Role of Angiotensin-Nephrilysin Inhibition for Treatment of Heart Failure

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This is a knowledge based activity.
See the end of the article for CE details.
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Goal:
The goal of this article is to appraise available evidence from three major clinical trials, and other sources, supporting combination use of angiotensin receptor-nephrilysin inhibition in the treatment of heart failure.

Learning Objectives:
Upon completion of this article the learner should be able to:

1. Describe the pharmacological rationale for combination angiotensin-nephrilysin inhibition.

2. State results from major clinical studies evaluating effectiveness of combination angiotensin-nephrilysin inhibition.

3. Analyze the results from major clinical studies evaluating effectiveness of sacubitril/valsartan for treatment of heart failure in terms of study strengths, limitations, and potential impact on practice.

4. Identify potential safety and tolerability concerns regarding sacubitril/valsartan.

Introduction

Heart failure is one of the most prevalent disease states in the United States, affecting nearly 6 million people with approximately 500,000 new cases (of all types) each year.¹ ² With over one million patients annually hospitalized, heart failure accounts for approximately $39 billion in health care costs.¹ The decline in heart function inevitably results in death, with mortality occurring in approximately half of patients within 5 years of diagnosis.² One explanation for the increase in heart failure diagnoses is due to advances in medical technology in the treatment of ischemic heart disease. Because more patients are surviving these acute events, they are living long enough to eventually develop heart failure.

Various factors contribute to the ventricular remodeling that leads to heart failure. One physiologic area of consideration is the renin-angiotensin-aldosterone system
(RAAS), a hormonal system that regulates blood pressure and fluid balance. Renin is normally secreted by juxtaglomerular cells in the kidneys in response to reduced renal blood flow. In circulation, plasma renin cleaves angiotensinogen—a peptide synthesized in the liver—into angiotensin I. Angiotensin I is then converted into angiotensin II by angiotensin-converting enzyme located in the lungs. Angiotensin II is the endogenous ligand for angiotensin receptor II (AT) receptors. Activation of the AT1 receptors located in the vasculature results in vasoconstriction and a subsequent rise in blood pressure. Additionally, angiotensin II stimulates aldosterone secretion from the adrenal cortex. Aldosterone acts on the renal tubules to increase sodium and water reabsorption, resulting in increased fluid retention and blood pressure. Under normal physiologic conditions, RAAS helps maintain renal and other vital organ perfusion in times of dehydration or hemorrhage. However, when abnormally active, RAAS can contribute to ventricular remodeling that results in heart failure. Uncontrolled hypertension caused by RAAS activation and subsequent fluid and sodium retention increases the force the heart must work against, as well as stroke volume. When left unchecked over time, the ventricle walls can stretch too far, becoming weak and unable to effectively pump blood out of the ventricle chamber. This results in heart failure with reduced ejection fraction. Another type of heart failure occurs when the ventricle walls become hypertrophied, leading to decreased ventricular chamber size and less blood available to physically fill the chamber. This results in heart failure with preserved ejection fraction.

Neprilysin

There are two known natriuretic peptides: atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). ANP is a 28-amino acid peptide stored and released by atrial myocytes in response to increased atrial pressure (due to intravascular fluid overload), angiotensin II stimulation, and sympathetic stimulation. ANP is the endogenous ligand for the natriuretic peptide receptor (NPR). NPRs are found in the distal renal tubules, smooth muscle of the vasculature, and the heart. When activated, NPR enhances sodium excretion, causes smooth muscle relaxation, and decreases contractility of the heart. This results in enhanced glomerular filtration rate, diuresis, and vasodilation, decreasing blood pressure and cardiac output. Since NPR only affects sodium excretion, ANP has potassium-sparing effects. Activation of NPR receptors of the heart results in decreased contractility and decreased cardiac hypertrophy. ANP also decreases renin release from juxtaglomerular cells, which decreases angiotensin II levels, and, ultimately, inhibits RAAS activation. These combined effects lead to a decreased workload of the heart, potentially slowing the progression of heart failure. BNP is a 32-amino acid peptide synthesized in the ventricles of the heart and the brain. It is released by similar mechanisms to ANP (i.e., increased fluid volume and filling pressure) and has similar physiologic actions.

Neprilysin is a circulating enzyme that is responsible for degradation of the natriuretic peptides, including ANP and BNP, as well as other endogenous peptides including bradykinin, substance P, glucagon, and most notably, angiotensin II. Inhibiting this enzyme in patients with heart failure is postulated to increase circulating levels of
ANP and BNP, enhancing the previously described benefits of these peptides. Since neprilysin is also responsible for breakdown of angiotensin II, higher concentrations of angiotensin II may result from inhibition of this enzyme without concomitant use of an ACE inhibitor or ARB. It is suspected that early studies of neprilysin inhibitors as monotherapy were not successful for this reason.

Current Standards of Care

Treatment guidelines for heart failure group patients into the New York Heart Association (NYHA) functional classes, which take patients’ capacity for exercise and symptom status, such as shortness of breath, into account. NYHA class I patients have no limitation of physical activity and ordinary activity does not cause symptoms. Class II patients have a slight limitation of physical activity—they are comfortable at rest, but ordinary physical activity such as exercise results in symptoms. Class III patients have a marked limitation of physical activity, and less than ordinary activity, such as activities of daily living (ADL), cause symptoms of heart failure. Class IV patients are unable to carry out any physical activity, including ADLs, without symptoms or experience symptoms at rest.

Pharmacotherapy for heart failure with reduced ejection fraction is centered around beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and aldosterone antagonists. These agents have been shown to reduce mortality in this patient population, and should be initiated and titrated to their optimal doses in all classes of heart failure to slow the progression of the disease. Loop diuretics are also added to drug regimens for fluid removal and symptom improvement. New studies have examined other physiologic targets that may provide mortality benefit to heart failure patients, including those with preserved ejection fraction. One target currently being investigated is neprilysin inhibition.

Clinical Studies

A systematic search using PubMed was conducted in order to identify randomized, controlled trials (RCTs) assessing combination therapy with neprilysin inhibitors and either an ACE inhibitor or ARB for treatment of heart failure. Studies had to assess ejection fraction, clinical outcomes, or both to be included. The search identified four major RCTs.

The earliest studies to evaluate neprilysin inhibition in the treatment of heart failure were the Inhibition of Metaloprotease by omaPatrilat in a Randomized Exercise and Symptoms Study of herat failure (IMPRESS) and Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trials, published in 2000 and 2002, respectively. The study drug, a dual inhibitor of neprilysin and ACE, was investigated in patients with heart failure with reduced ejection fraction. Two more recent studies have investigated an investigational angiotensin receptor-neprilysin inhibitor (ARNI), previously known as LCZ696, a combination drug containing sacubitril, a neprilysin inhibitor, and valsartan, an ARB. A 2012 study called the Prospective comparison of ARNI with ARB on Management Of Heart FailUre with preserved ejectioN fracTion (PARAMOUNT) studied the effects of neprilysin inhibition on the subset of heart failure patients with preserved ejection fraction. A 2014 study called the Prospective Comparison of ARNI with
ACEI to Determine Impact of Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) evaluated heart failure patients with reduced ejection fraction.\textsuperscript{11}

IMPRESS was a randomized, double-blind, multicenter trial of 573 patients with NYHA class II-IV heart failure with decreased ejection fraction who received either the dual neprilysin/ACE inhibitor omapatrilat 10 mg daily or lisinopril 5 mg daily, with titration in both arms to target doses of 40 mg daily or 20 mg daily, respectively, as tolerated.\textsuperscript{8} Patients were randomized in a 1:1 ratio and received treatment for 12 weeks. The primary endpoint was change in exercise duration. The key secondary endpoint was a combined composite of death and worsening heart failure.

Baseline characteristics were well-distributed, with similar mean ejection fractions (28.4 ± 7.5% vs. 27.8 ± 7.5%), NYHA class (64% class II, 35% class III vs. 62% class II, 38% class III), concomitant medication (i.e., similar proportions of diuretics [80%], ACE inhibitors [99%], beta blockers [30%]).\textsuperscript{8} Mean change in exercise duration at 12 weeks was 24 s with omapatrilat and 31 s with lisinopril (p=0.45). Results were also similar for the composite primary endpoint (19% vs. 24%, hazard ratio 0.75, 95% confidence interval [CI] 0.52 to 1.07).

Strengths of IMPRESS included appropriate design (e.g., randomization, blinding, active control) and primary endpoint, considering the brief study duration; however, the secondary endpoint was highly subjective and incorporated a number of possible events (e.g., hospitalization, supplemental diuretics) as “worsening heart failure.” Few statistically or clinically significant results were obtained, limiting the role of omapatrilat based on this study.

OVERTURE was a randomized, double-blind, multicenter trial of 5770 patients with NYHA class II-IV heart failure with an ejection fraction of 30% or less who received either omapatrilat 10 mg daily or enalapril 2.5 mg twice daily, with titration in both arms to target doses of 40 mg daily or 10 mg twice daily, respectively, as tolerated.\textsuperscript{9} Patients were randomized in a 1:1 ratio and followed for a mean of 14.5 months. The primary endpoint was composite incidence of death or hospitalization for heart failure requiring intravenous treatment. Secondary endpoints included all-cause mortality, composite incidence of cardiovascular death or hospitalization, and composite incidence of cardiovascular death, myocardial infarction, stroke, or myocardial revascularization.

Baseline characteristics between the omapatrilat and enalapril groups were well distributed, with similar mean ejection fractions (23.5 ± 5.3% vs. 23.5 ± 5.4%), NYHA class (48% class II, 48% class III, 4% class IV in both groups), concomitant medication (i.e., similar proportions of diuretics [99% in both groups], ACE inhibitors [90% vs. 91%), beta blockers [51% vs. 52%], spironolactone [42% in both groups], and aspirin [48% vs. 47%]), and blood pressure (124 ± 18/74 ± 11 mmHg vs. 123 ± 18/74 ± 10 mmHg).\textsuperscript{9} More patients in the enalapril group also received digoxin (66% vs. 59%).

The primary endpoint occurred in 31.7% of the omapatrilat group and 33.7% of the enalapril group (hazard ratio 0.94; 95% CI: 0.86-1.03, p=0.187).\textsuperscript{9} All-cause mortality occurred in 16.5% in the omapatrilat group and 17.6% of the enalapril group (hazard
The combined risk of cardiovascular death or hospitalization occurred in 40.8% of the omapatrilat group and 44.2% in the enalapril group (hazard ratio 0.91; 95% CI: 0.84-0.99, p=0.024). Cardiovascular death, myocardial infarction, stroke, or myocardial revascularization occurred in 18.6% of the omapatrilat group and 20.0% of the enalapril group (hazard ratio 0.93; 95% CI: 0.83-1.05, p=0.233).

Adverse events reported with omapatrilat at substantially different frequencies compared to enalapril included heart failure (22.6% vs. 25.6%), dizziness (19.4% vs. 13.9%), hypotension (19.5% vs. 11.5%), impaired renal function (6.8% vs. 10.1%), fatigue (8.1% vs. 9.6%), cough (9.7% vs. 9.0%), angina (8.2% vs. 8.9%), musculoskeletal pain (8.9% vs. 8.7%), nausea/vomiting (7.2% vs. 7.7%), edema (5.3% vs. 6.8%), and upper respiratory infections (8.2% vs. 6.7%). The most serious adverse effect was angioedema, occurring in 0.8% of the omapatrilat group and 0.5% of the enalapril group. The study drug was withdrawn in 17.9% of the omapatrilat group and 17.0% of the enalapril group because of an adverse event. Mean systolic blood pressure decreased in both groups (-3.6 vs. -5.2 mmHg) at the end of titration, but was similar in both groups during the maintenance phase of the study. The study authors noted hypotension and dizziness were reported more frequently in the omapatrilat group, even though blood pressure was reduced more with enalapril during the titration phase, which could suggest that the once daily dosing of omapatrilat may not have resulted in persistent vasodilatory effects.

Although the study participants were blinded to treatment arms, the study did not explain how it addressed the different dosing schedules. Additionally, the target dose of enalapril was 10 mg twice daily; current clinical practice guidelines allow for titration to 20 mg twice daily. Ultimately, the results from the OVERTURE trial were not favorable for omapatrilat, demonstrating it was no more effective than enalapril in reducing death or hospitalization from heart failure and resulting in more hypotensive events and greater potential for angioedema. The lack of benefit relative to enalapril, as well as increased reports of omapatrilat-associated angioedema (since omapatrilat inhibits ACE, aminopeptidase, and neprilysin, resulting in increased circulating bradykinin) in hypertension studies, ultimately led to withdrawal of omapatrilat from the drug approval pipeline.

PARAMOUNT was a phase 2 randomized, double-blind, multicenter trial of 301 patients with NYHA class I-III heart failure with an ejection fraction of 45% or higher to receive Entresto® (sacubitril/valsartan) or valsartan alone. ARBs are typically associated with lower incidence of angioedema than ACE inhibitors, and the study aimed to determine if this combination would provide better patient outcomes than the OVERTURE trial and other omapatrilat studies. Prior to randomization, patients were enrolled in a 2 week run in phase in which they continued their background treatments. After randomization, patients were started on sacubitril/valsartan 50 mg twice daily or valsartan 40 mg twice daily in a 1:1 ratio, and titrated to final doses of sacubitril/valsartan 200 mg twice daily or valsartan 160 mg twice daily. Sacubitril/valsartan 200 mg provides similar systemic exposure to valsartan as valsartan 160 mg. Patients could continue background therapy at the discretion of their physicians.
and were followed up at weeks 12 and 36. The primary endpoint was the change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP), a marker of left ventricular wall stress, assessed at 12 weeks. Secondary endpoints included changes in various echocardiograph measures, change in blood pressure, change in NYHA class, and change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

Baseline characteristics between the groups were similarly distributed, with similar mean ejection fractions between sacubitril/valsartan and valsartan (58% ± 7.3 vs. 58% ± 8.1), NYHA functional class (approximately 1% in class I, 80% in class II, and 20% in class III), median blood pressure (136/80 mmHg vs. 136/78 mmHg), and concomitant medications (i.e., similar proportions of patients receiving ACE inhibitors [56% vs. 53%], ARBs [38% vs. 41%], diuretics [100% in each group], beta blockers [79% vs. 80%], and aldosterone antagonists [19% vs. 23%]).

There were more patients in the valsartan group who had a previous admission for heart failure (45% vs. 40%).

With regard to the primary endpoint, the mean NT-proBNP level at 12 weeks in the sacubitril/valsartan group was 605 pg/mL, a 23% reduction from baseline (783 pg/mL), compared to an NT-proBNP level of 835 pg/mL, a 3% reduction from baseline (862 pg/mL) in the valsartan group. The ratio of change (i.e., the comparative reduction in mean NT-proBNP between groups) between sacubitril/valsartan and valsartan was 0.77 (95% CI; 0.64 to 0.92; p=0.005). The mean NT-proBNP level at 36 weeks in the sacubitril/valsartan group was 496 pg/mL, a 35% reduction from baseline (763 pg/mL), compared to 607 pg/mL in the valsartan group, a 26.8% reduction from baseline (822 pg/mL). The ratio of change at 36 weeks was 0.85 (95% CI; 0.65 to 1.09; p=0.20). Blood pressure was reduced by an average of 9.3/4.9 mmHg in the sacubitril/valsartan group compared to 2.9/2.1 mmHg in the valsartan group (p=0.001 for systolic and p=0.09 for diastolic blood pressure differences). There were no significant differences in most echocardiograph measures between groups. Ejection fraction change from baseline at 36 weeks between sacubitril/valsartan and valsartan 2.7% vs 3.1% (p=0.69). Change in relative wall thickness was 0.01% vs. 0.01% (p=0.96). However, left atrial volume was significantly reduced with sacubitril/valsartan at 36 weeks (-4.6 vs. 0.37 mL; p=0.003). The proportion of patients with an improvement in NYHA functional class was similar between groups at week 12 (p=0.11) and higher with sacubitril/valsartan at week 36 (p=0.05). Specific results were not provided. Although specific figures were not provided, the study found no difference in the KCCQ score between groups.

Adverse events from sacubitril/valsartan were not significantly different from valsartan (64% vs. 73%; p=0.14). Serious adverse events occurred in 15% of patients received sacubitril/valsartan compared to 20% of patients receiving valsartan (p=0.32), with similar rates of death between groups (1% vs. 1%; p=0.99). Other adverse events of interest included symptomatic hypotension (19% vs. 18%; p=0.88), renal dysfunction (2% vs. 5%; p=0.34), discontinuation for any adverse event (10% vs. 11%; p=0.90), and hyperkalemia (8% vs. 6%; p=0.50). Angioedema occurred in one patient on sacubitril/valsartan, who didn’t require hospitalization, and no patients on valsartan.
Strengths of this study include its multicenter, multinational design. The baseline characteristics of the study were well-balanced with similar proportions of patients in each NYHA functional class. However, since patients were allowed to continue background therapy with physician discretion, it is unknown if there were any differences in treatments during the study. Although the baseline treatments were similar in both arms of the study, it is unknown if any changes occurred during the trial. Since this was a phase II trial, it is unknown based solely on these results whether the improvements in surrogate markers and minor benefits in terms of NYHA functional class will translate into benefit on mortality and other clinical outcomes.

PARADIGM-HF was a phase III, randomized, double-blind trial of 8,442 patients with NYHA class II-IV heart failure with an ejection fraction of 35% or less who received either enalapril or sacubitril/valsartan. Prior to the study, patients were required to take a stable dose of a beta-blocker and an ACE inhibitor equivalent to at least 10 mg of enalapril daily. Prior to randomization and treatment, all patients began a run-in phase of enalapril 10 mg twice daily for a median duration of 15 days followed by a run-in phase of sacubitril/valsartan 100 mg twice daily, titrated to 200 mg twice daily for a median duration of 29 days. Patients who had no unacceptable side effects of the target doses of the two study drugs were then randomly assigned in a 1:1 ratio to receive enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily and were evaluated every 2 to 8 weeks during the first 4 months of treatment, then every 4 months thereafter.

The primary outcome was the composite incidence of death from cardiovascular causes or a first hospitalization for heart failure. Three interim analyses were conducted after accrual of one third, one half, and two thirds of the events, and the safety monitoring committee specified a trial stopping guideline for a compelling benefit with sacubitril/valsartan if a one-sided P value of less than 0.0001 occurred after the first analysis and less than 0.001 at the second and third analyses. Secondary outcomes included death from any cause, change from baseline to 8 months in the clinical summary score of the KCCQ, time to new onset atrial fibrillation, and the time to the first occurrence of a decline in renal function (defined as end-stage renal disease or a decrease in the eGFR of at least 50%).

The baseline characteristics of the patients were similarly distributed, with similar systolic blood pressures in the sacubitril/valsartan and enalapril groups (122 ± 15 mmHg vs. 121 ± 15 mmHg), ejection fraction (29.6 ± 6.1% vs. 29.4 ± 6.3%), NYHA functional classes (Class I 4% vs. 5%, Class II 72% vs. 69%, Class III 23% vs. 25%), and concomitant medications (i.e., diuretics [80% in both groups], and beta-blockers [93% in both groups]. There were small differences in patients on mineralocorticoid antagonist (54% vs. 57%, p = 0.01), digoxin (29% vs. 31%, p = 0.04); however, implications of these minor differences are unclear and not explored by authors.

The trial was stopped early after a median follow up of 27 months after the third interim analysis because the study authors determined a compelling benefit with sacubitril/valsartan had been observed based on the safety committee’s specified parameters. At the time of closure, the
composite primary endpoint occurred in 21.8% in the sacubitril/valsartan group and 26.5% in the enalapril group, corresponding to a hazard ratio with sacubitril/valsartan of 0.80 (95% CI, 0.73-0.87; p < 0.001), and a number needed to treat of 22 patients for 27 months to avoid one event. Death from any cause occurred in 17.0% of the sacubitril/valsartan group compared to 19.8% in the enalapril group, corresponding to a hazard ratio of 0.84 (95% CI, 0.76-0.93; p < 0.001) and a number needed to treat of 36 patients for 27 months to avoid one event. Death from cardiovascular causes occurred in 13.3% of the sacubitril/valsartan group and 16.5% of the enalapril group, corresponding to a hazard ratio of 0.80 (95% CI, 0.71-0.89; p < 0.001) and a number needed to treat of 32 patients for 27 months to avoid one event.

The most common adverse event was symptomatic hypotension, which occurred in 14.0% of the sacubitril/valsartan group compared to 9.2% of the enalapril group (p<0.001). Symptomatic hypotension with systolic blood pressure less than 90 mmHg occurred more often with sacubitril/valsartan compared to enalapril (2.7% vs. 1.4%; p < 0.001; number needed to harm 77). The following adverse events occurred more often with enalapril: serum creatinine at least 2.5 mg/dL (3.3% vs. 4.5%; p = 0.007), and serum potassium greater than 6.0 mmol/L (4.3% vs. 5.6%; p = 0.007). Angioedema events, including angioedema requiring no treatment or use of antihistamines (0.2% vs. 0.1%; p = 0.19), angioedema requiring catecholamine or glucocorticoid therapy without hospitalization (0.1% vs. 0.1%; p = 0.52), and angioedema requiring hospitalization without airway compromise (0.1% vs. less than 0.1%; p = 0.31), were similar between groups. However, it should be noted that patients at risk for angioedema were potentially screened out of the study during the run-in phase. Overall, fewer patients discontinued sacubitril/valsartan than enalapril because of an adverse event 10.7% vs. 12.3% (p=0.002).

Strengths of this study include study design (e.g., randomized, double-blind, appropriate active control), similar distribution of baseline characteristics, and a diverse patient population, resulting in good external validity. However, the study was designed with a run-in period which allowed patients to be screened out of the study for adverse events, such as angioedema, and intolerance, decreasing external validity. Since patients who could not tolerate either therapy during the run-in phase were not included in the study, the incidence of adverse events in the study may have been lower than what would be observed in practice. Additionally, approximately 75% of enrolled patients were classified in NYHA class I or class II heart failure. Concerns regarding the relatively mild nature of the population’s disease severity, as well as the fact that only approximately 600 and 500 patients were North American and African-American, respectively, have been raised. Patients in the control arm received a target dose of enalapril of 10 mg twice daily. This dose has been shown to reduce mortality and is a common target dose in clinical trials of enalapril for heart failure; however, 20 mg twice daily is a more aggressive target also recommended in clinical practice guidelines. It may be possible patients in the enalapril group would have received additional benefit from an increased dose; conversely, it is unclear how many patients reach this target dose, so results may reflect actual practice.
This study did not include heart failure patients with preserved ejection fraction (diastolic heart failure), so any potential benefit of the study drug to this patient population is not known. The ongoing Prospective comparison of ARNI with ARB Global Outcomes in Heart Failure with preserved ejection fraction (PARAGON-HF) study will enroll 4,300 patients in order to assess clinical benefits of sacubitril/valsartan for treatment of heart failure with preserved ejection fraction. Additionally, the study recruited patients with at least mildly elevated levels of natriuretic peptides, defined as a BNP ≥ 150 pg/mL or NT-proBNP ≥ pg/mL. A BNP of at least 100 pg/mL is suggestive of heart failure, therefore this study may have excluded some patients who had heart failure with lower BNP levels, and any potential benefit in these patients may be different.

Results from PARADIGM-HF, especially the clinically significant absolute reductions in the primary composite endpoint and all-cause mortality, strongly suggest that sacubitril/valsartan will be incorporated into clinical practice guidelines as a preferred agent for patients with reduced ejection fraction. The number needed to treat results for the primary composite endpoint, all-cause mortality, and cardiovascular mortality (i.e., 22, 36, 32) are highly favorable relative to the number needed to harm results for symptomatic hypotension (i.e., 77), the main safety result statistically more common with sacubitril/valsartan. Sacubitril/valsartan may supplant ACE inhibitors for many patients; however, the relative lack of representation of patients with NYHA class III and IV heart failure and African-Americans may preclude early adoption in those populations. Patients should also be carefully screened for risk factors for angioedema prior to switching to or initiating sacubitril/valsartan, even though rates were similar to control patients, due to the run-in and exclusion practices in PARADIGM-HF that resulted in high possibility that high risk patients were excluded from the study and the theoretical increased risk for angioedema with nephrilysin inhibitors. Prospective patients should also be evaluated for risk of symptomatic hypotension, given the increased risk for that adverse event in PARADIGM-HF.

Additional Considerations

Sacubitril/valsartan has also been studied for the treatment of hypertension in 100 mg, 200 mg, and 400 mg once daily doses. A 2010 study found significantly greater reductions with 200 mg sacubitril/valsartan once daily compared to 160 mg valsartan once daily in the mean sitting systolic blood pressure (-5.28 mmHg; 95% CI: -8.28 to -2.28) and the mean sitting diastolic blood pressure (-2.97 mmHg; 95% CI: -4.88 to -1.07, p < 0.0001); and 400 mg sacubitril/valsartan vs. 320 mg valsartan in systolic (-6.01 mmHg; 95% CI: -9.01 to -3.02) and diastolic (-2.70 mmHg; 95% CI: -4.61 to -0.80) mean sitting blood pressures. A 2013 study published by Kazuomi et al found a mean change of -11.86, -12.57, and -15.38 mmHg in systolic blood pressure; and -7.84, -7.29, and -8.76 mmHg in diastolic blood pressure in the 100 mg, 200 mg, and 400 mg sacubitril/valsartan dose respectively compared to placebo (all p < 0.0001) in Asian patients. In the context of treatment of heart failure, it is important to note that these results, and those of previously discussed clinical trials, underscore the importance of close monitoring of these patients for hypotension.
Neprilysin has also been implicated in the progression of Alzheimer’s disease (AD).\textsuperscript{15} Amyloid-β (Aβ) deposits in the brain, a hallmark of the disease, are normally degraded by neprilysin. A 2006 post-mortem study of 15 AD and 23 normal patients investigated whether decreased neprilysin levels contributed to the accumulation of Aβ in Alzheimer’s patients and in the normal aging process. Their findings suggested an inverse correlation with neprilysin and Aβ levels, as well as a significant age-dependent decrease in neprilysin levels in the temporal cortex of normal and AD patients. However, investigators found no difference in the rate of decline in neprilysin with age between normal and AD patients. The relationship of neprilysin inhibition in heart failure patients and potential for developing AD remains to be seen since the PARADIGM-HF trial ended too early to determine any association, and considering the relevance of these concerns especially for elderly patients.

Conclusion

Sacubitril/valsartan was approved by the US Food and Drug Administration (FDA) in July 2015 under the FDA priority review program.\textsuperscript{16} Some researchers estimate that Novartis\textsuperscript{®}, the manufacturer, could expect to gain almost $2 billion in sales by 2022, with almost 20\% of all heart failure patients treated with the drug, largely replacing ACEIs and ARBs as standard of care.\textsuperscript{17} However, its potential has been met with some skepticism. While the PARADIGM-HF trial was stopped early because of a relative risk reduction of 20\%, the absolute risk difference of about 4.8\% has been called a “marginal” benefit by some in the medical community. Some have also criticized the selection of the enalapril as the comparative agent in the PARADIGM-HF trial, since it is one of the oldest and least potent ACE inhibitors. Others pointed out that the dose of enalapril (10 mg twice daily) was lower than one generally recommended in heart failure patients (20 mg twice daily). Finally, others raise concern about the intersection of neprilysin inhibition and the development of Alzheimer’s disease.\textsuperscript{18}

Combination neprilysin and angiotensin receptor inhibition with sacubitril/valsartan has shown promising results in the reduction of mortality and morbidity in heart failure patients with reduced ejection fraction based on the results of the PARADIGM-HF trial.\textsuperscript{11} With significant reductions in the rates of death and hospitalization associated with heart failure complications,\textsuperscript{1,2} use of sacubitril/valsartan will likely provide substantial benefit to this population of heart failure patients. It is expected that sacubitril/valsartan will be incorporated into future clinical practice guidelines as a preferred agent for this population; however, potential barriers to integration into practice relative to ACE inhibitors and ARBs include higher cost (estimated annual cost of $4,500\textsuperscript{19}) and lack of long term clinical experience.
SUGGESTED LEARNING ACTIVITIES

Activity 1: Develop a diagram or figure that combines the pharmacological effects of ANP and BNP at their three primary sites of action, the RAAS, and the effects of neprilysin inhibition. [Learning Objective 1]

Activity 2: Develop a table with a row for each described study, and a column for each key piece of data (e.g., design, methods, results) in order to develop a study guide to recall key study information. [Learning Objective 2]

Activity 3: Identify three specific ways you would improve the design or methods of both PARAMOUNT and PARADIGM-HF, given the information provided. [Learning Objective 3]

Activity 4: List 5 key safety and tolerability concerns for sacubitril/valsartan, and other neprilysin inhibitors. Which are based on known pharmacology of the drug and which are based on findings from RCTs? [Learning Objective 4]

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References


