New and Emerging Therapies for Chronic Heart Failure

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www.fshp.org
Disclosure

• I do not have any relevant financial relationships to report
Pharmacist Objectives

• Discuss the mechanism of action for new and emerging heart failure (HF) therapies

• Evaluate pivotal approval trials of the new HF medications

• Examine special considerations for initiation of newly approved therapy
Technician Objectives

• Become familiar with pathophysiology of HF and the medication targets

• Understand classifications of HF

• List storage and handling considerations
Heart Failure (HF)

• Complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood
  – Manifests as dyspnea, fatigue, and fluid retention

• Most patients have symptoms due to impaired left ventricular (LV) myocardial function
Epidemiology

- ~5.1 million persons with HF
- >650,000 new cases annually

- Incidence increases with age
  - 20% lifetime risk for Americans >40 years of age

- African Americans at highest risk
  - Caucasian women at lowest risk
Financial Impact

• Primary diagnosis in >1 million hospitalizations annually
  – Patients at high risk of all-cause rehospitalization and 25% readmission rate at 1 month

• In 2013, HF costs exceeded $30 billion
  – Physician office visits cost $1.8 billion
HF in the Hospitalized Patient

• Acute decompensated HF
  – Leading cause of hospitalization in patients >65 years of age
  – Largest % of HF-related expenditures directly attributable to hospital costs

• 50% recurrent hospitalization at 6 months

• 1-year mortality rate of approximately 30%
Health-Related Quality of Life and Functional Status

• ↓ health-related quality of life (HRQOL)
  – Physical functioning and vitality

• Lack of improvement in HRQOL after discharge is a powerful predictor of rehospitalization and mortality

• Women with HF have consistently been found to have poorer HRQOL than men
Mortality

• Absolute mortality rate ~50% at 5 years
  – 7% of all cardiovascular deaths

• HF is mentioned in 1 of every 9 death certificates in the US
Risk Factors

• Hypertension
  – #1 cause
• Diabetes Mellitus

• Metabolic Syndrome

• Atherosclerotic Disease

• Acute Myocardial Infarction
Causes of Heart Failure

- Ischemic Heart Disease
- Cardiac Structural Abnormalities
  - Cardiomyopathies
    - Dilated
    - Familial
    - Endocrine and Metabolic
    - Toxic
    - Tachycardia-Induced
    - Peripartum
    - Inflammation-Induced
- Myocarditis
- Iron Overload
- Amyloidosis
- Cardiac Sarcoidosis
- Stress
HF and Ejection Fraction

• Heart Failure with Reduced Ejection Fraction (HFrEF)
  – Clinical diagnosis of HF and EF <40%

• Heart Failure with Preserved Ejection Fraction (HFpEF)
  – Variably classified as EF ≥40%, ≥45%, ≥50%, and ≥55%
  – Largely a diagnosis of exclusion
## Classification

### Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF&lt;sup&gt;38&lt;/sup&gt;</th>
<th>NYHA Functional Classification&lt;sup&gt;46&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B  Structural heart disease but without signs or symptoms of HF</td>
<td>I  No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C  Structural heart disease with prior or current symptoms of HF</td>
<td>I  No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
<tr>
<td>D  Refractory HF requiring specialized interventions</td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.
Progression of HF

- Myocardial Infarction
- Arrhythmias and Ventricular Dysfunction
- Sudden Death
- Stage B (structural damage/echo but asymptomatic)
- Remodeling
- Heart Failure
- Stage C & D
- Pump Failure
- Death
- Sudden Death

- Atherosclerosis
- Remodeling
- Left Ventricle Hypertrophy Diastolic Dysfunction

- Risk Factors:
  - Hypertension
  - Coronary Artery Disease
  - Valvular disease
  - Obesity
  - Diabetes
  - Kidney disease

- Stage A
What Causes Mortality

• Sudden or arrhythmic cardiac death (SCD)
  – Death within one hour of the onset of cardiovascular collapse in a previously stable patient
  – ~30-50% of all cardiac deaths

• Progressive pump failure
  – Cardiac death with preceding symptomatic or hemodynamic deterioration
Evaluation

• Thorough history and physical exam
  – Serial monitoring of vitals and volume status, CBC, CMP, and TSH
• Measurement of BNP or NT-proBNP can help establish prognosis or disease severity in chronic HF
• EKG
• Chest X-ray to assess heart size and pulmonary congestion
• Echocardiogram
Signs and Symptoms

• Dyspnea
  – With or without exertion
• Fatigue and weakness
• Edema in legs, ankles and feet
• Rapid or irregular heartbeat
• Exercise intolerance
• Increased need to urinate at night
• Sudden weight gain from fluid retention
• Lack of appetite and nausea
Diagnosis

• Framingham Heart Failure Diagnostic Criteria
  – Major criteria (requires 1)
    • Acute pulmonary edema
    • Cardiomegaly
    • Hepatojugular reflex
    • Neck vein distention
    • Paroxysmal nocturnal dyspnea or orthopnea
    • Pulmonary rales
    • Third heart sound (S3 gallop rhythm)
  – Minor criteria (requires 2)
    • Ankle edema
    • Dyspnea on exertion
    • Hepatomegaly
    • Nocturnal cough
    • Pleural effusion
    • Tachycardia (Heart Rate >120 beats per minute)

Treatment: Non-pharmacological

• Education (Class 1 LOE: B)
  – Social support

• Sodium restriction (Class IIa LOE: C)
  • <4grams/day
  • To reduce congestive symptoms

• Treatment of sleep disorders (Class IIa LOE: B)
  – Obstructive sleep apnea

• Physical activity/cardiac rehabilitation (Class Ia LOE: A)
Stage A Treatment

• Treatment of elevated blood pressure (Class I LOE: A)

• Treatment of dyslipidemia and vascular risk (Class I LOE: A)

• Treatment of diabetes mellitus and obesity (Class I LOE: C)

• Treatment of other conditions (Class I LOE: C)
  – Atrial fibrillation, alcohol and tobacco use
Stage B Treatment

• Considerations from stage A plus:
  – ACEi/ARB (Class 1 LOE: A)
    • Prevent symptomatic HF and ↓ mortality in all patients with a recent/remote history of MI or ACS
    • Prevent symptomatic HF in patients with reduced EF regardless of MI history
  – β- blocker (Class 1 LOE: A)
    • Reduce mortality with recent/remote history of MI or ACS
    • Prevent symptomatic HF in patients with reduced EF regardless of MI history
Stage C Treatment

• Pharmacologic treatment of HFrEF
  – Same as stages A and B, as appropriate
  – Guideline directed medical therapy (GDMT)
Stage C Treatment HFrEF

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
>50 mL/min and K+ <5.0 mEq/dL
Add
Class I, LOE A
Aldosterone
Antagonist
Stage C Treatment-HFrEF

• **ACEi (Class I LOE: A)**
  – ↓ risk of death and ↓ hospitalization in HFrEF
    • Seen in mild, moderate, and severe symptoms, and +/- CAD
  – Should be given in all patients except:
    • Life-threatening allergic reaction (angioedema)
    • Pregnancy
  – Use with caution in:
    • Low systemic blood pressure (systolic <80 mmHg)
    • Bilateral renal artery stenosis
    • Serum creatinine >3 mg/dL
    • Potassium >5 mEq/L
  – No differences shown among available ACEi
    • Initiate low dose and titrate to target dose
ACEi Mechanism of Action

Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery

Kidney → Renin → Angiotensinogen → AI

Cardiac & Vascular Hypertrophy
Systemic Vasoconstriction

Increased Blood Volume
Renal Sodium & Fluid Retention

Adrenal Cortex
Pituitary
Aldosterone

Thirst
ADH

http://cvpharmacology.com/vasodilator/ACE
Stage C Treatment-HFrEF

- ARB (Class 1 LOE: A)
  - Reasonable alternative to ACEi if patient is ACEi-intolerant or already on an ARB
  - ↓ hospitalization and mortality
  - Same contraindications and cautions as ACEi
    - Do not have dry cough adverse event (AE)
    - Potential for angioedema
  - Start at low dose and titrate
    - Typically double dose until at target dose
Stage C Treatment-HFrEF

• β-blockers (Class I LOE: A)
  – Long term use can ↓ HF symptoms, ↑ clinical status, and enhance overall well-being
  – ↓ risk of death and hospitalization in patients +/- CAD and DM
    • Benefits shown in patients already on ACEi
  – Not a class effect
    • 3 effective agents
      – Metoprolol succinate
      – Bisoprolol
      – Carvedilol
  – Start low and slowly titrate to target dose
  – AE include fluid retention and worsening HF; fatigue; bradycardia or heart block; and hypotension
B-blocker Mechanism of Action

http://cvpharmacology.com/cardioinhibitory/beta-blockers
Stage C Treatment-HFrEF

For all volume overload, NYHA class II-IV patients

Add

Class I, LOE C
Loop Diuretics
Stage C Treatment-HFrEF

• Loop diuretics (Class I LOE: C)
  – NYHA class II-IV
  – Furosemide, torsemide, bumetanide
  – ↑ urinary sodium excretion and ↓ physical signs of fluid retention
    • Effect on morbidity and mortality unknown
  – Titrate dose until ↑ urine output and ↓ weight, generally by 0.5 to 1.0 kg daily
    • Patients should have daily weights
  – AE: fluid and electrolyte depletion
Loop diuretics Mechanism of Action

http://cvpharmacology.com/diuretic/diuretics
Stage C Treatment-HFrEF

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
Stage C Treatment-HFrEF

- Aldosterone receptor antagonists (Class I LOE: A)
  - NYHA class II-IV
  - Spironolactone and eplerenone
  - RALES trial showed 30% ↓ in all-cause mortality as well as ↓ risk of SCD and hospitalizations with spironolactone use in patients with chronic HFrEF and LVEF <35%
    - Benefit shown in patients already on ACEi and β-blocker
  - AE:
    - Hyperkalemia
      - Caution in patients with high K⁺ and CrCl < 30 ml/min
    - Gynecomastia
Aldosterone Receptor Antagonist
Mechanism of Action

http://tmedweb.tulane.edu/pharmwiki/doku.php/treatment_of_heart_failure
Stage C Treatment-HFrEF

For persistently symptomatic African Americans, NYHA class III-IV

Add

Class I, LOE A
Hydral-Nitrates
Stage C Treatment-HFrEF

• Hydralazine and isosorbide dinitrate (Class I LOE: A)
  – NYHA class III or IV
  – Survival benefit in African Americans who remain symptomatic despite use of ACEi, β-blockers, and aldosterone antagonists
  – May be considered in patients intolerant to ACEi/ARBs
  – Dosed 3x daily in fixed combination
    • 37.5 mg of hydralazine and 20 mg of isosorbide dinitrate
      – Can be given separately if combination unavailable
    • Adherence
  – AE: Headache, dizziness, and GI
Hydralazine and Isosorbide Dinitrate Mechanism of Action

Stage C Treatment-HFrEF

• Digoxin (Class IIa LOE: B)
  – Can be beneficial to ↓ HF hospitalizations
    • No mortality benefit
  – May consider addition when symptoms persist despite GDMT
  – Initiate at low dose
    • Narrow therapeutic index – goal range 0.5 to 0.9 ng/mL
      – Toxic at >2 ng/ml
  – AE: Cardiac arrhythmias, GI, neurological complaints
Digoxin mechanism of action

http://www.cvpharmacology.com/cardiostimulatory/digitalis
Selected Landmark Trials

• ACEi
  – CONSENSUS
  – SOLVD
  – AIRE
  – TRACE

• ARB
  – CHARM
  – VALIANT

• β-Blocker
  – MERIT-HF
  – COPERNICUS
  – COMET
  – SENIORS

• Aldosterone receptor antagonist
  – RALES
  – EPHESUS
# Stage C Treatment - HFrEF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times</td>
<td>50 mg 3 times</td>
<td>122.7 mg/d&lt;sup&gt;422&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice</td>
<td>10 to 20 mg twice</td>
<td>16.6 mg/d&lt;sup&gt;413&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg once</td>
<td>40 mg once</td>
<td>N/A</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg once</td>
<td>20 to 40 mg once</td>
<td>32.5 to 35.0 mg/d&lt;sup&gt;445&lt;/sup&gt;</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once</td>
<td>8 to 16 mg once</td>
<td>N/A</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice</td>
<td>20 mg twice</td>
<td>N/A</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once</td>
<td>10 mg once</td>
<td>N/A</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once</td>
<td>4 mg once</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
<td>32 mg once</td>
<td>24 mg/d&lt;sup&gt;420&lt;/sup&gt;</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
<td>50 to 150 mg once</td>
<td>129 mg/d&lt;sup&gt;421&lt;/sup&gt;</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
<td>160 mg twice</td>
<td>254 mg/d&lt;sup&gt;108&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
### Stage C Treatment - HFrEF

<table>
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<tr>
<th>Drug</th>
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<th>Mean Doses Achieved in Clinical Trials</th>
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</thead>
<tbody>
<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25.0 mg once</td>
<td>25 mg once or twice</td>
<td>26 mg/d&lt;sup&gt;425&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
<td>42.6 mg/d&lt;sup&gt;446&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
<td>8.6 mg/d&lt;sup&gt;117&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>50 mg twice</td>
<td>37 mg/d&lt;sup&gt;447&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg once</td>
<td>80 mg once</td>
<td>N/A</td>
</tr>
<tr>
<td>Metoprolol succinate extended release</td>
<td>12.5 to 25 mg once</td>
<td>200 mg once</td>
<td>159 mg/d&lt;sup&gt;448&lt;/sup&gt;</td>
</tr>
<tr>
<td>(metoprolol CR/XL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydralazine and isosorbide dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination&lt;sup&gt;424&lt;/sup&gt;</td>
<td>37.5 mg hydralazine/20 mg</td>
<td>75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily</td>
<td>~175 mg hydralazine/90 mg isosorbide dinitrate daily</td>
</tr>
<tr>
<td></td>
<td>isosorbide dinitrate</td>
<td>dinitrate 3 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate&lt;sup&gt;449&lt;/sup&gt;</td>
<td>Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg, 3 or 4 times daily</td>
<td>Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses</td>
<td>N/A</td>
</tr>
</tbody>
</table>
• Other drug therapy
  – Anticoagulation (Class I LOE: A)
    • Chronic HF with atrial fibrillation and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy
      – Not recommended in patients without atrial fibrillation
  – Statins (Class III LOE: A)
    • Not beneficial as adjunctive therapy when prescribed solely for diagnosis of HF
  – Omega 3 fatty acids (Class IIa LOE: B)
    • Reasonable to use as adjunctive therapy in NYHA class II–IV symptoms and HFrEF or HFpEF
Stage C Treatment-HFrEF

• Devices
  – Implantable cardiac defibrillator (Class I LOE: A)
    • Reduce mortality with LVEF ≤35%, NYHA class II or III symptoms despite GDMT, and >1 year life expectancy
  – Cardiac resynchronization therapy (Class I LOE: A/B)
    • Pacemaker
      – LVEF ≤35%, sinus rhythm, left bundle-branch block with QRS duration ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT
Stage C Treatment-HFpEF

- Blood pressure management (Class I LOE: B)
  - Systolic and diastolic control
    - ACEi/ARB and β-blocker use is reasonable
- Diuretics (Class I LOE: C)
  - Symptomatic relief of volume overload
- Coronary revascularization (Class IIa LOE: C)
  - CAD in which symptoms or demonstrable myocardial ischemia is judged to have adverse effect on symptomatic HFpEF despite GDMT
- Management of atrial fibrillation (Class IIa LOE: C)
  - Improve symptomatic HF
Stage C Pharmacological Treatment

Summary

- **HFrEF**
  - Everyone unless CI:
    - ACEi/ARB + β-blocker
    - Aldosterone receptor antagonist (NYHA II-IV)
  - As appropriate
    - Loop diuretic
    - Hydralazine and isosorbide dinitrate
    - Digoxin

- **HFpEF**
  - GDMT for systolic and diastolic blood pressure control
Medications to Avoid in Stage C HF

- **Harm (Class III LOE: B)**
- **Calcium Channel Blockers**
  - Not recommended in HFrEF
    - Exception of amlodipine
- **Nonsteroidal Anti-Inflammatory Drugs**
  - Avoid due to sodium and fluid retention
  - Potential ↑ morbidity and mortality in HF patients using NSAIDs
- **Thiazolidinedione**
  - Regulate sodium reabsorption in the collecting ducts
  - Associated with ↑ in HF events
- **Steroids**
- **Antiarrhythmics except amiodarone and dofetilide**
Stage D

- Advanced HF
  - Patients with truly refractory HF
  - May be eligible for specialized, advanced treatment
  - Diagnosis requires thorough history and workup
Stage D

• Treatment
  – Fluid restriction (Class IIa LOE: C)
    • 1.5-2 L/day
  – Intravenous inotropic support (Class I LOE: C)
    • Maintain systemic perfusion and preserve end-organ performance
    • Bridge therapy
    • Palliative
  – Mechanical circulatory support (MCS) (Class IIa LOE: B)
    • Bridge to definitive therapy
    • Bridge to decision
    • Palliative
  – Cardiac transplant (Class I LOE: C)
Recently Approved Medications

• Sacubitril and Valsartan (Entresto®)

• Ivabradine (Corlanor®)
Sacubitril and Valsartan (Entresto®)

– Approved July 7, 2015 to reduce cardiovascular death and hospitalization in chronic HFrEF (NYHA II-IV)

• ARB-Neprilysin inhibitor
  – Neprilysin is a natural endopeptidase which degrades:
    • Natriuretic peptides
    • Bradykinin
    • Adrenomedullin
  – Inhibition counters neurohormonal overactivation that contributes to vasoconstriction, Na⁺ retention, and maladaptive remodeling

Effects of NEP Inhibition Alone

Offset by an Increase in Angiotensin II

- Beneficial physiological response
- Pathophysiological response

NEP inhibition alone

- Vasodilation
  - ↓ blood pressure
  - ↓ sympathetic tone
  - ↓ aldosterone levels
  - Natriuresis
  - Diuresis
  - Antifibrotic effects

- HF symptoms/progression

- Increase in Ang II
  - Vasoconstriction
  - ↑ blood pressure
  - ↑ sympathetic tone
  - ↑ aldosterone
  - ↑ sodium
  - Fibrosis

Neurohormonal imbalance remains
LCZ696: Dual NEP/RAAS Inhibition

**Neurohormonal Balance**

- **Beneficial physiological response**
  - NPs → NP system
  - NEP → Inactive fragments
  - Vasodilation: ↓ blood pressure, ↓ sympathetic tone, ↓ aldosterone levels, Natriuresis, Diuresis

- **Pathophysiological response**
  - RAAS → Ang II
  - AT$_1$ receptor
  - Vasoconstriction: ↑ blood pressure, ↑ sympathetic tone, ↑ aldosterone, ↑ sodium

→ HF symptoms/progression
→ Neurohormonal balance
Sacubitril and Valsartan (Entresto®)

• Formulations
  – Sacubitril 24mg and valsartan 26mg
  – Sacubitril 49mg and valsartan 51mg
  – Sacubitril 97mg and valsartan 103mg

• Dosing
  – Initial: 49/51mg BID
    • 24/26mg BID if:
      – Not currently taking ACEi or ARB
      – Severe renal impairment (CrCl <30ml/min)
      – Moderate hepatic impairment (Child-Pugh B)
  – Target: 97/103mg BID
    • Titrate by doubling the dose every 2-4 weeks as tolerated
Sacubitril and Valsartan (Entresto®)

- AE: hypotension, hyperkalemia, cough, dizziness, and renal failure
- Drug-drug interactions
  - NSAIDS
  - K⁺ sparing diuretics
  - Lithium
- Contraindications
  - Pregnancy
  - Hypersensitivity
  - History of angioedema with previous ACEi/ARB
  - Concomitant use of ACEi or aliskirin in diabetes

  ----
  • Do not administer within 36 hours of switching from or to an ACE inhibitor due to potential for severe angioedema

Sacubitril and Valsartan (Entresto®)

• Availability
  – Bottle counts of 60 and 180 tablets
  – Blister packs of 100 tablets

• Storage
  • 77°F
  • Protect from moisture

• Price
  – ~$450 per 60 tablets (~$7.5 per tablet)

PARADIGM-HF Trial

- LCZ696 200mg BID (equivalent to 160mg Valsartan)
- Enalapril 10mg BID
  - In addition to beta-blockers and aldosterone receptor antagonists
- Three phases
  - Single-blind run-in period in which received enalapril
  - Single-blind run-in period in which received LCZ696
  - Randomized, double-blind treatment in two groups

## PARADIGM-HF Trial

### Selected baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>White</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>Black</td>
<td>5.1%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Asian</td>
<td>18%</td>
<td>17.8%</td>
</tr>
<tr>
<td>NYHA Class 1</td>
<td>4.3%</td>
<td>5%</td>
</tr>
<tr>
<td>NYHA Class 2</td>
<td>71.6%</td>
<td>69.3%</td>
</tr>
<tr>
<td>NYHA Class 3</td>
<td>23.1%</td>
<td>24.9%</td>
</tr>
<tr>
<td>NYHA Class 4</td>
<td>0.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>LVEF</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>Pretrial use of ACEi</td>
<td>78%</td>
<td>77.5%</td>
</tr>
<tr>
<td>Pretrial use of ARB</td>
<td>22.2%</td>
<td>22.9%</td>
</tr>
</tbody>
</table>

PARADIGM-HF Trial

• Primary outcome: Composite of death from cardiovascular causes or a first hospitalization for heart failure
  – LCZ696: 914 patients (21.8%)
  – Enalapril: 1117 patients (26.5%)
  – Hazard ratio in LCZ696 group of 0.80 (0.73-0.87 95% CI), P<0.001
  – 20% reduction in composite of CV death and hospitalization

Ivabradine (Corlanor®)

- Approved April 15, 2015 to reduce the risk of hospitalization for worsening HF in patients with:
  - Stable, symptomatic chronic HF with LVEF <35%
  - Sinus rhythm with resting heart rate ≥70bpm
  - On maximally tolerated beta-blocker or CI

- Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current, which regulates heart rate
  - No effect on myocardial contractility or ventricular repolarization

Ivabradine (Corlanor®)

Ivabradine (Corlanor®)

• Formulations
  – Ivabradine 5mg
  – Ivabradine 7.5mg

• Dosing
  – Initial:
    • 5mg BID
    • 2.5mg BID in patients with conduction defect or risk of bradycardia
  – Max dose: 7.5mg BID

Ivabradine (Corlanor®)

- AE: atrial fibrillation, visual disturbance, bradycardia

- Drug-drug interactions
  - Negative chronotropes

- Contraindications
  - Acute decompensated heart failure
  - Blood pressure <90/50mmHg
  - Sick sinus syndrome, sinoatrial block or 3rd degree AV block
  - Resting heart rate <60 bpm
  - Severe hepatic impairment
  - Pacemaker dependence

Ivabradine (Corlanor®)

- **Availability**
  - Bottle counts of 60 tablets

- **Storage**
  - 77°F

- **Price**
  - ~$450 per 60 tablets (~$7.50 per tablet)

SHIFT Trial

- Ivabradine 7.5mg BID
- Placebo
  - In addition to stable background therapy

- Two phases
  - 14 day run-in period to confirm inclusion and exclusion criteria
  - Randomized, double-blind treatment in two groups

### SHIFT Trial

#### Selected baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.7 ± 11.2</td>
<td>60.7 ± 11.5</td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
<td>77%</td>
</tr>
<tr>
<td>White</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Asian</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>HR</td>
<td>79.7 ± 9.5</td>
<td>80.1 ± 9.8</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>49%</td>
<td>49%</td>
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<tr>
<td>NYHA Class III</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>NYHA Class IV</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>LVEF</td>
<td>29.0 ± 5.1</td>
<td>29.0 ± 5.2</td>
</tr>
<tr>
<td>β-blocker</td>
<td>89%</td>
<td>90%</td>
</tr>
</tbody>
</table>

SHIFT Trial

• Primary outcome: composite of cardiovascular death or hospital admission for worsening heart failure
• Ivabradine: 793 patients (24%)
• Placebo: 937 (29%)
• Hazard ratio in Ivabradine group of 0.82 (0.75 – 0.90 95% CI), P<0.0001
• 18% reduction in composite of CV death and hospitalization
  – Driven primarily by hospitalizations

Serelaxin

• Recombinant form of naturally occurring human relaxin-2
  – ↑ levels of relaxin result in improved arterial compliance and cardiac output with enhanced renal blood flow via dilation of afferent and efferent arterioles
• Not FDA approved
  – Pending Phase III trial data expected in 2016

Place in Therapy

• Role not yet discussed in guidelines

• Sacubitril and valsartan
  – Patients on optimal therapy with persistent symptoms and/or hospitalizations
  – Initiation of HFrEF therapy

• Ivabradine
  – Patients with contraindications to β-blockers
    • Asthma, COPD
  – NOT in place of β-blockers
Review

• Patients can be transitioned immediately from an ACEi to sacubitril and valsartan
  – FALSE

• Sacubitril and valsartan and ivabradine are approved for treatment of HFpEF
  – FALSE

• An adverse effect of ivabradine is visual disturbance
  – True
Key Takeaways

- **Treatment of HFrEF**
  - ACEi/ARB + β-blocker + aldosterone antagonist
    - GDMT as indicated per patient characteristics

- **Treatment of HFpEF**
  - GDMT for systolic and diastolic blood pressure control

- **Sacubitril and valsartan (Entresto®)**
  - ↓ risk of CV death and hospitalization in HFrEF NYHA Class II-IV

- **Ivabradine (Corlanor®)**
  - ↓ risk of hospitalization via heart rate control
References


New and Emerging Therapies for Chronic Heart Failure

Andrew Stoessel, PharmD

www.fshp.org