New Agents in the Treatment of Heart Failure Guideline Updates: Should we follow the PARADIGM SHIFT or follow our hearts?

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Objectives:
1. Describe the epidemiology and pathophysiology associated with heart failure
2. Discuss the clinical presentation of heart failure
3. Evaluate previous guideline recommendations for the treatment of heart failure
4. Formulate a recommendation regarding guideline updates and novel heart failure agents
## Epidemiology

I. Estimated 5.7 million people in the United States with heart failure (HF)\(^1\)
   a. Each year, over 550,000 new cases are diagnosed\(^2\)
   b. More often in men than women
   c. Increasing incidence with age

II. Incidence expected to increase 38% by the year 2030\(^3\)-\(^4\)

III. In 2009, one in nine deaths included HF as contributing cause\(^5\)

IV. Approximately 50% of people with HF die within five years of diagnosis\(^5\)

V. HF carries an estimated cost of $32 billion each year\(^5\)
   a. Health care services, medications to treat HF, and missed days of work

## Pathophysiology

I. HF creates a weakened heart, which ultimately leads to the inability to deliver oxygen- and nutrient-rich blood to the body

II. Chronic and progressive in nature

III. Compensatory mechanisms initially help temporarily mask symptoms but later lead to further disease progression
   a. Tachycardia and increased contractility\(^6\)
      i. Assists with maintenance of cardiac output (CO)
      ii. Activated via the sympathetic nervous system and norepinephrine (NE) release
      iii. Negative impact
         1. Increasing oxygen demand
         2. Decreasing filling time
         3. Precipitation of cardiac arrhythmias
         4. Increases myocardial cell death
   b. Fluid retention and increased preload\(^7\)
      i. Optimizes stroke volume (SV)
      ii. Fluid retention
         1. Decreased CO and, therefore, decreased renal perfusion leading to the initiation of the renin-angiotensin-aldosterone system (RAAS)
         2. Renin then converts angiotensinogen to angiotensin I, which is converted to angiotensin II via angiotensin converting enzyme (ACE)
         3. Angiotensin II then leads to aldosterone release, increasing both sodium and fluid retention
      iii. Increased preload
         1. Inability of the heart to respond appropriately to changes in preload
         2. A normal heart responds to increases in preload by increasing SV
         3. At a certain point in HF, increases in preload do not appropriately increase SV and instead lead to symptoms of pulmonary or systemic congestion
      iv. Negative impact
         1. Increasing pulmonary congestion
         2. Increasing systemic congestion and edema
   c. Vasoconstriction and increased afterload\(^7\)
      i. Prevents blood flow to nonessential organs
      ii. Caused by neurohormones such as NE, angiotensin II, endothelin-1, neuropeptide Y, urotensin II, and arginine vasopressin
      iii. Negative impact
         1. Further decrease in CO
         2. Increasing compensatory mechanisms
   d. Ventricular hypertrophy and remodeling\(^6\)-\(^7\)
      i. Key components in the pathogenesis and progression of HF
      ii. Caused by the heart's attempt to maintain CO and oxygen demand
      iii. Negative impact
         1. Diastolic and systolic dysfunction
         2. Increased fibrosis, myocardial ischemia, myocardial cell death, and risk of arrhythmia
Clinical Presentation

I. Left- versus right-sided HF
   a. Left-sided
      i. Left ventricular dysfunction
      ii. Pulmonary edema due to the blood backing up on the lungs
      iii. Shortness of breath, pulmonary crackles, and orthopnea
   b. Right-sided
      i. Right ventricular dysfunction
      ii. Systemic volume overload
      iii. Jugular venous distention (JVD), peripheral edema, and weight gain

II. Heart Failure with Reduced Ejection Fraction (HFrEF) versus Heart Failure with Preserved Ejection Fraction (HFpEF)

Table 1. Classification of HFrEF versus HFpEF

<table>
<thead>
<tr>
<th>Classification</th>
<th>LVEF(%)</th>
<th>Literature support</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>≤40</td>
<td>• Systolic HF</td>
<td>• LV* loses ability to contract normally and the heart is not able to pump adequately to push enough blood into circulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most clinical trials enrolled these patients</td>
<td>o Normal to low blood pressure (BP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Where efficacious therapies have been demonstrated</td>
<td>o S₃ gallop</td>
</tr>
<tr>
<td>HFpEF</td>
<td>≥50</td>
<td>• Diastolic HF</td>
<td>• LV* loses ability to relax normally and the heart can’t properly fill during the resting period between each beat</td>
</tr>
<tr>
<td>HFpEF borderline</td>
<td>41 to 49</td>
<td>• Characteristics, treatment patterns, and outcomes are similar to those with HFpEF</td>
<td>o Increased preload: severe hypertension</td>
</tr>
<tr>
<td>HFpEF improved</td>
<td>&gt;40</td>
<td>• HFpEF patients who previously had HFrEF</td>
<td>o S₄ gallop</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Further research needed to characterize this group</td>
<td></td>
</tr>
</tbody>
</table>

1. LVEF, left ventricular ejection fraction; LV, left ventricle

Etiology and Precipitating Factors

I. Etiology
   a. Idiopathic
   b. Myocarditis
   c. Ischemic heart disease
   d. Infiltrative disease
   e. Cardiomyopathy
   f. Hypertension
   g. Human immunodeficiency virus (HIV)
   h. Substance abuse

Table 2. Causes of HFrEF and HFpEF

<table>
<thead>
<tr>
<th>Systolic dysfunction: Reduced EF</th>
<th>Diastolic dysfunction: Preserved EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in muscle mass (e.g. MI*)</td>
<td>Increased ventricular stiffness</td>
</tr>
<tr>
<td>Dilated cardiomyopathies</td>
<td>Ventricular hypertrophy</td>
</tr>
<tr>
<td>Ventricular hypertrophy</td>
<td>Infiltrative myocardial diseases</td>
</tr>
<tr>
<td>Pressure overload</td>
<td>MI*</td>
</tr>
<tr>
<td>Volume overload</td>
<td>Mitral or tricuspid valve stenosis</td>
</tr>
<tr>
<td></td>
<td>Pericardial disease</td>
</tr>
</tbody>
</table>

EF, ejection fraction; MI, myocardial infarction
Diagnosis

I. Plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test, especially in the non-acute setting, when echocardiography is not immediately available\textsuperscript{12,13}
   a. Negative predictive values are similar and high in both the non-acute and acute settings
   b. Helpful in ruling out HF but not in establishing diagnosis

II. Elevated NPs help establish an initial working diagnosis and identify those who require further cardiac investigation\textsuperscript{12}
   a. Non-acute setting
      i. B-type natriuretic peptide (BNP) >35 pg/mL
      ii. N-terminal pro-BNP (NT-proBNP) >125 pg/mL
   b. Acute setting
      i. Higher values should be used
      ii. BNP >100 pg/mL
      iii. NT-proBNP >300 pg/mL

III. Electrocardiogram (ECG) increases the likelihood of HF diagnosis, but has low specificity\textsuperscript{12,13}
   a. Helpful with identifying underlying etiology
   b. HF is unlikely with a normal ECG
   c. Mainly recommended to rule out HF

IV. Echocardiography is most useful to establish the diagnosis in patients with suspected HF\textsuperscript{12,13}
   a. Provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and pulmonary hypertension

Classification and Staging

I. Classes: symptom based
II. Stages: disease progression

Table 3. Classifications and Staging of HF\textsuperscript{14}

<table>
<thead>
<tr>
<th>NYHA Functional Classification</th>
<th>AHA Stages of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain</td>
<td>Stage A No identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF</td>
</tr>
<tr>
<td>Class II Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain</td>
<td>Stage B Structural heart disease strongly associated with the development of HF but who have never shown signs or symptoms</td>
</tr>
<tr>
<td>Class III Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain</td>
<td>Stage C Current or prior symptoms of HF are present and associated with underlying structural heart disease</td>
</tr>
<tr>
<td>Class IV Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest</td>
<td>Stage D Advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association

Goals of Heart Failure Management

I. Reduced versus preserved ejection fraction (EF)
   a. No effective regimen has been identified for the treatment of HFpEF\textsuperscript{14}
   b. Studies have evaluated this area of research, however, no medication has yet to demonstrate improvements in morbidity and mortality\textsuperscript{15} (see appendix A)

II. Symptom control\textsuperscript{16}
   a. Diuretics
   b. Digoxin
   c. Angiotensin converting enzyme inhibitors (ACE I)/Angiotensin receptor blocker (ARB)
III. Hospitalization risk reduction
   a. ACE I/ARB
   b. Beta blocker
   c. Oral nitrates plus hydralazine
   d. Aldosterone antagonist
   e. Digoxin

IV. Survival improvement
   a. ACE I/ARB
   b. Beta blocker
   c. Oral nitrates plus hydralazine
   d. Aldosterone antagonist

Medication Review

I. Beta blockers
   a. Historically considered contraindicated in HF
   b. More recent data supports beta blocker use in patients with HF (see appendix B)
   c. Indicated for all stable patients with HF and reduced LVEF in the absence of contraindications or intolerance to beta blocker therapy
      i. Bradycardia
      ii. Heart block
      iii. Hemodynamic instability
   d. Carvedilol, bisoprolol, and metoprolol succinate demonstrated benefits in HF (see appendix B)
      i. Decrease in morbidity and mortality
      ii. Improvement in left ventricular (LV) function
      iii. Reduction in hospitalizations and symptoms
   e. Initiate when patient is not volume overloaded or having an acute HF exacerbation

Table 4. Beta Blocker Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Titration</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>Initial dose 1.25mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Increase by 1.25mg weekly until 5mg once daily, then 2.5mg every 4 weeks to target dose</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Initial dose 3.125 mg BID</td>
<td>25 mg BID</td>
</tr>
<tr>
<td></td>
<td>Doubled every 2 weeks to target dose</td>
<td>(titrate as tolerated to 50 mg twice daily if ≥ 85 kg)</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>Initial dose 12.5mg once daily ≥ NYHA class III HF; 25mg once daily &lt; NYHA class III HF</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Doubled every 2 weeks until target dose</td>
<td></td>
</tr>
</tbody>
</table>

BID, twice daily

II. ACE I
   a. Inhibits the production of angiotensin II, a vasoconstrictor, and increases concentrations of the vasodilator bradykinin by preventing its breakdown
   b. First agents to demonstrate mortality benefit in HF and have served as background therapy for all HF trials
   c. Improvements in morbidity, mortality, disease progression, and quality of life (see appendix C)
      i. Clinical effects demonstrated in symptomatic and asymptomatic LV dysfunction and LV dysfunction after MI

Table 5. ACE I Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg daily</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg daily</td>
<td>10 mg daily</td>
</tr>
</tbody>
</table>

TID, three times daily
III. ARBs
   a. Indicated for patients unable to tolerate ACE I therapy\textsuperscript{13,29-32} (see appendix D)
      i. Not an alternative in patients with hypotension, hyperkalemia, or renal insufficiency
   b. Act by blocking the binding of angiotensin II to the AT\(_1\) receptors\textsuperscript{13}
      i. Promotes vasodilation
      ii. Decreases the effects of aldosterone
   c. No impact on bradykinin/bradykinin-related adverse effects associated with ACE inhibitors such as cough\textsuperscript{13}
   d. Primary clinical trials supporting the use of these agents in HFrEF used either valsartan or candesartan pharmacotherapy\textsuperscript{33-35} (see appendix D)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4-8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20-40 mg BID</td>
<td>160 mg BID</td>
</tr>
</tbody>
</table>

Table 6. ARB Drug Information\textsuperscript{39}

IV. Aldosterone antagonists
   a. Spironolactone and eplerenone
   b. Indicated to improve symptoms in patients with EF <35\%\textsuperscript{36}
   c. Inhibit sodium reabsorption and potassium excretion in the kidneys
   d. Decreasing cardiac fibrosis and ventricular remodeling\textsuperscript{36}
   e. Associated with improvement of symptoms, reduction of HF hospitalization risk, and increased survival\textsuperscript{36}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg once daily</td>
</tr>
</tbody>
</table>

Table 7. Aldosterone Antagonist Drug Information\textsuperscript{36}

V. Oral nitrates plus hydralazine
   b. Self-described African Americans with HFrEF and moderate to severe symptoms, despite therapy with ACE I, diuretics, and beta blockers\textsuperscript{13,37}
   c. Possible alternative in ACE I- or ARB-intolerant patients, as demonstrated in clinical trials
   d. Assists with normalization of increased oxidative stress and reduced nitric oxide signaling with the hydralazine and nitrate components, respectively, preventing HF progression\textsuperscript{38}
   e. Benefits of reductions in mortality and hospitalizations, and improvement in quality of life (see appendix E)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Hydralazine 25–75 mg three or four times daily</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Isosorbide dinitrate 10–40 mg three times daily</td>
</tr>
<tr>
<td>BiDil</td>
<td>Hydralazine 37.5 mg + isosorbide dinitrate 20 mg (target of 2 tablets three times daily)</td>
</tr>
</tbody>
</table>

Table 8. Hydralazine+isosorbide Dinitrate Drug Information\textsuperscript{38}

VI. Diuretics
   a. Compensatory mechanisms in HF stimulate excessive sodium and water retention, which can lead to pulmonary and systemic congestion\textsuperscript{39,42}
   b. No data to support survival prolongation or progression of disease alteration\textsuperscript{13,41}
   c. Increased dosing often required in acute decompensated HF (ADHF) in order to achieve the same level of sodium excretion\textsuperscript{41}
   d. Loop diuretic medications
      i. Increase excretion of sodium and water at the ascending loop of Henle
      ii. More effective in achieving symptomatic relief compared to thiazide diuretics\textsuperscript{41}
      iii. Considered first-line treatment in patients with volume overload\textsuperscript{41}
   e. Monitoring\textsuperscript{16}
      i. Renal function
      ii. Electrolytes
      iii. CHF symptoms related to volume overload
      iv. Diuretic response
      v. Diuretic resistance
Table 9. Loop Diuretic Drug Information\textsuperscript{20}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavail. (%)</th>
<th>Initial dosing</th>
<th>Max dosing</th>
<th>Duration in hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>10-67</td>
<td>20-40 mg once or BID</td>
<td>600mg</td>
<td>6-8 (PO);2 (IV)</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80-100</td>
<td>0.5-1 mg once or BID</td>
<td>10mg</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80-100</td>
<td>10-20 mg daily</td>
<td>200mg</td>
<td>12 to 16</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>100</td>
<td>25-50 mg once or BID</td>
<td>200mg</td>
<td>12 (PO); 2 (IV)</td>
</tr>
</tbody>
</table>

VII. Digoxin
   a. Historically a mainstay in HF due to positive inotropic effects\textsuperscript{13}
      i. Previously found to improve cardiac function, quality of life, exercise tolerance, and HF symptoms in patients with HFrEF in normal sinus rhythm
   b. Inhibits the Na-K-ATPase pump in myocardial cells, increasing intracellular sodium, promoting sodium-calcium exchange, and leading to an increase in intracellular calcium concentration\textsuperscript{13}
      i. Results in improved myocyte contractility and overall left ventricular (LV) systolic function\textsuperscript{44}
   c. More recent data failed to demonstrate positive outcomes in HF\textsuperscript{44}
      i. Withdrawing digoxin worsens functional status, exercise capacity, and LVEF in patients with HF\textsuperscript{44}
      ii. Digoxin reduces hospitalization rate, but does not impact mortality among patients with HFrEF\textsuperscript{45}

Previous Treatment Recommendations

I. Patients with symptomatic HFrEF should be treated with\textsuperscript{46}
   a. An ACE I
   b. A beta blocker
   c. A diuretic
   d. An aldosterone antagonist

II. Benefits include\textsuperscript{46}
   a. Slowing HF progression
   b. Reducing morbidity and mortality
   c. Symptom improvement

III. Other agents previously mentioned should be considered on a case by case basis

Guideline Updates

I. 2016 American Heart Association/American College of Cardiology Focused Update (AHA/ACC) and the European Society of Cardiology recommendations\textsuperscript{12,47}
   a. Class I recommendation\textsuperscript{48}
      i. Replacement of an ACE I or ARB with sacubitril/valsartan to further reduce morbidity and mortality risks in patients with chronic, symptomatic HFrEF (NYHA class II or III), who are tolerating an ACE I or ARB
   b. Class IIA recommendation\textsuperscript{49}
      i. Ivabradine can be beneficial in patients to reduce HF hospitalization in patients with chronic, stable HFrEF (EF ≤ 35%, NYHA class II or III)
      ii. Ivabradine use supported in patients receiving a beta blocker at maximum tolerated dose in sinus rhythm with a heart rate of ≥70 beats per minute (BPM) at rest \textsuperscript{50,51}

New Heart Failure Agents

I. Sacubitril/valsartan (Entresto\textsuperscript{TM})\textsuperscript{52}
   a. Mechanism
      i. An angiotensin receptor–neprilysin inhibitor (ARNI)
      ii. Sacubitril, a neprilysin inhibitor, provides a new mechanism in the treatment of HF
         a. Endogenous vasoactive peptides are increased leading to vasodilation
         b. Decreased sodium retention
         c. Decreased maladaptive remodeling
      iii. Neprilysin inhibition, in combination with the inhibition of the renin-angiotensin system via valsartan, demonstrated superior effects compared to either agent alone
b. Indication
   i. Chronic NYHA Class II-IV with EF ≤35%
   ii. Concurrent treatment with beta blocker at a stable dose
   iii. Previous trial of an ACE I or ARB at a dose equivalent to enalapril 10 mg twice daily (see appendix F) or valsartan 160 mg twice daily (see appendix G), respectively

c. Dosing
   i. Initial dose sacubitril/valsartan:
      a. ACE I/ARB naïve: 24/26 mg twice daily
      b. Previous ACE I/ARB therapy: 49/51 mg twice daily
   ii. Available strengths: 24/26 mg, 49/51 mg, 97/103 mg
   iii. Valsartan is more bioavailable in sacubitril/valsartan than other products
      a. Valsartan 26 mg, 51 mg, and 103 mg in Entresto is equivalent to 40 mg, 80 mg, and 160 mg in other formulations, respectively

d. Dose adjustments
   i. Renal adjustments
      a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m²: 24 mg/26 mg twice daily; double dose every 2 to 4 weeks to target dosage of 97 mg/103 mg twice daily, as tolerated
   ii. Hepatic adjustments
      a. Severe hepatic impairment: Use not recommended
      b. Moderate hepatic impairment: 24 mg/26 mg twice daily; double dose every 2 to 4 weeks to target dosage of 97 mg/103 mg twice daily, as tolerated
      c. Mild hepatic impairment: No adjustment necessary

e. Safety
   i. Boxed Warning: fetal toxicity
   ii. Contraindications
      a. Hypersensitivity to any component of sacubitril/valsartan
      b. History of angioedema with an ACE I or ARB
      c. Concomitant use of other agents that act on RAAS
   iii. Warning/Precautions
      a. Angioedema
      b. Hypotension
      c. Hyperkalemia
      d. Impaired kidney function

f. First formulated with ACE I
   i. Omapatrilat, an ACE I and neprilysin combination, demonstrated some benefit
   ii. Angioedema was more common in the omapatrilat groups and risk outweighed benefit
   iii. Led to the investigation of an ARB in combination with the neprilysin inhibition, sacubitril/valsartan

II. Ivabradine (Corlanor™)
   a. Mechanism
      i. Ivabradine is a selective inhibitor of the If, pacemaker current, ion channel found in cardiac pacemaker cells of the sinoatrial node
      ii. Reduces heart rate while maintaining myocardial contractility and atrioventricular conduction
   b. Indication
      i. LVEF ≤35%
      ii. Sinus rhythm with resting heart rate ≥70 BPM
      iii. Either on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use
c. Dosing
   i. Initial: 5 mg twice daily for two weeks
   ii. Further adjustments based on heart rate
       a. Resting rate >60 BPM: increase dose by 2.5 mg twice daily
       b. Resting rate 50 to 60 BPM: continue current dose
       c. Resting rate <50 BPM or signs/symptoms of bradycardia: reduce dose by 2.5 mg twice daily
   iii. Maximum dose of 7.5 mg twice daily

d. Dose adjustments
   i. Renal adjustment
       a. Creatinine clearance (CrCl) > 15 mL/min: no adjustment required
   ii. Hepatic impairment
       a. Mild to moderate: no adjustment required
       b. Severe: contraindicated

e. Safety
   i. Contraindications
       a. ADHF
       b. BP <90/50 mmHg
       c. Sick sinus syndrome, sinoatrial block or 3rd degree atrioventricular block, unless a functioning demand pacemaker is present
       d. Resting heart rate <60 BPM prior to treatment
       e. Severe hepatic impairment (Child-Pugh C)
       f. Pacemaker dependence (heart rate maintained exclusively by the pacemaker)
       g. Concomitant strong cytochrome CYP3A4 inhibitors
   ii. Warnings/Precautions
       a. Fetal toxicity
       b. Atrial fibrillation
       c. Bradycardia and conduction disturbances

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**Clinical Question**

Should we follow the PARADIGM SHIFT or follow our hearts?

### Purpose
To determine if sacubitril/valsartan is superior to enalapril for reducing the risks of death and hospitalizations due to HF

### Design
Randomized, double-blind, double-dummy, parallel-group, active-controlled, two-arm trial

### Population
**Inclusion criteria:**
- 18 years or older
- NYHA class II-IV HF
- EF of ≤40% (later changed to ≤35% in an amendment)
- Participants were also required to have at least one of the following: BNP of ≥150 pg/mL or an NT-proBNP level ≥600 p/mL or, if they had been hospitalized for HF within the previous 12 months, a BNP of at least 100 pg/mL or an NT-proBNP ≥400 pg/mL.
- At least 4 weeks before screening, required to take a stable dose of a beta blocker and an ACE I (or ARB) equivalent to at least 10 mg of enalapril daily

**Exclusion criteria:**
- Symptomatic hypotension
- Systolic BP <100 mm Hg at screening or 95 mm Hg at randomization
- eGFR <30 ml/min/1.73 m² randomization, or a decrease of eGFR by >25% (amended to 35%) between screening and randomization
- Potassium level of ≥5.2 mmol/L at screening or 5.4 mmol/L at randomization
- History of angioedema or unacceptable side effects during receipt of ACE I or ARBs

### Outcomes
**Primary outcome:** composite death from cardiovascular (CV) causes or hospitalization for HF
**Secondary outcomes:** time to death from any cause, change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to a new onset of atrial fibrillation, time to the first occurrence of a decline in renal function

### Methods
- 8442 patients included in the current analysis cohort
  - 43 participants were ultimately excluded
- Eligible participants were switched from previous ACE I/ARB therapy to enalapril 10mg BID for two weeks
- Participants then received sacubitril/valsartan for four to six weeks
- Patients with no side effects during either run in period were enrolled and randomly assigned to the treatment groups
  - 600 participants with adverse reactions in the enalapril run-in
  - 547 participants with adverse reaction in the sacubitril/valsartan run-in
- Participants randomly assigned 1:1 to enalapril 10mg BID or sacubitril/valsartan 200mg BID
  - Doses were reduced in those who experienced unacceptable side effects
- Patient evaluations occurred every two to eight weeks during the first four months, and increased to every four months thereafter

### Results
<table>
<thead>
<tr>
<th>Primary composite</th>
<th>LCZ696 N=4187 (%)</th>
<th>Enalapril N=4212 (%)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV causes or first hospitalization for worsening HF</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.8 (0.73-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.8 (0.71-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening HF</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>
Secondary outcomes | LCZ696 N=4187 (%) | Enalapril N=4212 (%) | HR* (95% CI) | P Value
--- | --- | --- | --- | ---
Death from any cause | 711 (17.0) | 835 (19.8) | 0.84 (0.76-0.93) | <0.001
Change in KCCQ clinical summary score at 8 mo | -2.99±0.36 | -4.63±0.36 | 1.64 (0.63-2.65) | 0.001
New-onset atrial fibrillation | 84 (3.1) | 83 (3.1) | 0.97 (0.72-1.31) | 0.83
Decline in renal function | 94 (2.2) | 108 (2.6) | 0.86 (0.65-1.13) | 0.28

Mo, month; HR, hazard ratio, LCZ696, sacubitril/valsartan

Table 11. Adverse events

| Hypotension | LCZ696 N=4187 (%) | Enalapril N=4212 (%) | P Value |
|---|---|---|---
| Symptomatic | 588 (14) | 388 (9.2) | <0.001 |
| Symptomatic with SBP <90mm Hg | 112 (2.7) | 59 (1.4) | <0.001 |
| Cough | 474 (11.3) | 601 (14.3) | <0.001 |

Elevated SCr

| ≥2.5 | 139 (3.3) | 188 (4.5) | 0.007 |
| ≥3.0 | 63 (1.5) | 83 (2.0) | 0.1 |

Elevated K

| >5.5 | 674 (16.1) | 727 (17.3) | 0.15 |
| >6 | 181 (4.3) | 236 (5.6) | 0.007 |

Angioedema

| No treatment or use of antihistamines only | 10 (0.2) | 5 (0.1) | 0.19 |
| Use of catecholamines or glucocorticoids without hospitalization | 6 (0.1) | 4 (0.1) | 0.52 |

Authors' Conclusion

Sacubitril/valsartan was superior to ACE inhibition alone in reducing risk of death and hospitalization for HF patients. This provides evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of RAAS alone in patients with chronic HF.

Critique

Strengths:
- Study design
- Blinded
- Sample size
- Evaluated readmission as an endpoint

Limitations:
- Run-in phase
- Early discontinuation of trial
- Enalapril dosing
- Valsartan equivalent
- Cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) was low
- African American population

Take home

A significant benefit was demonstrated with the utilization of Entresto however, caution should be utilized in those with historically low BP readings, hyperkalemia, and renal dysfunction.


Purpose

To determine the ability of ivabradine to reduce CV risk in patients with stable coronary artery disease with a LVEF <40%

Design

Randomized, double-blind, placebo-controlled, parallel-group trial

Gossett 10
Population

Inclusion criteria:
- 55 years or older (≥18 years if diabetic)
- History of coronary artery disease (CAD)
- LVEF <40%
- End-diastolic short-axis internal dimension of greater than 56 mm by echocardiography
- In sinus rhythm with HR of ≥ 60 BPM
- Stable angina/HF symptoms for ≥ 3 months
- Receipt of appropriate CV medication at stable doses for ≥ 1 month

Exclusion criteria:
- MI or coronary revascularization within previous 6 months
- Stroke or cerebral transient ischemic attack in previous 3 months
- Implanted pacemaker, cardioverter, or defibrillator
- Valvular disease likely requiring surgery in the following 3 years
- Sinoatrial block
- Congenital long QT
- Complete atrioventricular block
- Severe or uncontrolled hypertension
- NHYA Class IV
- Current treatment with strong CYP P450 3A4 inhibitors

Outcomes

Primary outcome: composite of CV death, admission to hospital for acute MI, and admission to hospital for new onset or worsening HF

Secondary outcomes: all-cause mortality, cardiac death, CV death, admission to hospital for new-onset or worsening HF, the composite of admission to hospital for fatal and non-fatal acute myocardial infarction or unstable angina, coronary revascularization, CV death, admission to hospital for HF, and admission to hospital for MI

Methods

- 10,917 patients included in the current analysis cohort
  - 5479 in ivabradine arm
  - 5438 in placebo arm
- Run-in period of 14 days, patients then randomly assigned to each group stratified by treatment center and if patients were on a beta blocker at enrollment
- Initial treatment dose of ivabradine was 5mg BID compared to matching placebo
  - Doses were increased after 2 weeks in patients with a resting heart rate of ≥60 BPM to 7.5mg BID
  - Dose reductions from 7.5mg BID to 5mg BID in patients who had a heart rate <50 BPM at any follow-up visit and the 5mg dose was completely discontinued if heart rate remained <50 BPM
- All patients continued to receive appropriate conventional CV medical treatment throughout the study

Results

- Primary endpoint demonstrated no difference between groups for the composite endpoint
- Majority of secondary endpoints lacked statistical significance with the exception of the prespecified group with heart rate ≥70 BPM for coronary endpoints

Table 12. Coronary endpoints in subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup with heart rate of ≥70 BPM</th>
<th>Ivabradine N=2699</th>
<th>Placebo N=2693</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to hospital for MI, n(%)</td>
<td>85 (3.1)</td>
<td>131 (4.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission to hospital for MI or unstable angina, n(%)</td>
<td>143 (5.3)</td>
<td>182 (6.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>Coronary revascularization, n(%)</td>
<td>76 (2.8)</td>
<td>108 (4)</td>
<td>0.016</td>
</tr>
</tbody>
</table>
### Table 13. Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong></td>
<td>N=5479</td>
<td>N=5438</td>
</tr>
<tr>
<td>Drug discontinuation, n(%)</td>
<td>1528 (28)</td>
<td>856 (16)</td>
</tr>
<tr>
<td>Discontinuation due to bradycardia, n(%)</td>
<td>705 (13)</td>
<td>79 (2)</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>146 (21)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Subgroup with heart rate &gt;70 BPM</strong></td>
<td>N=2699</td>
<td>N=2693</td>
</tr>
<tr>
<td>Drug discontinuation, n(%)</td>
<td>627 (23)</td>
<td>430 (16)</td>
</tr>
<tr>
<td>Discontinuation due to bradycardia, n(%)</td>
<td>149 (6)</td>
<td>21 (1)</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>34 (23)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Authors’ Conclusion**
Reduction in heart rate with ivabradine provided no improvement in cardiac outcomes in all patients with stable coronary artery disease and left-ventricular systolic dysfunction. However, reduction of CAD was demonstrated in patients with heart rates of 70 BPM or greater.

**Critique**
- **Strengths:**
  - Evaluated heart rate in relation to CV risk
  - Study design
- **Limitations:**
  - Run-in and tolerability
  - Beta blockers utilized not listed

**Take Home**
In a specific subset of patients, those with a heart rate >70 BPM, ivabradine was found to be effective at reducing the risk of coronary events, fatal and nonfatal MI, and coronary revascularization.

---


**Purpose**
To evaluate the impact of ivabradine in reducing CV death or hospital admission for worsening HF

**Design**
Event-driven, multinational, randomized, double-blind, placebo-controlled, parallel-group trial

**Population**
- **Inclusion criteria:**
  - 18 years or older
  - Sinus rhythm
  - Resting heart rate of >70 BPM after a 5 min rest period or two consecutive visits
  - Stable, symptomatic, chronic HF of 4 or more weeks’ duration
  - Admission to hospital for worsening HF within the previous 12 months
  - LVEF of ≤35%
  - Optimal/stable background treatment for at least 4 weeks
- **Exclusion criteria:**
  - HF attributed to congenital heart disease or primary severe valvular disease
  - Recent (<2 months) MI
  - Ventricular or atrioventricular pacing operative for >40% of the day
  - Atrial fibrillation/flutter
  - Symptomatic hypotension

**Outcomes**
- **Primary outcome:** composite of CV death or hospital admission for worsening HF
- **Secondary outcomes:** composite of CV death or hospital admission for worsening HF in patients receiving at least 50% of the target daily dose of a beta blocker, all-cause death, any CV death, hospital admission for worsening HF, all-cause admission to hospital, any CV admission, and death from HF, and the composite of CV death, hospital admission for worsening HF, or hospital admission for non-fatal MI

**Methods**
- 6558 participants randomized
  - 3241 in ivabradine arm
  - 3264 in placebo arm
- Two week run-in period to enable confirmation of inclusion/exclusion criteria
- Starting dose of ivabradine was 5mg twice a day, compared to matching placebo, dosing increased to 7.5mg twice daily in the first 2 weeks of the study unless resting heart rate was ≤60 BPM
  - Participants with heart rates <50 BPM were decreased to 2.5 mg twice daily
Results

- Primary composite endpoint:
  - Significant difference in the primary composite with the effect driven by hospital admissions for worsening HF

<table>
<thead>
<tr>
<th>Table 14. Efficacy endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CV death or hospital admission for worsening HF</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mortality endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>CV mortality</td>
</tr>
<tr>
<td>Death from HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospital admission</td>
</tr>
<tr>
<td>Hospital admission for worsening HF</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
</tr>
<tr>
<td>CV death, or hospital admission for worsening HF, or non-fatal MI</td>
</tr>
</tbody>
</table>

HR, hazard ratio

- Secondary endpoint:
  - In those with ≥50% of beta blocker target dose
    - No difference in primary endpoint between groups
    - Significant reduction in hospitalizations due to HF

- Subgroup analysis:
  - Positive treatment effect noted only in those with a heart rate ≥77 BPM

- Safety data

<table>
<thead>
<tr>
<th>Table 15. Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Ivabradine group</strong></td>
</tr>
<tr>
<td>N=3232 (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Phosphenes</td>
</tr>
<tr>
<td><strong>Placebo group</strong></td>
</tr>
<tr>
<td>N=3260 (%)</td>
</tr>
</tbody>
</table>

Author’s Conclusion

Results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in HF and confirm the important role of heart rate in the pathophysiology of HF.

Critique

Strengths:
- Study design
- Was not stopped early, even with observed benefit
- Targeted population

Limitations:
- Applies to patients only in sinus rhythm
- Proportion of elderly patients was low
- US sites not included
- Beta blocker as background therapy
- Beta blockers utilized
- Inclusion of CRT/ICD was low
**Take Home**

Ivabradine is useful in reducing CV death or hospital admission for worsening HF, death from HF, and hospital admissions as an add on agent in patients on beta blocker therapy. Ivabradine should not be utilized as a replacement for beta blockers.

**Summary**

I. Well known, evidence based therapeutic regimen for HF involved ACE I or ARB, beta blocker, diuretics, and aldosterone antagonists for symptom improvement, reduction of hospitalization risk, and increased survival

II. Recent guideline updates from AHA/ACC and ESC have recommended
   a. Replacement of ACE I/ARB therapy for sacubitril/valsartan to reduce morbidity and mortality in NYHA class II-III HFpEF patients currently tolerating and ACE I/ARB
   b. Addition of ivabradine in NYHA Class II-III patients with a LVEF ≤35%, in sinus rhythm, and a resting heart rate ≥70 BPM on a maximally tolerated beta blocker dose

**Recommendation**

I. Sacubitril/valsartan
   a. Evaluation of a patients renal and hepatic function, history of blood pressure readings, current ACE I/ARB dose, and most recent EF and BNP are necessary data to collect

   Table 16. Sacubitril/valsartan recommendations for use

<table>
<thead>
<tr>
<th>Contraindication to sacubitril/valsartan</th>
<th>Consider sacubitril/valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>If any criteria are met:</td>
<td>If all criteria are met:</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min/1.73m²</td>
<td>eGFR &gt;30 mL/min/1.73m²</td>
</tr>
<tr>
<td>Moderate hepatic impairment</td>
<td>No or mild hepatic impairment</td>
</tr>
<tr>
<td>NYHA Class I or IV</td>
<td>NYHA Class II or III</td>
</tr>
<tr>
<td>EF &gt;35%</td>
<td>EF ≤35%</td>
</tr>
<tr>
<td>Equivalent dose of &gt; or &lt; enalapril 10mg</td>
<td>Equivalent dose of enalapril 10mg BID</td>
</tr>
<tr>
<td>BNP &lt;150pg/mL</td>
<td>BNP ≥150pg/mL</td>
</tr>
<tr>
<td>ACE I/ARB naïve patients</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist naïve</td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypotension or SBP &lt;100</td>
<td></td>
</tr>
<tr>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>Contraindication to use</td>
<td></td>
</tr>
</tbody>
</table>

   b. Other areas of consideration
      i. African American patients
      ii. Implantable devices
      iii. Hyperkalemia
      iv. Renal function

II. Ivabradine
   a. Ivabradine could be considered in patients optimized on an <50% of evidence-based beta blocker target dose, in sinus rhythm, and with a heart rate ≥70 BPM

III. Concomitant use
   a. Sacubitril/valsartan in preference to ivabradine
   b. Do not recommend utilization together at this time due to lack of data


57. Alldredge JM, Tendera MF, Adams JF, Freemantle NF, Polonski LF, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHEF) study. European heart journal JID - 8006263. 0329(0195 - 668; 0195 - 668).


70. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2001;112:2426.


### Appendix A. HFpEF Literature Review\(^{57, 64}\)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>EF + Patient factors</th>
<th>Staging</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP-CHF</td>
<td>EF &gt;40% + Age ≥70 years</td>
<td>NYHA: I-IV</td>
<td>Perindopril 4mg vs. placebo</td>
<td>Insufficiently powered to determine effects on composite all-cause mortality and HF related hospitalizations. Significant ↓ in hospitalizations for HF, NYHA class staging, and 6-minute walk tests.</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>EF ≥45% + Age ≥60 years</td>
<td>NYHA: II-IV</td>
<td>Irbesartan vs. placebo</td>
<td>No difference in primary endpoint of death from any cause or hospitalization for CV cause.</td>
</tr>
<tr>
<td>CHARM-PRESERVED</td>
<td>EF &gt;40%</td>
<td>NYHA: II-IV</td>
<td>Candesartan vs. placebo</td>
<td>No difference in composite endpoint of CV death or hospitalizations for HF ↓ in secondary endpoint of hospitalizations for HF.</td>
</tr>
<tr>
<td>COHERE</td>
<td>EF &gt;40%</td>
<td>NYHA: I-IV</td>
<td>Candesartan vs. placebo</td>
<td>Less severe HF symptoms ↓ hospitalizations.</td>
</tr>
<tr>
<td>OPTIMIZE-HF</td>
<td>EF ≥40% + Eligible for BB + Age ≥65 years</td>
<td>Not reported</td>
<td>Patients discharged from hospital on BB therapy</td>
<td>No significant effect on time to death, time to first re-hospitalization, composite time to death or first re-hospitalization.</td>
</tr>
<tr>
<td>SENIORS</td>
<td>EF &gt;40% + Age ≥70 years</td>
<td>Not reported for subgroup</td>
<td>Nebivolol daily vs placebo</td>
<td>No significant decrease in primary endpoint of death or CV hospitalization.</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>EF ≥45% &quot;Symptomatic HF&quot;</td>
<td>NYHA II-IV</td>
<td>Spironolactone vs. placebo</td>
<td>Non-significant reduction in composite CV mortality, aborted cardiac arrest, or hospitalization for the management of HF.</td>
</tr>
<tr>
<td>DIG-PEF</td>
<td>EF &gt;45%</td>
<td>Not reported for subgroup</td>
<td>Digoxin vs. placebo</td>
<td>No significant difference in combined outcome of death or hospitalization for worsening HF.</td>
</tr>
</tbody>
</table>

### Appendix B. Review of beta blocker studies\(^{65, 71}\)

<table>
<thead>
<tr>
<th>CLINICAL TRIAL NAME</th>
<th>POPULATION/TREATMENT ARMS</th>
<th>TRIAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol (1996)</td>
<td>NYHA II-IV, EF ≤35% Carvedilol vs placebo</td>
<td>48% ↓ In mortality and disease progression</td>
</tr>
<tr>
<td>MERIT-HF (1999)</td>
<td>NYHA II-IV, EF ≤40% Metoprolol ER vs placebo</td>
<td>34% ↓ in all-cause mortality</td>
</tr>
<tr>
<td>CIBIS II (1999)</td>
<td>NYHA III-IV, EF ≤35% Bisoprolol vs placebo</td>
<td>34% ↓ in all-cause mortality</td>
</tr>
<tr>
<td>COPERNICUS (1996)</td>
<td>Severe HF, EF ≤25% Carvedilol vs placebo</td>
<td>35% ↓ in all-cause mortality 24% ↓ in rate of death or hospitalization</td>
</tr>
<tr>
<td>COMET (2003)</td>
<td>NYHA II-IV, EF ≤35% Metoprolol IR vs carvedilol</td>
<td>Carvedilol ↓ all-cause mortality vs metoprolol IR</td>
</tr>
<tr>
<td>CIBIS III (2005)</td>
<td>NYHA II-III, EF ≤35% Bisoprolol vs enalapril</td>
<td>Bisoprolol-first non-inferior to enalapril-first in ITT but not in per-protocol analysis</td>
</tr>
<tr>
<td>MOCHA (1996)</td>
<td>NYHA II-III, EF ≤35% Carvedilol IR 6.25 mg BID vs 12.5 mg BID vs 25 mg BID vs placebo</td>
<td>Dose-related improvements in LV function, mortality, and hospitalization rates seen in carvedilol arms</td>
</tr>
</tbody>
</table>

\(^{ITT, intension to treat}\)
### Appendix C. Review of ACE I Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Drugs</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)</td>
<td>Severe HFpEF and NYHA class IV symptoms</td>
<td>Enalapril vs placebo</td>
<td>31% ↓ in 12-month mortality in enalapril group</td>
</tr>
<tr>
<td>SOVLD (1991)</td>
<td>EF ≤35% and NYHA class II-IV symptoms</td>
<td>Enalapril vs placebo</td>
<td>↓4-year mortality by 16% and ↓ HF hospitalizations</td>
</tr>
<tr>
<td>SOVLD Prevention (1992)</td>
<td>EF ≤35% and NYHA class II-IV symptoms</td>
<td>Enalapril vs placebo</td>
<td>20% ↓ in combined incidence of death or HF hospitalizations in the enalapril group</td>
</tr>
<tr>
<td>ATLAS (1999)</td>
<td>NYHA class II to IV HF and an EF of ≤30%</td>
<td>High-dose vs low-dose lisinopril</td>
<td>high-dose lisinopril experienced a ↓ of 12% hospitalization or death for any reason and 24% ↓ hospitalizations for HF</td>
</tr>
</tbody>
</table>

### Appendix D. Review of ARB Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Drugs</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB in HF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-HeFT (1999)</td>
<td>NYHA class II, III, or IV with an EF &lt;40%</td>
<td>Valsartan vs placebo</td>
<td>↓mortality and morbidity and risk of hospitalization in valsartan group</td>
</tr>
<tr>
<td>CHARM alternative (2003)</td>
<td>NYHA II-IV and LVEF ≤40%</td>
<td>Candesartan vs placebo</td>
<td>20% ↓ in CV mortality and 40% ↓ in hospitalization for HF</td>
</tr>
<tr>
<td>ARB vs ACE I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIMAAL (2002)</td>
<td>ACC/AHA stages B, C, D; EF ≤35% and previous MI</td>
<td>Losartan vs captopril</td>
<td>No significant difference in mortality, sudden death, or hospital admission</td>
</tr>
<tr>
<td>ELITE (1998)</td>
<td>Age ≥65; NYHA II-IV and EF ≤40% Never received an ACE inhibitor and stable CV therapy</td>
<td>Losartan vs captopril</td>
<td>Losartan was found to be superior in regards to tolerability and in regards to secondary endpoints of mortality and hospitalizations compared to captopril</td>
</tr>
<tr>
<td>ELITE II (2000)</td>
<td>≥60 years; NYHA II–IV HF and EF ≤40%</td>
<td>Losartan vs captopril</td>
<td>No significant difference in main efficacy parameters</td>
</tr>
<tr>
<td>VALIANT</td>
<td>ACC/AHA stages B, C, D, EF ≤35% and 0.5 to 10 days status post MI</td>
<td>Valsartan vs captopril</td>
<td>Mortality from any cause, death from any CV cause, recurrent MI, or hospitalization for HF was similar between groups</td>
</tr>
</tbody>
</table>

### Appendix E. Review of Hydralazine + isosorbide dinitrate studies

<table>
<thead>
<tr>
<th>Clinical Trial Name</th>
<th>Population/Treatment Arms</th>
<th>Trial Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT-I (1986)</td>
<td>Reduced exercise tolerance, EF ≤45%</td>
<td>↓ overall mortality in patients taking digoxin and diuretics</td>
</tr>
<tr>
<td>V-HeFT-II (1991)</td>
<td>NYHA I-IV, EF ≤45%</td>
<td>↓ mortality with enalapril vs isosorbide dinitrate + hydralazine in patients taking digoxin and diuretics</td>
</tr>
<tr>
<td>A-HeFT (2004)</td>
<td>NYHA III-IV, African American</td>
<td>43% ↑ survival in hydralazine + isosorbide arm</td>
</tr>
</tbody>
</table>

### Appendix F. Enalapril dosing equivalents

<table>
<thead>
<tr>
<th>Enalapril 5 mg is equivalent to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>benazepril 10 mg</td>
</tr>
<tr>
<td>captopril 50 mg</td>
</tr>
<tr>
<td>fosinopril 10 mg</td>
</tr>
<tr>
<td>lisinopril 10 mg</td>
</tr>
<tr>
<td>moexipril 7.5 mg</td>
</tr>
<tr>
<td>perindopril 4 mg</td>
</tr>
<tr>
<td>quinapril 10 mg</td>
</tr>
<tr>
<td>ramipril 2.5 mg</td>
</tr>
<tr>
<td>Trandolapril 2 mg</td>
</tr>
</tbody>
</table>
Appendix G. Valsartan dosing equivalents

Equivalent Dosages to Valsartan 80mg

<table>
<thead>
<tr>
<th>Equivalent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>candesartan</td>
<td>16 mg</td>
</tr>
<tr>
<td>eprosartan</td>
<td>600 mg</td>
</tr>
<tr>
<td>irbesartan</td>
<td>150 mg</td>
</tr>
<tr>
<td>losartan</td>
<td>50 mg</td>
</tr>
<tr>
<td>olmesartan</td>
<td>20 mg</td>
</tr>
<tr>
<td>telmisartan</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

Appendix H. Sacubitril/valsartan in HFpEF


**Purpose**

- To evaluate the efficacy and safety of sacubitril/valsartan in HFpEF patients

**Outcomes**

- **Primary outcome:** change in NT-proBNP from baseline to 12 weeks
- **Secondary outcomes:** changes in LVEF and volumes, left atrial volume, measures of diastolic function, and BP

**Results**

- **NTproBNP reduction:**
  - 12 weeks: statistically significant reduction from 783 at baseline to 605
  - Prespecified subgroup analysis revealed only patients with diabetes in NTproBNP at week 12

<table>
<thead>
<tr>
<th>NT-proBNP at week 12*</th>
<th>NT-proBNP at week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>134</td>
</tr>
<tr>
<td>Valsartan</td>
<td>132</td>
</tr>
</tbody>
</table>

*statistically significant

- No significant changes in LV size or function, diastolic function, LV mass, or tricuspid regurgitant velocity
- NYHA classification was not significantly different at week 12 or 36
- Left atrial volume size and atrial dimension were significantly reduced (p=0.003 and p=0.034, respectively) in the sacubitril/valsartan group at 36 weeks
  - Changes most apparent in those without atrial fibrillation
- Greater BP reduction occurred in the sacubitril/valsartan group at both time points
  - Decrease in systolic BP of 9.3/4.9 mmHg and 2.9/2.1 mmHg for each group, respectively, at 12 weeks (p=0.001 and p=0.09 for systolic and diastolic BP, respectively)
  - Decrease in BP by 7.5/5.1 and 1.5/0.34 for each group, respectively at 36 weeks (p=0.006 and p=0.001 for systolic and diastolic BP, respectively)
- Safety:
  - Hypotension, renal dysfunction and hyperkalemia did not vary between groups
  - eGFR decreased to a greater extent in sacubitril/valsartan group
  - Urinary albumin creatinine ratio increased to greater extent in sacubitril/valsartan group

**Take Home**

- Sacubitril/valsartan was more effective at reducing atrial remodeling, BP, and NYHA classification at week 36; benefits in clinical status and CV endpoints is not known