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Role of Angiotensin Receptor-Neprilysin Inhibition in Heart Failure

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Abstract
Purpose of Review Numerous evidence-based medical and device therapies proven to reduce morbidity and mortality have advanced care for heart failure with reduced ejection fraction (HFrEF). The primacy of this approach has now been superseded by striking new data resulting in the approval of the combination of valsartan and sacubitril, a neprilysin inhibitor (also known as LCZ696), in 2015 for the treatment of HFrEF. LCZ696 is a novel heart failure drug that simultaneously inhibits the renin-angiotensin system and potentiates the natriuretic peptide system.
Recent Findings In the Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, LCZ696 significantly improved cardiovascular outcomes compared to current guideline-directed medical therapy. Compared to an angiotensin-converting enzyme (ACE) inhibitor, LCZ696 was associated with a 20 % reduction in cardiovascular mortality (number needed to treat [NNT] 32) and a similar reduction in total mortality (NNT 36). Morbidity benefits of the drug were seen within 1 month of initiation. However, hypotension due to enalapril or the LCZ696 regimen during a run-in phase eliminated 20 % of patients. Safety concerns included the risk of angioedema and the theoretical concern of neurocognitive dysfunction due to the protean effects of neprilysin inhibition. The role of LCZ696 in patients with asymptomatic left ventricular systolic dysfunction is uncertain. LCZ696 is currently being evaluated in patients with heart failure with preserved ejection fraction, with promising initial results.
Summary LCZ696 represents a novel mechanistic approach to targeting heart failure with reduced ejection fraction, and ongoing studies will address its use in other cardiovascular populations.

Keywords Heart failure · Neprilysin inhibition · Clinical trial · Natriuretic peptides

Introduction

The prevalence of heart failure in the USA is 5.1 million, and this number will likely rise by 25 % by 2030, with a total projected cost of nearly $70 billion [1]. The lifetime risk of developing heart failure at the age of 40 is roughly 20 % and is increased substantially in individuals of African descent and in those with hypertension [2, 3]. Nearly 25 % of patients hospitalized for heart failure are readmitted within 30 days, and 5-year mortality rates remain roughly 50 % independent of ejection fraction [1, 4]. While significant advances in the treatment of heart failure with reduced rejection fraction (HFrEF) have been made over the past 30 years, since 2004, no new pharmacologic agent had been approved. Recently, a novel agent, LCZ696 (sacubitril/valsartan), a of combination angiotensin receptor blocker (ARB)-neprilysin inhibitor (NEPi), or ARNI, was shown to improve outcomes in HFrEF when compared to enalapril. LCZ696 is currently being studied in a phase 3 randomized controlled trial in heart failure with preserved ejection fraction (HFpEF), after a phase 2 trial demonstrated improved surrogate endpoints. Neprilysin

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inhibition, therefore, has the potential to change the landscape of heart failure pharmacotherapy. Here, we review the role of natriuretic peptides in the pathophysiology of heart failure providing a mechanistic rationale for the development of LCZ696. We highlight preclinical studies and clinical trials leading to the approval of LCZ696 and discuss current limitations as well as future directions for this novel approach for treating heart failure.

Heart Failure and the Natriuretic Peptide System

A variety of compensatory mechanisms are activated in HFrEF which aim to restore cardiac output and enhance end-organ perfusion. These mechanisms include activation of the renin-angiotensin-aldosterone system (RAAS), adrenergic nervous system, cytokines, and natriuretic peptides (NPs) [5, 6]. While initially beneficial in restoring vital organ perfusion, the chronic effects of this cascade lead to increased ventricular preload and afterload, ultimately causing progressive cardiac dilatation, dysfunction, and clinical heart failure symptoms. Activation of the RAAS system leads to the downstream formation of the potent vasoconstrictor angiotensin II (Ang II). Ang II acts locally and systemically, inducing vasoconstriction (via AT 1 receptors) and cellular proliferation (via AT 2 receptors). Ang II leads to increased peripheral vasoconstriction and fluid retention and also exerts direct effects on the myocardium, leading to myocardial fibrosis [7].

In addition to Ang II, activation of RAAS leads to formation of aldosterone, which increases sodium reabsorption in the distal kidney and leads to myocardial fibrosis (via collagen production), prothrombosis, and endothelial dysfunction [6]. Accordingly, mortality in heart failure is related to circulating levels of Ang II, aldosterone, norepinephrine, and epinephrine, and these effects are attenuated by angiotensin-converting enzyme inhibitors (ACEi) [8]. Interestingly, ACEi do not completely attenuate plasma aldosterone production despite uptitration of ACEi [9]. Thus, sequential blockade of Ang II formation with ACEi and mineralocorticoid receptors with aldosterone antagonists (plus evidence-based beta blockers) are now cornerstones of guideline-based treatment of HFrEF.

Natriuretic peptides (NPs) are a family of hormones that are thought to be counter-regulatory to the aforementioned RAAS and sympathetic nervous system activation. To date, three NPs have been identified in humans—atrial NP (ANP), brain NP (BNP), and C-type NP (CNP) [10]. ANP and BNP are released primarily from the heart—ANP from the atria and BNP from the ventricles—although both can be synthesized in either chamber under pathologic conditions [11, 12]. C-type NP is produced mainly by endothelial cells and may have a role in cardiac remodeling following acute myocardial infarction [13]. ANP and BNP are released in response to elevated wall stress [14]. Both ANP and BNP have multiple mechanisms of action, via guanylyl cyclase coupled receptors which increase intracellular cGMP, including vasodilation, natriuresis, and diuresis.

In the setting of volume expansion or pressure overload, release of BNP results in improved myocardial relaxation and opposes the vasoconstriction, sodium retention, and antidiuretic effects of the RAAS [15, 16]. NPs reduce renin release from the renal juxtaglomerular cells, decreasing Ang II [17, 18]. In animal models, ANP inhibits myocardial fibrosis mediated by aldosterone [19]. Since it is secreted in the setting of increased ventricular wall stress, BNP as a biomarker is highly specific for the diagnosis of heart failure and correlates with poor prognosis [20].

Exogenous Administration of Natriuretic Peptides

Given the positive natriuretic and diuretic effects of NPs, as well as their role in attenuation of the upregulated RAAS, investigators have examined the impact of administration of exogenous synthetic NPs in heart failure. In the VMAC trial, 489 patients with acute decompensated heart failure (ADHF) received intravenous (IV) nesiritide (recombinant human BNP), IV nitroglycerine, or placebo. When added to standard care in hospitalized patients with ADHF, nesiritide led to decrease in PCWP compared to both placebo and nitroglycerin but showed no difference in dyspnea or overall clinical status [21]. Moreover, analysis of VMAC and two other randomized trials raised concerns over trends toward increased death in patients randomized to nesiritide, possibly related to hypotension as well as renal dysfunction [22]. Such concerns led to the pivotal ASCEND-HF trial, in which 7141 patients hospitalized with ADHF were randomized to nesiritide or placebo. While nesiritide was not associated with increase in death, repeat hospitalization, or worsening renal failure, it was associated with increased hypotension and did not improve clinical symptoms [23]. Based on the above experiences, clinical use of nesiritide is sparse and limited to adjunctive management of acute decompensated heart failure in selected patients.

Neprilysin Inhibition

Another approach to increase NP levels has been to prevent endogenous NP degradation by inhibiting neprilysin, the enzyme responsible for its degradation. Neprilysin is a membrane bound zinc metalloendopeptidase originally isolated from the kidney brush border of rabbits in 1974 [24]. In addition to degrading ANP and BNP, neprilysin acts on numerous other substrates including adrenomedullin, substance P, Ang I and II, bradykinin, and endothelin-1 [25–27]. Two early NEPis, candoxatril and ecadotril, were developed and tested

in a variety of cardiovascular populations and showed conflicting results. Candoxatril acutely increased endogenous levels of ANP and BNP, as well as increased plasma cGMP, promoting natriuresis and diuresis, and lowering CVP, but with no predictable effect on lowering blood pressure, its intended goal [28, 29]. When administered to patients with clinical heart failure, candoxatril increased ANP levels, suppressed aldosterone, decreased right atrial pressure and PCWP, and increased cardiac output [30]. However, in a clinical trial of 279 patients with HFrEF to assess safety and efficacy, while plasma and urinary cGMP levels were increased, there were more deaths in patients receiving ecadotril with no evidence of clinical efficacy [31]. Early clinical use of neprilysin inhibition alone was stopped as the drug did not consistently lower blood pressure as expected and had less than anticipated clinical efficacy in improving heart failure symptoms [32]. Further work revealed that due to its multiple substrates including Ang II, unopposed neprilysin inhibition may have resulted in undesirable vasoconstriction, countering its intended clinical effect both in hypertensive and heart failure populations [33].

Given untoward effects of unopposed neprilysin inhibition, a dual neprilysin and renin-angiotensin system inhibitor—omapatrilat—was developed. Preclinical models suggested that dual blockade of RAAS and neprilysin resulted in reduction in cardiac preload and afterload greater than either drug alone [34]. This was associated with an increase in cardiac output, decrease in peripheral vascular resistance, and significant decrease in blood pressure [35]. In initial small clinical trials, omapatrilat was found to improve functional status, improve ejection fraction, LV end systolic wall stress, and reduce systolic blood pressure (SBP) in patients with HFrEF. Dose-dependent reductions in PCWP, SBP, and SVR were also noted, with no significant adverse events [36].

In a study of 573 patients with NYHA class II–IV heart failure and EF < 40 % on ACEi randomized to omapatrilat or lisinopril for 24 weeks in the IMPRESS trial, there was a trend toward significance in the combined endpoint of death or heart failure hospitalization ($p = 0.052$), and a positive benefit in composite of death, heart failure admission, or study drug discontinuation ($p = 0.035$; 0.52 [0.28–0.96]). Omapatrilat improved NYHA functional class more than lisinopril in patients with NYHA class III and IV heart failure [37]. In the much larger OVERTURE trial, 5770 patients with NYHA class II–IV heart failure were randomized to omapatrilat or enalapril for 14.5 months, with a primary endpoint of death or hospitalization for HF requiring IV diuretics. Omapatrilat was not found to be more effective than ACEi, but post hoc analyses observed a decrease in the primary endpoint in favor of omapatrilat. More importantly, however, there was a trend toward increased incidence of angioedema ($n = 24$ vs 14) in the omapatrilat group [38]. In the larger OCTAVE hypertension trial of 25,301 patients randomized to omapatrilat or enalapril, a 3-fold increase in risk of angioedema was noted (2.17 vs 0.68 %) and was even higher in individuals of African descent [39]. As a result, omapatrilat was tabled from FDA approval, and dual neprilysin renin-angiotensin system inhibitors were largely abandoned.

Development and Initial Clinical Trials with LCZ696

The increased risk of angioedema from dual neprilysin ACE inhibition was attributed to increased circulating concentration of bradykinin resulting from inhibition of two proteases that degrade it—ACE and neprilysin. However, unexpectedly, omapatrilat also inhibited aminopeptidase P, a third enzyme involved in bradykinin breakdown [40]. Accordingly, there was hope that by combining neprilysin inhibition with an ARB (a class of drug that does not increase bradykinin levels and is already associated with lower rates of angioedema than ACEi), the clinical benefits of omapatrilat could be maintained without the increased risk of angioedema. LCZ696 (Entresto®) is a 1:1 combination of the ARB, valsaratan, and the NEPi prodrug, sacubitril (AHU377), which is rapidly cleaved to the active metabolite LBQ657 [41]. Because valsartan blocks AT II rather than ACE, and because LBQ657, the active metabolite of sacubitril, does not inhibit aminopeptidase P, the risk of angioedema was thought to be substantially decreased [42]. Furthermore, valsartan has been shown to provide independent mortality benefit in patients with HFrEF intolerant of an ACEi [43]. In healthy humans, LCZ696 treatment was associated with increases in plasma cGMP, renin concentration and activity, and angiotensin II levels, illustrating the benefit of having dual neprilysin and ARB blockade [41]. Figure 1 summarizes the effects of LCZ696 in patients with chronic heart failure.

PARADIGM-HF

The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was designed to determine whether LCZ696 would reduce morbidity and mortality in patients with HFrEF compared to ACE-inhibitor-based therapy. Inclusion criteria included patients with NYHA functional class II–IV, EF < 40 %, and NT-pro BNP > 600 pg/ml (or >400 pg/ml if hospitalized for heart failure within the prior 12 months). Patients were required to be on a stable dose of beta-blocker and ACEi/ARB. Importantly, patients were excluded if they had SBP < 100 mm Hg at screening or <95 mm Hg at randomization, GFR < 30 ml/min/1.73 m^2, or potassium >5.4 mEq/l. The trial design included a run-in period, in which patients were switched from the ACEi or ARB they were previously receiving to single-blinded treatment with enalapril

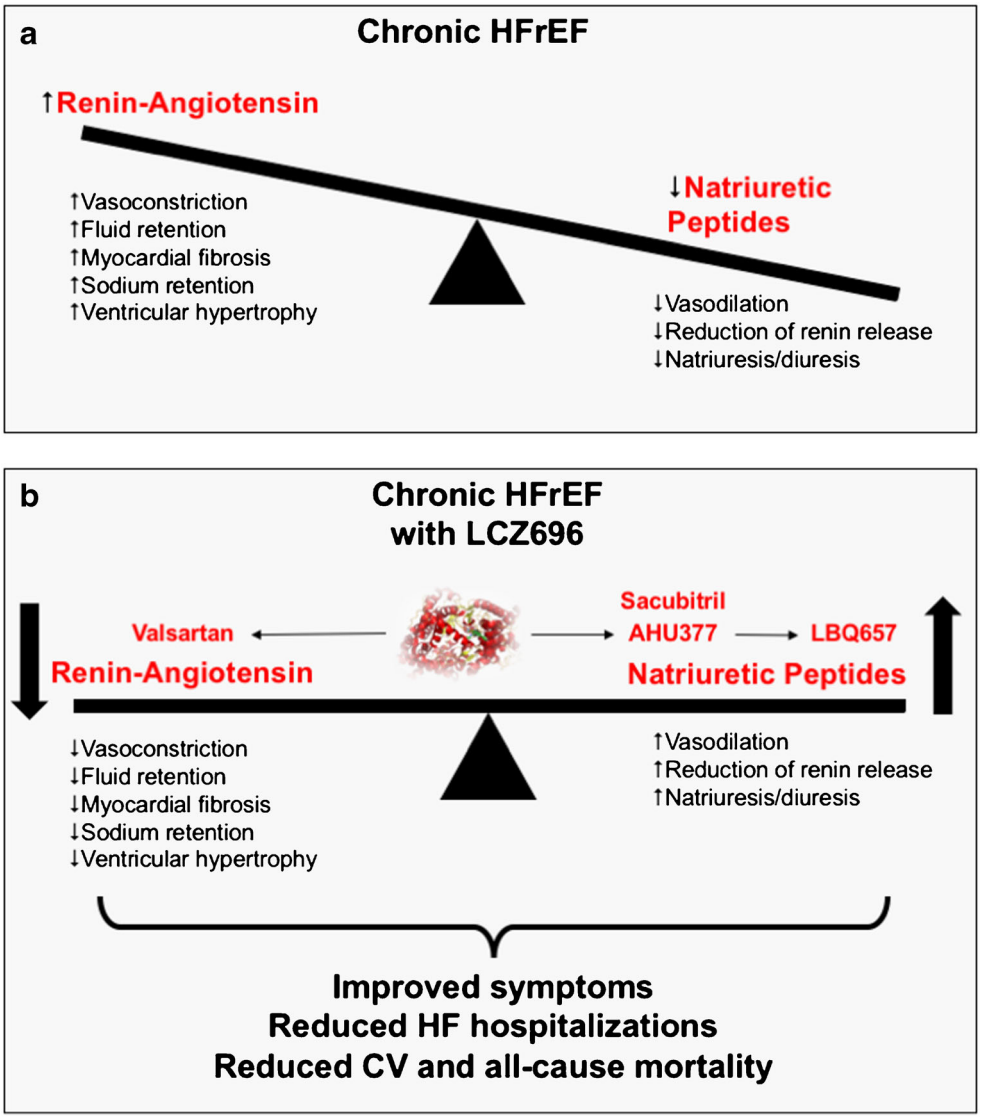

Fig. 1 Effects of LCZ696 on neurohormonal and natriuretic peptide systems. Neurohormonal and natriuretic peptide systems are dysregulated in chronic heart failure (**a**). Through dual inhibition of the angiotensin receptor by valsartan and neprilysin by sacubitril, LCZ696 restores the relative balance of these two opposing systems to promote vasodilation, natriuresis, and a reduction in myocardial fibrosis (**b**). *HFrEF* heart failure with reduced ejection fraction, *HF* heart failure, *CV* cardiovascular

10 mg daily for 2 weeks. If enalapril was well tolerated at this dose, study participants were then switched to single-blinded treatment with LCZ696 for 4–6 weeks (initially at 100 mg BID, then increased to 200 mg BID, corresponding to 51 mg and 103 mg of valsartan, respectively). Patients who tolerated the entire run-in period were eligible for final randomization. The primary endpoint was a composite of cardiovascular death or first hospitalization for heart failure. Secondary endpoints included death from any cause, change in Kansas City Cardiomyopathy Questionnaire clinical summary score, new-onset atrial fibrillation, or worsening renal function. Ultimately, 8442 patients were randomized, with a mean LVEF of 30 %. The study population was predominantly NYHA functional class II (70 %), with less than 1 % class IV.

The trial was stopped early due to an overwhelming benefit with LCZ696. After a median follow-up time of 27 months, the primary outcome occurred in 914 patients (21.8 %) in the LCZ696 group and 1117 patients (26.5 %) in the enalapril group (hazard ratio 0.80; 95 % confidence interval [CI], 0.73 to 0.87; $p = 0.0000002$). A number needed to treat (NNT) of 21 (over a median of 27 months) was observed in the LCZ696 arm compared with the enalapril group. Death from cardiovascular causes was reduced by 20 %. First hospitalization for heart failure was reduced by 21 %. Importantly, LCZ696 reduced all-cause mortality by 16 %. LCZ696 was also associated with decreased heart failure symptoms. Modest rates of angioedema were noted in the LCZ696 treatment arm ($n = 19$ vs 10), but this difference was not significant, and there were no episodes leading to airway compromise. Symptomatic hypotension was more common in the LCZ696 group (14 vs 9.2 %; $p < 0.001$) but was not associated with increased rates of drug discontinuation. Renal failure and hyperkalemia were more common in the enalapril arm [44].

Several post hoc analyses of the PARADIGM-HF trial revealed that LCZ696 was associated with reduction in both sudden cardiac death as well as death due to worsening heart

failure [45•]. Compared to enalapril, LCZ696 was associated with 16 % decreased need to intensify medical treatment for heart failure ($p = 0.003$) and 34 % fewer emergency department visits for worsening heart failure ($p = 0.001$). The patients receiving LCZ696 had 23 % fewer hospitalizations for worsening heart failure ($p < 0.001$), were 18 % less likely to require intensive care ($p = 0.005$), and were 31 % less likely to require intravenous positive inotropic agents ($p < 0.001$). LCZ696 was also associated with a 22 % risk reduction in the need to have implantation of a heart failure device or cardiac transplantation, although this reduction did not achieve statistical significance ($p = 0.07$). Importantly, the reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days following randomization [46••]. LCZ696 led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (NT-pro BNP and troponin) compared to enalapril [46••].

Post hoc analysis on age and cardiovascular outcomes and tolerability revealed that in all pre-specified age categories, the primary outcome was reduced in favor of LCZ696. Furthermore, while rates of hypotension, renal impairment, and hyperkalemia increased with age, the absolute differences between treatment groups remained consistent [47]. Finally, a putative placebo analysis was conducted using the placebo arms from SOLVD-T (ACEi vs placebo) and CHARM-Alternative (ARB vs placebo). This analysis revealed that for the primary composite outcome of cardiovascular death or heart failure hospitalization in PARADIGM-HF, the relative risk reduction with LCZ696 vs placebo from SOLVD-T was 43 % (95 % CI 34–50 %; $p < 0.0001$), and for all-cause mortality, the reduction compared with a putative placebo was 28 % (95 % CI 15–39 %; $p < 0.0001$). Putative placebo analyses based on CHARM-Alternative gave similar relative risk reductions of 39 % (95 % CI 27–48 %; $p < 0.0001$) for the composite outcome of cardiovascular death or heart failure hospitalization and 26 % (95 % CI 11–39 %; $p < 0.0001$) for all-cause mortality [48].

Limitations of PARADIGM-HF

Several limitations should be considered when attempting to generalize the data from PARADIGM-HF. Perhaps the most important was the study run-in period, which ensured that patients tolerated both high-dose LCZ696 and enalapril before entering randomization. Nearly 20 % of patients were removed from the study during either the 2-week (median 15 days) enalapril run-in or the 4-week (median 29 days) LCZ696 run-in period. This period served to identify patients that were particularly susceptible to either hypotension or renal dysfunction and hyperkalemia. This run-in period likely sub-selected a group of more stable heart failure patients who were ultimately included in the randomization. Additionally, the close monitoring of patients during this run-in phase would be difficult to achieve in an outpatient clinical setting.

Thus, PARADIGM-HF contained a predominantly NYHA class II population. Patients tended to be younger than prior trials (median age 64) and were generally well nourished (BMI 28 kg/m^2). Nearly 40 % of patients had never been previously hospitalized for heart failure. Yet, post hoc stratification of the trial participants using two common heart failure risk scores revealed that many PARADIGM-HF subjects were indeed high risk for adverse outcomes, and that the benefit of LCZ696 over enalapril was seen in all risk groups [49]. Patients were excluded if they had a systolic blood pressure of <100 mm Hg at the time of enrollment, which would exclude a significant proportion of outpatients with HFrEF who are on maximal guideline-directed medical therapy. Furthermore, patients with ADHF were not enrolled, and thus, the effect of LCZ696 in this group remains unknown. Generalizability to more severely symptomatic heart failure patients is limited as 70 % of patients in PARADIGM-HF had NYHA class II symptoms, with fewer than 1 % functional class IV. Additionally, rates of device therapy, including implantable cardiac defibrillations (ICDs) and cardiac resynchronization therapy (CRTs) were 15 and 7 %, respectively, much lower than would be expected in an ambulatory heart failure population. Both therapies are associated with reduced mortality in heart failure, with CRT-D also being associated with more acute improvement in symptoms. The low rates of device therapy may have increased the treatment effect of LCZ696.

This trial contained predominantly male participants (78 %) with very low enrollment of individuals of African descent (5.1 %). The low enrollment of patients of African descent is notable for two reasons. First, individuals of African descent represent a unique heart failure population whose response to other evidence-based heart failure therapies has generally differed from other race/ethnic groups. Therapies such as combination hydralazine and isosorbide dinitrate have shown profound benefit in individuals of African descent, which has not been replicated in other populations [50]. In a subgroup analysis of PARADIGM-HF, both the primary endpoint and death from cardiovascular causes were no different between LCZ696 and enalapril in individuals of African descent; however, the study was not powered to detect this difference, and only 500 individuals of African descent were included in the study. Furthermore, the low rate of inclusion of individuals of African descent in the study may have decreased the observed rates of angioedema, an adverse event known to occur more frequently and severely in these individuals. As well, there are no published data describing any potential drug-drug interactions of LCZ696 and the combination of isosorbide dinitrate and hydralazine. If both work through upregulation of cGMP, hypotension may be a concern.

An additional safety issue brought up by the trial was the potential for increased risk of neurocognitive dysfunction due to LCZ696. Neprilysin is the major enzyme responsible for the degradation of amyloid beta (Aβ) peptides, which are involved in the development of Alzheimer's disease. Inhibition of neprilysin in animal models resulted in increase in Aβ and plaque-like deposits in the brain 30–50 times higher than normal [51]. Conversely, gain of function mutations of neprilysin may be associated with decrease risk in Alzheimer's disease [52]. Neprilysin levels are decreased in areas of the brain typically affected by Alzheimer's and areas with increased Aβ deposition [53]. LBQ657 does cross the blood-brain barrier and has been shown to increase amyloid beta peptides in the CSF in monkeys [54]. In human participants, Aβ1-42 or Aβ1-40 were not increased in response to LCZ696 although levels of Aβ1-38 did increase [55]. Although adverse neuro-cognitive effects were not increased in patients receiving LCZ696 in PARADIGM-HF, there was no formal assessment of executive function during the trial. There are some concerns that heart failure patients may be at particular risk of increased CSF concentrations of LCZ696 due to increased blood-brain barrier permeability as a result of age, cerebrovascular disease, hypertension, and diabetes [56]. Due to these concerns, the trial of LCZ696 in HFpEF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF), will specifically include assessment of cognitive function as well as neurological imaging as part of the study protocol.

LCZ696 and HFpEF

LCZ696 represents an intriguing option in HFpEF, where to date, none of the HFrEF guideline directed medical therapies have clearly demonstrated mortality benefit. Most recently, spironolactone was shown to decrease heart failure hospitalization in HFpEF, with a decrease in cardiovascular mortality in patients enrolled in the Americas [57]. These findings underscore the importance of RAAS blockade in this population [58]. PARAMOUNT was a randomized, double-blind, parallel group, active controlled phase 2 trial. Participants were >40 years old with LVEF > 45 % and had documented history of heart failure signs or symptoms and NT-pro BNP > 400 pg/ml, on diuretic therapy, and with SBP <140 mmHg. Patients were excluded if LVEF had previously been <45 %, or if they had isolated right heart failure, primary valvular disease, or coronary artery disease with revascularization within 3 months. Eligible patients were enrolled in a 2-week single-blind run-in period. Subsequently, 308 patients were randomized to LCZ696 50 mg BID or valsartan 40 mg BID and titrated to final doses of LCZ696 200 mg BID or valsaratan 160 mg BID. The primary endpoint was change in NT-proBNP at 12 weeks. The trial included patients with a mean age of 70 years, 55 % female, and 80 % NYHA class II. At 12 weeks, NT-pro BNP was significantly reduced in the LCZ696 group (ratio 0.77, CI 0.64–0.92, $p = 0.005$). While SBP was significantly reduced, there was no change in LV size, function or mass, diastolic function, functional class, or quality of life at 12 weeks. However, at 36 weeks, there was a reduction in left atrial volume and improvement in NYHA functional class [59••].

Several post hoc analyses of the PARAMOUNT trial data provided insight into possible mechanisms driving the trial outcomes. LCZ696 was shown to lower both SBP and DBP significantly at 36 weeks compared with valsaratan. However, the effect of the LCZ696 on NT-proBNP, left atrial volume, functional class, and eGFR was independent of reduction in SBP, implicating the drug-specific dual modulation of RAAS and NPs as the more likely mechanism [60]. Despite the reduction in blood pressure, GFR actually decreased less in the LCZ696 compared to valsartan ($p = 0.002$), and there was a trend toward fewer episodes of worsening renal function ($p = 0.18$) [60]. Finally, high sensitivity troponin T levels, known to be elevated in patients with decompensated heart failure and associated with greater structural abnormalities and worse outcomes in HFrEF were examined in PARAMOUNT participants [61]. Troponin elevation was found in 55 % of participants and was associated with older age, diabetes, higher NT-pro BNP levels, lower GFR, and larger left atrial size, and LV volume and mass. LCZ696 treatment reduced high sensitivity troponin T to a greater extent at 12 weeks (12 % reduction; $p = 0.05$) and at 36 weeks (14 % reduction; $p = 0.03$) compared with valsartan [62].

The promising findings of PARAMOUNT provided rationale for the larger PARAGON-HF. It is critical to note that PARAMOUNT is the first phase 2 trial conducted in HFpEF. All other large-scale clinical trials in HFpEF did not conduct a phase 2 trial prior to conducting the definitive phase 3 trial. The pivotal phase 3 PARAGON trial, which is currently ongoing, will enroll 4300 patients to assess clinical outcomes with LCZ696 compared to valsaratan in patients with HFpEF. Patients will be included if they are 55 years or older, have LVEF > 45 %, heart failure functional class II–IV, symptoms of heart failure requiring diuretics, the presence of left ventricular hypertrophy or left atrial enlargement on echocardiography, and elevated NT-pro BNP. The primary endpoint will be a composite of cardiovascular death and total heart failure hospitalizations. Secondary endpoints will include reduction in composite endpoint of cardiovascular mortality, total nonfatal heart failure hospitalization, stroke, and myocardial infarction, improving NYHA functional

class, delayed time to new onset atrial fibrillation, and time to all-cause mortality [63].

Unanswered Questions and Future Directions

Several unanswered questions remain with clinical use of LCZ696. PARADIGM-HF included only patients with stage C HFrEF with persistent symptoms and functional limitation, already prescribed guideline directed doses of currently approved heart failure therapies. It remains unclear how this novel medication should be incorporated in the stepwise treatment of stage C HFrEF. Given the benefit of this medication over ACEi, consideration may be given to initiating this medication from the outset in treatment naïve symptomatic patients with newly diagnosed HFrEF. For patients already on ACEi or ARB therapy, clarification is needed as to when to consider transitioning to LCZ696, particularly in the less symptomatic patients. Real-world experience with drug washout and monitoring may prove challenging as even in a well-monitored clinical trial; 20 % of patients were unable to tolerate a transition to LCZ696. Furthermore, whether this medication should be considered in stage B HFrEF or in the much larger group of at risk stage A patients will require attention and perhaps dedicated clinical trials. LCZ696 showed significant reduction in blood pressure compared to valsartan alone in hypertensive patients [64]. For patients with stage D HFrEF or acute decompensated heart failure, further work is needed to determine whether LCZ696 can be safely used without causing symptomatic hypotension. Table 1 summarizes the major ongoing clinical trials with LCZ696.

As previously mentioned, individuals of African descent have not been well represented in most heart failure trials, as was the case with PARADIGM-HF. In subgroup analysis, LCZ696 was no better than enalapril, and concerns for angioedema in this population still remain. How to integrate LCZ696 with current guidelines therapies in individuals of African descent, particularly in conjunction with hydralazine and isosorbide dinitrate, will need attention. PARAGON will enroll a higher number of individuals of African descent to help further address the angioedema concerns. Patients with obesity also merit specific consideration as their lower levels of endogenous NPs suggest a particular benefit from neprilysin inhibition. Unfortunately, despite representing a large proportion of the HFpEF population, patients with obesity are excluded from PARAGON. Finally, given concerns over the potential neurocognitive effects of LCZ696—particularly in elderly patients who represent a majority of patients with HFpEF—the Food and Drug Administration has mandated a separate clinical trial to assess neurocognitive effects of LCZ696 in patients with HFpEF [65].

Conclusions

LCZ696 is the first drug in nearly 10 years to gain approval for the treatment of HFrEF and represents a novel approach as a first in class dual inhibitor of neprilysin and the angiotensin receptor. With overwhelming evidence of benefit in symptomatic patients with HFrEF in PARADIGM-HF, LCZ696 is currently approved to improve symptoms and decrease the risk of heart failure hospitalization or death when added to background therapy including beta-blockers and mineralocorticoid antagonists. However, lingering questions over its use remain. One in five potential patients was unable to tolerate LCZ696 or enalapril during a 6-week run-in period, raising concerns of tolerability of this drug in a broad heart failure population. The role of LCZ696 in the management of asymptomatic left ventricular systolic dysfunction (stage B) as well as ADHF is not clear, as these patients were excluded from the trial. Furthermore, the use of LCZ696 in individuals of African descent in whom combination hydralazine/nitrates are the cornerstone of therapy remains to be seen. While the results of PARAMOUNT suggest a promising role for LCZ696 in the treatment of HFpEF, we await the results of PARAGON-HF to demonstrate positive clinical outcomes in this challenging patient population. In conclusion, PARADIGM-HF and the work leading up to the development of LCZ696 suggest that

Table 1 Major ongoing clinical trials of LCZ696 in heart failure

Trial	Hypothesis	Completion
PARAGON-HF	Efficacy and safety of LCZ696 compared to Valsartan in HFpEF	2019
PARADISE-MI	Effect of LCZ696 on cardiovascular death, HF hospitalization, and new onset HF in patients at high risk for HF following a myocardial infarction	2020
TRANSITION	Effect of initiation of LCZ696 in patients following recent hospitalization for HFrEF	2018
PIONEER	Effect of in-hospital initiation of LCZ696 on NT-proBNP (compared to enalapril) in patients with HFrEF following an acute decompensation	2018

HF heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *NT-proBNP* N-terminal pro-brain natriuretic peptide

combined neprilysin-ARB therapy represents a powerful novel mechanism for treatment of heart failure and is likely to fundamentally change guideline-based medical therapy.

Compliance with Ethical Standards

Conflict of Interest Stuart B. Prenner and Clyde W. Yancy declare that they have no conflict of interest.

Sanjiv J. Shah declares personal fees for consultancy work from Novartis, Bayer, Merck, and AstraZeneca.

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

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- • Of importance
- •• Of major importance

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