Review Article

Angiotensin Receptor Neprilysin Inhibition in Heart Failure: Mechanistic Action and Clinical Impact

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ABSTRACT

Heart failure (HF) is an increasingly common syndrome associated with high mortality and economic burden, and there has been a paucity over the past decade of new pharmacotherapies that improve outcomes. However, recent data from a large randomized controlled trial compared the novel agent LCZ696, a dual-acting angiotensin receptor blocker and neprilysin inhibitor (ARNi), with the well established angiotensin-converting enzyme (ACE) inhibitor enalapril and found significant reduction in mortality among the chronic reduced ejection fraction HF population. Preclinical and clinical data suggest that neprilysin inhibition provides beneficial outcomes in HF patients by preventing the degradation of natriuretic peptides and thereby promoting natriuresis and vasodilatation and counteracting the negative cardiorenal effects of the up-regulated renin-angiotensin-aldosterone system. Agents such as omapatrilat combined neprilysin and ACE inhibition but had increased rates of angioedema. Goals of an improved safety profile provided the rationale for the development of the ARNi LCZ696. Along with significant reductions in mortality and hospitalizations, clinical trials suggest that LCZ696 may improve surrogate markers of HF severity. In this paper, we review the preclinical and clinical data that led to the development of LCZ696, the understanding of the underlying mechanistic action, and the robust clinical impact that LCZ696 may have in the near future. (*J Cardiac Fail 2015;21:741−750*)
Key Words: Angiotensin receptor neprilysin inhibition, LCZ696, heart failure.

Heart failure (HF) is a common disease that currently affects 5.7 million Americans and will affect an estimated >8 million adults, with a projected total cost of almost $70 billion, by 2030.[1] Over the past 30 years, there has been significant improvement in survival rates after the diagnosis of HF,[2] but the 5-year mortality rate remains high at ∼50%[1] and the syndrome is associated with significant morbidity. The reduction in HF mortality in recent decades can be largely attributed to the discovery and implementation of optimal medical therapy including

inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors[3] or angiotensin II receptor blockers (ARBs),[4] beta-blockers,[5,6] and aldosterone receptor blockers.[7] However, the past decade had been essentially void of any new pharmacotherapy offering an additional mortality benefit in HF patients until the recently published Prospective Comparison of ARNi (Angiotensin Receptor−Neprilysin Inhibitor) With ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[8] The trial demonstrated a reduction in mortality when comparing the long-term effects of LCZ696, a 1st-in-class agent that delivers simultaneous angiotensin receptor blockade (valsartan) and neprilysin inhibition (sacubitril), versus enalapril in addition to current standard of care therapy.[8] Neprilysin is a neutral endopeptidase (NEP) that is responsible for degradation of several vasoactive peptides, including natriuretic peptides (NPs),[9] and has been the therapeutic target of numerous agents over the last several decades. In this paper, we review the preclinical and clinical data related to the mechanistic action of neprilysin
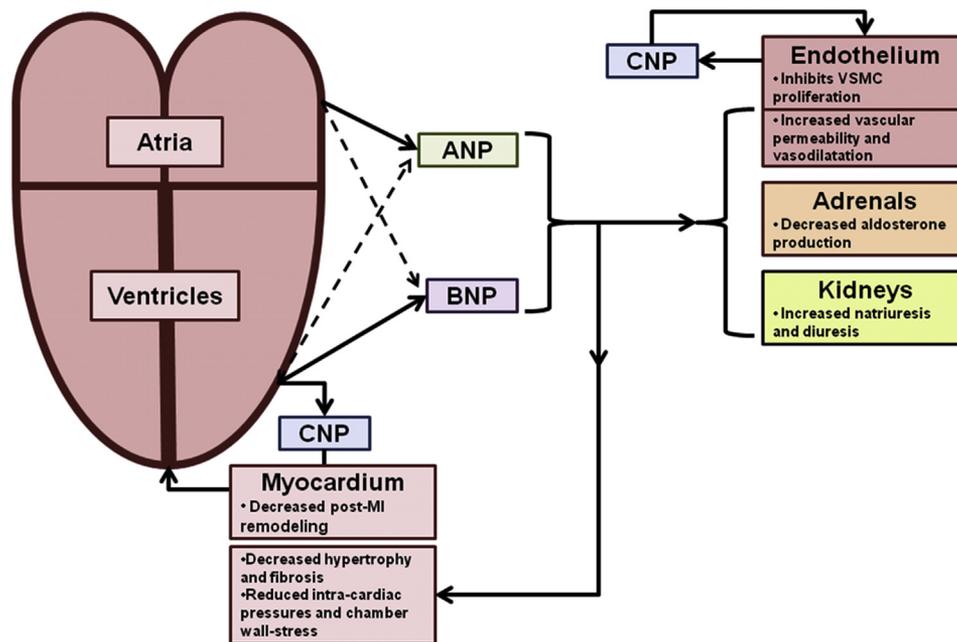
Fig. 1. Origins and sites of action of natriuretic peptides in heart failure. A-Type natriuretic peptide (ANP) is predominantly released from the atria, B-type natriuretic peptide (BNP) is predominantly released from the ventricles, and C-type natriuretic peptide (CNP) is predominantly found locally in myocardium and endothelium with minimal systemic release. In states of cardiac stress and volume overload (eg, heart failure), both ANP and BNP may be released from either cardiac chambers (dashed lines). ANP and BNP act on the endothelium to increase vascular permeability and vasodilatation, on the adrenals to inhibit aldosterone production, on the kidneys to promote natriuresis and diuresis, and at the level of myocardium to inhibit fibrosis and cellular hypertrophy leading to decreased intra-cardiac pressure and chamber wall-stress. CNP also acts on the myocardium to inhibit fibrosis and cellular hypertrophy and may decrease post−myocardial infarction (MI) remodeling. CNP acts locally on the endothelium to inhibit vascular smooth muscle cell (VSMC) proliferation as well as promote vascular permeability and vasodilatation.

inhibition combined with angiotensin receptor blockade and the clinical impact of this novel therapy in HF patients.

Natriuretic Peptides

Because one of the actions of ARNIs is to modulate NP levels, mechanistic data need to be placed in the context of the contemporary understanding of the role of NPs in HF. NPs in HF have been reviewed previously.[10] Although other NPs, such as renally produced urodilatin, may play an important role in HF[11] there are 3 main NPs that originate from cardiac tissue, A-type (or atrial) natriuretic peptide (ANP), B-type (or brain) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP; Fig. 1). In healthy subjects, ANP is mainly secreted from the atria and BNP from the ventricles, however, in patients with left ventricular (LV) dysfunction both peptides are secreted from the LV in response to wall tension to promote natriuresis, diuresis, vasodilatation, and RAAS blockade via aldosterone and renin inhibition.[10,12] These peptides therefore block the negative cardiac effects of angiotensin II (Ang II) and aldosterone in HF patients, including sodium retention, vasoconstriction, and endothelial dysfunction.[13,14] Whereas ANP and BNP predominantly serve as circulating hormones, CNP is derived from endothelial cells and synthesized in cardiac fibroblasts and may have important

antiremodeling effects in the myocardium by means of local regulation of collagen synthesis and cellular hypertrophy inhibition.[15,16] These actions are all mediated by means of NP receptors via the cyclic guanosine monophosphate (cGMP) second messenger system.[17] However, as HF advances, there is inadequate activation of or a diminished response to NPs coupled with further activation of the RAAS, which ultimately overcomes the beneficial effects of the NPs and leads to neurohormonal imbalance.[18,19]

Because serum levels of NPs become elevated in HF patients, assays were developed to assess these biomarkers to diagnose and offer prognostic information related to acute decompensated heart failure (ADHF).[20] Despite high levels of circulating NPs, ADHF patients are thought to be in a state of relative BNP insufficiency[10] owing to relatively higher levels of the high-molecular-weight proBNP, which has less biologic activity than the low-molecular-weight BNP,[21] as well as increased cellular phosphodiesterase, which inhibits the downstream affects of BNP on target cells.[22]

In canine models of HF, the acute administration of subcutaneous BNP significantly improved several hemodynamic measurements, natriuresis, and diuresis.[23] These observations and additional preclinical work led to the development of nesiritide, a recombinant human BNP. A study of 489 patients with ADHF compared intravenous

nesiritide with intravenous nitroglycerin or placebo as therapy adjunctive to standard of care.[24] Nesiritide significantly improved pulmonary capillary wedge pressure (PCWP) and cardiac index at 1 hour after infusion, and although the difference in PCWP remained at 24 hours, patients reported no significant difference in dyspnea between the nesiritide and nitroglycerin groups. Eventually, pooled analysis of several randomized controlled trials questioned the safety of nesiritide regrading hypotension and renal dysfunction.[25] These data provided the rationale for the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial.[26] The ASCEND-HF trial compared nesiritide and placebo in 7,141 patients with ADHF. There was no significant benefit in early dyspnea relief or 30-day outcomes in the nesiritide group.[26] Low-dose nesiritide as renal adjuvant therapy in patients admitted with ADHF and concomitant renal dysfunction was evaluated in the recently completed Renal Optimization Strategies Evaluation (ROSE) trial.[27] Despite the theoretic benefit of enhancing diuresis and preserving renal function, patients receiving nesiritide had no difference in decongestion or renal function at 72 hours compared with placebo. These data have limited the use of nesiritide to adjunctive therapy with diuretics for dyspnea relief in acute HF.[28] Thus, although short-term high-dose BNP may be of minimal benefit in acute HF, there may remain a benefit of sustained modest elevations of NPs in chronic HF. As such, the role of NPs as biomarkers in HF is more widely accepted.

Neprilysin Inhibition

Considering earlier success with RAAS blockade in HF via ACE inhibition and ARB use, as well as signs of benefit with NP infusions, inhibition of the degradation of NPs was evaluated for potential therapeutic benefits. NPs are removed from circulation via receptor-mediated clearance and extracellular proteases.[9] The major enzyme contributing to the extracellular degradation is known as neprilysin (NEP), also referred to as neutral endopeptidase, enkephalinase, or EC 3.4.24.11.[29] Neprilysin is a membrane-bound zinc metalloendopeptidase that was originally isolated in 1974 from the kidney brush border of rabbits[30] and has since been found to be widely distributed in mammalian cells.[31,32] Evidence suggests that ANP and CNP are the preferred substrates of neprilysin, whereas BNP is more slowly degraded.[33,34] In addition to the NPs, other vasoactive peptides that have been identified as neprilysin substrates include adrenomedullin, substance P, Ang I and II, bradykinin,[35] and endothelin-1.[36,37] Thus, although inhibition of neprilysin would increase levels of NPs and other compensatory peptides, leading to the desirable effects noted above, there may also be increased levels of peptides, yielding undesirable effects, such as vasoconstriction[38] with Ang II and endothelin-1 or possible side effects such as angioedema[39] with increased levels of bradykinin. Several agents have been developed that act via neprilysin inhibition. Two agents investigated in the HF population included

candoxatril and ecadotril. The development program for candoxatril was discontinued after mixed clinical results,[40−44] and ecadotril was found to have no clinical benefit, and in 2 patients taking the highest dose it potentially led to the rare side effect of drug-induced aplastic anemia, which limited further investigation.[45]

Omapatrilat

Taken together, the numerous substrates of neprilysin and earlier studies with mixed clinical effects of neprilysin inhibition alone on the RAAS and related vasoactive peptides led to the development of vasopeptidase inhibitors which contain both neprilysin and ACE inhibitor properties,[46] including omapatrilat.[47] Attenuation of the RAAS via ACE inhibition has proven cardiac and mortality benefits in HF patients,[3,48] and both inhibition of neprilysin and ACE leads to greater cardiorenal benefits (eg, improved natriuresis and diuresis and lower levels of Ang II and aldosterone) in preclinical models of HF, likely via increased levels of NPs and other vasodilating peptides, such as bradykinin, while simultaneously preventing the conversion of Ang I to Ang II.[49−52] In a post−myocardial infarction (MI) rodent model, omapatrilat decreased myocardial fibrosis compared with placebo and decreased LV hypertrophy compared with captopril.[53] A small study in humans with normotensive patients suggested that omapatrilat increased urinary levels of ANP and yielded similar inhibitory effects as fosinopril regarding the conversion of Ang I to Ang II.[54]

Initial trials of omapatrilat in HF patients reported no major adverse side effects,[55−57] improvement in reported functional status,[55] improved left ventricular ejection fraction (LVEF), natriuresis, and diuresis,[55] and even a nonsignificant trend favoring omapatrilat in rates of death and HF-related admissions compared with lisinopril.[57] Again, when compared with lisinopril, similar effects were found regarding levels of the substrates Ang II and endothelin-1.[57] The OVERTURE trial consisted of 5,770 New York Heart Association (NYHA) class II−IV HF patients randomized to omapatrilat or enalapril for 14.5 months (Table 1).[58] The trial was designed to detect a primary end point of death or hospitalization for HF requiring intravenous treatment and found omapatrilat to be noninferior, but a post hoc analysis that used a broader definition for HF-related hospitalizations found a statistically significant decrease in the end point among patients taking omapatrilat. Furthermore, there was a decrease in the number of patients who died or were hospitalized for any cardiovascular reason in the omapatrilat group compared with the enalapril group. The authors reported similar adverse event profiles, but noted a trend of 24 versus 14 cases of angioedema with omapatrilat compared with enalapril.[58] The data from the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) was suggestive of a potential benefit with omapatrilat compared with enalapril, and warranted further investigation. The Omapatrilat Cardiovascular Treatment Versus Enalapril (OCTAVE) trial randomized 25,301

Table 1. Vasopeptidase Trials Outcomes: Omapatrilat vs Enalapril

Trial (year)	n	Design	Duration	Inclusion Criteria	Comparison	Primary End Point	Outcomes (Omapatrilat vs Enalapril)
OVERTURE (2002)[58]	5,770	Randomized, double-blinded	~14.5 mo	NYHA II–IV for ≥2 mo or LVEF ≤30% + HF hospitalization within 12 mo	40 mg omapatrilat daily (82.5% reached target dose) vs 10 mg enalapril twice daily (86.4% reached target dose)	Composite of all-cause mortality or HF-related hospitalization	• 2% ARR and 0.94 HR ($P = .187$) in primary end point • 3.4% ARR and 0.91 HR ($P = .024$) in death or hospitalization for CVD • 24 (0.8%) vs 14 (0.5%) cases of angioedema
OCTAVE (2004)[59]	25,302	Randomized, double-blinded	24 wk	Adults with treated or untreated HTN based on JNC-VI criteria	20–80 mg omapatrilat daily vs 10–40 mg enalapril daily, titrated to meet blood pressure goal of <140/<90 mm Hg	Reduction in SBP at wk 8 and the need for new adjunctive antihypertensive therapy by wk 24	• 3.6 mm Hg reduction in mean SBP at 8 wk • 19% vs 27% of patients required adjunctive antihypertensive therapy • 274 (2.17%) vs 86 (0.68%) cases of angioedema

ARR, absolute risk reduction; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; HTN, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; SBP, systolic blood pressure.

hypertensive patients to 24 weeks of omapatrilat or enalapril, and although they did find an improvement in blood pressure in the omapatrilat arm, they also noted a 3-fold increase in the risk of angioedema (2.17% vs 0.68%) that was particularly prevalent among smokers and black patients.[59] Subsequent rodent studies suggested that omapatrilat also inhibits the bradykinin-metabolizing enzyme aminopeptidase P (APP)[60] and that the combined inhibition of neprilysin, ACE, and APP may be the mechanism causing elevated levels of bradykinin leading to angioedema.[61] Thus, while there appear to be clinical benefits, the inherent risks of angioedema led to the United States Food and Drug Administration (FDA) to reject the New Drug Application for omapatrilat in 2002.[62]

LCZ696

The aforementioned data provided the rationale for a therapeutic approach that continued to use neprilysin and RAAS inhibition without directly affecting ACE or APP, and led to the development of a dual ARNi.[63] A novel drug is known as LCZ696, a single agent that contains the molecular moieties of the ARB valsartan and the neprilysin inhibitor AHU377 (ie, sacubitril), which is the prodrug for active LBQ657 (Fig. 2).[63] In HF patients with a reduced ejection fraction (EF), the use of an ARB in those intolerant of an ACE inhibitor is an approved 1st-line therapy,[28] and valsartan has been shown to potentially have beneficial effects in the HF population.[64]

Preclinical studies of AHU377 versus placebo confirmed an increase in cGMP, natriuresis, and diuresis in response to exogenous ANP administration.[65] Other preclinical work confirmed a rapid increase in plasma concentrations of both valsartan (peak 1.6–4.9 h) and LBQ657 (peak 1.8–2.7 h) after oral administration of LCZ696, followed by an acute decrease in blood pressure and dose-dependent increase in ANP levels.[63] Healthy human volunteers receiving escalating doses of LCZ696 were noted to have significant acute increases in plasma cGMP levels that returned to baseline by 24 hours as well as dose-dependent increases in plasma renin concentration, renin activity, and Ang II that were sustained after 12 days.[63] The effects on RAAS-mediated neurohormonal levels were similar to those seen previously with valsartan[66] and likely mediated through loss of the normal feedback inhibition via the Ang II type 1 receptor.[13] These early data with LCZ696 in the context of previously demonstrated beneficial effects of neprilysin inhibition by means of other agents provided the rationale to proceed with larger phase III studies of LCZ696 without additional phase II work.

LCZ696 Clinical Trials

Hypertension

The first large-scale clinical trial with LCZ696 consisted of 1,328 adult patients with mild to moderate hypertension and examined resting diastolic blood pressure (DBP) across
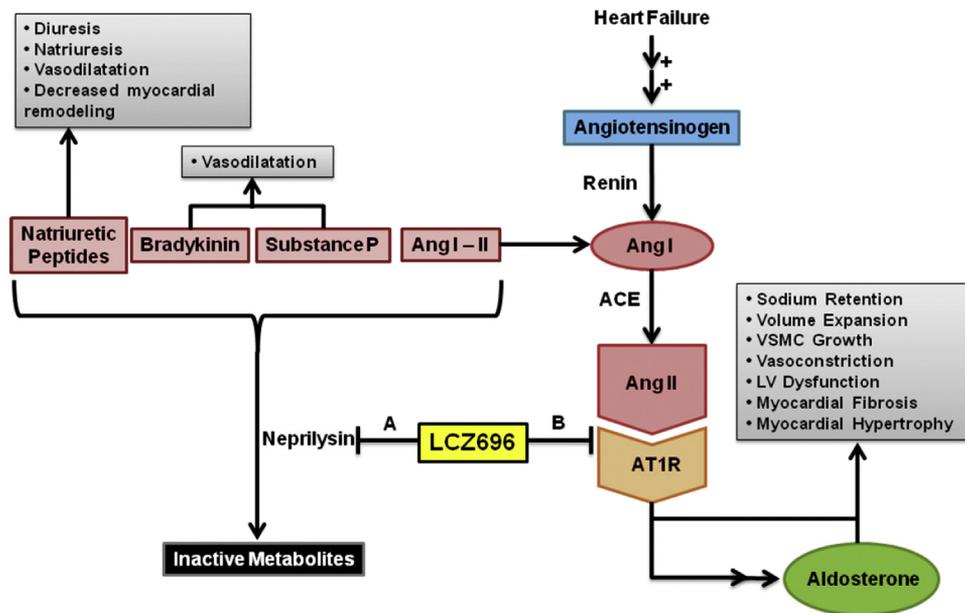
Fig. 2. Sites of action of LCZ696. LCZ696 exerts dual effects via the neprilysin inhibitor AHU377 (*A*), which serves as the prodrug for active LBQ657, and the active moiety of the angiotensin (Ang) II type 1 receptor (AT1R) inhibitor valsartan (*B*). LCZ696 prevents the degradation of several vasoactive substrates, including natriuretic peptides, bradykinin, substance P, and Ang I and II, as well as inhibiting the downstream effects of Ang II. This mechanism counteracts states of volume overload and the activated RAAS via increased diuresis, natriuresis, vasodilatation, and inhibition of downstream Ang II and aldosterone effects. ACE, angiotensin-converting enzyme; AT1R, angiotensin II type 1 receptor; LV, left ventricular; VSMC, vascular smooth muscle cell.

3 single-dose pairwise comparisons of LCZ696 versus valsartan (Table 2).[67] The authors paired equivalent doses in line with data revealing a linear relationship between a range of doses that include 400 mg of LCZ696 providing an equivalent exposure to 320 mg of valsartan.[63] Patients received varying doses of LCZ696, valsartan, AHU377, or placebo once daily. The investigators found that the mean reduction in resting measurements of DBP and systolic blood pressure (SBP) was greater with AHU377 compared with placebo and with LCZ696 versus the appropriate comparator dose of valsartan. There were significantly higher levels of ANP in LCZ696 doses >100 mg compared with valsartan and placebo. Consistent with RAAS blockade and earlier data, plasma renin concentration was increased from baseline in all patients receiving LCZ696 or valsartan, but there was not an increase in aldosterone concentration. The authors reported no cases of angioedema, and in general, LCZ696 was well tolerated. But notably their sample population contained only ∼8% black patients, despite the higher prevalence of angioedema among black patients in previous omapatrilat studies.[59] Furthermore, the generalizability of this study to patients with HF or other cardiovascular disease is limited because those patients were actively excluded.[67]

Another similarly designed trial evaluating the effect of LCZ696 on hypertension studied 389 adult Asian patients with mild to moderate hypertension.[68] The study was also powered to detect a primary end point of a change in mean difference of DBP across 3 single-dose pairwise comparisons of LCZ696 versus placebo. Patients received either varying LCZ696 doses or placebo once daily. There were statistically significant differences across all doses of LCZ696 in the reduction from baseline measurements of clinic DBP and SBP. The authors also reported that LCZ696 was well tolerated with no cases of angioedema. Limitations of this study are similar to the above trial, including the absence of black patients, potentially reducing the ability to detect angioedema. Furthermore, the investigators failed to include an active comparator arm, making their data more predictable regarding to blood pressure–lowering ability, and they did not report data on hard clinical outcomes.[68]

Heart Failure With Preserved Ejection Fraction

The first published randomized double-blind trial with LCZ696 in HF patients compared the agent with valsartan in a parallel group study of patients with HF with a preserved ejection fraction ≥45% (HFpEF), referred to as the Prospective Comparison of ARNi With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial.[69] Patients had NYHA functional class II–III symptoms, were ≥40 years old, and were required to have an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of >400 pg/mL and to be on concomitant diuretic therapy. Major exclusion criteria included any previous LVEF measurement $<45\%$, isolated right-sided HF due to pulmonary disease, other causes of dyspnea, primary valvular or myocardial diseases, or coronary artery or cerebrovascular disease needing revascularization within 3 months of screening or during the trial

Table 2. LCZ696 Randomized Double-Blind Clinical Trials

Study (Year)	n	Patients	Duration	Comparison	Outcomes	Limitations
Ruilope et al (2010)[67]	1,328	• Multinational • Mean age 53 y • 87% white • 57% male • Mild to moderate uncomplicated HTN	8−13 wk; after 8 wk, 1,215 patients randomized to continue treatment vs placebo	100 mg LCZ696 daily vs 80 mg valsartan daily; 200 mg LCZ696 daily vs 160 mg valsartan daily; 400 mg LCZ696 daily vs 320 mg valsartan daily vs 200 mg ahu377 daily vs placebo	• At 8 wk LCZ696 significantly decreased mean resting DBP (−2.17 mm Hg) and SBP (−4.20 mm Hg) vs valsartan • AHU377 and LCZ696 >100 mg significantly increased plasma ANP vs placebo • LCZ696 and valsartan significantly increased plasma renin concentration vs placebo • AHU377 did not change plasma renin concentration vs placebo • No cases of angioedema	• Noninvasive hemodynamic monitoring • Only ∼8% black patients in sample population • Limited generalizability to HF population with exclusion of serious structural or functional cardiac disease
Kario et al (2014)[68]	389	• Asian country based • Mean age 52 y • 71% male • Mild to moderate uncomplicated HTN	8 wk	100 mg, 200 mg, or 400 mg LCZ696 daily vs placebo	• LCZ696 significantly decreased mean clinic DBP (−7.29 to −8.76 mm Hg) and SBP (−11.86 to −15.38 mm Hg) vs placebo • Significantly decreased 24-h, daytime, and nighttime ambulatory DBP, SBP, and PP (all $P < .0001$) vs placebo • No cases of angioedema	• Noninvasive hemodynamic monitoring • Only Asian patients in sample population • Lack of comparator arm • Limited generalizability to HF population with exclusion of significant CVD or previous HF
PARAMOUNT (2012)[69]	301	• Multinational • Mean age 71 y • HFpEF (LVEF ≥45%) • 79.4% NYHA II • 43.5% male • Geometric mean NT-proBNP 830.6 pg/mL • 100% diuretic use	1−36 wk	200 mg LCZ696 twice daily vs 160 mg valsartan twice daily	At 12 wk: • LCZ696 significantly decreased NT-proBNP and SBP • No significant change in NYHA class or left atrial volume or size At 36 wk: • LCZ696 significantly decreased SBP and left atrial size and volume and improved NYHA class • At either point, no change in LV size, function, or mass or quality-of-life scores • 1 case of angioedema with LCZ696	• Not designed or powered to detect clinical end points (surrogate markers only) • High rates of ARBs or ACE inhibitors (94%) and beta-blockers (79%) in HFpEF population • Older patient population compared with other LCZ696 trials
PARADIGM-HF (2014)[8]	8,442	• Multinational • Mean age 64 y • HFrEF (LVEF ≤35%) • 70% NYHA II • 78% male • Median NT-proBNP 1,608 pg/mL • 100% ACE inhibitor or ARB use • 93% beta-blocker use	27 mo (median)	200 mg LCZ696 twice daily vs 10 mg enalapril twice daily	• ARR 4.7%, NNT 21 in LCZ696 arm for composite of CV death or HF hospitalization • ARR 3.2%, NNT 32 in LCZ696 arm for any CV death • ARR 2.8%, NNT 36 in LCZ696 arm for preventing 1st HF hospitalization or any death • At 8 mo, LCZ696 arm had improved KCCQ scores • 10.7% vs 12.3% AEs causing drug discontinuation in LCZ696 vs enalapril groups • 19 vs 10 cases of angioedema in LCZ696 vs enalapril ($P = .13$)	• Run-in phase used to ensure drug tolerability at target doses • Only ∼5% black patients in sample population

ACE, angiotensin-converting enzyme; AE, adverse event; ARB, angiotensin receptor blocker; ANP, A-type natriuretic peptide; avg, average; CV, cardiovascular; DBP, diastolic blood pressure; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NNT, number need to treat; NT-proBNP, N-terminal pro-brain natriuretic peptide; PP, pulse pressure; RRR, relative risk reduction; other abbreviations as in Table 1.

period. The trial randomized 301 patients to receive a target dose of either 200 mg LCZ696 or the bioequivalent dose of valsartan (160 mg) twice daily for up to 36 weeks and was powered to detect a primary end point of a change in NT-proBNP levels at 12 weeks. There was a significant decrease in NT-pro-BNP levels in the LCZ696 group at 12 weeks, with a ratio of change of 0.77 (P = .005), but, although levels were still decreased, the difference was no longer significant at 36 weeks. Although the investigators found a significant reduction in SBP, there was no change in LV size, function, or mass, diastolic function, NYHA functional class, or quality of life scores at 12 weeks. At 36 weeks, there was a reduction in left atrial volume and improvement in NYHA functional class in the LCZ696 group compared with the valsartan group. There were similar adverse event rates among patients receiving LCZ696 compared with valsartan (15% vs 20%).[69] The trial was not designed or powered to detect clinical outcomes, but it has provided the rationale for larger ongoing clinical outcomes studies.

Several post hoc analyses of the PARAMOUNT trial data have been published that provide further insight into the mechanistic effects of LCZ696.[70–72] The effects of LCZ696 on decreasing NT-proBNP at 12 weeks and improving left atrial volume, NYHA functional class, and estimated glomerular filtration rate (eGFR) at 36 weeks were all independent from the improvement seen in SBP.[70] Troponin assays are an established predictor of clinical outcomes and measurement of subclinical myocardial injury, and in acute decompensated and chronic HFrEF,[73] compared with valsartan patients, those receiving LCZ696 had a statistically significant 12% and 14% reduction in high-sensitivity troponin T (hs-TnT) at 12 and 36 weeks, respectively.[71] The change in hs-TnT significantly correlated with changes in NT-proBNP at 36 weeks but not at 12 weeks. Although this study was short term, limiting any mortality analysis, it provides indirect evidence that LCZ696 leads to a reduction in myocardial wall stress, potentially by means of the up-regulation of NPs.[71]

Heart Failure With Reduced Ejection Fraction

The PARADIGM-HF trial is the largest LCZ696 HF trial to date and randomized 8,442 patients in double-blind fashion to receive 200 mg LCZ696 or 10 mg enalapril twice daily in addition to standard of care for a median follow-up of 27 months.[8] Eligible patients had NYHA functional class II–IV symptoms and LVEF ≤40% (which was changed to ≤35% by protocol amendment), were taking an ACE inhibitor or ARB, beta-blocker (if tolerated), and mineralocorticoid receptor antagonist (if indicated), and had a plasma BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or if hospitalized for HF in the past 12 months those cutoff levels reduced by one-third. Patients were excluded if they had resting or symptomatic hypotension, decreased eGFR ($<$ 30 mL min^{-1} 1.73 m^{-2}), hyperkalemia, or history of angioedema or unacceptable side effects to ACE inhibitors

or ARBs. Patients had a run-in period to ensure tolerability of the target dose of each drug, during which 12% of patients withdrew due to an adverse event, and the authors reported higher adjusted withdrawal rates in the enalapril group. The primary end point was a composite of death from cardiovascular causes or hospitalization for HF, and the trial was stopped early after meeting prespecified stringent criteria that included a significant reduction in all-cause mortality within the LCZ696 group.

Regarding the primary end point, there was an absolute risk reduction (ARR) of 4.7% with a number needed to treat (NNT) of 21 (over a median of 27 mo) in the LCZ696 arm compared with the enalapril group. There was also an ARR of 3.2% with an NNT of 32 to prevent 1 death from any cardiovascular cause, and ARRs of 2.8% with an NNT of 36 to prevent a 1st hospitalization for worsening HF or a single death from any cause. Rates of adverse events leading to drug discontinuation were 10.7% vs 12.3% (P = .03) in the LCZ696 compared with the enalapril group. Compared with enalapril, more patients receiving LCZ696 experienced an episode of symptomatic hypotension (14% vs 9.2%; P < .001), but overall hypotension was a cause for permanent discontinuation of therapy in only 0.9% of the LCZ696 group and 0.7% of the enalapril group (P = .38). The LCZ696 group had 19 cases of angioedema compared with 10 in the enalapril group, but this difference was not statistically significant. Importantly, there were no cases of serious angioedema with airway compromise or requiring mechanical airway protection. Overall, the study provided strong evidence for superiority of the ARNi compared with RAAS inhibition with an ACE inhibitor, in addition to guideline-directed therapy, regarding mortality and HF hospitalizations. Furthermore, although the run-in period may have excluded patients from the final adverse event rate, the overall number of patients excluded was small and even higher in the enalapril group, and therefore seems unlikely to have largely affected the safety profile of LCZ696. However, similarly to previous studies of LCZ696 in hypertension,[67] the PARADIGM-HF study had a low prevalence of black patients (5.1%), which may have limited the investigators' ability to detect a difference in angioedema.

Additional analysis of the PARADIGM-HF data examined the effect of LCZ696 on nonfatal clinical deterioration, also referred to as worsening HF.[74] In the LCZ696 arm compared with the enalapril arm, fewer patients had an intensification of outpatient therapy (ARR 1.9%, NNT 53) and an emergency department visit for HF (ARR 1.2%, NNT 83). The LCZ696 arm also had fewer patients requiring intensive care (ARR 1.7%, NNT 59) and intravenous inotropes (ARR 1.5%, NNT 67). Thus, compared with enalapril, LCZ696 is not only more effective at reducing mortality, but it can decrease signs and symptoms of nonfatal clinical deterioration.

Because it would be unethical to withhold an ACE inhibitor or ARB in patients with HFrEF, the authors also used

the PARADIGM-HF data to examine the effects of LCZ696 compared with putative placebos via indirect comparisons with 2 earlier placebo-controlled trials that used the ACE inhibitor enalapril and the ARB candesartan.[75] With the use of the putative placebo from the enalapril trial, the relative risk reduction (RRR) with LCZ696 on the primary composite of cardiovascular death or HF hospitalization was 43%, with RRRs of 34% for cardiovascular death, 49% for HF hospitalization, and 28% for all-cause mortality. All the effects seen were statistically significant. The authors found similar statistically significant reductions with the use of the putative placebo from the candesartan trial, with RRRs of 39% for the composite outcome, 32% for cardiovascular death, 46% for HF hospitalization, and 26% for all-cause mortality. This analysis adds further evidence to support beneficial effects of LCZ696 on important clinical outcomes in HF patients, including reductions in mortality and HF hospitalizations.[75]

Conclusion and Future Directions

With the total cases and economic burden of HF continuing to rise, there is an overwhelming need for new therapies that can reduce morbidity and mortality. The robust effect on mortality reduction seen with the novel-acting ARNi LCZ696 promises to alter the trajectory of HF for individual patients and perhaps for society at large. Early preclinical and clinical work with earlier neprilysin inhibitors suggest that this effect is uniquely mediated through simultaneous potentiation of the endogenous NPs and inhibition of the RAAS via Ang II type 1 receptor blockade. The use of an ARB rather than an ACE inhibitor has led to a more favorable side effect profile, specifically fewer cases of serious angioedema.

Future studies are needed to investigate these effects across the broader continuum of patients with HF, such as those with ADHF and more advanced symptoms. Unanswered questions also remain on the economic impact of LCZ696 and on best practices for implementation of LCZ696 into routine clinical care. Furthermore, although the above trials suggest improvement in surrogate markers of HF severity within the HFpEF population, we will have to await the results of the ongoing PARAGON-HF trial (NCT01920711), currently enrolling 4,300 patients in a multicenter, randomized, double-blind, parallel-group study comparing LCZ696 and valsartan and examining the effects on cardiovascular death and HF hospitalizations. Although there remain some unanswered questions, LCZ696 has the potential to replace ACE inhibitors or ARBs as adjunctive therapy in patients with chronic, stable, but symptomatic HF with LVEF ≤40%. In fact, as of July 7, 2015, the FDA has approved LCZ696 (trade name Entresto) for use in chronic HFrEF patients with NYHA functional class II−IV symptoms.[76] The labeling states that the agent should be used in conjunction with other HF therapies but in place of ACE inhibitors or ARBs, and that it is contraindicated in patients with a history of ACE inhibitor− or ARB-induced angioedema. The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice daily with up-titration after 2−4 weeks to the target dose of 97/103 mg twice daily. A reduced starting dose of 24/26 mg twice daily is recommended for patients currently not taking or previously taking a low-dose ACE inhibitor or ARB, with doubling of the dose every 2−4 weeks, as tolerated, until the target dose is reached. Physicians will need to be careful regarding to patient selection, because there is unlikely to be a run-in phase in routine clinical practice and patients more susceptible to hypotension and angioedema should be screened carefully before initiation of therapy.

Disclosures

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