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Combined Neprilysin and Angiotensin Inhibitor for the Treatment of Heart Failure

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Abstract

Heart failure (HF) is a highly prevalent disease state worldwide that can progress into a disabling condition. It is pertinent to have a treatment regimen that is effective in lowering the number of HF exacerbations and, therefore, hospital readmission rates. A novel medication currently in clinical trials, LCZ696, blocks both neprilysin and angiotensin type I receptors. The overall effects are an inhibition of the breakdown of natriuretic peptides which leads to a decrease in renin and aldosterone release. This, combined with the antagonization of angiotensin type I receptors, leads to a decrease in blood pressure, blood volume and systemic vascular resistance. The PARAMOUNT trial compared the therapeutic effectiveness of LCZ696 to valsartan monotherapy. This study demonstrated that patients taking LCZ696 had better improvements in symptoms and biomarkers. The PARADIGM-HF trial compared LCZ696 to enalapril. LCZ696 showed significant reductions in cardiac death, hospitalizations and HF symptoms over enalapril. Although this new medication looks promising as a future treatment option for HF patients, additional studies should be completed to look at the long-term patient outcomes associated with LCZ696.

Key Terms

Cardiac Output; Heart Failure; Natriuretic Peptides; Neprilysin; Renin-angiotensin System; Enalapril; Omapatrilat; Valsartan

Introduction

Cardiovascular disease has been the number one cause of death in the United States almost every year since 1935.1 Heart failure (HF), characterized by a lack of blood perfusion due to decreased cardiac output, is a debilitating condition worldwide. Fortunately, through extensive drug development, scientists and clinicians have been able to slow the decline of cardiac function. Currently, angiotensin-converting-enzyme inhibitors (ACE-I) are the first line therapy options for HF patients based on recommendations from the 2013 American College of Cardiology Foundation/American Heart Association guidelines.2 They are effective in preserving Left Ventricular Ejection Fraction (LVEF) and decreasing hypertension symptoms associated with HF.

However, recent research points to a novel approach in better managing HF. In clinical trials, LCZ696, a dual neprilysin and angiotensin blocker, has consistently demonstrated clinical effectiveness in many cardiac parameters. Future studies need to be conducted before LCZ696 is introduced into the market and incorporated into the guidelines as an alternative option to ACE-I, the current mainstay treatment for HF.

Epidemiology

With a prevalence of more than 5.8 million people in the United States and 23 million people worldwide, HF is a serious public health concern.3 Each year, there are more than 550,000 new cases diagnosed in the United States alone. Heart failure prevalence is highest among black and Hispanic populations.2 Male and female populations have a similar incidence and prevalence of HF. However, women more commonly develop HF later in life and tend to survive longer with the disease than men. Even though HF can occur at any age, the prevalence is only about 1 to 2 percent in populations younger than 55 years of age and increases to approximately 10 percent in populations over 75 years of age. Heart failure is a complicated clinical syndrome that is the consequence of a structural or functional cardiac disorder. It results in an impaired ability of the heart to pump blood sufficiently enough to meet the requirement of metabolizing tissues.2,3 There are different types of HF which may result in various outcomes. Left-sided HF can cause fluid backup in the lungs resulting in shortness of breath, while right-sided HF can cause fluid backup into the abdomen and lower extremities causing edema.4 Heart failure can also be classified as systolic or diastolic. Systolic HF, also known as HF with reduced ejection fraction, occurs when the left ventricle cannot contract with enough force to pump out adequate amounts of blood. Diastolic HF, also known as HF with preserved ejection fraction, occurs when the left ventricle does not fill completely. Many conditions can damage the heart resulting in HF including coronary artery disease, myocardial infarction, hypertension, obesity, arrhythmias and other chronic diseases such as diabetes and dyslipidemia. Following are tables of both the ACCF/AHA Stages of HF and the New York Heart Association (NYHA) Functional Classification from the ACCF/AHA Practice Guidelines.2

Table 1. ACCF/AHA Stages of HF.2

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>At high risk for HF with no structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease without symptoms of HF</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
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**Table 2. NYHA Functional Classification.**

<table>
<thead>
<tr>
<th>NYHA Functional Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause HF symptoms.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes HF symptoms.</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without symptoms of HF, or experience HF symptoms at rest.</td>
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With numerous possible causes of HF, it can be difficult to diagnose. A compilation of data from a patient’s medical history, physical examination and chest radiograph along with the presence of indicating symptoms and elevated filling pressures are used when diagnosing HF. Symptoms a patient with HF may experience include dyspnea at rest or during exertion, fatigue or weakness, edema in the lower extremities, tachycardia, chest pain or palpitations. When a patient presents with these symptoms, a family history as well as serial assessments of weight, jugular venous pressure and vital signs should be obtained. Risk factors are also taken into consideration and include conditions that can damage the heart muscle. These risk factors include sleep apnea, viral infections, obesity, alcohol or tobacco use and use of the diabetes medications rosiglitazone and pioglitazone, which can increase edema and worsen HF. Many diagnostic tests are used to identify the causative conditions or risk factors of HF. One test used to distinguish between systolic and diastolic HF is an echocardiogram, which measures the ejection fraction and produces a video image of the heart to show how well it is pumping blood.

Hospitalization for treatment intensification is usually required for periodic exacerbations of HF. Almost 1 million hospitalizations for HF occur each year and it is the most frequent cause for hospitalization of patients over 65 years of age. Readmission rates of HF patients are 25 percent within 30 days of initial hospitalization and can reach up to 50 percent within six months. Both initial hospitalization and readmission rates for HF patients continue to rise. It is difficult to establish a robust risk model for readmission because there are many factors to consider that vary from patient to patient. There are, however, some clinical predictors for readmission. If levels of cardiac biomarkers (such as natriuretic peptides and cardiac troponins) remain high at discharge, readmission is likely. Worsening renal function during the course of hospitalization for HF is a strong predictor of readmission. Having lower hospital readmission rates would improve the patient’s quality of life and also benefit the hospital financially. New treatment options to help reduce hospital readmission rates are needed. One new option is LCZ696, which targets the renin-angiotensin-aldosterone system.

**Pharmacology**

In the renin-angiotensin-aldosterone system (also known as RAAS), renin from the kidney is responsible for the rate limiting step, which is the conversion of angiotensinogen to angiotensin I (ANG I). From this point, ANG I is converted to angiotensin II (ANG II) via the angiotensin converting enzyme (ACE), which is produced in the lung. Eventually, ANG II binds to the angiotensin type 1 receptor (AT1) as seen in Figure 1A.

![Figure 1A Renin-Angiotensin-Aldosterone System](image-url)
Once ANG II binds to its receptor, different areas of the body are affected, including the cardiovascular system, sympathetic nervous system and pituitary gland. In general, ANG II promotes cell growth and proliferation, inflammatory response and oxidative stress. In the cardiovascular system, ANG II causes vasoconstriction, which leads to an increase in blood pressure and cardiac contractility. This can lead to vascular and cardiac hypertrophy. As ANG II travels to the adrenal cortex, it facilitates aldosterone secretion which helps regulate sodium and potassium balance. These two electrolytes ultimately influence the extracellular volume. With aldosterone release, more sodium and water is reabsorbed in the distal convoluted tubule and collecting duct. This process promotes the excretion of potassium. ANG II also activates the sympathetic nervous system, which promotes vasoconstriction and increases blood pressure. Furthermore, ANG II increases vasopressin, also known as antidiuretic hormone (ADH), which is released from the pituitary gland and increases water reabsorption. Lastly, while ANG II is activating different systems, it also inhibits the atrial natriuretic peptide (ANP) and nitric oxide. When ANP and nitric oxide are inhibited, the body's natural way of decreasing renin and promoting vasodilation is prevented.

Since ANG II affects many locations in the body (especially the heart), angiotensin II receptor blockers (ARB) are important in patients with HF. As seen in Figure 1B, the mechanism of action is selective inhibition of ANG II by competitive antagonism of the ANG II receptors, more specifically the AT1 receptor. When ANG II is blocked from attaching to the receptor, the actions mediated by AT1 receptors are inhibited. This leads to a reduction in blood pressure by decreasing the systemic vascular resistance. The sympathetic nervous system activity is reduced as well. There is an inhibition of aldosterone release from the adrenal gland and, therefore, less sodium is reabsorbed when ANG II cannot bind to the AT1 receptor. While the RAAS is working, the natriuretic peptides system maintains cardiovascular homeostasis such as the vascular tone, cardiovascular remodeling and fluid regulation. The natriuretic peptides system is the body's natural defense to overactive RAAS or sympathetic nervous system. This system consists of three peptides: ANP, B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). Atrial natriuretic peptide is made in the atria and responds to atrial distention while BNP is produced in the ventricular myocytes and responds to volume overload. C-type natriuretic peptide is secreted from the vascular endothelium and responds to cytokines. Overall, the natriuretic peptides system decreases the release of renin and aldosterone, which leads to the suppression of RAAS. Due to the suppression of RAAS, the blood pressure and blood volume are decreased. While the sympathetic nervous system activity is inhibited, the parasympathetic nerve activity increases. When natriuretic peptides are released, the opposite effects of sympathetic nervous system and RAAS occurs such as vasodilation and decrease in renin secretion (see Figure 2A).

Neprilysin (NEP) is an enzyme that degrades the natriuretic peptides specifically ANP and CNP. In addition, NEP degrades ANG II, bradykinin and substance P. Bradykinin and substance P are vasoactive peptides and are responsible for vasodilation. One of the treatments for HF is NEP inhibitors, as shown in Figure 2B, which increase natriuretic peptides and allow more vasodilation to occur. Since ANG II degradation is also inhibited, there can be an increase in vasoconstriction. Therefore, NEP inhibitors depend on the balance between the vasoconstrictor and vasodilator effects.

The angiotensin receptor neprilysin inhibitor (ARNI) may serve as a novel treatment option for HF management and is currently in clinical trials. This drug is currently called LCZ696 and must be taken orally in order to become activated. As seen in Figure 3, once LCZ696 is in the body, it dissociates into valsartan and Sacubitril (AHU377), which is an ARB and a prodrug, respectively. Sacubitril (AHU377) is enzymatically cleaved into LBQ657, which is the active form of the neprilysin inhibitor. While LBQ657 is inhibiting neprilysin, the valsartan blocks the angiotensin type 1 receptor. Since NEP inhibitors are dependent on the balance between the vasoconstrictor and vasodilator effects, the valsartan blocks any of the vasoconstrictor effects while the vasodilator effects are activated.
Treating HF solely through the means of increasing NEP appears to be therapeutically insufficient. The ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF) trial assessed nesiritide's role in the prevention of rehospitalizations and improvements of dyspnea symptoms in HF patients. As a double-blind, placebo-controlled trial, 7,141 patients who were hospitalized with acute HF were randomly assigned to either nesiritide (recombinant natriuretic peptide) or placebo for 24 to 168 hours. Nesiritide slightly improved symptomatic dyspnea at six hours (P=0.03) and 24 hours (P=0.007) compared to placebo. However, there was no significant difference in 30-day mortality rate (3.6 percent with nesiritide versus 4.0 percent with placebo; absolute difference of -0.4 percentage points; 95 percent confidence interval, -1.3 to 0.5) or rates of worsening renal function, as defined by greater than 25 percent decrease in estimated glomerular filtration rate (GFR). Additionally, nesiritide was associated with increased rates of hypotension. Thus, the use of nesiritide should not be the standard treatment for HF patients. Similarly, ecadotril, a NEP inhibitor, showed little to no improvements in HF symptoms and quality of life in a placebo-controlled trial including 279 patients. Patients on ecadotril showed no difference in the six minute walk test (6MWT) compared to placebo patients. The 6MWT is an outcome measure typically utilized in clinical trials to assess the efficacy of HF treatments. Lastly, ecadotril is not frequently used in practice due to its serious side effect profile ( aplastic anemia at higher doses). Candoxatril, another NEP inhibitor, was tested in 11 healthy men and did not demonstrate a promising therapeutic option. Although central venous pressure was reduced, systolic pressure was increased, most likely due to increased levels of epinephrine and endothelin.

Omapatrilat was the first combination drug manufactured to target both neprilysin and ACE. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial compared its efficacy to an ACE-inhibitor (enalapril) in a randomized, double-blind trial of 5,770 patients. The omapatrilat group demonstrated a 9 percent lower risk of cardiovascular death or hospitalization (P=0.024) and a 6 percent lower risk of mortality. (P=0.339). Although showing much promise, omapatrilat does not demonstrate a definite clinical superiority over enalapril in reducing a primary clinical event (death and rehospitalization). Omapatrilat was shown to have a higher occurrence of angioedema which led to its withdrawal from the market. Angioedema most likely resulted due to increased plasma concentrations of bradykinin. Bradykinin induces vasodilation and vascular permeability. As a result, angiotensin receptor blockers (ARBs) were further studied as a combination product due to a decreased risk of angioedema.

LCZ696 is the first combined drug to incorporate inhibition of neprilysin and angiotensin receptor blockade. It was extensively studied in HF with HFP EF and HF with HFr EF patients. The PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of HF with Preserved Ejection Fraction) trial was a randomized, parallel group, double-blind study which compared LCZ696's therapeutic effectiveness to valsartan monotherapy. Patients included in this study were required to be classified as a NYHA class II to III (see Table 1 and Table 2), have a left ventricular ejection fraction greater than 45 percent and have an N-terminal B-type natriuretic peptide (NT-proBNP; marker of ventricular wall stress) greater than 400 pg/ml. Change in serum NT-proBNP concentrations 12 weeks from baseline.
was the primary endpoint in this study. Patients were then followed through 36 weeks for additional endpoints. At the start of the trial, 308 patients were randomized to LCZ696 200 mg twice daily or valsartan 160 mg twice daily (both doses were bioequivalent). After 12 weeks, NT-proBNP levels were significantly reduced in the LCZ696 group compared to valsartan group (p=0.005). At 36 weeks, LCZ696 patients had better improvements in left atrial size, greater improvements in NYHA class, and greater reductions in blood pressure. Additionally, GFR was higher in patients receiving LCZ696 compared to patients receiving valsartan. Further prospective studies need to be conducted in order to assess whether these observed effects would translate to improved patient outcomes. Future experiments should increase the duration of follow-up in order see the long-term clinical benefits of LCZ696.

In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF) trial, 8,442 patients were randomly assigned to receive either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily). Patients were required to be classified as a NYHA class II to III, have a left ventricular ejection fraction of less than 40 percent and have a NT-proBNP level of greater
than 600 pg/ml. Other inclusion criteria were GFR greater than 30 ml/min/1.73 m², systolic blood pressure greater than 95 mmHg and potassium less than 5.4 mmol/L. The primary endpoint was the composite of death from cardiovascular causes or hospitalizations from HF. There were 558 deaths from cardiovascular causes in the LCZ696 patients and 693 deaths in the enalapril patients. LCZ696 was found to reduce hospitalizations by 21 percent and decrease symptoms and physical limitations of HF (P= 0.001). This study ended early due to the clear and "overwhelming benefits" of LCZ696 over enalapril.

From these clinical trials, LCZ696 has consistently demonstrated its clinical efficacy via improvements in many cardiac parameters. Dual inhibition of neprilysin and the renin-angiotensin-aldosterone system provides a new method to effectively and safely treat HF patients.

Pharmacist Role

Although LCZ696 has been well-tolerated by patients overall, it is still imperative that pharmacists counsel patients on the potential side effects and the importance of adherence to their medication regimen. A potential adverse reaction is hypotension, so patients should be consulted about the symptoms of low blood pressure including dizziness; syncope; blurred vision; nausea; cold, clammy, pale skin and rapid, shallow breathing. Angioedema rarely occurred in trials, but patients should be educated on signs and symptoms so they may seek care early to avoid airway compromise. Medication noncompliance is a risk factor for hospital admission. Counseling on the importance of HF medication adherence helps the patients to understand why they are taking the medication because they may not always physically feel an impact.

It is important that pharmacists educate their patients not only about the medications they are taking but also about their disease states and how lifestyle modifications can impact them. Stressing the benefits of weekly physical activity, dietary sodium and fluid restriction and staying within a healthy weight to patients can help reduce the incidence of HF exacerbations. Encouraging patients to find a support system has been shown to reduce hospitalizations and mortality because patients are more likely to adhere to their treatment regimen and live a healthier lifestyle. Being the most accessible health care providers to some patients, pharmacists should follow-up with recently discharged HF patients to help reduce hospital readmission and HF exacerbations through improved patient education.

Conclusion/Outlook for the Future

Each year there are many new cases of HF, a disease responsible for increased hospital readmission rates. Currently, ACE-I are used to control HF, which is insufficient alone. A novel drug, LCZ696, may be an alternative to the current first line therapies of ACE-I and ARB for HF, specifically HFrEF. LCZ696 is an angiotensin receptor neprilysin inhibitor, which inhibits neprilysin through LBQ657 and blocks the AT1 receptor through valsartan. Overall, LCZ696 had less cardiovascular mortality and HF hospitalizations compared to other monotherapies. In addition, patients tolerated this drug better than omapatrilat, which had higher incidence of angioedema. In comparison to enalapril, LCZ696 had less hospitalizations and less physical limitations in patients. Currently, LCZ696 has been studied in patients with HFrEF; however, longer follow-up is needed in order to determine long-term effects of LCZ696. Pharmacist should be anticipating the use of this novel drug and educate patients on ways to improve their quality of life through medications and lifestyle modifications. Overall, pharmacists can help reduce hospital readmission and HF exacerbations through improved patient education.