A New Mechanism of Action in Heart Failure: Angiotensin-Receptor Neprilysin Inhibition

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Abstract

Objective: To evaluate the efficacy, safety, and clinical significance of sacubitril/valsartan (Entresto) in patients with heart failure with a reduced ejection fraction (HFrEF). **Data Sources:** An extensive search was conducted on Ovid MEDLINE using keywords and medical subject headings *LCZ696*, *sacubitril/valsartan*, *angiotensin-receptor neprilysin inhibitor*, and *Entresto*. **Study Selection and Data Extraction:** The search was conducted to retrieve clinical trials comparing sacubitril/valsartan to current guideline-directed therapy for HF. Articles using the limits of clinical trials “all” (phase I to IV), in English, and published within the past 5 years were reviewed. Supplemental sources included the Entresto package insert via the manufacturer’s website. Primary end points included all-cause mortality and time to first hospitalization. Safety end points included incidence and severity of angioedema, cough, hyperkalemia, increased serum creatinine, and hypotension. **Data Synthesis:** This review critiques both clinical and statistical significance of the “Prospective Comparison of ARNi with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure” or PARADIGM-HF and other phase II to III clinical trials. Sacubitril/valsartan showed a 20% reduction in cardiovascular death and first hospitalization from HF compared with enalapril. Despite an overall reduction in adverse events, sacubitril/valsartan had increased occurrences of hypotension and nonserious angioedema. **Conclusion:** Sacubitril/valsartan is a viable option for newly diagnosed New York Heart Association (NYHA) class II to III and is an alternative to patients who are currently being treated with the maximum doses of current gold standard treatment. Clinicians initiating sacubitril/valsartan must monitor patients closely for signs, symptoms, and history of hypotension and angioedema.

Keywords

angiotensin-receptor neprilysin inhibitor, enalapril, Entresto, heart failure, *LCZ696*, natriuretic peptide, HFrEF, sacubitril/valsartan

Background

Heart failure (HF) continues to be a major concern, affecting more than 5 million people in the United States. According to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), there are greater than 650 000 new cases of HF per year, and the incidence continues to rise.¹ HF is a progressive disease that impairs cardiac structure and function. As the disease progresses, cardiac output becomes insufficient to provide the body with an adequate amount of oxygen.² Etiology and risk factors include long-standing hypertension, myocardial infarction, arrhythmias, valvular disorders, congenital malformations, and chronic diseases such as thyroid problems, sleep apnea, cocaine use, smoking, and alcohol abuse.² Common signs and symptoms of HF include dyspnea, exercise intolerance, fatigue, and fluid retention. There are 2 different organizations that classify the

severity of HF. The ACCF/AHA classifies the stages of HF by structural heart disease, whereas the New York Heart Association (NYHA) classification is based on functional symptoms.²

There are 2 different types of HF: systolic HF and diastolic HF. Systolic HF, also known as HF with a reduced ejection fraction (HFrEF), makes up the majority (~70%) of HF conditions. Systolic HF is classified as having an ejection fraction of $\leq 40\%$ and occurs when the left ventricle cannot contract normally, causing a decreased ability to pump blood into circulation.³ Diastolic HF, also known as HF with a preserved

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ejection fraction (HFpEF), is classified as having an ejection fraction of $\geq 50\%$, but can also be called borderline HFpEF at 41% to 49% or improved HFpEF at $>40\%$. This occurs when the left ventricle cannot relax normally, causing the heart to lose its ability to fill with blood, during diastole.³ Current therapy for HFrEF includes diuretics for fluid retention, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), β -blockers, aldosterone antagonists, hydralazine/isosorbide dinitrate, and digoxin.¹ Only ACE inhibitors, ARBs, β -blockers, aldosterone antagonists, and hydralazine/isosorbide dinitrate are proven to reduce mortality in patients with HFrEF.¹ The approach when treating HFpEF is different from that for treating HFrEF, in which options include diuretics to relieve symptoms and treating underlying comorbidities leading to HF.¹

Current first-line therapy for HFrEF includes ACE inhibitors or ARBs plus a β -blocker, as shown previously in The Cooperative North Scandinavian Enalapril Study (CONSENSUS) and Studies of Left Ventricular Dysfunction (SOLVD) trial to reduce mortality, morbidity, and hospitalizations.¹ The CONSENSUS trial compared enalapril with placebo, in addition to standard therapy, in patients with severe HFrEF and NYHA class IV symptoms and showed a 40% reduction in mortality at 6 months for enalapril. The SOLVD trial further demonstrated a mortality benefit in patients with moderate HFrEF.⁴ The SOLVD trial compared enalapril with placebo, in addition to standard therapy, in patients with an EF of $\leq 35\%$, and showed a 16% decrease in mortality and reduction in hospitalizations at 4 years.⁵ In addition, aldosterone antagonists are recommended in patients with NYHA class II to IV HF, who have a left-ventricular ejection fraction (LVEF) of 35% or less, unless contraindicated, as the Emphasis-HF trial displayed a reduction in morbidity and mortality.^{1,6} Although the current first-line treatment has been effective, HFrEF is still associated with increased hospitalizations, high mortality rates, and many long-term complications, such as kidney and liver damage, stroke, myocardial infarction, and death.¹

Prior to the combination of neprilysin inhibitor and ARBs, previous combinations with ACE inhibitors were considered. This combination is referred to as vasopeptidase inhibitors. Omapatrilat, a vasopeptidase, was studied in patients with hypertension, cardiovascular disease, and HF. The Omapatrilat and Enalapril in Patients with Hypertension (OCTAVE) trial compared the combination to enalapril in patients with hypertension.⁷ The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial compared the combination in patients with HFrEF.⁸ Both of these trials showed increased amounts of severe angioedema. The proposed mechanism is the dual inhibition of bradykinin breakdown by ACE inhibitors via the renin angiotensin aldosterone system and further lack of breakdown as a result of the inhibition of the neprilysin enzyme leading to increased cases and severity of

angioedema.⁹ Combining neprilysin with valsartan, an angiotensin II type 1 receptor antagonist, prevents the dual inhibition of bradykinin and leads to reduced cases of angioedema.⁹

This article delivers a clinical review on sacubitril/valsartan (Entresto), a novel medication for HFrEF. Sacubitril/valsartan is a combination drug that uses an ARB plus a neprilysin inhibitor, termed *ARNi* (angiotensin receptor neprilysin inhibitor).¹⁰ This medication, formerly known as LCZ696, was originally developed by Novartis and was granted priority review on designation by the US Food and Drug Administration (FDA) in February of 2015. On July 7, 2015, sacubitril/valsartan was approved to reduce the risk of cardiovascular death and hospitalization in NYHA classes II to IV in HFrEF patients because of the drug's significant safety and efficacy.¹¹

Data Source

A search of Ovid MEDLINE (January 2010 to November 2015) using keywords *LCZ696*, *sacubitril/valsartan*, *angiotensin-receptor neprilysin inhibitor*, and *Entresto* was carried out to conduct a clinical trials search. Articles using the limits of clinical trials "all" (phase I to phase IV), using human subjects, in English, and for the past 5 years were reviewed. Supplemental sources included the Entresto package insert via the manufacturer's website.

Pharmacology

Sacubitril/valsartan is a combination drug consisting of sacubitril and valsartan. Valsartan inhibits the angiotensin II receptor type 1, causing vasodilation, reducing secretion of vasopressin, reducing production and secretion of aldosterone, and increasing the excretion of sodium and water by the kidneys, which leads to a reduction in blood volume.¹² The prodrug sacubitril, inhibits neprilysin. Neprilysin is an endopeptidase that converts the active natriuretic peptides into inactive forms. Blocking this enzyme increases levels of natriuretic peptides, bradykinin, and adrenomedullin, which counteracts neurohormonal overstimulation preventing vasoconstriction, sodium retention, and maladaptive remodeling (Figure 1).¹²

Sacubitril/valsartan is cocrystallized (1:1 molar ratio) with a molecular mass of 5748.03 g/mol, which is stable in both solid and aqueous forms (pH of 5-7).¹³ Sacubitril/valsartan has an oral bioavailability of $>60\%$.³ The neprilysin inhibition portion of the drug, sacubitril, is further metabolized into the active metabolite LBQ657 by plasma esterases. The peak plasma concentration of the active moiety, LBQ657, is reached within 2 hours. Sacubitril has a half-life of 1.4 hours; LBQ657 has a half-life of 11.5 hours; and valsartan has a half-life 9.9 hours.¹² Sacubitril/valsartan is given twice daily and reaches steady state within 3 days.

Figure 1. TOP: Combination of sacubitril (neprilysin inhibitor) and valsartan (angiotensin II receptor antagonist) BOTTOM: Activation of prodrug sacubitril to LBQ657 (sacubitrilat) by de-ethylation via plasma esterases.

The formulation of valsartan in sacubitril/valsartan has a more potent blockage of angiotensin II AT₁ receptors than valsartan alone because of higher bioavailability than other formulations, leading to greater vasodilation, reduction in the secretion of vasopressin, and reduction in the production and secretion of aldosterone. The 26, 51, and 103 mg of valsartan in sacubitril/valsartan is equivalent to evidence-based doses of 40, 80, and 160 mg of valsartan alone because of the fact that the valsartan in sacubitril/valsartan is more readily absorbed than valsartan in other marketed tablet formulations.¹⁴ In clinical trials, patients who took sacubitril/valsartan with or without food did not see a change in absorption, which allows the drug to be taken without regard to food. Sacubitril/valsartan is highly bound to plasma proteins. Given its molecular size and high protein binding sacubitril/valsartan is likely to be poorly dialyzable. The volume of distribution of the sacubitril component is 103 L and that of the valsartan component is 75 L. Approximately 60% of sacubitril and 13% of valsartan is excreted unchanged in the urine. Approximately 42% of sacubitril and LBQ657 and 86% of valsartan are excreted through the feces.¹⁴

Clinical Trials

Phase II Trials

The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction: A

Phase 2 Double-Blind Randomized Controlled Trial (PARAMOUNT-HF) assessed the efficacy and safety of sacubitril/valsartan compared with valsartan HFpEF, with the primary outcome of reduction in NT-proBNP (brain natriuretic peptide) from baseline to 12 weeks. PARAMOUNT-HF was a 36-week, multicenter, randomized, double-blind, double-dummy superiority trial that assessed patients with NYHA class II to III HF, LVEF of 45% or greater, and NT-proBNP of >400 pg/mL.¹⁵ Patients were excluded from the trial if they had previous ejection fraction of <45%, isolated right HF caused by pulmonary disease, dyspnea resulting from noncardiac causes, primary valvular or myocardial diseases, or CAD needing revascularization within 3 months of screening.¹⁵ Prior to randomization, there was a 2-week placebo run-in period where patients continued their baseline treatments. However, ACE inhibitors and ARBs had to have been discontinued 24 hours prior to randomization. There were 301 patients randomized to receive either sacubitril/valsartan 50 mg titrated to 200 mg orally twice daily or valsartan 40 mg titrated to 160 mg orally twice daily over 36 weeks, with 12 weeks being the main study period.¹⁵

Using ANCOVA to measure the primary outcome with an a priori *P* value of ≤0.05, the trial found that sacubitril/valsartan was superior to valsartan in reducing NT-proBNP at 12 weeks. In the sacubitril/valsartan group, NT-proBNP was reduced from 783 to 605 pg/mL, compared with 862 to

835 pg/mL in the valsartan group. The ratio of change from sacubitril/valsartan to valsartan was statistically significant at 0.77: $P = 0.005$; 95% CI = 0.64-0.97. A follow-up at 36 weeks showed no statistical difference between the 2 groups, potentially undermining the statistical and clinical significance of NT-proBNP reduction. In addition to the reduction in NT-proBNP, the authors of the trial also documented a reduction in left-atrial size in patients receiving sacubitril/valsartan after 36 weeks, which could be a sign of reverse left-atrial remodeling. Furthermore, there was an improvement in NYHA class at 36 weeks in patients taking sacubitril/valsartan compared with valsartan alone. The secondary end points of any severe adverse events (AEs) between the study groups had a P value of 0.32 and lacked CIs, making the data inconclusive.¹⁵ Because of the findings of a reduction in NT-proBNP, reverse left-atrial remodeling, and an improvement in NYHA class, further phase III testing is warranted to discuss the benefits of sacubitril/valsartan in the potential reduction in left-ventricular pressure and wall stress in patients with HFpEF.

Phase III Trials

The PARADIGM-HF was a phase III trial conducted to determine if long-term effects of sacubitril/valsartan on morbidity and mortality in patients with HFrEF were superior to enalapril, based on the composite primary end points of death from cardiovascular causes and first hospitalizations from HF. The criteria of the PARADIGM-HF trial were based on the SOLVD treatment group. The SOLVD and OVERTURE trials allowed the authors to bypass phase II trials and determine an effective comparator dose of enalapril 10 mg twice daily.^{5,8,16}

The phase III trial was designed to be a multicenter, active-controlled, double-blind, randomized, superiority trial but was ended early after the 27th-month median follow-up because of overwhelming benefits. Inclusion criteria were the following: patients had to be at least 18 years old and with NYHA class II, III, or IV symptoms; ejection fraction of 40% or less (changed to 35% or less by randomization); and BNP of at least 150 pg/mL or NT-proBNP of at least 600 pg/mL (or if they had been hospitalized for HF within 12 months, BNP of at least 100 pg/mL or NT-proBNP of at least 400 pg/mL). Patients taking ACE inhibitors or ARBs were considered but were required to take a stable dose of a β -blocker and ACE inhibitor (or ARB) equivalent to enalapril 10 mg for at least 4 weeks before screening. Exclusion criteria were symptomatic hypotension, systolic blood pressure <100 mm Hg at screening or <95 mm Hg at randomization, estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² of body surface area at screening or at randomization or a decrease in eGFR of more than 25% (changed to 35%) between screening and randomization, serum potassium >5.2 mmol/L at screening or >5.4 at

randomization, history of angioedema, or unacceptable side effects during ACE inhibitor or ARB treatment.¹⁷

There were 2 run-in periods prior to randomization. The first was 2 weeks of single-blind treatment with enalapril 10 mg orally twice a day. The second run-in was 2 weeks of sacubitril/valsartan 100 mg orally twice daily, titrated up to 200 mg orally twice daily for an additional 2 weeks. Patients received a 36-hour washout period to avoid the risk of angioedema in between the run-in period and prior to starting the study drug. During the run-in period, 12% of patients withdrew from the trial because of AEs, such as cough, hyperkalemia, renal dysfunction, and hypotension. There were 8442 patients randomized into 2 groups. The first group of 4187 patients was assigned to receive sacubitril/valsartan 200 mg orally twice daily, and the second group of 4212 patients was assigned to receive enalapril 10 mg orally twice daily.^{17,18}

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for HF. The secondary outcomes were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), the time to a new onset of atrial fibrillation, and the time to the first occurrence of a decline in renal function. The KCCQ is a self-administered, 23-question survey that measures a patient's physical function; frequency, severity, and recent changes of symptoms; social function; self-efficacy and knowledge; and quality of life. An overall summary score is derived from those measures and is quantified to a range of 0 to 100, with the higher scores reflecting better health status. The mean age was 64 years; 66% of the patients were white; and the mean LVEF was 29.5%.¹⁷

At the end of the 27 months, the primary outcome of death from cardiovascular causes or first hospitalization for worsening HF was significantly lower in the sacubitril/valsartan group (21.8%) compared with the enalapril group (26.5%) using Kaplan-Meier estimates: $P < 0.001$ and 95% CI = 0.80 (0.73-0.87). A total of 21 patients needed to be treated with sacubitril/valsartan for 27 months to prevent 1 occurrence of death from cardiovascular cause or first hospitalization from worsening HF compared with enalapril. There were a total of 558 deaths from cardiovascular causes in the sacubitril/valsartan group (13.3%) compared with 693 deaths in the enalapril group (16.5%); $P < 0.001$ and 95% CI = 0.80 (0.71-0.89). The absolute risk reduction in mortality was 3% when compared with the gold standard, enalapril. There were 537 patients (12.8%) receiving sacubitril/valsartan who were hospitalized for HF, which was significantly lower than the 658 patients receiving enalapril: $P < 0.001$ and 95% CI = 0.79 (0.71-0.89). The secondary outcome of death from any cause was lower in the sacubitril/valsartan group (17%) compared with the enalapril group (19.8%); $P < 0.001$ and 95% CI = 0.84 (0.76-0.93). Moreover, the sacubitril/valsartan group (-2.99) showed a

Table 1. Frequency of Adverse Events in PARADIGM-HF.

	Sacubitril/ valsartan, n = 4187	Enalapril, n = 4212	P Values
Symptomatic hypotension	14%	9.25%	<0.001
Serum creatinine >2.5 mg/dL	3.3%	4.5%	0.007
Elevated serum K ⁺	16.1%	17.3%	0.15
Cough	11.3%	14.3%	<0.001
Angioedema	0.45%	0.23%	0.19

lesser decrease in the mean change from baseline to month 8 in the KCCQ clinical summary score than the enalapril group (-4.63): $P = 0.001$ and 95% CI = 1.64 (0.63-2.65). New onset of atrial fibrillation occurred in 84 patients of the sacubitril/valsartan group and 83 patients of the enalapril group, with no statistically significant differences; $P = 0.84$. There were also no statistically significant differences in the decline of renal function between the sacubitril/valsartan group (94 patients) and the enalapril group (108 patients); $P = 0.28$. There was a decreased adverse drug reaction profile for sacubitril/valsartan versus enalapril. Sacubitril/valsartan had decreased adverse effects related to renal impairment, hyperkalemia, and cough compared with enalapril, but there were more occurrences of hypotension and nonserious angioedema. In the sacubitril/valsartan group, 588 patients (14%) experienced symptomatic hypotension, compared with 388 patients (9.2%) in the enalapril group ($P < 0.001$). Although the sample sizes were small and, therefore, no conclusion should be drawn, the safety data of non-serious angioedema should be noted. In the sacubitril/valsartan group, there were 3 times more hospitalizations and almost 2 times more need for medical intervention without hospitalizations because of angioedema compared with the enalapril group. In the sacubitril/valsartan group, 10.7% of patients stopped the trial because of AEs, compared with 12.3% in the enalapril group ($P = 0.03$).¹⁷ Table 1 lists the frequency of AEs experienced in the clinical trial.

Packer et al¹⁹ analyzed the results of PARADIGM-HF in Angiotensin Receptor Neprilysin Inhibition Compared with Enalapril on the Risk of Clinical Progression in Surviving Patients with Heart Failure to assess the effects of sacubitril/valsartan compared with enalapril on the clinical deterioration in surviving HFrEF patients. They looked to determine if ARNi was superior to ACE inhibitors in the prevention of clinical progression. The substudy results showed that fewer sacubitril/valsartan-treated patients ($n = 520$) had worsening HF, requiring additional therapy, intravenous therapy, or increasing doses of diuretics than enalapril-treated patients ($n = 604$): $P = 0.003$ and 95% CI = 0.84 (0.74-0.94). A total of 53 patients need to be treated with sacubitril/valsartan for 27 months to prevent 1 patient from worsening HF leading to increased medical treatment. Also,

patients on sacubitril/valsartan ($n = 102$) had a fewer number of emergency department visits for HF and hospital admissions compared with enalapril ($n = 150$): $P = 0.001$ and 95% CI = 0.66 (0.52-0.85).¹⁹ Overall, the sacubitril/valsartan group had 30% lower visits among all emergency department visits when compared with enalapril. These statistically significant differences reflect the superiority of sacubitril/valsartan over enalapril in the clinical progression of HFrEF. The PARADIGM-HF trial showed that sacubitril/valsartan was superior in reducing death from cardiovascular causes and first hospitalizations from HF, and the latter subgroup analysis showed that there was a reduction in clinical progression of the disease. In slowing the progression of this disease, treatment with sacubitril/valsartan could possibly stabilize the course of HF and improve patient's quality of life.

The results of the PARADIGM-HF and other phase III trials appear promising because there are statistically significant differences in important clinical end points when comparing sacubitril/valsartan with current first-line therapy of ACE inhibitors. The reduction in the primary end points of death from cardiovascular causes, first hospitalization from worsening HF, and clinical progression of HFrEF is encouraging for this newly approved medication. There are, however, limitations and concerns regarding the landmark trial. The fact that the phase II trial was bypassed is particularly concerning because there were no studies to assess safety. This, added with the high number of dropouts during the run-in period ($n = 977$), makes it difficult to extrapolate tolerability of sacubitril/valsartan in clinical practice.¹⁷ The PARADIGM-HF trial had mostly enrolled patients who were NYHA class II, making up 71.6% of the patients, and only had 0.8% of patients in the NYHA class IV functional class. This is a cause for concern because most of the patients were clinically stable, and it remains unknown how the novel medication truly works in those with severely progressed disease. Moreover, the trial was done predominantly in Caucasian Europeans (66% Caucasian, only 7% from North America). There is a higher risk of angioedema in African Americans, but African Americans only made up 5% of the population studied in the phase III trials. Within the study, 5.6% (3/54) of African Americans had angioedema, with 1 patient requiring hospitalization.²⁰ The trial also had a majority of male participants (~78%), with a mean age of about 64 years. Also, inhibiting neprilysin would inhibit the breakdown of β -amyloid, which builds up in the brain, as seen in Alzheimer's disease.²¹ The results of the PARADIGM-HF trial show the relative risk reduction to be a 20% decrease in mortality from baseline. It is important to note, however, that the absolute risk reduction was a 3% reduction in mortality when compared to the gold standard, enalapril. The PARADIGM-HF trial was too short to assess cognitive outcomes, but precaution should be taken, with close

monitoring. It should also be noted that the manufacturer, Novartis, funded this trial, but the trial was reviewed by an independent data and safety monitoring committee, and the analyses were replicated by an independent academic statistician. The authors of the trial also assumed responsibility for the accuracy and completeness of the study.¹⁷ With that being said, the new mechanism of action along with the decreased incidences of AEs, increased efficacy, and proven reduction in mortality makes sacubitril/valsartan a viable option in treating HFrEF, with monitoring of hypotension, angioedema, cough, serum creatinine, and serum potassium. Postmarketing safety data are needed to determine where exactly in clinical practice this new agent will be placed. From these data, sacubitril/valsartan may be an option for HFrEF patients who have previously tolerated full doses of ACE inhibitors or ARB therapy and have no experience of symptomatic hypotension.

Currently, there is a lack of effective treatment for reducing the morbidity and mortality for HFpEF. Treating HFpEF is done empirically and mostly aims at treating symptoms and underlying comorbidities.²² Normally, BNPs are released because of cardiac stretch from increased myocardial wall tension to protect the heart from volume and pressure overload. In HFpEF, that protective mechanism is seen to be deficient.²² Therefore, by inhibiting the breakdown of natriuretic peptides, via ARNi, there could be beneficial results in using sacubitril/valsartan in treating HFpEF. NT-proBNP is an important clinical end point in this disease state because it is a marker of left-ventricular wall stress, AEs are associated with increased NT-proBNP, and reduced NT-proBNP is associated with better outcomes. As previously discussed in the PARAMOUNT-HF trial, there was a statistically significant reduction in NT-proBNP; reverse left-atrial remodeling was seen; and there was improvement in NYHA class, with a similar safety profile compared with valsartan. To determine if these findings would translate to improved outcomes in HFpEF patients, there is an ongoing phase III trial in the recruitment stage with an aimed completion date of May 2019. The Prospective Comparison of ARNi with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial hopes to determine the long-term efficacy and safety comparison of sacubitril/valsartan with valsartan. This multicenter, randomized, double-blind, active-controlled superiority trial will compare ARNi and ARBs in reducing death from cardiovascular causes and total hospitalizations in NYHA class II to IV patients with HFpEF.²³

Drug-Drug Interactions

Sacubitril/valsartan is contraindicated in patients who are currently on ACE inhibitors for increased risk of angioedema and hypotension.²⁴ The Valsartan Heart Failure (Val-HeFT) trial showed that combining an ACE inhibitor and an ARB (such as

valsartan) in patients being treated with a β -blocker increased mortality; therefore, the ACCF/AHA guidelines do not recommend the combination of ACE inhibitors and ARBs in treating HFrEF.¹ The manufacturing label recommends waiting 36 hours after discontinuing ACE inhibitors to initiate sacubitril/valsartan.²⁴ This recommendation is based on the run-in period protocol used in the PARADIGM-HF trial.¹⁷ Duplicate therapy of sacubitril/valsartan and ARBs should also be avoided. Sacubitril/valsartan is contraindicated in diabetic patients and patients with renal impairment ($\text{eGFR} < 60 \text{ mL/min/m}^2$) on aliskiren.²⁴ Health care providers should monitor sacubitril/valsartan with potassium-sparing diuretics for increased potassium levels. Use of NSAIDs with sacubitril/valsartan can lead to increased renal impairment. Taking sacubitril/valsartan and lithium can lead to increased lithium toxicity.²⁴

Availability, Dosage, and Administration

Entresto is available at the lowest dose of sacubitril 24 mg and valsartan 26 mg orally twice daily and can be titrated to the maximum dose in adult and geriatric patients to sacubitril 97 mg/valsartan 103 mg orally twice daily.¹⁴ The manufacturers recommend sacubitril/valsartan for patients who continue having signs and symptoms of HF on the maximum doses of ACE inhibitors or ARBs. These patients will initiate sacubitril 49 mg/valsartan 51 mg tablet orally twice a day. After 2 to 4 weeks, patients who tolerate the dose can titrate up to the maximum dose.²⁴

There is no dose adjustment for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh Class B) should initiate therapy at the lowest dose. Sacubitril/valsartan should be avoided in patients with severe hepatic impairment. Patients with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ should start at the lowest dose and then double the dose every 2 to 4 weeks until the target dose is reached.¹⁴

Monitoring

One of the major concerns with neprilysin inhibitors is the risk of angioedema. Within the PARADIGM-HF run-in period, the median time to angioedema occurred 10 days after the first dose of sacubitril/valsartan ($n = 12$ [80%] in the enalapril arm and $n = 5$ [50%] in the sacubitril/valsartan arm). The data for blacks and nonblacks remained consistent with the above findings.²⁰ In the PARADIGM-HF, of the double-blind randomized groups, the sacubitril/valsartan arm had greater incidences of angioedema compared with the enalapril arm. Times to first case of angioedema were a median of 87 (52-464) days and 256.5 (44-384) days, respectively.^{17,21} Although the incidences of life-threatening angioedema were limited, giving this medication to patients who

have a history of angioedema is contraindicated. If there are any signs or symptoms of angioedema, discontinue the medication immediately.

In alignment with current HF medications, sacubitril works on the kidney, and therefore, serum creatinine should be monitored closely. Additionally, the valsartan component of the medication also requires monitoring for increased potassium levels. Clinicians should also monitor patients' BUN levels.²⁴

Adverse drug reactions for sacubitril/valsartan include hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), orthostasis (2.1%), falls (1.9%), and angioedema (0.5% in all patients, 2.4% in African American patients). Sacubitril/valsartan is contraindicated in patients with hypersensitivity to either component and history of angioedema with previous ACE inhibitor or ARB therapy.²⁴

Special Populations

Sacubitril/valsartan holds a Black Box Warning for fetal toxicity and should not be used in pregnant patients.¹⁴ Valsartan is contraindicated in pregnancy. No controlled data in human pregnancy exists, but fetal toxicity has been shown in animal data. There have been cases reported where pregnant women have taken valsartan, which resulted in spontaneous abortion, oligohydramnios, and newborn renal dysfunction.²⁵ Further studies need to be completed in humans to determine if sacubitril/valsartan appears in breast milk. Previous studies show valsartan in animal milk, and therefore, sacubitril/valsartan should not be used in women who are lactating.²⁵

Formulary Considerations

Sacubitril/valsartan will be available in bottles of 60 and 180 tablets and a 100-tablet blister package. The lowest dose is available as a white tablet, the transition dose as a yellow tablet, and the highest dose as a pink tablet.¹⁴ Sacubitril/valsartan is estimated to cost \$12.50 a day or about \$4500 a year, with 2 tablets taken daily. Novartis plans to negotiate with insurance companies to make the medication more affordable.¹⁴ Despite these efforts, some retail pharmacies offer enalapril for less than \$10 for a 30-day supply and less than \$110 a year. Many clinicians will need to see drastic improvements in ejection fraction and HF signs and symptoms to justify the cost of this new medication and authorize use in patients. Additionally, it should be noted that pharmacoeconomic data are lacking to help guide clinicians to make formulary decisions.

Discussion

The new FDA approval of sacubitril/valsartan (Entresto) offers 3 dosing regimens for patients with HFrEF NYHA

class II to IV. In clinical practice, sacubitril/valsartan will be used in patients who are still experiencing worsening HF symptoms and reduced ejection fraction despite clinical improvement on stable doses of β -blockers and additional evidence-based medications.

Sacubitril/valsartan offers a new mechanism of action, along with a decreased adverse effect profile, increased efficacy, and proven reduction in mortality as seen in phase III trials. These positive attributes of sacubitril/valsartan makes it a viable option for treating NYHA class II to IV HF.¹ Patients on ACE inhibitors or ARBs will need to be tapered off their current medication and started on sacubitril/valsartan 49 mg/51 mg orally twice daily and titrated up the maximum dose.²⁴ Health care providers will continue to monitor for similar AEs, such as hypotension, angioedema, and elevated serum potassium and serum creatinine.¹⁴

Although sacubitril/valsartan offers potential in HF patients, further studies need to be performed to ensure extrapolation in more diverse patient populations. Whereas the PARADIGM-HF trial utilized the KCCQ for symptomatic progression, further studies need to evaluate symptom control and health-related quality of life. Before starting sacubitril/valsartan, health care providers should perform a thorough past medical history to rule out incidences of angioedema. In addition to sacubitril/valsartan's new mechanism, additional physiological mechanisms are now available for HF. The FDA approved ivabradine in April 2015 for the treatment of worsening HF by targeting sinus node function. Ivabradine blocks hyperpolarization cyclic nucleotide-gated channels, bypassing effects on myocardial contraction in patients with systolic function abnormalities.²⁶ As with sacubitril/valsartan, patient-specific parameters are warranted. Ivabradine should only be given to patients in sinus rhythm with resting heart rate ≥ 70 beats per minute and who are either on maximally tolerated doses of β -blockers or have a contraindication to β -blocker use. Ivabradine should be dose adjusted to reach a goal of 50 to 60 beats per minute.²⁷ Vitamin D supplementation has also been proposed to reduce mortality in HF patients. Many studies have shown increased mortality rates in HF patients with vitamin D deficiency.^{28,29} The literature shows mixed reviews on vitamin D supplementation and improvement in LV performance and exercise tolerance.²⁸ The future role of vitamin D supplementation requires further research. These additional mechanisms provide a new age of medications alongside gold standard HF medications, and patient-specific parameters may decrease mortality and morbidity in HF patients.

The place of sacubitril/valsartan in therapy will not only be for newly diagnosed NYHA class II to IV HF patients but patients who have tried additional evidence-based medications with mortality reduction for HF. Patients must first be able to tolerate an ACE inhibitor or ARB plus β -blocker $\pm$ an aldosterone antagonist. Ambulatory care facilities provide the framework to closely titrate sacubitril/valsartan based on

patient-specific medical profiles. Continuous management in the ambulatory care setting allows health care providers to not only titrate the medication but also closely monitor patients for AEs. Regardless of initial starting dose, within 6 months, patients will be in the target dose of sacubitril/valsartan. Patients may experience cardiovascular protection and decreased hospitalizations at the maximum dose. As far as compliance is concerned, twice-daily dosing of sacubitril/valsartan is comparable to the evidence-based treatment of twice-daily dose of ACE inhibitors and ARBs in HF patients. With the increased use of patient adherence programs and monthly copay plans, patients will be able to determine a medical plan that works best for the individual.

The 2014 Canadian HF guidelines placed a high recommendation for sacubitril/valsartan prior to its FDA approval.³⁰ These guidelines encourage the use of sacubitril/valsartan over ACE inhibitors and ARBs in patients with an ejection fraction <40%, elevated BNP, HF hospitalization within the past year, and on appropriate evidence-based medicine. The guidelines recommend the same potassium and renal cutoffs as the PARADIGM-HF exclusion criteria.²⁹ American and European guidelines have not been updated to include recommendations regarding sacubitril/valsartan.

Conclusion

Sacubitril/valsartan may change the current standard of HF treatment. Although the long-term benefits of sacubitril/valsartan in controlling HF patients seem favorable, additional studies are needed to determine its use, efficacy, safety, and tolerability in diverse populations. Sacubitril/valsartan may serve as a viable option for newly diagnosed NYHA classes II to III and as an alternative to patients who are currently being treated with the maximum doses of current gold standards of therapy.

Declaration of Conflicting Interests

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