

8-1-2017

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Recommended Citation

Yandrapalli, S., Aronow, W., Mondal, P., & Chabbott, D. (2017). The Evolution of Natriuretic Peptide Augmentation in Management of Heart Failure and the Role of Sacubitril/valsartan. *Archives of Medical Science : AMS*, 13 (5), 1207-1216. <https://doi.org/10.5114/aoms.2017.68813>

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The evolution of natriuretic peptide augmentation in management of heart failure and the role of sacubitril/valsartan

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Submitted: 30 March 2016

Accepted: 11 May 2016

Arch Med Sci 2017; 13, 5: 1207–1216

DOI: <https://doi.org/10.5114/aoms.2017.68813>

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Abstract

Heart failure (HF) is one of the leading causes of morbidity, mortality, and health care expenditures in the US and worldwide. For three decades, the pillars of treatment of HF with reduced ejection fraction (HFrEF) were medications that targeted the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Prior attempts to augment the natriuretic peptide system (NPS) for the management of HF failed either due to lack of significant clinical benefit or due to the unacceptable side effect profile. This review article will discuss the NPS, the failure of early drugs which targeted the NPS as therapies for HF, and the sequence of events which led to the development of sacubitril plus valsartan (Entresto; LCZ696; Novartis). LCZ696 has been shown to be superior to the standard of care available for treatment of HFrEF in several substantial hard endpoints including heart failure hospitalizations, cardiovascular mortality, and all-cause mortality.

Key words: sacubitril/valsartan, Entresto, LCZ696, heart failure with reduced ejection fraction, natriuretic peptide system.

Introduction

Heart failure (HF) is the inability of the heart to pump an adequate supply of blood to meet the demands of the body. The HF is a clinical syndrome characterized by impaired myocardial function and progressive maladaptive neurohormonal activation of the cardiovascular and renal systems leading to circulatory insufficiency. The HF is one of the leading causes of morbidity, mortality, and health care expenditures in the US and worldwide [1–4]. The HF is classified on the basis of ejection fraction (EF) into HF with reduced EF (HFrEF) with an EF < 50%, and HF with preserved EF (HFpEF) with an EF ≥ 50%. Over the last century there has been significant progress in identifying the neurohormonal systems responsible for the development of heart failure including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) (Figure 1). Beta-adrenergic blockers (β-blockers) targeting the SNS, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone antagonists targeting the RAAS have become the cornerstone of medical therapy for chronic HFrEF

[5]. These drugs have been shown to reduce both morbidity and mortality [5]. However, with improved survival of patients with acute myocardial infarction and a growing elderly population, heart failure will continue to increase in prominence as a major health issue in the United States and the world [1].

The newest and most promising medication for the treatment of chronic HF_{rEF} is sacubitril/valsartan (LCZ696), a drug that targets the natriuretic peptide system (NPS) in addition to the RAAS (Figure 1) [6]. This article will briefly discuss the NPS, explain the reasons behind the failure of the early agents that targeted the NPS, and will then proceed to review the development and current physiological understanding of LCZ696 in the treatment of HF.

Treatment of heart failure

The HF as a disease entity was first described in texts dating back to ancient Egypt, Greece, and India [7]. The first medical therapy for HF was digitalis, an extract from the Foxglove plant [8]. From the early 1900s, diuretics were used in addition to digoxin [9]. These medications treated the symp-

tom of HF and did not target the neuro-hormonal pathways causing the HF syndrome. Since then, ACEIs [10, 11], β -blockers [12–14], aldosterone antagonists [15–17], ARBs [18, 19], and the combination of isosorbide dinitrate and hydralazine [20] have been approved for the treatment of HF_{rEF}.

Natriuretic peptide system (NPS)

Currently, the cornerstones of HF therapy are drugs that modulate the SNS and RAAS. However, since the early 1980s, there has been significant clinical interest in the NPS as a key hormonal pathway critical to the development and possible treatment of HF. Natriuretic peptides (NPs) are endogenous protein molecules that cause urinary sodium excretion, with the exception being C-type NP, which does not exert a marked effect on sodium or water excretion [21]. The NPS consists of the three main NPs secreted from the heart: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [22]. ANP is primarily secreted from the atria, BNP from the ventricles and CNP from endothelial cells and cardiac fibroblasts [22]. ANP and BNP are circulating hormones released from the atrium and ven-

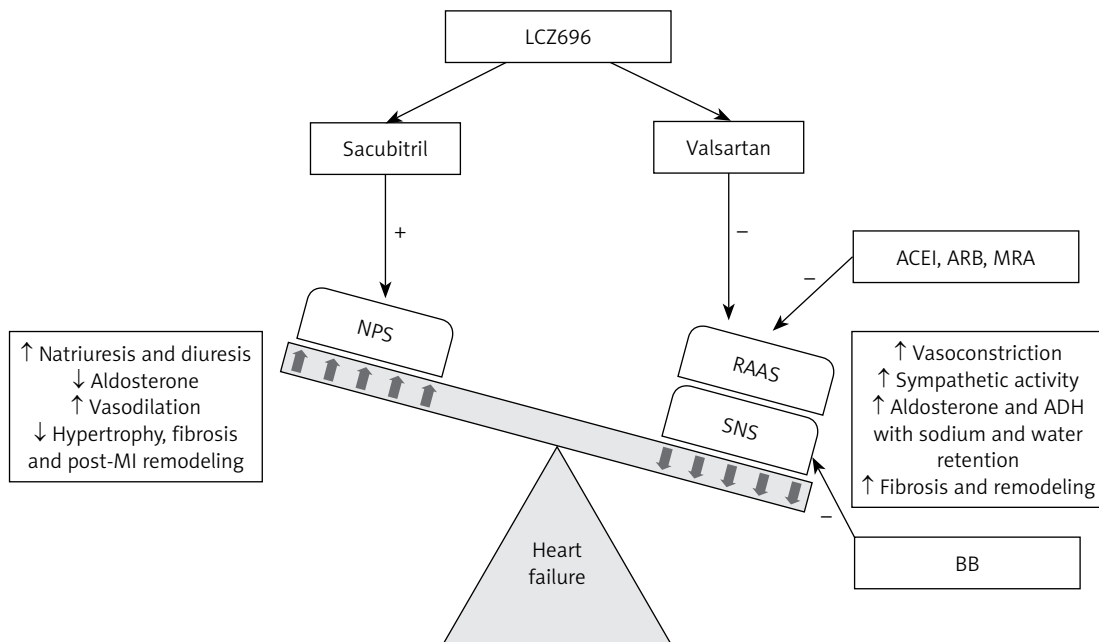


Figure 1. Neuro-hormonal interactions in heart failure and their role in contributing to the progression of heart failure. Heart failure activates the SNS and the RAAS, which leads to increased sympathetic tone and vasoconstriction, thereby increasing the afterload on the failing heart. RAAS activation leads to an increase in secretion of aldosterone and ADH causing fluid retention, edema, and fibrotic changes in the failing myocardium. Together, the SNS and the RAAS result in pathophysiological and clinical worsening of HF. ACEI, ARB, MRA, and BB reduce the effects of the RAAS and the SNS. The failing heart also activates the NPS, which promotes sodium and water excretion, vasodilatation, and decreased aldosterone secretion, and inhibits fibrotic changes in the failing myocardium. The effects of the NPS are antagonistic to those of the SNS and the RAAS. LCZ696 acts by augmenting the NPS and inhibiting the RAAS, thereby improving the symptoms and inhibiting the progression of HF

NPS – natriuretic peptide system, RAAS – renin-angiotensin-aldosterone system, SNS – sympathetic nervous system, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, MRA – mineralocorticoid receptor antagonist, BB – β -adrenergic blocker, ADH – antidiuretic hormone, “+” indicates augmentation, “-” indicates inhibition, “↑” indicates increase, “↓” indicates decrease.

tricles in response to stretch and fluid overload, and these hormones counteract the volume overloaded state by promoting natriuresis, diuresis, vasodilation, and RAAS blockade via aldosterone and renin inhibition [22]. ANP and BNP decrease preload via diuresis and decrease afterload via vasodilation and RAAS blockade. CNP acts locally and exhibits vasodilatory and anti-remodeling effects on the myocardium [23]. These hormonal actions prevent the classic pathologic structural changes associated with HF including cardiovascular remodeling, ventricular hypertrophy, and fibrosis [24].

In contrast to the detrimental effects of activation of the SNS and the RAAS, activation of the NPS appears to have a beneficial role in the prevention of progression of HF. Understanding of the beneficial effects of NPS prompted the creation of human synthetic ANP (carperitide) and human recombinant BNP (nesiritide). Intravenous infusion of carperitide is used as a treatment for acute decompensated heart failure in Japan without good evidence to support this practice [25]. Although infusions of nesiritide have shown promising results in a few studies [26, 27], nesiritide failed to show significant clinical benefit in larger trials [28–30]. The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial compared nesiritide and placebo in the treatment of acute decompensated heart failure. The results of this trial showed no significant benefit in early dyspnea relief, 30-day mortality or readmission rates in the nesiritide group, but showed an increase in hypotension [28]. On the basis of the available data the NPs were widely accepted as biomarkers of HF but not therapeutic options [5].

Nephrilysin inhibition

When intravenous infusion of NPs did not demonstrate significant clinical significance in treating HF, the focus shifted to developing inhibitors of enzymes that degrade endogenous NPs. Clearance of circulating NPs is via receptor-mediated clearance and enzymatic degradation by extracellular proteases [31]. Nephrilysin (NEP) is a large membrane-bound neutral endopeptidase responsible for cleaving NPs [31]. NEP, also known as enkephalinase, atriopeptidase, EC 3.4.24.11, and CD10 [31], is present in many tissues [24, 32], and is most abundant in the renal cortex [33]. NEP contributes to the extremely short half-life of ANP of approximately 2 min [33]. ANP and CNP are more readily degraded, whereas BNP is relatively resistant to the action of NEP [34]. From a physiologic standpoint, inhibiting NEP represented an approach to augment endogenous NP levels and activity.

Thiorphan, an NEP inhibitor (NEPI), was synthesized in 1980 [35], and subsequent studies in animals [36] and humans [37] demonstrated that NEP inhibition increased ANP levels with associated natriuresis, diuresis and blood pressure reduction. Additionally, NEP inhibition suppressed the activation of aldosterone [38], demonstrating the important interaction between NPS and the RAAS [33]. In a study of 9 patients with severe chronic HF (EF < 30%), intravenous candoxatrilat (an NEPI) increased circulating ANP, improved natriuresis and diuresis, and reduced right atrial pressure and pulmonary capillary wedge pressure, without affecting the arterial blood pressure [39]. The positive results from this trial prompted investigations using oral NEPIs. However, studies of oral ecdodril [40, 41] and oral candoxatril [42] failed to show significant benefit in patients with chronic HF and essential hypertension, respectively. A few studies showed inconsistent effects of NEPIs on blood pressure [42, 43].

In addition to degrading NPs, NEP also degrades a large number of other vasoactive peptides including vasodilators such as adrenomedullin and bradykinin and vasoconstrictors such as angiotensin I, II, and endothelin-1 [44, 45]. The beneficial effects of augmenting endogenous NPs were offset by the NEPI-mediated enhancement of vasoconstrictor substances, importantly angiotensin II, and, thereby, enhancing the RAAS. Based on these observations, it was evident that lone NEP inhibition showed little effect on blood pressure and only modest benefits [45] in the treatment of HF (Figure 2).

The rise and fall of omapatrilat

The rational solution to this dilemma was to further inhibit angiotensin II in addition to NEP in an effort to prevent the detrimental effects of NEP inhibition on the RAAS. Preliminary animal studies with combined selective NEPI and captopril (an ACEI) showed greater blood pressure reduction [46], improved systemic hemodynamics [47], and improved left atrial filling pressures [48].

After the synthesis of an orally active combined ACEI-NEPI in 1994 [49], multiple studies examined the effects of an orally active vasopeptidase inhibitor – omapatrilat. This class of drugs was referred to as vasopeptidase inhibitors as they have dual inhibitory effects on 2 key enzymes involved in the metabolism of vasoactive peptides [50]. Omapatrilat improved natriuresis, diuresis, left ventricular EF, and functional class in chronic HF patients [51]. The IMPRESS (Inhibition of Metallo Protease by BMS-186716 in a Randomized Exercise and Symptoms Study in Subjects With Heart Failure) trial, a phase II randomized clinical trial that compared omapatrilat with lisinopril in 573 HFrEF pa-

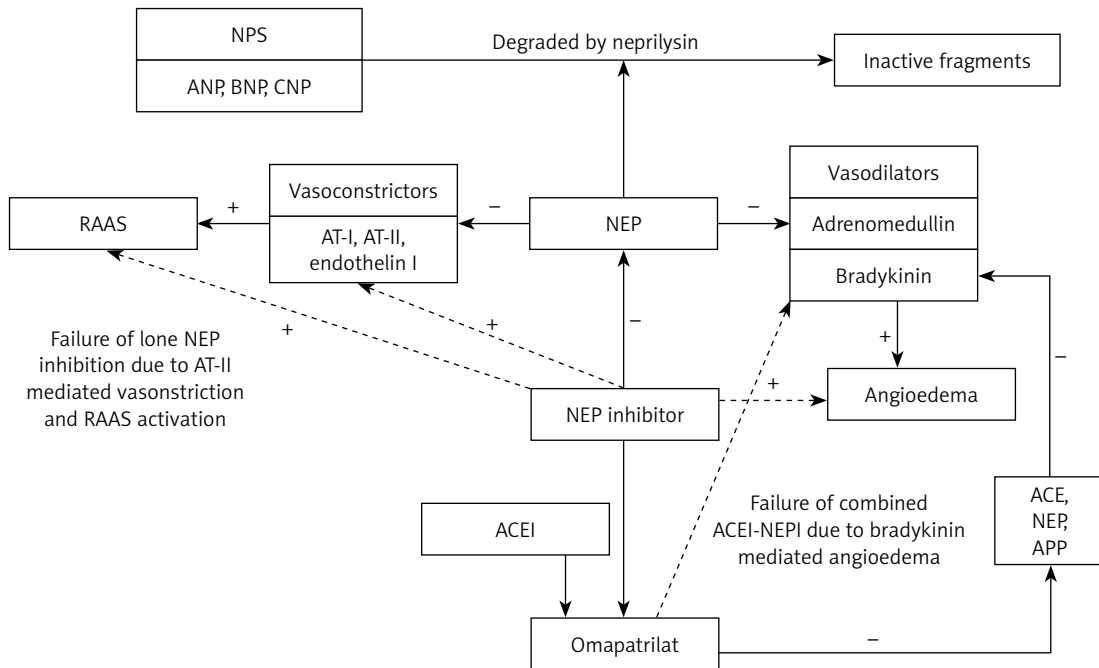


Figure 2. Physiological mechanisms behind the failure of lone neprilysin inhibition, and combined angiotensin converting enzyme – neprilysin inhibitors, as potential therapies in the management of heart failure. The beneficial effects of augmenting endogenous natriuretic peptides with NEPI were offset by the NEP-mediated enhancement of vasoconstrictor substances, especially AT-II, which enhanced the RAAS pathway. Bradykinin is inactivated by various enzymes including ACE, NEP, and APP, all of which are inhibited by omapatrilat. The synergism of ACE inhibition with NEP inhibition led to a large increase in the levels of bradykinin, thereby causing angioedema

NPS – natriuretic peptide system, ANP – A-type natriuretic peptide, BNP – B-type natriuretic peptide, CNP – C-type natriuretic peptide, RAAS – renin-angiotensin-aldosterone system, AT-I – angiotensin I, AT-II – angiotensin II, NEP – neprilysin, ACE – angiotensin converting enzyme, APP – aminopeptidase P, ACEI – angiotensin converting enzyme inhibitor, NEPI – neprilysin inhibitor, “+” indicates increase/augmentation, “-” indicates inhibition, continuous line indicates direct action, dotted line indicates indirect action.

tients, showed that omapatrilat had a non-significant benefit in the composite of first occurrence of death or admission for worsening HF [52, 53].

The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial was a phase III randomized double-blind trial that compared omapatrilat with enalapril in 5770 patients with New York Heart Association (NYHA) class II–IV HF for a mean duration of 14.5 months [54]. Results from the OVERTURE trial showed that omapatrilat was neither superior nor inferior to enalapril in reducing the primary endpoint of combined all-cause mortality and HF hospitalizations requiring intravenous treatment [54]. Post hoc analysis using a broader definition for HF hospitalizations (as used in the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial) showed a 11% reduction (nominal $p = 0.012$) in the primary endpoint [54]. Secondary analysis favored omapatrilat in reducing cardiovascular-related death or cardiovascular-related hospitalizations [54]. Although the adverse effect profiles were similar, angioedema was more frequent in patients taking omapatrilat (0.8%) compared to the enalapril group (0.5%). Encouraging results from the OVERTURE trial prompted larger clinical trials.

The Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial was a randomized, controlled, double-blind trial that compared omapatrilat and enalapril for 24 weeks in 25,302 hypertensive patients [55]. Although omapatrilat significantly lowered blood pressure, angioedema was more frequent with omapatrilat (2.17%) than with enalapril (0.68%), particularly in African-Americans (5.53% vs 1.62%) [55].

ACEI can potentially cause angioedema by inhibiting the metabolism of bradykinin [56, 57]. Subsequently, it was identified that omapatrilat also inhibits aminopeptidase P (APP), which is involved in bradykinin metabolism [58]. Bradykinin is inactivated by various enzymes including ACE, NEP, and APP, all of which are inhibited by omapatrilat [59]. The synergism of ACE inhibition with NEP inhibition led to a large increase in the levels of bradykinin [59], causing angioedema, a concern that stalled the approval and further development of a combined ACEI-NEPI as a therapy for HF (Figure 2).

LCZ696 and the early clinical trials

The discovery of the role of NPS in the progression of HF and the idea of combined RAAS and

NEP inhibition remained exciting and promising, but the trials discussed demonstrated that omapatrilat was associated with angioedema [55]. The logical solution to this problem was a combination of an ARB and NEPI which would inhibit the RAAS and enhance the NPS without inhibiting ACE or APP. By using this combination, the endogenous bradykinin would be metabolized by the uninhibited ACE, thereby not greatly increasing the risk of angioedema. Results from an animal study published later supported this hypothesis [60].

LCZ696 is a novel, orally active, first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) which combines valsartan (an ARB) and sacubitril in a 1 : 1 ratio [61]. Sacubitril (AHU377) is a pro-drug, which upon ingestion is rapidly metabolized to an active NEPI moiety, LBQ657 [61]. Phase I and II studies of LCZ696 showed that after oral administration of LCZ696, peak plasma concentrations were reached rapidly for valsartan (1.6–4.9 h), sacubitril (0.5–1.1 h), and its active moiety LBQ657 (1.8–3.5 h), followed by an acute blood pressure reduction [61]. LCZ696 treatment was associated with increases in plasma ANP and cGMP, diuresis, blood pressure reduction, increased renin concentration and activity, and increased angiotensin II levels, providing evidence for NEP inhibition and angiotensin receptor blockade [61, 62]. LCZ696 was considered safe and well tolerated, and data from these studies supported its further clinical development for hypertension and HF.

A phase III trial compared LCZ696 with valsartan in 1328 subjects with mild to moderate hypertension [63]. The primary endpoint of this study was the mean difference across the 3 single-dose pairwise comparisons of LCZ696 versus valsartan (100 mg vs. 80 mg, 200 mg vs. 160 mg, and 400 mg vs. 320 mg) in mean sitting diastolic blood pressure during the 8-week treatment period. Part of the study population received either AHU377 or placebo once daily. Data from this study showed that reduction in systolic, diastolic, and pulse pressures, both sitting and ambulatory, was greater with LCZ696 than with either valsartan or AHU377 [63]. A similarly designed trial comparing LCZ696 with placebo in 389 Asian subjects with mild to moderate hypertension achieved similar results [64]. Although LCZ696 was well tolerated in both trials without reports of angioedema, only a small percentage of study patients were black [63, 64], in whom the incidence of angioedema was greater according to the OCTAVE trial [65]. Also the generalizability of these data to patients with HF is limited because such patients were excluded from these trials.

The PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fracTion) trial was a phase II randomized double-blind trial of 301 patients

with NYHA class II–IV HFpEF that compared N-terminal pro BNP (NT-proBNP) levels after 12 weeks of treatment with either LCZ696 or valsartan [65]. NT-proBNP is a precursor molecule for BNP and is not a substrate for NEPI [66]. Baseline NT-proBNP was greater than 400 pg/ml in the study population. At 12 weeks, NT-proBNP was significantly reduced in the LCZ696 group (hazard ratio (HR) = 0.77, $p = 0.005$). After 36 weeks of treatment, the LCZ696 group demonstrated a decrease in left atrial volume and size and greater improvement in NYHA functional class. The adverse event rate was similar in both groups. Post hoc analysis suggested that the NT-proBNP lowering effect of LCZ696 was independent of systolic blood pressure reduction [67]. Encouraging results from these early trials prompted further larger trials.

The paradigm-heart failure trial

The medical and pharmaceutical community looked forward to further studies investigating the clinical benefit of LCZ696 in HF patients. The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) was a phase III double-blind trial that randomized 8442 patients with NYHA class II–IV HF and an EF of $\leq 40\%$ (later amended to $\leq 35\%$) to receive twice daily dosing of either 200 mg of LCZ696 or 10 mg of enalapril in addition to standard medical therapy for HF [6]. Enalapril was chosen as it was the most widely studied RAAS blocker in patients with chronic HFpEF, and the target dose of enalapril in PARADIGM-HF was similar to the dose used in the SOLVD treatment trial. The majority of the study population was receiving β -blockers and mineralocorticoid receptor antagonists. The primary endpoint was a composite of death from cardiovascular causes or hospitalization for HF.

The PARADIGM-HF trial was initiated without a phase-II safety trial and hence the investigators employed steps to test the tolerability of LCZ696 before randomization. Patients taking any dose of ACEI or ARB were considered for participation in the study, but prior to screening, patients were required to be on a stable dose of an ACEI or an ARB that was the therapeutic equivalent of 10 mg of enalapril daily for at least 4 weeks. Patients that met screening criteria then entered an initial run-in period where they were switched from their prior ARB or ACEI to 10 mg of enalapril twice daily for 2 weeks. If this regimen was tolerated, a second run-in period was implemented where participants were started on a single blind treatment of LCZ696 for an additional 4–6 weeks. Initially the dose of LCZ696 was 100 mg twice daily, which was increased to 200 mg twice daily. If participants tolerated both the study medications (LCZ696 and

enalapril), they were then randomly assigned to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. This methodology allowed the investigators to obtain data regarding the safety and tolerability of target doses of the study drugs.

The study was stopped early after a median follow-up of 27 months due to the significant clinical benefit observed with LCZ696, which at that time met the pre-specified cutoff for an immense benefit. At 27-month follow-up, LCZ696 was associated with a 20% (HR = 0.80, $p < 0.001$) decrease in the primary endpoint compared to enalapril (absolute risk reduction (ARR) 4.7%). The number needed to treat over 27 months to prevent 1 occurrence of a primary endpoint was 21. When compared to enalapril, LCZ696 reduced death from any cardiovascular cause by 20% (ARR 3.2%, HR = 0.8, $p < 0.001$) and HF hospitalizations by 21% (HR = 0.79, $p < 0.001$), and improved the symptoms and quality of life as measured on the Kansas City Cardiomyopathy Questionnaire. There was a 16% (HR = 0.84, $p < 0.001$) reduction in all-cause mortality in the LCZ696 arm. In terms of side effects, 14% of patients receiving LCZ696 experienced hypotension compared to 9% in the enalapril group ($p < 0.001$). However, the number of patients who discontinued therapy due to hypotension was not significantly different (0.9% in the LCZ696 group vs. 0.7% in the enalapril group). Non-serious angioedema occurred more frequently in the LCZ696 group although the difference was not significant (19 cases vs. 10 cases in the enalapril group). Significantly fewer patients developed cough (11.3% in the LCZ696 group vs. 14.3% in the enalapril group, $p < 0.001$), elevated serum potassium > 6.0 mmol/l (4.3% in the LCZ696 group vs. 5.6% in the enalapril group, $p = 0.007$), or elevated serum creatinine ≥ 2.5 mg/dl (3.3% in the LCZ696 group vs. 4.5% in the enalapril group, $p = 0.007$) in the LCZ696 group.

Additional analysis of the paradigm-heart failure trial

The PARADIGM-HF investigators also compared the effects of LCZ696 with putative placebos using the treatment arms of the SOLVD treatment trial and the Candesartan in Heart Failure-Assessment in Reduction in Mortality and Morbidity-Alternative (CHARM-Alternative) trial as references for comparison with enalapril (an ACEI) and candesartan (an ARB), respectively [68]. For the primary composite outcome of cardiovascular death or HF hospitalization in the PARADIGM-HF trial, the relative risk reduction with LCZ696 versus a putative placebo from the SOLVD treatment trial was 43% ($p < 0.0001$) with similarly large effects on cardiovascular death (34%; $p < 0.0001$),

heart failure hospitalization (49%; $p < 0.0001$), and all-cause mortality (28%; $p < 0.0001$). Putative placebo analyses based on the CHARM-Alternative trial showed relative risk reductions of 39% ($p < 0.0001$) for the composite outcome of cardiovascular death or heart failure hospitalization, 32% ($p < 0.0001$) for cardiovascular death, 46% ($p < 0.0001$) for heart failure hospitalization, and 26% ($p < 0.0001$) for all-cause mortality [68].

Secondary analyses of data from the PARADIGM-HF trial were also encouraging. When compared to enalapril, LCZ696 exhibited additional clinical benefits in parameters that quantify HF disease progression, including reduced worsening of NYHA functional class (≥ 1 class) at 1 year ($p = 0.023$), reduced need for intensification of medical treatment of HF (HR = 0.84, $p = 0.003$) and reduced requirement of intensive care (18% rate reduction; $p = 0.005$) or intravenous inotropic support (31% risk reduction, $p < 0.001$) [69]. LCZ696 was associated with significant reductions in emergency department visits (HR = 0.66; $p = 0.001$) and 23% fewer hospitalizations for worsening HF ($p < 0.001$) [69]. Significant reductions in the levels of NT-proBNP and troponins were observed, which indicates reduced heart stress. Non-significant reductions in the need for implantation of a HF device and cardiac transplantation were also observed [69]. LCZ696 was superior to enalapril in reducing both sudden cardiac death (HR = 0.80, $p = 0.008$) and death from worsening heart failure (HR = 0.79, $p = 0.034$), independent of whether the patient had an implantable cardioverter-defibrillator [70]. The superiority of LCZ696 over enalapril was apparent irrespective of glycemic status [71], left ventricular EF [72], HF risk scores [73], systolic blood pressure [74], and age [75].

LCZ696 investigated at the tissue level

Investigators examined the mechanistic actions of LCZ696 at the tissue level. Von Lueder *et al.* randomized post-myocardial infarction adult male Sprague-Dawley rats to treatment for 4 weeks with LCZ696 or a vehicle [76]. At the conclusion of the study, the LCZ696 group demonstrated higher left ventricular EF and function, lower left ventricular end diastolic diameter, and lower heart mass. Additionally, the LCZ696 group had markedly reduced fibrosis in the peri-infarct area and remote myocardium, which can be interpreted as reduced cardiac remodeling. This study demonstrated the ARNI-mediated inhibition of hypertrophy and fibrosis leading to attenuation of cardiac remodeling and myocardial dysfunction. Suematsu *et al.* investigated the effects of LCZ696 therapy in diabetic mice with HFrEF in comparison with valsartan or control [77]. In this study, LCZ696 improved cardiac function with the reduc-

tion of fibrosis. The investigators attributed this to the suppression of local transforming growth factor- β by the sacubitril moiety of LCZ696. These studies further support the pathophysiological basis for the beneficial effects of LCZ696 observed in the PARADIGM-HF trial.

Criticism of the PARADIGM-HF trial

The PARADIGM-HF trial is not without criticism, especially in regards to the study population. The study population in the PARADIGM-HF trial was predominantly white (66%), male (78%), NYHA functional class II HF (70%), and had a mean age of 64 years. Only 60 patients (< 1%) had NYHA functional class IV HF at baseline, and only 5% of the study population was black. These factors might reduce the generalizability of the data from the trial as HF patients are usually older individuals with varying NYHA functional class. In the United States population, non-Hispanic black patients have a higher rate of HF-related mortality as compared to others [4]. In the OCTAVE trial, black patients had an increased frequency of angioedema with omapatrilat [55]. The lower proportion of black patients in the PARADIGM-HF trial may have limited the ability of this trial to detect a significant difference in the frequency of angioedema with LCZ696.

It is also important to consider the high dropout rate of 20% during the run-in phases in the study [6]. This dropout rate may reduce the generalizability of the study to the target patient population. Physicians should thereby be cautious in selecting patients for treatment with LCZ696, as a significant number of HF patients may not be able to tolerate the drug, and a run-in period is not feasible in regular clinical practice.

Lastly, NEP plays a critical role in maintaining the homeostasis of amyloid- β peptide (A β) in the brain [78]. NEPI might lead to accumulation of A β in the brain, favoring the development of Alzheimer's dementia [79]. Although the incidence of cognition-related adverse effects was not increased by LCZ696 in the PARADIGM-HF trial [6], the duration of the trial was not long enough to assess this problem. Such data should be available from the PARAGON-HF (Prospective comparison of angiotensin receptor-neprilysin inhibitor with ARB Global Outcomes in HF with preserved ejection fraction) trial (NCT01920711), which includes serial cognitive function testing in its design. Also phase IV safety data of LCZ696 might shed more light on this association.

Current role of LCZ696 in heart failure and the future of LCZ696

The United States Food and Drug Administration approved LCZ696 for the treatment of HF.

Although the drug is not yet approved for clinical use in Canada, the Canadian HF guidelines recommend the use of LCZ696 in place of an ACEI or an ARB in patients with mild to moderate HF, an ejection fraction < 40%, an elevated natriuretic peptide level or hospitalization for HF in the past 12 months, serum potassium < 5.2 mmol/l, and an estimated glomerular filtration rate \geq 30 ml/min and treated with appropriate doses of guideline-directed medical therapy, with close surveillance of serum potassium and creatinine (Conditional Recommendation; High-Quality Evidence) [80].

Further studies are testing LCZ696 on more selective patient populations. The PARAMETER (Prospective Comparison of an Angiotensin-Receptor Neprilysin Inhibitor With an Angiotensin-Receptor Blocker Measuring Arterial Stiffness in the Elderly) study was designed to assess the short-term (12 weeks) and long-term (52 weeks) effects of LCZ696 compared with olmesartan (an ARB), on measures of central aortic hemodynamics and arterial stiffness in older patients with systolic hypertension and an increased pulse pressure [81]. The study met the primary endpoint of significant reduction in central aortic systolic pressure with 12 weeks monotherapy in the LCZ696 group compared to the olmesartan group, although this significance did not persist at 52 weeks [81]. The phase III PARAGON-HF trial is currently recruiting participants to evaluate the efficacy and safety of LCZ696 compared to valsartan on morbidity and mortality in NYHA class II–IV HF patients with a left ventricular EF > 45% (ClinicalTrials.gov NCT01920711). This trial is based on the results from the PARAMOUNT trial. The UK Heart and Renal Protection III (UK HARP-III) trial (ISRCTN 11958993) will compare LCZ696 against irbesartan (an ARB) in patients with proteinuric chronic kidney disease to assess the short-term safety and efficacy of LCZ696 in this population [82]. If the results from the UK HARP-III trial favor LCZ696, longer duration studies to evaluate the effects of LCZ696 in delaying the progression of CKD to end-stage renal disease can be planned. Such beneficial effects can improve outcomes of HF patients with concomitant CKD.

Conclusions

The treatment of HF has been revolutionized with medications physicians are familiar with and trust such as the β -blockers, the ACEIs, the ARBs and aldosterone antagonists. Despite pharmacological advances, HF continues to increase in incidence and remains a leading cause of morbidity and mortality and economic burden. In this scenario, there is definitely a need for newer therapies that can reduce the burden of HF on the community. Although the initial attempts of NP

enhancement for HF management have failed, the combination RAAS inhibitor and NPS enhancer sacubitril/valsartan performed significantly better than the current standard of care ACEI in the PARADIGM-HF trial. Although one trial might not be sufficient to change the guidelines, the results from the PARADIGM-HF trial provide affirmation that targeting the NPS in addition to the SNS and the RAAS provides substantial benefit to patients with HFREF. Further large trials testing LCZ696 on specific patient populations will provide more data regarding the beneficial effects of combining NPS augmentation with RAAS inhibition in patients with cardiovascular disease.

Conflict of interest

The authors declare no conflict of interest.

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