Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition

Scott A. Hubers, MD; Nancy J. Brown, MD

Abstract—Heart failure affects ≈5.7 million people in the United States alone. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and aldosterone antagonists have improved mortality in patients with heart failure and reduced ejection fraction, but mortality remains high. In July 2015, the US Food and Drug Administration approved the first of a new class of drugs for the treatment of heart failure: Valsartan/sacubitril (formerly known as LCZ696 and currently marketed by Novartis as Entresto) combines the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril in a 1:1 ratio in a sodium supramolecular complex. Sacubitril is converted by esterases to LBQ657, which inhibits neprilysin, the enzyme responsible for the degradation of the natriuretic peptides and many other vasoactive peptides. Thus, this combined angiotensin receptor antagonist and neprilysin inhibitor addresses 2 of the pathophysiological mechanisms of heart failure: activation of the renin-angiotensin-aldosterone system and decreased sensitivity to natriuretic peptides. In the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, valsartan/sacubitril significantly reduced mortality and hospitalization for heart failure, as well as blood pressure, compared with enalapril in patients with heart failure, reduced ejection fraction, and an elevated circulating level of brain natriuretic peptide or N-terminal pro-brain natriuretic peptide. Ongoing clinical trials are evaluating the role of valsartan/sacubitril in the treatment of heart failure with preserved ejection fraction and hypertension. We review here the mechanisms of action of valsartan/sacubitril, the pharmacological properties of the drug, and its efficacy and safety in the treatment of heart failure and hypertension. (Circulation. 2016;133:1115-1124. DOI: 10.1161/CIRCULATIONAHA.115.018622.)

Key Words: heart failure ■ natriuretic peptides ■ pharmacology ■ prescription drugs

Heart failure affects ≈5.7 million people in the United States, and the number is projected to grow to >8 million by the year 2030. Several compensatory mechanisms occur in patients with heart failure, including ventricular remodeling and neurohormonal activation. Over time, however, these compensatory mechanisms become maladaptive and lead to worsening heart failure. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin AT₁ receptor blockers (ARBs), β-blockers, and aldosterone antagonists, designed to target these maladaptive compensatory changes, have demonstrated a mortality benefit in patients with heart failure with reduced ejection fraction. Despite these many treatment options, mortality from heart failure remains high, and ≈50% of individuals with heart failure die within 5 years of diagnosis. Recently, increasing the beneficial effects of natriuretic peptides in heart failure has gained considerable interest as a therapeutic approach for the treatment of heart failure. On July 7, 2015, the US Food and Drug Administration approved valsartan/sacubitril, a novel complex of the ARB valsartan with an inhibitor of neprilysin (neutral endopeptidase-24.11), the enzyme responsible for the degradation of natriuretic peptides and many other vasoactive peptides (Figure 1). In this review, we summarize the evidence for valsartan/sacubitril in the treatment of heart failure with reduced ejection fraction and highlight the potential for its use in heart failure with preserved ejection fraction and hypertension.

Mechanisms of Action of Valsartan/Sacubitril

Valsartan/sacubitril is the first of a new class of drugs that have been referred to as angiotensin receptor–neprilysin inhibitors. The class name is a misnomer because ARBs are not enzyme inhibitors. A more accurate name for the class would be angiotensin receptor antagonist/neprilysin inhibitors. The combined angiotensin receptor antagonist/neprilysin inhibitor was developed to address 2 pathophysiological mechanisms underlying heart failure: activation of the renin-angiotensin-aldosterone system (RAAS) and decreased sensitivity to natriuretic peptides.

The mechanisms of action of ARBs such as valsartan have been studied extensively, are reviewed elsewhere, and are not addressed in detail here. In brief, ARBs decrease vasoconstriction and aldosterone production and increase natriuresis
by blocking vascular and adrenal AT\textsubscript{1} receptors. ARBs also decrease cardiac, vascular, and renal injury by decreasing AT\textsubscript{1}, mineralocorticoid receptor–, or aldosterone-mediated hypertrophy, inflammation, and fibrosis. During angiotensin receptor blockade, angiotensin II concentrations are increased as a result of a lack of feedback inhibition of renin production, and angiotensin II may exert favorable or unfavorable effects through non-AT\textsubscript{1} receptors. With long-term administration of ARBs, as with long-term administration of ACE inhibitors, circulating aldosterone concentrations “escape” back to baseline levels, providing the rationale for the concurrent use of mineralocorticoid receptor antagonists.

Beneficial effects of nephrilysin inhibition have been attributed to decreased degradation of the natriuretic peptides. Natriuretic peptides cause vasodilation by stimulating particulate guanylate cyclase to produce cGMP. In heart failure, administration of valsartan/sacubitril decreased N-terminal pro-brain natriuretic peptide (NT-proBNP) but increased brain natriuretic peptide (BNP), providing indirect evidence that BNP degradation was decreased. In addition, in a dose-escalation study in healthy volunteers, there was a significant increase in cGMP at all doses of valsartan/sacubitril compared with baseline. Natriuretic peptides are cleared from circulation by binding to the natriuretic peptide receptor C and degraded by nephrilysin. Nephrilysin has a higher affinity for atrial natriuretic peptide (ANP) and C-type natriuretic peptide than for BNP (Table I in the online-only Data Supplement).

In the kidney, in addition to increasing renal blood flow and glomerular filtration, natriuretic peptides inhibit sodium reabsorption in the proximal and distal nephron. In addition, natriuretic peptides act to suppress the renin-angiotensin and sympathetic systems and to decrease secretion of endothelin. The natriuretic peptides also exert anti-inflammatory, antifibrotic, and antihypertrophic effects in vitro in cardiomyocytes or cardiac fibroblasts. In cultured adipocytes, ANP and BNP promote lipolysis and increase the synthesis and secretion of adiponectin.

As heart failure progresses, responsiveness to natriuretic peptides, in particular ANP and BNP, decreases. Resistance to natriuretic peptides can result from downregulation of natriuretic peptide receptors, increased clearance of BNP by nephrilysin or the natriuretic peptide receptor C, or decreased downstream signaling. Expression of phosphodiesterase 5, which degrades cGMP, is also increased in experimental heart failure, and phosphodiesterase 5 inhibition restores sensitivity to exogenous BNP. In addition, decreased processing of proBNP to active BNP 1-32 may contribute to diminished natriuresis and vasodilation in patients with heart failure. Decreased degradation of natriuretic peptides with valsartan/sacubitril could overcome natriuretic resistance resulting from any one of these mechanisms.

Pharmacological strategies to enhance the actions of natriuretic peptides in humans have included exogenous administration of endogenous peptides or degradation-resistant peptides, as well as the development of nephrilysin inhibitors. Nesiritide or recombinant BNP was approved for the treatment of acutely decompensated heart failure in the United States in 2001. Concerns about hypotension, a lack of mortality benefit, its short half-life, and the requirement for intravenous administration have limited its use. Nephrilysin inhibitors thus offered an attractive alternative approach to increasing natriuretic peptides, and in humans, administration of a nephrilysin inhibitor potentiates the natriuretic effect of ANP without altering vascular resistance.

Early studies of nephrilysin inhibition in the treatment of heart failure and hypertension provided disappointing results.

**Figure 1.** Effects of valsartan/sacubitril through inhibition of nephrilysin (NEP) and blockade of the renin-angiotensin-aldosterone system. Red represents antagonism/inhibition. ACE indicates angiotensin-converting enzyme; ADM, adrenomedullin; Ang I, angiotensin I; Ang II, angiotensin II; ANP, atrial natriuretic peptide; APP, aminopeptidase P; ARB, angiotensin receptor blocker; AT,R, angiotensin type 1 receptor; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; and NEPi, nephrilysin inhibitor.
For example, a dose-ranging study of ecadotril did not show benefit in heart failure, and there was a numeric increase in deaths in patients receiving the neprilysin inhibitor. Candoxatril, the first orally bioavailable neprilysin inhibitor, increased blood pressure and endothelin concentrations in healthy volunteers. In addition to degrading vasodilator peptides, neprilysin catalyzes the conversion of angiotensin I to angiotensin (1–7) and degrades endothelin (Figure 1 in Table I in the online-only Data Supplement). The observation that candoxatril potentiates the pressor response to angiotensin II also suggested that increased angiotensin II offset potentiated the vasodilator response to intravenous adrenergic model. In a heart failure model in sheep, neprilysin inhibition increases in vasodilator peptides during neprilysin inhibition and provided the impetus for combining drugs with activity against the RAAS with neprilysin inhibitors. An increased incidence of the side effect of angioedema during combined ACE and neprilysin inhibition (so-called vasopeptidase inhibition), presumably resulting from decreased degradation of bradykinin and substance P, led in turn to the development of valsartan/sacubitril.

In addition to cleaving the natriuretic peptides, neprilysin cleaves peptides such as bradykinin, substance P, vasoactive intestinal peptide, glucagon, neurotensin, adrenomedullin, and amyloid-β (Aβ) peptide (Figure 1 and Table I in the online-only Data Supplement). Bradykinin contributes to many beneficial effects of ACE inhibitors, including blood pressure reduction and endothelial fibrinolytic function, and to adverse events. The contribution of bradykinin to the effects of combined AT1 receptor blockade/neprilysin inhibition has not been studied.  

Data Supplement). Bradykinin while preserving natriuresis and diuresis.  

Figure 2. Structure of valsartan/sacubitril using a ball-and-stick model. Carbon atoms are represented in gray; sodium, purple; carboxylate and carbonyl oxygen, red; and water oxygen, green. Hydrogen atoms are not shown. Reproduced from Gu et al with permission from the publisher. Copyright © 2010, American College of Clinical Pharmacology.

Pharmacokinetics of Valsartan/Sacubitril

Valsartan/sacubitril is composed of the dipeptidic ARB valsartan and the neprilysin inhibitor prodrug sacubitril [chemical formula: (2R,4S)-5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methyl-pentanoic acid ethyl ester] in a 1:1 ratio (Figure 2). It is synthesized by dissolution of the 2 drugs, followed by the addition of aqueous sodium hydroxide solution to induce crystallization. Crystal valsartan/sacubitril contains 6 sacubitril and 6 valsartan moieties in their anionic forms, 18 penta- and hexa-coordinated sodium cations, and 15 water molecules, and it has been described as a sodium supramolecular complex. After ingestion, valsartan/sacubitril dissociates to valsartan and sacubitril, which is further converted by esterases to the active inhibitor of neprilysin LBQ657.

In multiple dosing studies in healthy volunteers, plasma concentrations of valsartan peaked at 1.6 to 4.9 hours after dosing; sacubitril, at 0.6 to 0.9 hours; and LBQ657, at 1.8 to 2.7 hours. Valsartan/sacubitril can be administered with or without food. Administration of valsartan as valsartan/sacubitril increases its bioavailability ≈40% in humans. For example, the Cmax and area under the concentration curve (AUC) of valsartan after a single dose of 400 mg valsartan/sacubitril (194 mg sacubitril and 206 mg valsartan) are equivalent to those achieved after a dose of 320 mg valsartan alone. Similarly, the valsartan doses given in valsartan/sacubitril 100 mg (51 mg valsartan) and valsartan/sacubitril 200 mg (103 mg valsartan) are bioequivalent to 80 and 160 mg valsartan given alone.

After sacubitril is converted to LBQ657, it is not further metabolized; neither is valsartan. After oral administration, 52% to 68% of sacubitril is excreted in the urine and 37% to 48% in the feces, in both cases primarily as LBQ657. Eighty-six percent of valsartan and its metabolites are excreted in the feces. Valsartan, sacubitril, and LBQ657 have mean elimination half-lives of 9.9, 1.4, and 11.5 hours, respectively. The apparent volume of distribution of valsartan is 75 L compared with 103 L for sacubitril. Approximately 94% to 97% of valsartan, sacubitril, and LBQ657 are bound to plasma proteins.

The pharmacokinetics of valsartan/sacubitril after a single dose of 400 mg are similar in men and women. The Cmax and AUC of valsartan in valsartan/sacubitril are increased 24% and 30%, respectively, in subjects ≥65 years of age compared with subjects 18 to 45 years old. The Cmax of LBQ657 is similar in the 2 age groups, whereas the AUC of LBQ657 is 42% greater in subjects ≥65 years of age compared with 18- to 45-year-old subjects. The Cmax and AUC of LBQ657 are increased in patients with renal insufficiency, and a lower starting dose of valsartan/sacubitril 50 mg (24/26 mg) is recommended in patients with severe renal impairment (estimated glomerular filtration rate <30 mL·min⁻¹·1.73 m⁻²). In moderate hepatic impairment (Child-Pugh class B),...
the AUCs of valsartan and LBQ657 are increased, and a low starting dose is advised.

Coadministration of valsartan/sacubitril with drugs that inhibit CYP450 does not significantly affect the pharmacokinetics of valsartan/sacubitril because neither of its components are metabolized by CYP450. In vitro studies reveal that sacubitril inhibits 2 members of the family of cellular uptake transporters called organic anion transporting poly-peptides (OATPs), namely OATP1B1 and OATP1B3.³⁹ These 2 transporters are expressed on the basolateral membrane of hepatocytes and are involved in the hepatic clearance of many drugs, including furosemide and statins.⁴¹–⁴³ Valsartan/sacubitril appears to reduce the Cmax of furosemide by ≤50% and the AUC by 25%, whereas the Cmax and AUC of atorvastatin are significantly increased.³⁹ Valsartan/sacubitril also reduces the Cmax and AUC of hydrochlorothiazide and metformin. Given the widespread use of these drugs in patients with cardiovascular disease, further studies investigating drug-drug interactions with valsartan/sacubitril are warranted. Although OATP1 contributes to the clearance of valsartan,⁴⁴ inhibition of OATP1 by sacubitril does not likely contribute to its increased bioavailability when administered as valsartan/sacubitril because concurrent administration of valsartan and sacubitril, not in valsartan/sacubitril, does not have the same effect.

**Efficacy**

**Heart Failure With Reduced Ejection Fraction**

The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was a prospective, multicenter trial in which 8442 patients with a reduced ejection fraction and New York Heart Association class II through IV were randomized to treatment groups of either valsartan/sacubitril 200 mg twice daily or enalapril 10 mg twice daily.⁴⁵–⁴⁷ Patients were required to have ejection fraction of ≤40% (later reduced to ≤35%) and to be taking a stable dose of a β-blocker and an ACE inhibitor (6532 patients) or an ARB (1892 patients) for at least 4 weeks before screening. Patients were required to have a plasma BNP level of at least 150 pg/mL or an NT-proBNP concentration of at least 600 pg/mL. Patients who had been hospitalized previously for heart failure could have a BNP of at least 100 pg/mL or an NT-proBNP level of at least 400 pg/mL. The study included a single-blind run-in period in which each patient received enalapril for at least 2 weeks (median, 15 days) and then valsartan/sacubitril for 4 to 6 weeks (median, 29 days) to assess tolerability. The mean age of patients was 64 years, and 87% were male. The majority of patients were white (66%) or Asian (18%), and a small proportion were black (>5%). At randomization, 82% of patients were taking a diuretic, 94% were on a β-blocker, and 58% were taking a mineralocorticoid receptor antagonist. After a median follow-up of 27 months, 21.8% of patients in the valsartan/sacubitril group experienced the primary composite outcome of either death resulting from cardiovascular causes or hospitalization for heart failure compared with 26.5% in the enalapril group, a relative risk reduction of 20% (P<0.001; Figure 3).⁴⁵ There was a significant interaction between New York Heart Association class at randomization and the effect of treatment on this end point (P=0.03). Treatment with valsartan/sacubitril was associated with a 21% reduction in risk for heart failure admission (P<0.001) and an improved Kansas City Cardiomyopathy Questionnaire symptom score compared with treatment with enalapril (P=0.001). All-cause mortality was significantly lower in the valsartan/sacubitril group (17% in the valsartan/sacubitril group versus 19.8% in the enalapril group; P=0.0009). There was no difference between the 2 treatment groups in the incidence of new-onset atrial fibrillation or in decline in renal function.

Mean systolic blood pressure (SBP) was 3.2±0.4 mm Hg lower in the valsartan/sacubitril group compared with the enalapril group (P<0.001), raising the possibility that the doses of valsartan/sacubitril and enalapril administered were not therapeutically equivalent. Inclusion of the between-group difference in blood pressure as a time-dependent covariate did not negate the benefit of valsartan/sacubitril, however. Of note, <1% of patients randomized had New York Heart Association class IV heart failure, which limits inference of the mortality and morbidity benefit in this group. There was a higher rate of symptomatic hypotension in the valsartan/sacubitril group than in the enalapril group (14% versus 9.2%; P<0.001), whereas cough, elevated serum creatinine (≥2.5 mg/dL), and hyperkalemia were significantly more frequent in the enalapril treatment group. Angioedema occurred in 19 patients in the valsartan/sacubitril group and in 10 patients in the enalapril group during the double-blind treatment period.

**Heart Failure With Preserved Ejection Fraction**

Solomon et al⁶ studied the effects of valsartan/sacubitril in patients with heart failure and preserved ejection fraction in the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial. This trial randomized patients with New York Heart Association class II through IV heart failure, an ejection fraction of at least 45%, and an NT-proBNP level >400 pg/mL to receive either valsartan/sacubitril 200 mg twice daily or valsartan 160 mg twice daily. Randomization was preceded by a 2-week placebo run-in period. The primary end point was change in NT-proBNP, which is not a substrate of nephrilysin and therefore could serve as a biomarker of wall stress even in the presence of nephrilysin inhibition. Increased NT-proBNP levels are associated with adverse outcomes in patients with chronic heart failure.⁴⁸ Fifty-seven percent of randomized patients were women, and the mean age was 71 years. Most patients were taking ACE inhibitors (54%) or ARBs (39%) before randomization.

NT-proBNP was significantly reduced after 12 weeks in the valsartan/sacubitril group compared with the valsartan group (ratio of change LCZ696/valsartan, 0.77; 95% confidence interval, 0.64–0.92; P=0.005).⁶ The difference in NT-proBNP between the 2 groups was not sustained at 36 weeks. Left atrial size at 36 weeks was significantly decreased in the valsartan/sacubitril group compared with the valsartan group (average left atrial volume decrease of 4.6 mL in the valsartan/sacubitril group versus an increase of 0.37 mL in the valsartan group; P=0.003). The decrease in left atrial size was postulated to reflect improved left ventricular filling pressures...
in patients receiving valsartan/sacubitril. It is important to note that blood pressure was reduced to a significantly greater degree in the valsartan/sacubitril group (−9.3±14/−2.9±11 mmHg in the valsartan group; P=0.001 for SBP and P=0.09 for diastolic blood pressure [DBP] difference). The use of concomitant loop diuretics was increased in the valsartan group. There were no significant differences between treatment groups in other echocardiographic end points, in a clinical composite assessment, or in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire. The incidence of adverse events was similar in the 2 groups. Estimated glomerular filtration rate declined to a greater extent in the valsartan group, whereas urinary albumin/creatinine ratio increased to a greater extent in the valsartan/sacubitril group. There was 1 case of angioedema in the valsartan/sacubitril group and none in the valsartan group. Although this trial was not powered to evaluate for clinical outcomes, it set the stage for the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON)-HF trial, a current study designed to evaluate the efficacy and safety of valsartan/sacubitril compared with valsartan in patients with heart failure with preserved ejection fraction (NCT01920711; the Table provides a list of clinical trials involving valsartan/sacubitril).

Hypertension

Ruilope et al examined the effect of an 8-week treatment with valsartan/sacubitril in mild to moderate hypertension, defined by a mean sitting DBP of 90 to 109 mmHg after washout of antihypertensive medications or 95 to 109 mmHg in untreated patients. Eighty-seven percent of the patients studied were white, and 57% were male. Patients underwent a 2-week washout period, followed by a 2-week single-masked treatment with placebo, before randomization to 1 of 8 treatment groups: placebo, sacubitril 200 mg, valsartan/sacubitril 100 mg, valsartan/sacubitril 200 mg, valsartan/sacubitril 400 mg, valsartan 80 mg, valsartan 160 mg, or valsartan 320 mg. The placebo-subtracted change in SBP and DBP from baseline was similar after 8 weeks of treatment with valsartan/sacubitril 100 mg and valsartan 80 mg.
<table>
<thead>
<tr>
<th>Trial No.</th>
<th>Title</th>
<th>Patient Population (n)</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01035255</td>
<td>Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF)</td>
<td>HFpEF (8442)</td>
<td>Enalapril</td>
<td>Published by McMurray et al⁴⁵</td>
</tr>
<tr>
<td>NCT00549770</td>
<td>Efficacy and Safety of LCZ696A in Patients With Essential Hypertension</td>
<td>Essential hypertension (1328)</td>
<td>Valsartan, sacubitril, placebo</td>
<td>Published by Ruilope et al⁴⁹</td>
</tr>
<tr>
<td>NCT01193101</td>
<td>Efficacy and Safety of LCZ696 Compared to Placebo in Patients With Essential Hypertension</td>
<td>Essential hypertension (389)</td>
<td>Placebo</td>
<td>Published by Kario et al⁵⁰</td>
</tr>
<tr>
<td>NCT00887588</td>
<td>Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT)</td>
<td>HFpEF (301)</td>
<td>Valsartan</td>
<td></td>
</tr>
<tr>
<td>NCT01785472</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients With Essential Hypertension</td>
<td>Essential hypertension (1438)</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01599104</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension</td>
<td>Essential hypertension (1161)</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01281306</td>
<td>An 8-Week Study to Evaluate the Dose Response of AHU377 in Combination With Valsartan 320 mg in Patients With Mild-to-Moderate Systolic Hypertension</td>
<td>Essential hypertension (910)</td>
<td>Valsartan, sacubitril, placebo</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01615198</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients With Essential Hypertension</td>
<td>Essential Hypertension (588)</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01922089</td>
<td>Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients (TITRATION)</td>
<td>HFpEF (498)</td>
<td>NA</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01692301</td>
<td>Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients With Hypertension</td>
<td>Essential hypertension (454)</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01876368</td>
<td>Efficacy and Safety of LCZ696 Compared to Olmesartan in Essential Hypertensive Patients Not Responsive to Olmesartan</td>
<td>Essential hypertension (376)</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01256411</td>
<td>A Long-Term (12 mo) Safety, Tolerability and Efficacy Study of LCZ696 in Patients With Essential Hypertension</td>
<td>Essential hypertension (341)</td>
<td>NA</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01663233</td>
<td>Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Combination With Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine</td>
<td>Essential hypertension (266)</td>
<td>Amlodipine</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01870739</td>
<td>A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects With Hypertension</td>
<td>Essential hypertension (124)†</td>
<td>Olmesartan</td>
<td>Completed, no published results</td>
</tr>
<tr>
<td>NCT01920711</td>
<td>Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON)-HF</td>
<td>HFpEF (4300)†</td>
<td>Valsartan</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02226120</td>
<td>Safety and Tolerability During Open-label Treatment With LCZ696 in Patients With CHF and Reduced Ejection Fraction</td>
<td>HFpEF (3714)†</td>
<td>NA</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02468232</td>
<td>Study of Efficacy and Safety of LCZ696 in Japanese Patients With Chronic Heart Failure and Reduced Ejection Fraction</td>
<td>HFpEF (220)†</td>
<td>Enalapril</td>
<td>Currently recruiting</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; and NA, not applicable.

*Trials registered with ClinicalTrials.gov.
†Estimated enrollment.
sacubitril 200 mg reduced SBP and DBP to a greater extent than the bioequivalent 160 mg valsartan (−11.00/−6.14 versus −5.69/−3.17 mm Hg; \( P=0.0006 \) for SBP and \( P=0.0023 \) for DBP). Valsartan/sacubitril 400 mg reduced SBP and DBP significantly more than 320 mg valsartan (−12.50/−6.85 versus −6.44/−4.15 mm Hg; \( P<0.0001 \) and \( P=0.0055 \) for SBP and DBP, respectively). A subset of patients also underwent ambulatory blood pressure monitoring. LCZ626 200 mg and 400 mg reduced ambulatory SBP to a significantly greater extent than valsartan 160 mg and 320 mg, respectively. The 200- and 400-mg doses of valsartan/sacubitril reduced both placebo-subtracted sitting and ambulatory pulse pressure significantly more than valsartan 160 and 320 mg. In a trial of Asian patients with essential hypertension, Kario et al.\(^{50} \) found similar reductions in SBP and DBP with valsartan/sacubitril 200 mg (−12.57/−7.29 mm Hg compared with placebo).

Treatment with sacubitril 200 mg alone or the 2 higher doses of valsartan/sacubitril significantly increased ANP. Sacubitril and all doses of valsartan/sacubitril increased circulating concentrations of cGMP. Sacubitril alone did not affect plasma renin activity. Moreover, valsartan/sacubitril and bio-equivalent doses of valsartan increased plasma renin activity similarly, suggesting that the effect of valsartan/sacubitril on plasma renin activity resulted solely from loss-of-feedback inhibition of renin production during angiotensin receptor blockade. Plasma aldosterone concentrations did not differ among active treatment groups or from placebo.

**Safety and Adverse Effects**

Treatment with the combined ACE and neprilysin inhibitor omapatrilat was associated with a 3-fold increased risk of angioedema compared with treatment with an ACE inhibitor alone.\(^{30} \) This has been attributed to concurrent inhibition of at least 2 pathways involved in the degradation of bradykinin and substance P, major effectors of angioedema. Bradikynin is inactivated primarily by ACE but also by neprilysin and aminopeptidase P, whereas substance P is inactivated by ACE, neprilysin, and dipeptidyl peptidase IV. A polymorphism in the gene encoding for neprilysin has also been associated with ACE inhibitor–associated angioedema.\(^{51} \) Given that valsartan/sacubitril inhibits only neprilysin, the incidence of angioedema during valsartan/sacubitril may be expected to be lower than during vasopeptidase inhibition.

In the PARADIGM-HF trial, there were 19 confirmed cases of angioedema in patients treated with valsartan/sacubitril compared with 10 cases in patients treated with enalapril (0.5% with valsartan/sacubitril versus 0.2% with enalapril; \( P=0.13 \)). No patient in either group developed airway compromise or required endotracheal intubation. It should be noted, however, that 6532 of 8442 patients enrolled in the trial were previously treated with an ACE inhibitor and that all patients were exposed to enalapril during the single-blind run-in period. The rate of angioedema during each run-in portion of the trial was 0.1%. Including a high proportion of patients who tolerated exposure to an ACE inhibitor or sacubitril, either before the study or during the run-in phase, may have introduced selection bias and led to an underrepresentation of angioedema in the trial, because ≥50% of cases of ACE inhibitor–associated angioedema occurred within the first week of treatment initiation.\(^{52} \) In addition, the incidence of angioedema in the PARADIGM-HF trial may underestimate the incidence in the general population. Just 5% of patients in PARADIGM were black, a group at increased risk of ACE inhibitor– and vasopeptidase inhibitor–associated angioedema.\(^{53,54} \) Indeed, rates of angioedema were higher in blacks treated with valsartan/sacubitril compared with nonblacks.\(^{39} \) The use of valsartan/sacubitril in patients who were not previously taking ACE inhibitors also may lead to a higher rate of angioedema in clinical practice.

Rates of angioedema in patients taking valsartan/sacubitril may be increased by drug-drug interactions if patients inadvertently take an ACE inhibitor while taking valsartan/sacubitril. The current recommendation is to discontinue ACE inhibitor use at least 36 hours before valsartan/sacubitril is started; a longer washout period is desirable because ACE inhibitors have a prolonged duration of action.

Symptomatic hypotension was the most common adverse event reported with valsartan/sacubitril in the PARADIGM-HF and PARAMOUNT trials, with a frequency of 18% and 19%, respectively. A similar rate of hypotension (19.5%) was found with omapatrilat in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), a trial designed to compare omapatrilat with enalapril in chronic heart failure.\(^{55} \) The higher rate of hypotension with valsartan/sacubitril compared with enalapril in the PARADIGM-HF trial did not lead to a significant difference in discontinuation of the drug (0.9% of valsartan/sacubitril patients discontinued the drug as a result of hypotension compared with 0.7% in the enalapril group; \( P=0.38 \)). In a study assessing factors leading to the hypotensive effect of RAAS inhibition with captopril, Hodsman et al.\(^{56} \) found a greater blood pressure reduction in patients with renin-dependent states (ie, low sodium intake and volume depletion). Therefore, it is recommended that volume and sodium depletion states be corrected before valsartan/sacubitril is started to minimize its hypotensive effects.

Like ACE inhibitors and ARBs, valsartan/sacubitril can cause hyperkalemia, cough, and worsening renal function. In the PARADIGM-HF trial, the frequency of hyperkalemia, defined as a serum potassium ≥5.5 mmol/L, was 16.1% in patients taking valsartan/sacubitril, which was not significantly different compared with enalapril. Concurrent use of potassium-sparing drugs increases the frequency of hyperkalemia. Valsartan/sacubitril had a significantly lower rate of cough than enalapril (11.3% with valsartan/sacubitril versus 14.3% with enalapril; \( P<0.001 \)). Using data from the PARAMOUNT trial, Voors et al.\(^{57} \) found that patients treated with valsartan/sacubitril had a lower decline in estimated glomerular filtration rate compared with patients treated with enalapril at 36 weeks (−1.5±13.1 versus −5.2±11.4 mL·min⁻¹·1.73 m⁻²; \( P=0.008 \)). There was a significant increase in the ratio of urine albumin to creatinine in the valsartan/sacubitril group (from 2.4 mg/mmol at baseline to 2.9 mg/mmol at 36 weeks), whereas the ratio of urine albumin to creatinine in the enalapril group did not change significantly (2.1 mg/mmol at baseline to 2.0 mg/mmol at 36 weeks; \( P \) between groups=0.016). Whether this reflects a marker disease progression or an effect of valsartan/sacubitril on vascular permeability remains unknown. Using
an ACE inhibitor or ARB with valsartan/sacubitril is not recommended because of the increased risk of adverse effects in trials of combined RAAS blockade. Valsartan/sacubitril does not affect the QT interval.

Drugs that inhibit the RAAS can cause harm to the fetus. Therefore, valsartan/sacubitril should not be administered to pregnant women.

Neprilysin is involved in the clearance of Aβ from the brain and cerebrospinal fluid (CSF). Administration of valsartan/sacubitril 400 mg/d to healthy subjects for 2 weeks increased CSF Aβ1-38 compared with placebo, but CSF Aβ1-40 and CSF Aβ1-42 concentrations did not change. In young cynomolgus monkeys, 2-week treatment with valsartan/sacubitril 50 mg/d increased CSF Aβ1-40, Aβ1-42, and Aβ1-38 levels but did not alter Aβ levels in the brain. In a 39-week toxicology study in cynomolgus monkeys, treatment with valsartan/sacubitril 300 mg/d did not result in Aβ accumulation in the brain.

Cost
The wholesale price of valsartan/sacubitril is estimated to be $4500/y or $12.50/d for twice-daily dosing. In comparison, the cost of the enalapril dose used in the PARADIGM-HF trial was about $3.89 daily. Lisinopril is one of the least expensive ACE inhibitors on the market, with a daily price of $1.56. Therefore, replacing a patient’s lisinopril with valsartan/sacubitril could potentially result in an 8-fold increase in drug costs. The Institute of Clinical and Economic Review published a report evaluating the cost-effectiveness of valsartan/sacubitril. The current estimate of cost savings resulting from a reduction of heart failure hospitalizations is $1043 per patient after 1 year of treatment with valsartan/sacubitril, or ≈25% of the annual drug cost. Assuming that 390000 patients receive valsartan/sacubitril in the first year, the estimated 1-year budget impact is $1.4 billion.

Conclusions
Valsartan/sacubitril, the first combined angiotensin receptor antagonist/neprilysin inhibitor, decreases mortality in patients with heart failure with reduced ejection fraction. Ongoing clinical trials will determine the efficacy in other conditions, including hypertension and heart failure with preserved ejection fraction. The coming years will bring additional information about this class of drugs. For example, is the beneficial effect of combined angiotensin receptor antagonist/neprilysin inhibition on mortality in heart failure with reduced ejection fraction dependent on superior blood pressure and afterload reduction? In addition, the long-term renal effects of combined angiotensin receptor antagonist/neprilysin inhibition are yet to be determined. Is the clinical benefit of valsartan/sacubitril driven by decreased degradation of natriuretic peptides, or are there other mechanisms by which combined angiotensin receptor antagonism and neprilysin inhibition improve heart failure? As previously noted, neprilysin degrades a number of vasoactive peptides in addition to the natriuretic peptides, and the contribution of these peptides to the effects of valsartan/sacubitril remains to be studied. Related to this, what will be the incidence of angioedema among patients treated with valsartan/sacubitril in the real-world setting? The answers to these questions are likely to be addressed in upcoming trials and will undoubtedly further our understanding of the pathophysiology of heart failure.

Sources of Funding
This work was supported by National Institutes of Health grants T32-GM-108554 (Dr Hubers) and R01-HL-125426 (Dr Brown).

Disclosures
Dr Brown served on an adjudication committee for angioedema for valsartan/sacubitril trials and serves as a consultant to Novartis. Dr Hubers reports no conflicts.

References


treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF).


Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition
Scott A. Hubers and Nancy J. Brown

Circulation. 2016;133:1115-1124
doi: 10.1161/CIRCULATIONAHA.115.018622
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/11/1115

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/06/24/CIRCULATIONAHA.115.018622.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
## SUPPLEMENTAL MATERIAL

### Supplemental Table: Peptide substrates of neprilysin relevant to cardiovascular and metabolic disease

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Cleavage sites</th>
<th>Km</th>
<th>Kcat</th>
<th>Kcat/Km</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin I</td>
<td>Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Asp-Arg-Val-Tyr-Ile-His-Pro-Phe</td>
<td>280</td>
<td>145</td>
<td>5.1</td>
<td>1</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg</td>
<td>92.2</td>
<td>6364</td>
<td>69.0</td>
<td>6</td>
</tr>
<tr>
<td>Protein</td>
<td>Peptide Sequence</td>
<td>Molar Mass (kDa)</td>
<td>Half-Life (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin 1</td>
<td>Cys-Ser-Cys-Ser-Ser-Leu-Met-Asp-Lys-Glu-Cys-Val-Tyr-Phe-Cys-His-Leu-Asp-Ile-Ile-Trp</td>
<td>2.3</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin 2</td>
<td>Cys-Ser-Cys-Ser-Ser-Trp-Leu-Asp-Lys-Glu-Cys-Val-Tyr-Phe-Cys-His-Leu-Asp-Ile-Ile-Trp</td>
<td>10.7</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin 3</td>
<td>Cys-Thr-Cys-Phe-Thr-Tyr-Lys-Asp-Lys-Glu-Cys-Val-Tyr-Tyr-Cys-His-Leu-Asp-Ile-Ile-Trp</td>
<td>2.5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrin (sulfated)</td>
<td>Pyr-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Ala-Tyr(SO₃H)-Gly-Trp-Met-Asp-Phe</td>
<td>57</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon-like peptide 1</td>
<td>His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Lys-Glu-</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7-36) amide</td>
<td>Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-NH₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANP indicates atrial natriuretic peptide; BNP, brain natriuretic peptide; and CNP, C-type natriuretic peptide. Arrow (↓) indicates a cleavage site. For a complete list of peptide substrates of neprilysin see http://merops.sanger.ac.uk/cgi-bin/substrates?id=M13.001

Km is the concentration of substrate needed to reach half maximum velocity; the lower the Km the greater the affinity of the enzyme for the substrate. Kcat/Km, or the specificity constant, conveys the relative rate of the enzyme neprilysin acting on the specific substrate.

Supplemental References


