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Entresto (Sacubitril/Valsartan): Angiotensin Receptor Neprilysin Inhibition for Treating Heart Failure

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Abstract
Purpose of Review Heart failure is a major and growing public health problem throughout the world. Sacubitril/valsartan is a new medication with proven benefit in chronic heart failure with reduced ejection fraction. In order to use it most effectively, a thorough understanding of this medication is essential for providers.
Recent Findings Recent evidence demonstrates a significant improvement in mortality and heart failure hospitalizations and an acceptable side effect profile with sacubitril/valsartan in patients with heart failure and reduced ejection fraction. The most frequent adverse reaction is hypotension, which rarely necessitates discontinuation of therapy. Trials are underway for additional indications for this medication.
Summary Sacubitril/valsartan is a safe and efficacious treatment for heart failure with reduced ejection fraction. Whether use of sacubitril/valsartan in heart failure with preserved ejection fraction and in post-myocardial infarction left ventricular dysfunction will improve outcomes will be determined by ongoing studies.

Keywords Heart failure · Neprilysin inhibitor · Angiotensin receptor blocker · Natriuretic peptides

This article is part of the Topical Collection on *Heart Failure*

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Introduction

Heart failure (HF) is pandemic throughout the world and it has important implications on global health. In the USA alone, more than 6.5 million adults have clinical manifestations of heart failure [1]. As the population ages in the future, the number of Americans with HF is likely to significantly increase. There are nearly 1 million yearly emergency department (ED) visits for HF in the USA, with 84% of them resulting in admission to the hospital [2]. Admission to an observation unit for HF has also become increasingly common. Between 2002 and 2010, 3.1% of ED visits for HF resulted in admission to an observation unit with a 10% yearly increase in likelihood of observation unit disposition [3]. Despite advances in treatment, the number of hospital admissions and ED visits for HF has not significantly decreased in the last 15 years and mortality attributed to heart failure remains unacceptably high [2].

Medical treatments with neurohormonal blocking agents that target the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS) have emerged over the past several decades as the cornerstones of therapy. Recently, a new class of medication that modulates neurohormonal effects, angiotensin receptor neprilysin inhibitors (ARNIs), has become available. The first of this class of drugs combines sacubitril, a neprilysin inhibitor, which inhibits degradation of peptide mediators that counteract the adverse effects of the RAAS and SNS, and the angiotensin receptor blocker (ARB) valsartan. When compared to an angiotensin converting enzyme inhibitor (ACEi) in the PARADIGM-HF (Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) study, the sacubitril/valsartan combination was found to be superior in improving both cardiovascular and overall survival, and in reducing hospital admission for patients with heart

failure with reduced ejection fraction (HFrEF) [4••]. The subsequent approval of the sacubitril/valsartan combination by regulatory agencies around the world has provided practitioners with a powerful new tool for the treatment of heart failure. To use it safely and effectively, a thorough knowledge of the physiology, pharmacology, indications, contraindications, and potential adverse reactions of this drug is essential. It is the goal of this review to provide information that will help practitioners utilize sacubitril/valsartan with confidence in patients with HFrEF.

Physiology of Neprilysin

Heart failure is a complex disease, which results in decreased quality of life, high morbidity, and early mortality. There have been many attempts to find new therapeutic targets for heart failure and these have been met with varying degrees of success. The recent positive outcomes seen in the PARADIGM-HF trial have established neprilysin inhibition (in combination with angiotensin receptor blockade) as an appealing new target for drug therapy.

Neprilysin, also known as membrane metalloendopeptidase and CD10, is a membrane-bound endopeptidase that alters the bioavailability of many vasoactive peptides. Although originally discovered in the kidney, neprilysin is widely distributed in the body including in the central nervous system, lung, and intestine and in neutrophils, fibroblasts, and endothelial cells [5]. Neprilysin degrades many peptides with varying physiologic roles including those with vasoactive properties (e.g., natriuretic peptides (NPs), bradykinin, substance P, adrenomedulin, glucagon, vasoactive intestinal peptide, and angiotensin II) [6, 7]. Inhibition of neprilysin results in increased levels of these peptides, many of which could potentially have beneficial effects in heart failure.

Widespread neurohormonal activation occurs in the setting of cardiac dysfunction and it tends to become more pronounced as heart failure progresses [8]. While early effects of neurohormonal activation may help support the failing cardiovascular system, sustained activation of many of these neurohormonal systems, particularly the RAAS and SNS, proves to be deleterious over time as the main effector molecules of these systems promote peripheral vasoconstriction, salt and water retention, and maladaptive cardiac remodeling. Other counter-regulatory neurohormonal systems activated in the setting of heart failure have the capacity to compensate for the adverse effects of the RAAS and SNS. Although the levels of the potentially beneficial peptides are elevated in HF patients, their effects are overwhelmed as the disease progresses. Clearance and inactivation of the compensatory peptides is mediated by renal mechanisms, dedicated clearance receptors, and enzymatic degradation. Neprilysin is a ubiquitous enzyme that has been shown to play an important role in the degradation of NPs and other compensatory peptides. Circulating neprilysin have been shown to be elevated in HF patients and to be associated with increased cardiovascular mortality and morbidity [9•]. Conceptually, neprilysin inhibition could have beneficial effects in patients with HF by augmenting levels of a wide variety of compensatory mediators including the family of NPs.

Natriuretic peptides are a family of hormones including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and others, that share similar structures and natriuretic, diuretic, and vasorelaxant functions. ANP is primarily synthesized in cardiac atrial myocardium while BNP is primarily synthesized and released from left ventricular myocardium in response to increased wall stress due to either dilation, or pressure from increased intravascular volume [10]. ProBNP is cleaved into the functionally inert N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the biologically active BNP. Because NPs are released in the setting of volume overload, measurement of serum levels of BNP and NT-proBNP have proven to be valuable biomarkers in the diagnosis of heart failure in patients presenting to the ED with dyspnea [11, 12]. They also have value in predicting prognosis in both acute and chronic heart failure [13–16]. NPs have an important compensatory role in heart failure by binding to receptors in heart, kidneys, brain, and the circulation system, producing cardiovascular protective effects by promoting natriuresis, diuresis, and vasodilation. The NPs have also been reported to have anti-fibrotic effects that may lead to improvements in cardiac structure and function over time [17–19].

Development of Therapeutic Inhibition of Neprilysin

Neprilysin inhibition represents an attractive therapeutic target to prevent breakdown of vasoactive peptides including NPs, thereby increasing their serum concentration and potentially augmenting beneficial compensatory effects. Initial attempts at therapeutic inhibition of neprilysin were ineffective or associated with significant adverse reactions. The first neprilysin inhibitor available orally, candoxatril, was associated with a dose-dependent increase in ANP, but failed to show reduction in blood pressure in patients with hypertension or a reduction in systemic vascular resistance in HF patients [20, 21]. These negative results were thought to be due to vasoconstriction caused by an increase in the concentration of angiotensin II, which is also degraded by neprilysin (Fig. 1).

The next attempt combined neprilysin inhibition with an ACEi. By blocking degradation of compensatory peptides and inhibiting RAAS simultaneously, omapatrilat was shown to be a potent anti-hypertensive medication that could improve hemodynamics in heart failure [22, 23]. Despite early positive results, omapatrilat failed to show improved outcomes in the OVERTURE (Omapatrilat Versus Enalapril Randomized

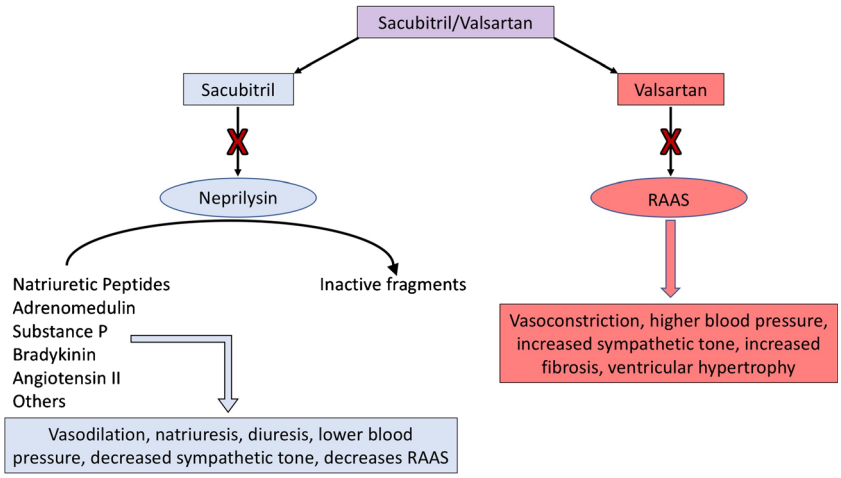

Fig. 1 Physiology of neprilysin and RAAS inhibition. The augmentation of compensatory peptides by neprilysin inhibition combined with blockage of RAAS by valsartan combine to have favorable effects in heart failure. *RAAS* renin angiotensin aldosterone system

Trial of Utility in Reducing Events) trial and was associated with higher rate and severity of angioedema [24]. The increased risk of angioedema seen with omipatrilat was thought to be due to increased concentrations of bradykinin, a peptide that is degraded by both angiotensin-converting enzyme and neprilysin. This safety concern ultimately led to discontinuation of further development of the drug.

Sacubitril/valsartan (brand name Entresto, formerly known as LCZ696) is a first-in-class ANRI. By combining a neprilysin inhibitor with an ARB instead of an ACEi, sacubitril/valsartan was designed to have reduced risk for angioedema compared to omapatrilat. Early studies provided evidence that sacubitril/valsartan was both safe and effective in treating hypertension. In a large randomized control trial comparing valsartan and sacubitril/valsartan, the investigational drug had greater reduction in systolic and diastolic blood pressure than valsartan with similar overall numbers of adverse events and no occurrences of angioedema [25].

Clinical Trials of Sacubitril/Valsartan in HFrEF

PARADIGM-HF, a randomized, double-blind trial of 8442 patients, was designed to test the hypothesis that treatment with sacubitril/valsartan was superior to an ACEi in reducing morbidity and mortality in patients with chronic but stable HFrEF. A detailed list of the inclusion and exclusion criteria for enrollment in PARADIGM-HF is provided in Table 1.

The study was designed with a single-blinded run-in period during which all patients initially received enalapril 10 mg twice daily followed by sacubitril/valsartan at a dose of 100 mg twice daily and then 200 mg twice daily. This design helped ensure that enrolled patients tolerated both agents at doses either known (enalapril) or believed (sacubitril/valsartan) to be effective prior to randomization in the trial. Patients who completed the run-in periods where then randomized in a double-blinded fashion to receive enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily [26].

Baseline characteristics of the study population were typical of patients with HFrEF and did not differ significantly between the treatment groups [4]. Selected baseline characteristics include:

- Mean ejection fraction, 29 ± 6%
- Ischemic cardiomyopathy, 60%
- Hypertension, 70%
- Diabetes, 34%
- 93% of patients were on a beta-blocker, 80% on a diuretic, and 55% were on a mineralocorticoid antagonist at baseline

The PARADIGM-HF trial was terminated early because of overwhelming evidence of the superiority of sacubitril/valsartan over enalapril for the composite primary endpoint, its components, and for all-cause mortality. At a mean follow up of 27 months, the primary outcome of death from cardiovascular causes or first hospitalization for worsening heart failure occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1117 patients (26.5%) in the enalapril group (hazard ratio 0.80; 95% confidence interval [CI], 0.73 to 0.87; $P = 0.0000004$) [4••]. A total of 558 deaths (13.3%) in the sacubitril/valsartan group and 693 deaths (16.5%) in the enalapril group were due to cardiovascular causes (hazard ratio 0.80; 95% CI, 0.71 to 0.89; $P < 0.001$). There were 537 patients (12.8%) receiving sacubitril/valsartan compared to 658 patients (15.6%) receiving enalapril who were hospitalized for HF (hazard ratio 0.79; 95% CI, 0.71 to 0.89; $P < 0.001$). All-cause mortality also was significantly lower in the sacubitril/valsartan group compared to the enalapril group (17.0 vs 19.8%; hazard ratio 0.84; 95% CI, 0.76 to 0.93; $P < 0.001$).

Table 1 ESC and AHA/ACA/HFSA Guidelines for ARNIs

Class	LOE	
		AHA/ACA/HFSA Guidelines [21 Yancey JACC 2016]
I	B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACEIs (LOE: A), OR ARBs (LOE: A), OR ARNI (LOE: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
III	B-R	ARNI should not be administered concomitantly with ACEIs or within 36 h of the last dose of an ACEIs.
III	C-EO	ARNI should not be administered to patients with a history of angioedema.
		ESC Guidelines [22 Ponikowski Eur Heart Jur 2016]
I	B	Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA.

AHA/ACA/HFSA American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, *Class I* strong recommendation, *Class III* harm, *LOE* level of evidence, *LOE B-R* moderate-quality evidence from 1 or more randomized control trial, *LOE C-EO* consensus of expert opinion based on clinical experience, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *ESC* European Society of Cardiology, *LOE B* data derived from a single randomized clinical trial or large non-randomized studies, *MRA* mineralocorticoid receptor antagonist

Subgroup analysis from this trial showed the benefit from sacubitril/valsartan with respect to the primary outcome and cardiovascular deaths in all relevant subgroups. Of particular importance to practitioners was the finding that sacubitril/valsartan was effective in reducing events even in patients considered to be at low risk based on New York Heart Association (NYHA) class II symptoms, lack of recent hospitalizations, and/or already receiving other medications or devices known to improve survival in HF (i.e., beta-blockers, mineralocorticoid receptor antagonists, intra-cardiac cardioverter defibrillators, cardiac resynchronization therapy). Sacubitril/valsartan also had a beneficial effect on quality of life, with a statically significant lesser decline in quality of life at 8 months as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. There were no significant differences, however, between sacubitril/valsartan and enalapril in new-onset atrial fibrillation or decline in renal function.

In PARADIGM-HF, sacubitril/valsartan was shown to be generally safe and well tolerated. Although sacubitril/valsartan group did have a higher proportion of patients with symptomatic hypotension (588 patients (14.0%) compared to 388 patients (9.2%) in the enalapril group; $P < 0.001$), this rarely resulted in discontinuation of either drug. Non-serious angioedema was also more frequent in the sacubitril/valsartan group, but this difference was not statistically significant and angioedema occurred rarely in both groups (19 patients (0.4%) in the sacubitril/valsartan group compared to 10 patients (0.2%) in the enalapril group; $P = 0.13$). Of note is the fact that angioedema was seen in 2.4% of black patients randomized to sacubitril/valsartan in the study. There were no cases of airway compromise due to angioedema in either group during the study. Several adverse events were less frequent in the sacubitril/valsartan group compared to the enalapril group. For example, there were fewer episodes of renal impairment, hyperkalemia, and cough compared to the enalapril group. Overall, significantly fewer patients in the sacubitril/valsartan group stopped their study drug after randomization due to an adverse event (10.7 vs 12.3%; $P = 0.03$).

In summary, PARADIGM-HF provided convincing evidence that sacubitril/valsartan was superior to what had been considered standard therapy for HFrEF patients with an acceptable safety profile. The reduction in cardiovascular mortality of 20% with sacubitril/valsartan over enalapril was similar in magnitude to what was seen in studies that established ACEis as first line therapy for heart failure [27]. These results demonstrated superiority of sacubitril/valsartan to ACEi alone. Subsequent analyses have shown that sacubitril/valsartan is likely to be a cost-effective approach for treating HFrEF patients [28]. In addition, if optimally implemented in the 2.2 million Americans with HFrEF who are estimated to be candidates for this therapy, ARNI therapy has been projected to prevent over 28,000 deaths a year in the USA alone [29•].

Indications and Dosing

The findings of PARADIGM-HF established sacubitril/valsartan as an important new therapy for treating HFrEF patients. Because of the approval of sacubitril/valsartan (and also

ivrabadine) by the United States Food and Drug Administration (FDA), the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (ACC/AHA/HFSA) released a focused update on new pharmacological therapy for heart failure. This update listed use of an ARNI, ACEi, or ARB as acceptable clinical strategies for RAAS inhibition with a class I recommendation for patients with chronic HFrEF [30]. In addition, it was recommended that in patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, that these agents should be replaced by an ARNI to further reduce morbidity and mortality. Similar recommendations were offered in the European Society of Cardiology (ESC) guidelines [31], although there were some differences between the documents. Full details of the ACC/AHA/HFSA and ESC guidelines are given in Table 2.

As sacubitril/valsartan becomes more widely used, a thorough knowledge of the indications, contraindications, adverse reactions, and details of treatment are important for physicians and health care providers. The doses of sacubitril/valsartan that are contained in available formulations are 24/26, 49/51, and 97/103 mg. It is worth noting that in the PARADIGM-HF trial, doses referred to total amount of both ingredients and the previously mentioned formulations were referred to as 50, 100, and 200 mg, respectively.

The initial doses of sacubitril/valsartan should be based on the previously tolerated dose of ACEi or ARB.

- In patients previously taking >10 mg/day of enalapril or >160 mg/day of valsartan (or the equivalent dose of another ACEi or ARB), the recommended starting dose of sacubitril/valsartan is 49/51 mg twice daily.
- In patients previously taking ≤10 mg/day of enalapril or ≤160 mg/day of valsartan (or the equivalent dose of another ACEi or ARB), the recommended starting dose of sacubitril/valsartan is 24/26 mg twice daily.
- Due the increased risk of angioedema seen with the combination of ACEi and neprilysin inhibitor in the clinical trial of omapatrilat, sacubitril/valsartan should not be administered with an ACEi and a 36-h washout period is recommended after the last dose of an ACEi prior to starting sacubitril/valsartan.
- In patients not currently taking an ACEi or ARB, the initial dose of sacubitril/valsartan should be 24/26 mg twice daily.
- In all cases, the starting dose should be doubled every 2 to 4 weeks as tolerated to the target maintenance dose of sacubitril/valsartan 97/103 mg twice daily. After starting the drug and after each dose increase, the patient should be queried for symptoms (particularly those related to hypotension) and blood should be obtained to measure electrolytes and renal function.

Table 2 PARADIGM-HF inclusion and exclusion criteria

Inclusion criteria

- Outpatients ≥18 year of age
- NYHA class II-IV symptoms and an ejection fraction initially 40% or less but later in the trial changed to 35% or less
- A BNP level ≥150 pg/ml (or a NT-proBNP level ≥600 pg/ml), or BNP ≥100 pg/ml (or NT-proBNP ≥400 pg/ml) if the patient had been hospitalized for heart failure within the last 12 months
- For 4 weeks prior to screening, patients were required to take a stable dose of a beta-blocker, unless contraindicated or not tolerated
- For 4 weeks prior to screening, patients were required to take an ACEi or ARB equivalent to at least 10 mg of enalapril daily

Exclusion criteria

- History of hypersensitivity, allergy to, or contraindication to the study drugs or other ACEIs, ARBs, of neprilysin inhibitors
- Previous history of intolerance to recommended target doses of ACEIs or ARBs
- Known history of angioedema
- Current acute decompensated heart failure
- Symptomatic hypotension and/or systolic blood pressure <100 mmHg at screening or <95 mmHg at randomization
- An eGFR <30 ml/min/1.73 m^2 of body-surface at screening or randomization, or a decrease in eGFR of >25% between screening and randomization
- A serum potassium level of >5.2 mmol/l at screening or randomization
- Acute coronary syndrome, stroke, transient ischemic attack, major cardiovascular surgery, percutaneous coronary intervention, or carotid angioplasty within 3 months of screening
- Coronary or carotid artery disease likely to require surgery or intervention within 6 months after screening
- Implantation of a cardiac resynchronization therapy device without 3 months prior to screening
- History of heart transplant, on a transplant list or presence of LVAD
- History of severe pulmonary disease
- Diagnosis of peripartum or chemotherapy induced cardiomyopathy
- Symptomatic bradycardia or second or third degree heart block without a pacemaker
- Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilation
- Presence of any other disease with a life expectancy of <5 years
- Pregnant or nursing (lactating) women
- Women of child-bearing age unless they are using two birth control methods

NYHA New York Heart Association, *BNP* B-type natriuretic peptide, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate, *LVAD* left ventricular assist device

No dose adjustment for sacubitril/valsartan is required when eGFR is ≥30 ml/min/1.73 m^2. When eGFR is <30 ml/min/1.73 m^2, the initial dose of sacubitril/valsartan should be 24/26 mg twice daily. No dosage adjustment is necessary for mild hepatic impairment (Child-Pugh class A). The initial dose in moderate hepatic impairment (Child-Pugh class B) recommended by the manufacturer is sacubitril/valsartan 24/26 mg twice daily. Use is not recommended in severe hepatic impairment (Child-Pugh class C) as sacubitril/valsartan has not been studied in this population.

Recommendations for monitoring patients on sacubitril/valsartan are based on guidelines for patients on an ACEi or ARB. Patients should have a baseline and periodic measurement of serum potassium, renal function, and blood pressure. In addition, blood pressure, renal function, and serum potassium should be assessed within 1 to 2 weeks after initiation or dose changes. Patients with low systolic blood pressure, low serum sodium, diabetes mellitus, or renal impairment should be monitored closely.

Contraindications

There are relatively few absolute contraindications to use of sacubitril/valsartan. Drugs that target the RAAS can cause injury or death to the developing fetus. Sacubitril/valsartan is contraindicated in pregnancy and should be discontinued as soon as possible once pregnancy is detected. Sacubitril/valsartan is not recommended during breast feeding as it is unknown if valsartan or sacubitril are found in breast milk.

Sacubitril/valsartan should not be given to patients with a history of angioedema. Trials with the neprilysin angiotensin converting enzyme inhibitor omapatrilat were associated with an unacceptably high rate of angioedema likely due to the combined effect on bradykinin levels. In PARADIGM-HF, angioedema was uncommon but there were more cases seen with the sacubitril/valsartan combination than with enalapril. Angioedema was more frequently seen in black patients in PARADIGM-HF, occurring at a rate of 2.4%. Patients should be cautioned about the possibility of experiencing angioedema with sacubitril/valsartan and those who have an episode of angioedema while on the drug should have the medication discontinued immediately.

Adverse Reactions

Most of the information regarding tolerance and side effects of sacubitril/valsartan comes from PARADIGM-HF. The database from this study, however, may under-estimate what is seen in clinical practice in that patients were recruited only after they were shown to be able to tolerate an ACEi or ARB at a dose equivalent to enalapril 10 mg per day for 4 weeks. In addition, there was a single-blind run-in period in the study in which patients who developed intolerable side effects to either 10 mg of enalapril twice daily or 200 mg twice daily of sacubitril/valsartan were excluded from the double-blind portion of the trial. During the run-in period of PARADIGM-HF, 12% of all patients withdrew due to adverse events, most commonly cough, hyperkalemia, renal dysfunction, or hypotension [4••]. After adjustment for length of therapy during the run-in period, the rate of withdrawal was higher in the enalapril group than in the sacubitril/valsartan group. After randomization, 10.7% of patients stopped the study drug due to an adverse event, a rate that was less than what was seen in the enalapril group in which 12.3% of patients stopped the study drug.

In the double-blind portion of the study, sacubitril/valsartan was associated with a lower rate of renal dysfunction, severe hyperkalemia, and cough than was seen with enalapril. However, symptomatic hypotension was more common in the sacubitril/valsartan group compared to the enalapril group. This was not an unexpected finding given that treatment with sacubitril/valsartan had previously been shown to reduce systolic and diastolic blood pressure to a greater degree than valsartan alone [25]. Although symptomatic hypotension was more common in the sacubitril/valsartan-treated patients than in those who received enalapril (14.0 vs 9.2%), the occurrence of this side effect rarely resulted in discontinuation of the drug in either study group. Overall, differences in systolic blood pressure between the sacubitril/valsartan group and the enalapril group were modest, with the mean systolic blood pressure being 2.7 ± 0.7 mmHg lower in the sacubitril/valsartan group compared to the enalapril group on average throughout the duration of the study.

Due to the potential effect of sacubitril/valsartan on serum potassium, renal function, and blood pressure, close monitoring in a clinical setting is necessary after initiation or dose adjustment. Based on experience with ACEi and ARBs, a rise in serum creatinine up to 20% starting a few days after initiation of therapy is not unusual and does not require discontinuation of therapy. Based on clinical experience of the authors, symptomatic and asymptomatic hypotension is not uncommon during treatment with sacubitril/valsartan. Patients who are depleted of salt and water due to diuretic therapy or other causes are more susceptible to the blood pressure-lowering effects of sacubitril/valsartan and caution should be used in initiating or uptitrating the drug in patients thought to be volume depleted. In most cases of hypotension, the reduction in blood pressure is small and therapy can be continued safely as the patient adjusts to a new lower blood pressure. In some instances, diuretics may need to be adjusted as the authors have observed that some patients require a lower dose after sacubitril/valsartan is started. Additional strategies include education about dehydration and adjustment of anti-hypertensive or other vasoactive medications. Overall, we have found that sacubitril/valsartan is generally well tolerated when there is close follow-up and careful attention to the patient symptoms and the results of laboratory tests.

Although not an adverse reaction, knowledge of the effect of sacubitril/valsartan on serum levels of BNP and NT-proBNP is important for health care providers, particularly if they are inclined to use natriuretic peptides to define or manage heart failure patients. Treatment with the neprilysin inhibitor sacubitril may lead to an increased serum level of BNP due to decreased degradation of the peptide. Alternatively, NT-proBNP is virtually resistant to degradation by neprilysin.

If using a biomarker to aid in the diagnosis of heart failure or to determine prognosis, it would be reasonable to use NT-proBNP instead of BNP until further studies clarify the diagnostic and prognostic criteria for natriuretic peptides in patients taking a neprilysin inhibitor.

Future Indications and Ongoing Studies

Currently, sacubitril/valsartan is used for treatment of chronic HFrEF to decrease mortality and HF hospitalizations. As further studies are completed, indications and uses for sacubitril/valsartan may also increase. Patients with HFpEF make up approximately 50% of patients with heart failure and there is evidence that this percentage appears to be increasing. Although long-term outcomes in the HFpEF population may not be as poor as in the HFrEF population, patients hospitalized with HFpEF have similar overall mortality compared to patients with HFrEF [32, 33]. Currently, no treatments for HFpEF have been shown to be beneficial in reducing mortality or reducing hospitalization rate. Theoretically, combined inhibition of neprilysin and an angiotensin receptor would seem to offer benefits beyond those seen with current treatment strategies that target the RAAS system alone.

The PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) trial was a randomized control pilot trial comparing sacubitril/valsartan to valsartan alone in patients with NYHA class II–III heart failure and ejection fraction 45% or higher [34]. The primary outcome was change in NT-proBNP level after 12 weeks of therapy. There was a significantly greater reduction in NT-proBNP as well as positive secondary outcomes of improved left atrial size and NYHA class in the treatment group compared to the valsartan group. This hypothesis-generating pilot study along with the highly favorable results of PARADIGM-HF prompted the outcomes trial PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction; NCT01920711). This large trial with a goal enrollment of 4600 patients will assess sacubitril/valsartan in comparison to valsartan in patients with heart failure and ejection fraction ≥45% with the primary study outcome being cardiovascular death or HF hospitalization. Trial results are anticipated in 2019.

Previous studies have shown that both ACEis and ARBs improve outcomes in patients post-myocardial infarction [35–38]. Sacubitril/valsartan is currently being studied in post-myocardial infarction patients in comparison to ramipril. The PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI; NCT02924727) trial will enroll approximately 4650 patients post-myocardial infarction with evidence of systolic dysfunction and without a previous history of chronic heart failure. Patients will be randomized to sacubitril/valsartan or ramipril with the primary outcome being cardiovascular death, hospitalization for HF, or outpatient HF. Results are also expected in 2019.

Conclusion

Heart failure is increasing in prevalence and adversely affects quality of life of patients who suffer from this condition. It is a frequent cause for ED presentation, hospital admission, and premature mortality. Sacubitril/valsartan is a first in class ARNI that has been shown to reduce mortality and HF hospitalization in chronic HFrEF. The ACC/AHA/HFSA guideline now recommends that patients with chronic HFrEF who have an indication for treatment should be transitioned from an ACEi or ARB to sacubitril/valsartan. As use of sacubitril/valsartan grows, an increasing number of patients will be taking this medication on presentation to the hospital. On admission for acute decompensated heart failure, it is reasonable to reduce the dose or hold sacubitril/valsartan if acute kidney injury or hypotension is present. If blood pressure and renal function are stable, however, sacubitril valsartan should be continued and even titrated up to the target dose during hospitalization. In patients admitted already on an ACEi or ARB, consideration should be given to switching to sacubitril/valsartan or starting the drug at the appropriate time in patients who are naïve to any therapy targeting the RAAS. Studies are currently underway to test the safety and efficacy of sacubitril/valsartan in HFpEF and post-myocardial infarction. The indications and use of this medication are likely to increase in the future and knowledge of the physiology, indications, dosing, adverse reactions, and contraindications of sacubitril/valsartan will become increasingly important for health care providers in the emergency room and hospital setting.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest. Dr. Greenberg has been a consultant for Novartis and is a member of their speakers bureau.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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