spironolactone 1722 1502 1168 870 614 330 53
Placebo 1723 1462 1145 834 581 331 53
TOPCAT Trial

Estimated Cumulative Proportion of Patients Hospitalized for Heart Failure

Placebo  
Spironolactone

Hazard ratio, 0.83 (95% CI, 0.69–0.99)  
P=0.04 by log-rank test

No. at Risk  
Spironolactone  
1722  1502  1167  869  613  330  53
  
Placebo  
1723  1464  1148  837  583  332  53
Patient Case

• LS is a 48 yo Caucasian F with ischemic cardiomyopathy (EF 20%) who presents to your clinic with chief complaint of dyspnea and fatigue that is limiting her physical activity (NYHA Class III). Her medications include lisinopril 40 mg daily, furosemide 40 mg BID, Carvedilol 25 mg BID and spironolactone 25 mg daily. Her most recent laboratory results and vitals signs are within level of normal. What is the best approach for management of her HF?
Patient Case

a. Increase lisinopril to 80 mg daily
b. Switch lisinopril to sacubitril/valsartan
c. Increase spironolactone to 50 mg daily
d. Add hydralazine/nitrates
Patient Case

a. Increase lisinopril to 80 mg daily
b. Switch lisinopril to sacubitril/valsartan
c. Increase spironolactone to 50 mg daily
d. Add hydralazine/nitrates
Patient Case

How do you transition from lisinopril to sacubitril/valsartan for this patient?
Pharmacist Learning Assessment

Describe which patient(s) described below are good candidate(s) for prescribing ivabradine?

a. 89 yo M with chronic atrial fibrillation and LVEF 30%

b. 70 yo F with NSR, resting HR > 70 bpm, and LVEF 60%

c. 55 yo M with NSR, resting HR 50 bpm, and LVEF 35%

d. 66 yo F with NSR, resting HR 90 bpm, and LVEF 25%
Pharmacist Learning Assessment

Describe which patient(s) described below are good candidate(s) for prescribing ivabradine?

a. 89 yo M with chronic atrial fibrillation and LVEF 30%

b. 70 yo F with NSR, resting HR > 70 bpm, and LVEF 60%

c. 55 yo M with NSR, resting HR 50 bpm, and LVEF 35%

d. 66 yo F with NSR, resting HR 90 bpm, and LVEF 25%
Pharmacist Learning Assessment

Which of the following statements is **CORRECT**?

a. Compared to losartan, sacubitril/valsartan is shown to reduce CV mortality by 20%

b. Sacubitril/valsartan is associated with statistically significant incidence of angioedema when compared to enalapril

c. Sacubitril/valsartan is generally associated with more hypotension compared to enalapril

d. Enalapril has lower risk of renal impairment and hyperkalemia compared to sacubitril/valsartan
Pharmacist Learning Assessment

Which of the following statements is **CORRECT**?

a. Compared to losartan, sacubitril/valsartan is shown to reduce CV mortality by 20%

b. Sacubitril/valsartan is associated with statistically significant incidence of angioedema when compared to enalapril

c. **Sacubitril/valsartan is generally associated with more hypotension compared to enalapril**

d. Enalapril has lower risk of renal impairment and hyperkalemia compared to sacubitril/valsartan
Technician Learning Assessment

What is an example of medications that should be avoided in patients with HF and reduced ejection fraction?

a) Lisinopril
b) Amlodipine
c) Prednisone
d) Simvastatin
Technician Learning Assessment

What is an example of medications that should be avoided in patients with HF and reduced ejection fraction?

a) Lisinopril
b) Amlodipine
c) Prednisone
d) Simvastatin
Which of the following is NOT considered an evidence-based drug therapy for management of HF with reduced ejection fraction?

a) Lisinopril
b) Carvedilol
c) Spironolactone
d) Amlodipine
Technician Learning Assessment

Which of the following is **NOT** considered an evidence-based drug therapy for management of HF with reduced ejection fraction?

a) Lisinopril  
b) Carvedilol  
c) Spironolactone  
d) Amlodipine
Questions?