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Sacubitril/Valsartan (Entresto®): A New Dual Therapy Approved For Chronic Heart Failure

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Heart Failure (HF) affects ~5.1 million Americans, with an estimated 870,000 new cases being diagnosed annually.[1,2] Left ventricular HF is separated into two main classifications with roughly equal prevalence: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). The estimated annual cost of HF is over $30 billion and this amount is likely to grow given that 1 in 5 Americans are projected to be over the age of 65 years by 2050.[1] Within this age group, HF is the leading cause of hospital admissions.[3] According to the American Heart Association, the 5-year mortality rate following a diagnosis of HF is staggeringly high at around 50%.[2] Thus, finding new, more efficacious treatments for chronic HF is imperative.

One therapeutic target that has been explored in recent decades is the natriuretic peptide (NP) system. Natriuretic peptides are released in response to myocardial stretch and overload, leading to an increase in cyclic guanosine monophosphate (cGMP). Several cardio-protective processes are mediated by cGMP, including vasodilation, inhibition of renin and aldosterone, and natriuresis.[4] One approach to increasing NP concentrations is through inhibiting neprilysin, an enzyme involved in NP metabolism. Sacubitril/valsartan (Entresto®; Novartis Pharmaceuticals; East Hanover, NJ) is a newly approved drug that is the first dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). The purpose of this article is to describe ARNi pharmacology, specifically focusing on sacubitril/valsartan, and review the efficacy and adverse events from clinical trials.

Pharmacology

Sacubitril/valsartan (previously known as LCZ696) is one of the first dual-acting pharmaceuticals that comes as a supramolecular complex containing the neprilysin inhibitor, sacubitril, and the angiotensin-receptor blocker (ARB), valsartan. This complex is made up of a 6:6:18:15 ratio of sacubitril, valsartan, sodium, and water molecules, respectively. The neprilysin inhibitor prodrug sacubitril (or AHU377) is metabolized into the active metabolite, also known as LBQ657.

The sacubitril/valsartan supramolecular complex is remarkably stable as a result of ionic and hydrogen bond formation, such that the structural stability is even maintained in water with very little degradation after one week.[5] As a result of being delivered as a component of this stable molecular complex, the amount of valsartan that dissociates and is absorbed is not equivalent to other oral tablet forms of valsartan. The complex increases valsartan exposure by about 40% compared to conventional valsartan tablets.[6,7]

Mechanism of Action

The two primary actions of sacubitril/vasartan affect the counter-regulatory RAAS and NP neurohormonal systems.[8] Sacubitril promotes the NP system while valsartan reduces RAAS activity by blocking angiotensin II type 1 (AT_1) receptors. Neprilysin, also known as neutral endopeptidase (NEP), is involved in metabolism of NPs into inactive compounds. Most of the pharmacological actions of NEP inhibition are a result of increased levels of atrial, B-Type, and C-Type NPs. Increased levels of the NPs result in increased natriuresis and diuresis in the kidneys, vasodilation, and renin-angiotensin-aldosterone system (RAAS) inhibition. These peptides also inhibit fibrosis and cellular hypertrophy in the myocardium, decreasing intra-cardiac pressure and the amount of stress on the chamber wall.[9] Other neprilysin substrates include angiotensin I-II, bradykinin, endothelin-1, and substance P. Inhibition of the breakdown of these substrates have contributed to the side effect profile of NEP inhibitors (discussed in more detail below).

As a result of being involved in the metabolism of a variety of substrates, the effects of neprilysin are widespread throughout different areas of the body and can be difficult to predict. An increase in angiotensin II and endothelin-1 can cause vasoconstriction and further downstream RAAS activation. Consequently, the addition of an angiotensin-converting enzyme inhibitor (ACEI) or an ARB is needed to negate the RAAS activation caused by neprilysin inhibition.

Elevated bradykinin is thought to be directly responsible for adverse effects such as cough and angioedema. Previous studies of omapatrilat (a combined NEP inhibitor/ACEI) demonstrated promising data in the OCTAVE (hypertension) and IMPRESS (HF) trials.[10,11] However, the drug was ultimately never approved because of concerns over an increased risk of angioedema, presumably due to the greater bradykinin concentrations observed with NEP inhibition than with ACE inhibition alone. Omapatrilat also inhibits aminopeptidase P (APP), which, like ACE, is involved in breaking down bradykinin.[9] In contrast, sacubitril appears to have no, or only minimal effects on APP and bradykinin. The minimal effect of sacubitril/valsartan compared to omapatri-

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Table 1 | Sacubitril/valsartan pharmacokinetic data.[6]

Property	Sacubitril	Sacubitril active metabolite	Valsartan
t_{max}	0.8 hours	1.3 hours	1.3 hours (4 hrs if separate)
$t_{1/2}$	1.4 hours	11.5 hours	9.9 hours
Bioavailability	≥60%	n/a	NR
Protein Binding	94% to 97%	94% to 97%	94% to 97%
Elimination	52%-68% in urine; 37-48% in feces		13% in urine; 86% in feces
Metabolism	By esterases to active metabolite	None	Minimal (20%)

NR = not reported; t_{max} = time to peak concentration; $t_{1/2}$ = half-life.

lat on bradykinin is supported by *in vivo* demonstration of the rank efficacy of bradykinin metabolism inhibitors as ACE > APP >> NEP.[12]

Pharmacodynamics

Neprilysin inhibition results in a maximum increase in cGMP usually observed 4 hours after administration of sacubitril/valsartan, although cGMP concentrations remain elevated at 12 hours after a 600 or 900 mg dose. Twenty-four hours after a dose, cGMP returns to baseline. Importantly, NEP inhibition does not affect N-terminal pro-BNP, an important prognostic biomarker in HF.[8] RAAS inhibition has been measured using biomarkers such as direct renin concentration (DRC) or plasma renin activity (PRA) and angiotensin II concentration. These biomarkers become elevated when blockade of the AT_1 receptor by valsartan reduces the normal feedback inhibition of renin release by angiotensin II. Overall, sacubitril/valsartan has been shown to improve hemodynamics and cardio-renal biomarkers.[8]

Pharmacokinetics

Sacubitril is the prodrug of the neprilysin inhibitor component of the complex, from which it dissociates along with valsartan shortly following oral administration. Conversion of sacubitril by esterase to an active metabolite occurs rapidly, as indicated by the short terminal half-life of sacubitril and the quick time to peak concentration (t_{max}) of the active metabolite. The time to steady state for all active components is about 3 days. Of note, the AUC of valsartan is 3-fold higher in this formulation with sacubitril than it is in all other single-drug oral formulations of valsartan.[6] **Table 1** provides a summary of pharmacokinetic data for sacubitril/valsartan.

Drug Interactions

Renin-angiotensin-aldosterone inhibitors should generally be avoided during treatment with sacubitril/valsartan. Although the combination of sacubitril and an ACEI has not been studied extensively, this combination could increase the risk for angioedema as has been seen previously with omapatrilat. Furthermore, the manufacturer recommends allowing 36 hours to pass when switching to or from an ACEI. The combination of sacubitril/valsartan and the direct renin inhibitor aliskiren should especially be avoided in diabetic patients. Due to the results of the ALTITUDE trial, concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus. Diabetic patients taking aliskiren with either an ACEI or an ARB reported more hyperkalemia, worsening renal impairment, and hypotension compared to placebo to the extent that the study was stopped early.[13]

The risk of nephrotoxicity is also increased with concomitant use of sacubitril/valsartan with NSAIDs.[7] Sacubitril/valsartan can increase the concentrations of certain cations in the blood as a result of the increased risk of nephrotoxicity. The risk of hyperkalemia is increased by sacubitril/valsartan, and concomitant use with spironolactone, triamterene, amiloride, potassium supplements, or any potassium-containing salt substitutes should be avoided. Patients taking lithium should also be monitored carefully to prevent lithium toxicity while taking sacubitril/valsartan.[7]

Sacubitril is also an inhibitor of OATP1B1 and OATP1B3 transporters[7], which are involved in the hepatic uptake of certain medications. Inhibition of these transporters can increase the plasma concentration of statins, fexofenadine, and erythromycin, among other drugs. [14]

Clinical Trials

Sacubitril/valsartan was evaluated in patients with HFrEF in the PARADIGM-HF trial, and in patients with HFpEF in the PARAMOUNT trial and the ongoing PARAGON-HF trial, all of which have been sponsored by Novartis. **Table 2** summarizes the baseline characteristics for patients enrolled in these trials and **Table 3** summarizes the design characteristics and principal results of these trials.

The PARADIGM-HF Trial

The Prospective comparison of ARNi with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial compared sacubitril/valsartan 200 mg twice daily to enalapril 10 mg twice daily in patients with symptomatic HFrEF.[14] Enalapril was chosen as the comparator drug because it had previously been shown to reduce mortality in chronic HFrEF in the CONSENSUS and SOLVD studies.[16,17] A dose of 200 mg of sacubitril/valsartan contains 97 mg of sacubitril and 103 mg of valsartan. Even though the target maintenance dose of valsartan for HF patients is 160 mg twice daily, the improved bioavailability of valsartan in the study drug allows for a comparable dose.

Patients were included in the PARADIGM-HF trial if they were at least 18 years old and diagnosed with chronic HFrEF (NYHA Class II-IV). They were also required to have NT-proBNP blood concentrations of at least 600 pg/mL, or 400 pg/mL if hospitalized within the last 12 months for HF. Patients were required to be stable on a β-blocker and also either an ACEI or ARB for at least 4 weeks prior to screening. Patients were excluded for having systolic blood pressure (SBP) <100 mm Hg at screening or <95 mm Hg at randomization, hyperkalemia (serum potassium >5.4 mmol/L), or an eGFR <30 mL/min/m² (or a decrease of 35% in eGFR between screening and randomization). Also excluded were patients who had a history of angioedema or ACEI/ARB intolerance.

Table 2 | Baseline patient characteristics in the PARADIGM-HF & PARAMOUNT trials.[15]

Characteristic	PARADIGM (n=8,442)	PARAMOUNT (n=301)
Hypertension	71%	95%
Diabetes	35%	41%
Atrial Fibrillation	36%	27%
HF Hospitalization	62%	40%
Prior MI	43%	21%
Stroke	9%	Not Measured
Medications		
Diuretic	80%	100%
Digitalis	29%	Not Measured
β-blocker	93%	79%
Aldosterone antagonist	54%	19%
Pre-Trial ACEI	78%	56%
Pre-Trial ARB	22%	38%

ACEI = angiotensin converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **HF** = heart failure; **MI** = myocardial infarction.

The primary outcome of the PARADIGM-HF trial was a composite of cardiovascular (CV) death or a first hospitalization for HF. A secondary outcome was the change from baseline to 8 months on Kansas City Cardiomyopathy Questionnaire (KCCQ) score, which measures symptoms and physical limitations in patients with HF, where higher scores indicate fewer limitations and/or symptoms. Other secondary outcomes were time to death from any cause, new onset of atrial fibrillation, and the first occurrence of a decline in renal function.

Patients in this study were, on average, 64 years old and predominantly white (66%) and male (88%). Most patients had NYHA class II HF (71.6%) and a mean left ventricular ejection fraction (LVEF) just under 30%. Additional patient characteristic data can be found in **Table 2**.

Due to the overwhelming benefit of sacubitril/valsartan over enalapril, the study was terminated early. The primary endpoint was reduced by 20% (HR 0.80; 95% CI 0.73 to 0.87; p<0.001) in the sacubitril/valsartan group over a median of 27 months.[15] The absolute risk reduction (ARR) was 4.7% for the composite primary endpoint, resulting in a number needed to treat of 21. Individually, risk of death from CV causes was 20% lower and first hospitalization for HF was 19% lower when comparing sacubitril/valsartan to enalapril. Death from any cause was also significantly reduced in the sacubitril/valsartan group compared with the enalapril group (HR 0.84; 95% CI 0.76 to 0.93; p<0.001).[9,15]

Further analyses of the PARADIGM-HF trial results also showed reductions in clinical worsening of HF in patients assigned sacubitril/valsartan. Clinical worsening was determined by comparing the need for intensification of outpatient medical treatment for HF, ED visits or hospitalizations for worsening HF, and the need for inotropic agents, HF devices, or cardiac transplantation. Intensification of outpatient therapy was defined as requiring the addition of a new drug or an increase in daily dose of a diuretic for more than one month. Sacubitril/valsartan performed better than enalapril on the need for intensification of outpatient HF treatment (HR 0.84; 95% CI 0.74 to 0.94; p=0.003). Not only did fewer patients require hospitalizations and ED visits for HF, but fewer patients had multiple hospitalizations or ED visits in the sacubitril/valsartan group.[18]

One limitation of this study is the use of a run-in period to ensure tolerability of the drugs at the target doses, which can increase the potential for selection bias and result in an underestimation of the side effect profile with "real world" use. Roughly 12% of patients withdrew during the run-in periods because of adverse effects. Another limitation was the lack of diversity among the study population with only about 5% being African American. The incidence of angioedema is higher in African Americans and underrepresentation of this population may have skewed the safety results.[9]

The PARAMOUNT Trial

The Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial compared sacubitril/valsartan 200 mg twice daily to valsartan 160 mg twice daily in patients with HFpEF.[3] Patients in this study were on average 71 years old and roughly 56% were women. Most patients had HF NYHA class II (81%) and an average LVEF of 58% (**Table 2**). Patients were included if they had an LVEF of at least 45% with a history of associated signs and symptoms of HF. Diuretic therapy was required, as was a systolic BP <140 mmHg, or systolic BP ≤160 mmHg if the patient was taking 3 or more antihypertensive medications at randomization. In addition, inclusion criteria included potassium concentration ≤5.2 mmol/L, eGFR ≥30 mL/min/1.73 m^2, and NT-proBNP ≥400 pg/mL. Exclusion criteria included a history of LVEF <45%, severe obesity, and several CV comorbid conditions (e.g., valvular or myocardial diseases).[3]

This phase II trial was powered only to measure surrogate endpoints and not hard clinical outcomes. The primary endpoint was the change in NT-proBNP, a biomarker of left ventricular wall stress, from baseline at 12 weeks.[8] Secondary endpoints of the PARAMOUNT trial include changes in various ECG measures, changes in blood pressure, NYHA class changes, clinical composite assessment, and quality of life using the KCCQ.

After 12 weeks of therapy, sacubitril/valsartan reduced NT-proBNP to a greater extent than did valsartan. Mean NT-proBNP concentrations at 12 weeks were 605 pg/mL for the sacubitril/valsartan group and 835 pg/mL for the valsartan group. The ratio of change (study drug/reference drug) was 0.77 (p=0.005). These differences persisted after controlling for differences in achieved blood pressure between the groups. Improvements in some of the secondary endpoints were significant after 36 weeks of treatment and included reductions from baseline left atrial width (0.15 cm), volume (4.6 mL), and volume index (2.6 mL/m^2). Reductions in left atrial size are associated with positive outcomes in HFpEF.[3]

Limitations of the PARAMOUNT trial included the use of surrogate biomarkers instead of clinical outcomes and a high incidence of β-blocker and ACEI/ARB use at baseline, which may not be representative of the actual HFpEF population. In addition, the inclusion/exclusion criteria ensuring a certain minimum concentration of NT-proBNP suggests that the results of this study may not apply to patients with HFpEF who do not have elevated NT-proBNP levels.

The PARAGON-HF Trial (Ongoing)

The Prospective comparison of ARNi with ARB Global Outcomes in heart failure with preserved ejectioN fraction (PARAGON-HF) is an ongoing outcomes study that started in July 2014, with an anticipated completion date of May 2019. The

Table 3 | Summary of Clinical Trials of Sacubitril/Valsartan in Heart Failure Patients

Study	PARADIGM-HF[19]	PARAMOUNT[20]	PARAGON-HF[21]
Completed	2014	2012	Ongoing
NCT	01035255	00887588	01920711
Sample size	8,442	301	Currently Enrolling
Study Details	• RCT • Double Blind	• Phase II RCT • Double Blind, Parallel-Group, Double-Dummy Design • Multi-Center	• Phase III RCT • Parallel Assignment • Single-blind run-in period(s) • Double-blind treatment period
Indication	HFrEF (LVEF ≤35%)	HFpEF (LVEF ≥45%)	HFpEF (LVEF ≥45%)
Inclusion Criteria	• Age ≥18 years • NYHA Class II-IV • NT-proBNP ≥600 pg/mL (400 pg/mL if hospitalized) • Appropriate concurrent medications	• Age ≥40 years • NT-proBNP >400 pg/mL • NYHA Class II-IV • Use of an ACEI or ARB, β-blocker, a diuretic. • Hypertension controlled • eGFR ≥30 mL/min/1.73 m^2 • K+ ≤5.2 mmol/L	• Age ≥55 years • LVEF ≥45% • Use of diuretic • Elevated NT-proBNP or a hospitalization for HF in the previous 9 months • Structural heart disease
Exclusion Criteria	• Hypotension • Hyperkalemia • eGFR <30 mL/min/1.73 m^2 • Prior Hx of Angioedema • ACEI or ARB intolerance	• LVEF <45% at any time • Dyspnea or edema from non-cardiac disease	• LVEF <45% at any time • Dyspnea or edema from non-cardiac disease • Uncontrolled hypertension
Patient Characteristics	• 78% Male • Mean Age: 64 Years • 70% NYHA Class II	• 43.5% Male • Mean Age: 71 Years • 79.4% NYHA Class II	Unknown (enrollment ongoing)
NT-proBNP	1608 pg/mL (Median)	830.6 pg/mL (Mean)	Unknown (enrollment ongoing)
Doses Compared	Sacubitril/valsartan 200 mg BID vs. enalapril 10 mg BID	Sacubitril/valsartan 200 mg BID vs. valsartan 160 mg BID	Sacubitril/valsartan 200 mg BID vs. valsartan 160 mg BID
Duration	27 months (stopped early)	12-36 weeks	Up to 57 months
Primary Outcome	Composite of CV death or HF hospitalization	Change in NT-pro BNP and SBP at 12 weeks.	Composite of CV death and total number of HF hospitalizations
Limitations	• Only 5% of the sample population were black. • Run-in period use may underestimate side effects.	• Surrogate markers used instead of clinical outcomes. • Study population may not represent clinical practice.	Unknown (study ongoing)

KCCQ = Kansas City Cardiomyopathy Questionnaire; **QoL** = quality of life; **LVEF** = left ventricular ejection fraction; **HF** = heart failure; **RCT** = randomized controlled trial; **CV** = cardiovascular

inclusion and exclusion criteria are similar to those of the PARAMOUNT trial. The study will investigate the effects of sacubitril/valsartan on mortality and morbidity in patients with HFpEF.[21]

Adverse Events

Due to the use of run-in periods during the clinical trials, the adverse event rates that have been published are likely lower than may be expected in real-world practice. In the PARADIGM-HF trial, patients taking sacubitril/valsartan reported more hypotension and non-serious angioedema than patients taking enalapril. However, fewer cases of hyperkalemia, renal impairment, and cough were reported in the sacubitril/valsartan group.[15]

The two most commonly reported adverse events of sacubitril/valsartan have been hypotension (18% to 19%) and hyperkalemia (8% to 12%). Concurrent use of high doses of diuretics and/or other causes of volume/salt depletion may increase the risk of hypotension. Volume or salt depletion should be corrected prior to starting sacubitril/valsartan, otherwise a lower starting dose should be used. To reduce the risk of hyperkalemia, potassium levels should be monitored periodically during treatment, especially in patients who have diabetes, severe renal impairment, hypoaldosteronism, or who are on a high-potassium diet.[7]

Other commonly reported side effects include cough and dizziness, which were reported at rates of 9% and 6%, respectively. Orthostasis occurred at a slightly higher rate in the sacubitril/valsartan group (2.1%) compared to the enalapril group (1.1%). Falls were reported in 1.9% of patients taking sacubitril/valsartan and 1.3% of patients taking enalapril, and may be an important counseling point in the elderly HF patients.

Rare but serious adverse effects that were reported include angioedema and impaired renal function. The incidence of angioedema in patients taking sacubitril/valsartan was less compared to rates observed in trials using omapatrilat. Patients at a higher

risk of developing angioedema include African Americans and smokers. To prevent severe adverse renal effects, kidney function should be monitored periodically. Patients may require a lower dose or may need to discontinue sacubitril/valsartan depending on their serum creatinine. Patients with renal artery stenosis may have increased blood urea and serum creatinine if given sacubitril/valsartan. In clinical trials, patients taking sacubitril/valsartan did not appear to have an increased incidence of impaired renal function when compared to the control groups.[7]

Laboratory abnormalities have also been reported while using sacubitril/valsartan. During the double-blind period of the PARADIGM-HF trial, 5% of patients in both treatment groups had hemoglobin or hematocrit decreases of >20%. Additionally during this period, increases in serum creatinine of >50% and serum potassium concentrations of >5.5 mEq/L were both observed in 16% of patients in each group. During the run-in periods, the increase in serum creatinine were seen in 2.2% of patients on sacubitril/valsartan and 1.4% of patients on enalapril. Potassium concentration was >5.5 mmol/L in 16% of patients taking sacubitril/valsartan in the PARAMOUNT trial, and ≥6 mmol/L in 3% of patients on the study drug. A 50% or more decrease in eGFR was also seen in 3% of patients taking sacubitril/valsartan.[7]

Indication & Usage

Place in Therapy

Currently, the only FDA-approved indication for sacubitril/valsartan is for reducing the risk of cardiovascular death and hospitalization for HF in patients with HFrEF (NYHA Class II-IV). The 2013 AHA guidelines recommend an ACEI (or ARB, if ACEI is not tolerated) as adjunct therapy for HFrEF (NYHA Class II-IV) or other patients with HF and a history of MI or ACS;[1] however, the most recent evidence supports the use of sacubitril/valsartan in place of an ACEI or ARB.[15,18] While relative risk reduction for mortality found in patients taking an ACEI or ARB compared to placebo is 16%[15], the PARADIGM-HF trial resulted in a reduction of about 21% when compared to enalapril over a 27 month period.[9] Mortality benefits in addition to the other improvements seen in the PARADIGM-HF trial discussed previously suggest a strong case for sacubitril/valsartan replacing ACEIs in the guidelines for HFrEF. Patients already taking and tolerating an ACEI or ARB are ideal candidates for starting sacubitril/valsartan, as long as a 36-hour washout period is allowed to pass between stopping and starting therapy.[7] However, it may be prudent to delay switching patients from an ACEI or ARB to sacubitril/valsartan until more data are available on the risks of using this drug. Switching from ACEI or ARB to an ARNi is not likely to significantly impact use of other indicated therapy.

Sacubitril/valsartan is not currently FDA-approved for HFpEF and while results from the PARAMOUNT trial suggest that it may have beneficial effects in HFpEF patients, this trial was not powered to examine clinical outcomes. Therefore, decisions about sacubitril/valsartan's place in HFpEF therapy await the results of the PARAGON-HF trial.[21]

Dosing & Administration

Sacubitril/valsartan is available as a non-scored, ovaloid, biconvex, film-coated tablet. Available strengths are summarized in **Table 4**. Of note, the strength is often listed as the sum of the strengths of sacubitril and valsartan (e.g., Entresto® 50 mg is actually 24 mg sacubitril and 26 mg valsartan). All strengths are packaged in bottles of 60 and 180 tablets as well as blister packs of 100 tablets. Tablets should be stored in a cool dry place at room temperature (15-30°C.)[7]

Table 4 | Available strengths of Entresto®.

Total Tablet Strength	Sacubitril Dose	Valsartan Dose	Tablet Color
50 mg	24 mg	26 mg	Violet White
100 mg	49 mg	51 mg	Pale Yellow
200 mg	97 mg	103 mg	Light Pink

The starting dose of sacubitril/valsartan should take into account the patient's renal and hepatic function in addition to their present use of either an ACEI or ARB. For most patients, including those previously on an ACEI or ARB at moderate or higher doses, the manufacturer-recommended starting dose is 100 mg (49 mg sacubitril/51 mg valsartan) by mouth twice daily, with or without food. If the patient is switching to sacubitril/valsartan from an ACEI or ARB, a washout period of 36 hours should be completed before initiating sacubitril/valsartan.[7] A lower starting dose of 50 mg (24 mg sacubitril/26 mg valsartan twice daily) should be used in patients who are not currently taking an ACEI or an ARB, or if they were previously taking low doses of an ACEI or ARB. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or moderate hepatic impairment (Child-Pugh B classification) should be started at a dose of 50 mg twice daily.

Titration to a maintenance dose of 200 mg twice daily can be achieved by doubling the daily dose every 2-4 weeks.[7] Although pharmacokinetics studies have supported once-daily dosing of sacubitril/valsartan, divided doses of the medication were used in the PARADIGM-HF study to avoid severe hypotension and ensure prolonged angiotensin-receptor blockade and neprilysin inhibition.[22] Finally, this medication is not recommended for women who are pregnant or breastfeeding given paucity of data on sacubitril in pregnant or breastfeeding women and that valsartan is classified in pregnancy risk category D.[7]

Conclusion

Sacubitril/valsartan (Entresto®) has been studied in large clinical trials for HF in response to an increasing need for novel therapies that can reduce morbidity and mortality, particularly in patients with HFpEF. The progression of HF is characterized, in part, by a neurohormonal imbalance due to inadequate activation of the NP system and/or reduced sensitivity to normal NP levels. In an effort to target this mechanism, the first-in-class FDA-approved ARNi, sacubitril/valsartan, increases NP levels by decreasing their enzymatic degradation. The PARADIGM-HF trial has clearly demonstrated the benefits of sacubitril/valsartan in patients with HFrEF. Although HF guidelines have not been updated since publication of this trial, it is plausible that future guideline updates will incorporate recommendations for sacubitril/valsartan in place of ACEI or ARB therapy in stable patients with HFrEF. The cost for this novel drug is expected to be approximately $375 per 30-day supply. Additional trials are currently underway to determine the benefits in HFpEF patients. With nearly half of all patients with HF having a preserved EF and the lack of treatment options proven to be effective at reducing morbidity and mortality in this population, the prospect of a potentially effective new class of drug being on the horizon for these patients is promising.

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