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Dual Angiotensin Receptor and Neprilysin Inhibition in Chronic Systolic Heart Failure: Understanding the New PARADIGM

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Abstract

Objective: To evaluate the clinical role of LCZ696, a novel angiotensin–neprilysin inhibitor, for the treatment of chronic heart failure with a reduced ejection fraction (HFrEF). **Data Sources:** A search of PubMed was conducted using a combination of the search terms *LCZ696, neprilysin inhibition, natriuretic peptide system, renin-angiotensin system*, and *heart failure with reduced ejection fraction*. Bibliographies of all retrieved articles were reviewed for relevant literature. All references included were published between 1980 and May 2015. **Study Selection/Data Extraction:** All studies and review articles that contained data describing the use of LCZ696 in HFrEF were reviewed. **Data Synthesis:** HFrEF remains a disease of high morbidity and mortality. Natriuretic peptide (NP) augmentation has emerged as a most promising, novel neurohormonal target in HFrEF. NPs provide vasodilatory, natriuretic, diuretic, and antiproliferative actions to help support the failing heart. Neprilysin, a neutral endopeptidase, is a primary pathway for NP metabolism. LCZ696 consists of the neprilysin inhibitor sacubitril (AHU377) and the angiotensin receptor blocker valsartan. Combined inhibition of the renin angiotensin aldosterone system and neprilysin augments the beneficial NP neurohormonal pathway while providing direct antagonism to increases in angiotensin II. In the PARADIGM HF trial, LCZ696 significantly improved morbidity and mortality over enalapril, a standard of care in HFrEF. Application of these results to clinical practice requires careful considerations of trial design, study patient population, and clinical monitoring. **Conclusions:** LCZ696 significantly improved morbidity and mortality in patients with chronic HFrEF but will require careful application to "real-world" populations of HFrEF.

Keywords

heart failure, systolic heart failure, left-ventricular systolic dysfunction, angiotensin receptor blocker, neprilysin, natriuretic peptide

Heart Failure and Its Impact

Heart failure is a clinical syndrome of dyspnea and fatigue secondary to impaired cardiac function.[1] Symptoms arise from a diminished cardiac output that is unable to meet the body's metabolic needs. Symptoms may or may not be associated with increased intravascular volume. Heart failure with reduced ejection fraction (HFrEF) is a subset of heart failure which occurs in the setting of impaired systolic function with a left-ventricular ejection fraction (LVEF) less than 40%.[1] As cardiac output falls, compensatory responses such as sodium and water retention, vasoconstriction, and ventricular remodeling temporarily stabilize patients but ultimately contributes to significant morbidity and mortality over time.[2]

The impact of heart failure on health care and society is substantial. It is estimated that more than 5 million American adults suffer from heart failure, with a projected increase to more than 8 million adults by 2030.[3] The symptoms of heart failure significantly reduce functional capacity and quality of life, leading to reoccurring hospital admissions for symptom management. Heart failure is a progressive disease that ultimately results in death from myocardial failure or malignant arrhythmia. Although survival after diagnosis has improved over time, mortality remains as high as 50% within 5 years.[3,4] Unfortunately, prognosis is equivocal or worse than many malignancies.[5]

The primary goals of treatment for HFrEF are to improve symptoms and quality of life, slow the progression of cardiac dysfunction, and reduce mortality.[6] The arsenal of available therapeutics has expanded significantly over the

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past 30 years, incrementally improving morbidity and mortality. Despite the advances, there continues to be a need for innovative therapeutic agents. In the PARADIGM-HF trial, a novel therapeutic approach consisting of dual angiotensin receptor and neprilysin inhibition resulted in significant improvement in clinical outcomes for HFrEF.[7] This review will discuss how the addition of a neprilysin inhibitor to traditional neurohormonal antagonism pharmacotherapy resulted in a potentially new treatment paradigm for HFrEF.

Data Sources and Selection

A search of PubMed was conducted using a combination of the search terms *LCZ696, neprilysin inhibition, natriuretic peptide (NP) system, renin-angiotensin system*, and *heart failure with reduced ejection fraction*. Bibliographies of all retrieved articles were reviewed for relevant published literature. Randomized clinical trials, observational studies, meta-analyses, and review articles were reviewed. All articles were in the English language. All references included were published between 1980 and May 2015.

Early Models of HFrEF

The understanding of heart failure pathophysiology has evolved over the years and with it came significant improvements in pharmacotherapy. Heart failure was first described with a cardiorenal model in which impaired renal perfusion triggered sodium and water retention, resulting in the congestive signs and symptoms often associated with heart failure.[2] At that time, diuresis was the primary treatment to control symptoms without known improvement in mortality.

Later invasive hemodynamic assessment of heart failure through right heart catheterization revealed that the syndrome was associated with increased cardiac filling pressures, decreased cardiac output, and excessive peripheral vasoconstriction.[2] This hemodynamic model of heart failure focused on increasing the capacity of the venous system to reduce preload and relieve cardiopulmonary congestion as well as decreasing afterload to reduce impedance and improve cardiac output.[2] New treatment modalities focused on medications with vasodilatory properties. The first major clinical trial in HFrEF, V-HEFT, investigated whether the α_1-antagonist prazosin or the combination venodilatory/arterial dilatory actions of hydralazine and isosorbide dinitrate improve mortality compared with placebo.[8] Whereas prazosin failed to affect mortality at any point in the trial, hydralazine/isosorbide demonstrated a 34% relative reduction in all-cause mortality at 2 years, which was nearly statistically significant ($P = 0.053$).[8] Combination vasodilatory treatment improved exercise capacity as well as LVEF.[8] Though improvement in patient symptoms is important, mortality reduction became the benchmark for future studies in heart failure.

The Neurohormonal Model

The success of hemodynamic modulating agents for HFrEF generated interest in angiotensin converting enzyme (ACE) inhibitors, given their balanced venous dilation and arterial dilation within a single medication taken once or twice daily. Early studies suggested that the ACE inhibitors enalapril and captopril effectively improved symptoms and functional capacity in HFrEF.[9]

In 1987, the landmark clinical trial CONSENSUS found that enalapril reduced the risk of all-cause mortality by 40% at 6 months compared with placebo in severe HFrEF ($P = 0.002$).[10] Consequently, enalapril was compared directly to hydralazine and isosorbide dinitrate in the V-HEFT II clinical trial to determine whether the mechanism of vasodilation mattered.[11] Vasodilation through ACE inhibition with enalapril demonstrated a greater mortality reduction compared with a direct vasodilator, primarily through a reduction in sudden cardiac death.[11] The results suggested that while vasodilation improves hemodynamics and symptoms, the therapeutic mechanism by which vasodilation occurs may alter the course of disease progression, leading to improved mortality.[12] This helped prompt a new treatment paradigm in HFrEF, now recognized as the neurohormonal model.

The neurohormonal model of heart failure suggests that after an initial myocardial insult, endogenous neurohormonal systems are activated in an effort to maintain hemodynamic stability.[12] The insult may be acute, as with myocardial infarction, or chronic, such as long-standing hypertension. Unfortunately, the neurohormonal systems only provide temporary hemodynamic stability. Long-term activation of the pathways ultimately leads to progressive myocardial dysfunction and death. One such neurohormonal system implicated in the progression of heart failure was the renin-angiotensin-aldosterone system (RAAS).

Renin-Angiotensin-Aldosterone System

RAAS is responsible for preserving cardiovascular stability through the modulation of vasoconstriction as well as sodium and water retention.[13] Renin, a proteolytic enzyme, is excreted from juxtaglomerular cells of the kidney in response to reduced renal perfusion pressure, reduced sodium to the distal tubule, or increases in renal sympathetic tone.[13] Upon its release, renin catalyzes the conversion of angiotensinogen to angiotensin I, the rate limiting step in the RAAS cascade. Angiotensin I is subsequently converted to biologically active angiotensin II by ACE. Angiotensin II exerts its end-organ effects through the angiotensin receptor (ATR) subtypes. ATR1 is the predominant receptor responsible for the physiological response to angiotensin II in various tissues.[13] Activation of ATR1 results in potent systemic vascular

Table 1. Major Trials of ACE Inhibitor or ARB Monotherapy in Left-Ventricular Systolic Dysfunction.[11-12,16-21]

Drug Class	Trial	Disease	Study Medication	Comparator	Number of Patients	Mortality (RRR)	Hospitalizations
ACE inhibitor	CONCENSUS (1987)	HF	Enalapril	Placebo	253	↓40%	NR
	SOLVD (1991)	HF	Enalapril	Placebo	2569	↓16%	↓26%
	V-HEFT II (1991)	HF	Enalapril	Hydralazine + Isosorbide	804	↓28%	ND
ARB	ELITE I (1997)	HF	Losartan	Captopril	722	↓46%	ND
	ELITE II (2000)	HF	Losartan	Captopril	3152	ND	NR
	VALHEFT Subgroup (2001)	HF	Valsartan	Placebo	366	↓67%	↓47%
	VALIANT (2003)	AMI	Valsartan	Captopril	14 703	ND	ND
	CHARM ALTERNATIVE (2003)	HF	Candesartan	Placebo	2028	↓20%	↓39%

Abbreviations: ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; HF, heart failure; ND, no difference; NR, not reported; RRR, relative risk reduction.

constriction, cell proliferation and remodeling within the ventricles and vasculature, and sodium retention through stimulation of aldosterone secretion and direct actions within the renal tubule.[13] Activation of ATR2 produces vasodilatory and antiproliferative actions, but the receptor is minimally expressed in adults.[13]

RAAS Pathophysiology in HFrEF

In patients with heart failure, RAAS activation has been directly related to severity of left-ventricular functional dysfunction.[14] In HFrEF, a reduction in cardiac output compromises renal perfusion, resulting in chronic compensatory activation of RAAS.[13] RAAS activation provides short-term hemodynamic support but is detrimental to long-term clinical outcomes. Hemodynamically, ATR1 stimulation in vasculature results in increased systemic vascular resistance, or cardiac afterload, in an attempt to maintain end-organ perfusion. Increasing impedance on the compromised heart facilitates progression of systolic dysfunction. Within the kidney, decreased renal perfusion leads to ATR1 stimulation in the renal tubules and adrenal cortex, creating a sodium avid state in an effort to increase intravascular volume and renal perfusion pressure. Under normal cardiac conditions, increased intravascular volume improves cardiac output through the Frank Starling relationship.[15] In HFrEF, elevated intravascular volume increases intracardiac pressures to such a degree that the weakened heart cannot tolerate, leading to worsening heart failure symptoms and further deterioration of cardiac function. Most important, extended periods of ATR1 activation within the cardiac tissue leads to adverse ventricular remodeling from excessive collagen production, hypertrophy, and fibrosis within the myocytes.[13] Indirectly, RAAS and angiotensin II have detrimental neurohormonal effects through activation of other neurohormonal systems such as norepinephrine, endothelin, and aldosterone.[13] Pharmacotherapeutic interference of the production and actions of angiotensin II became a logical and effective target for improving outcomes in HFrEF.

Angiotensin II as a Neurohormonal Target

Contemporary HFrEF management includes therapies that target the detrimental effects of excessive RAAS activation. Clinical trials involving the use of ACE inhibitors and angiotensin II receptor antagonists have demonstrated significant improvement in morbidity and mortality in HFrEF compared with placebo (Table 1). ACE inhibitors interfere with the conversion of angiotensin I to biologically active angiotensin II, leading to reduced ATR1 activation. Hemodynamically, ACE inhibition provides a balanced reduction in preload and afterload, leading to reduced cardiac filling pressures and improved cardiac output. More important, reduced ATR1 activation in the cardiac tissue slows maladaptive remodeling and disease progression.[13] The improvements in mortality achieved with ACE inhibitors have established the drug class as the standard against which other HFrEF therapies were measured and added to.

Although ACE inhibitors clearly demonstrate improved outcomes, angiotensin II can be produced through pathways that are not influenced by traditional ACE inhibitors, including systemic non-ACE pathways and tissue-level ACE pathways.[13] Angiotensin II receptor blockers (ARBs) displace angiotensin II from AT1 receptors in the vasculature and cardiac and renal tissues. Although they produce hemodynamic benefits similar to that of ACE inhibitors, ARBs theoretically result in greater interference of RAAS activation because ARBs antagonize both systemic and tissue-generated angiotensin II regardless of the pathway by which it was produced.[13] The theoretical benefits of ARBs did not translate into improved outcomes when compared directly with ACE inhibitors (Table 1). In addition, the combination of ACE inhibitors and ARBs have not consistently demonstrated mortality reduction in HFrEF.[22,23]

Despite their shortfalls when compared with and added to ACE inhibitors, ARBs are proven to be viable alternatives for patients who are ACE inhibitor intolerant for reasons other than hyperkalemia or acute kidney injury (Table 1). ACE inhibitor or ARB use is universally supported by guidelines worldwide as part of the backbone of HFrEF treatment.[1,6,24]

Additional Neurohormonal Targets

The success of ACE inhibition led to the pursuit of additional neurohormonal targets in HFrEF. After targeting RAAS, it was hypothesized that sympathetic nervous system (SNS) activation contributes significantly to heart failure progression, thus the SNS became the next neurohormonal pathway targeted in HFrEF. Although they were initially considered contraindicated in HFrEF, β-adrenergic antagonists were found to significantly improve morbidity and mortality in HFrEF when added to ACE inhibitors.[25-27] Aldosterone soon became a third neurohormonal target in HFrEF. In theory, inhibition of ACE should suppress the production and release of aldosterone. Contrary to this theory, evidence suggests that ACE inhibitors only transiently suppress the production of aldosterone, and therefore, direct aldosterone receptor antagonism may provide additional benefit.[28] The hypothetical benefit was confirmed in the RALES and EMPHASIS HF trials, which demonstrated significant improvements in morbidity and mortality with the addition of a mineralocorticoid receptor antagonist to ACE inhibitors and ACE inhibitors plus β-adrenergic antagonists, respectively.[29,30] Despite sophisticated multimodal pharmacotherapy with ACE inhibitors or ARBs, β-adrenergic receptor antagonists, and mineralocorticoid receptor antagonists, HFrEF morbidity and mortality remains unacceptably high.[30] The discovery of novel therapeutic targets remains essential in order to continue to improve outcomes.

Natriuretic Peptide System

Analogous to RAAS and SNS, the NP system is a neurohormonal pathway responsible for maintaining appropriate hemodynamics and plasma volume. The NP system consists of 3 major peptides: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP). NPs are genetically related with mature forms sharing an identical 17-amino acid ring.[31] Despite their structural similarities, NPs are differentiated by the tissues from which they originate, the stimulus for their release, and their physiological effects.

ANP is secreted mainly from atrial cardiac myocytes, whereas BNP is secreted from ventricular cardiac myocytes.[32] Very little CNP exists within cardiac myocytes, but high concentrations are found within the kidney, central nervous system, vasculature, and other tissues.[32] The primary trigger for the release of ANP and BNP is atrial and ventricular wall stress secondary to increased intracardiac pressures.[32] CNP is released in response to cytokines and endothelium-dependent agonists.[31] NP release can also be stimulated by angiotensin II and endothelin-1.[31]

NPs differ in their selectivity for NP-specific receptors, which delineates their respective physiological actions. ANP and BNP bind natriuretic peptide receptor (NPR) A, which is highly expressed in endothelial cells of the vasculature and the kidney.[32] In the vasculature, ANP and BNP have potent arterial and venous dilating actions that significantly reduce systemic blood pressure as well as cardiac filling pressures.[32] In the kidney, ANP and BNP have natriuretic and diuretic actions that reduce intravascular volume.[31] The physiological actions of CNP differ slightly from that of ANP and BNP because of its preference for NPR B. NPR B is primarily expressed in the vascular smooth muscle.[31] CNP actions are primarily hemodynamic and it is a far more potent venodilator than its NP counterparts.

Natriuretic Peptide System in HFrEF

NP serum levels, particularly BNP, correlate with the severity of LV dysfunction, symptoms, and prognosis of heart failure.[33] The primary physiological benefits of NPs in HFrEF include vasodilation, diuresis, natriuresis, and antiproliferative effects. The vasodilatory benefits of NPs include decreasing preload through increasing venous capacitance as well as increasing vascular permeability to displace intravascular fluid into the extravascular space.[34] Potent arterial vasodilation by ANP and BNP reduces systemic vascular resistance and improves cardiac output. The renal actions of ANP and BNP include increased diuresis and natriuresis, which offers further reduction in preload. In addition to their hemodynamic and volume benefits, NPs have favorable effects on cardiovascular remodeling by antagonizing growth factor–dependent DNA synthesis and cell proliferation of cardiac fibroblasts.[31]

Contrary to RAAS, the NP system is a neurohormonal pathway that provides beneficial hemodynamic and antiproliferative effects on the failing heart. The beneficial actions of NPs directly counteract the detrimental actions of RAAS and its primary product, angiotensin II. In addition NPs have been shown to directly suppress angiotensin II production through RAAS inhibition as well.[35] Traditionally, harmful neurohormonal pathways in HFrEF were targets for pharmacotherapeutic antagonism. Augmentation of a beneficial pathway, such as the NP system, represents a novel approach and a new paradigm in neurohormonal modulation for HFrEF. The NP system can be augmented through supplementation of exogenous NPs or by interfering with the metabolism of endogenous NPs. Although NP supplementation has inherent challenges

Table 2. Opposing Physiological Effects of Sole Neprilysin Inhibition.

Neprilysin Substrate	Plasma Levels	Vasodilation	Natriuresis/Diuresis	Cardiovascular Remodeling
ANP	↑	↑	↑	↓
BNP	↑	↑	↑	↓
CNP	↑	↑	↔	↓
Angiotensin-II	↑	↓	↓	↑
Endothelin-I	↑	↓	↔	↑

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide.

with bioavailability and cost, inhibition of metabolism remains a plausible therapeutic target for HFrEF.

Neprilysin as a Neurohormonal Target for HFrEF

Despite an elevation in NP production and release, heart failure is actually a state of NP deficiency. BNP assays commonly used in clinical practice detect biologically active BNP as well as the products of its metabolism. Studies comparing common assays with mass spectrometry found very low levels of biologically active BNP, with elevated levels of its degraded byproducts.[36] Excessive degradation of NPs likely contribute to the diminished physiological responses to their release in HFrEF. NPs are metabolized and eliminated through 2 primary mechanisms. The first mechanism is NPR C, a third NP receptor, which internalizes and degrades ANP, BNP, and CNP.[32] A second mechanism, neprilysin, has become a promising target to augment NP levels for therapeutic benefit in HFrEF.

Neprilysin, also known as neutral endopeptidase, is membrane bound metallopeptidase responsible for the catabolism of vasoactive peptides.[31] The enzyme predominates in the kidney but can be found in numerous tissues, including but not limited to the lung, vascular smooth muscle, and cardiac myocytes.[31] Although often associated with the NP system, neprilysin metabolizes numerous other substrates with vasoactive and renal actions. Neprilysin hydrolyzes the systemic vasoconstrictors endothelin-1 and angiotensin-II to inactive products.[37] As discussed previously, angiotensin-II is also a potent stimulus for sodium and water reabsorption. Apart from vasodilatory NPs, neprilysin is responsible for hydrolyzing other endogenous vasodilators, including bradykinin and adrenomedullin.[37] Finally, neprilysin is responsible for the conversion of angiotensin I to angiotensin (1-7).[37] Angiotensin (1-7) offsets many of the effects of angiotensin II through non-ATR pathways by providing direct vasodilatory, natriuretic, and antiproliferative actions.[13] Therefore, inhibition of neprilysin alone promotes opposing physiological actions (Table 2).

Early Pitfalls With Neprilysin Inhibition in HFrEF

Candoxatril

The opposing physiological effects of lone neprilysin inhibition were evident clinically in early studies of candoxatril, the first neprilysin inhibitor investigated in humans. Candoxatril was studied as monotherapy in patients with hypertension and heart failure. Overall, sole inhibition of neprilysin resulted in increased ANP, BNP, and cGMP levels, but at the expense of increased angiotensin-II and endothelin-I.[38] Although the net effect improved diuresis and natriuresis, it did not reduce SVR or systemic blood pressure. Some studies demonstrated increased SVR, leading to reduced cardiac output.[38] The favorable increase in circulating NPs achieved with neprilysin inhibition were hemodynamically offset by circulating vasoconstrictors, particularly angiotensin II. Apart from the hemodynamic shortfalls, chronic exposure to elevated angiotensin II could theoretically enhance the cardiovascular toxicity of RAAS, although this was never confirmed with long-term clinical trials. It was hypothesized that NP augmentation through neprilysin inhibition may require concomitant suppression of angiotensin II to yield improved outcomes in HFrEF.

Omapatrilat

After the failures of candoxatril, neprilysin inhibition was teamed with RAAS inhibition in an effort to suppress angiotensin II production and aldosterone release. Until recently, omapatrilat was the agent closest to demonstrating benefit in HFrEF. Omapatrilat is a vasopeptidase inhibitor with potent inhibitory action against neprilysin as well as ACE. Early dose titration studies in patients with reduced ejection fraction demonstrated increases in ANP and BNP, suggesting effective neprilysin inhibition.[39] Plasma ACE activity was diminished, with increases in renin activity supporting concomitant inhibition of ACE. In contrast to candoxatril, neurohormonal modulation with omapatrilat demonstrated dose-dependent improvements in LVEF, pulmonary capillary wedge pressure, and SVR, warranting

further investigation of clinical outcomes. The OVERTURE trial was the definitive, phase III study comparing omapatrilat and enalapril in HFrEF.[40] Omapatrilat was found to be noninferior but not superior in reducing the combined risk of death or hospitalization for heart failure. It has been hypothesized that omapatrilat's once-daily dosing led to excessive hypotension and inconsistent neprilysin inhibition.

Apart from its noninferiority, additional concerns emerged when in the hypertension trial, OCTAVE, omapatrilat demonstrated greater than a 3-fold increase in the incidence of angioedema compared with enalapril alone.[41] The relative risk was even higher in African Americans and smokers. Neprilysin, like ACE, is involved in the metabolism of bradykinin, a major mediator of angioedema through vasodilation and vascular permeability.[42] Additionally, omapatrilat inhibits aminopeptidase P, a third enzyme responsible for bradykinin and substance P degradation.[42] Because of excessive risk without profound benefit, omapatrilat was not approved by the FDA, sending dual RAAS and neprilysin inhibition back to the drawing board.

LCZ696 as the Answer

LCZ696 is the first-in-class dual angiotensin receptor blocker and neprilysin inhibitor to be studied in humans. The rationale for combination angiotensin receptor and neprilysin blockade is to achieve the dual neurohormonal modulation of RAAS and neprilysin without the increased risk of angioedema. Angiotensin receptor antagonists have demonstrated a lower risk of angioedema compared with ACE inhibitors.[43] The use of ARBs avoids concomitant inhibition of bradykinin degradation when added to neprilysin inhibitors.

LCZ696 contains the angiotensin receptor antagonist valsartan combined with the neprilysin inhibitor sacubitril (AHU377) in a 1:1 ratio.[44] Following oral administration of LCZ696 in healthy volunteers, valsartan and sacubitril are absorbed rapidly, with maximum plasma concentrations reached within 2 hours for both components.[44] Sacubitril is a prodrug that is rapidly metabolized to LBQ657, the biologically active inhibitor of neprilysin, via non-CYP pathways.[44] Peak LBQ657 concentrations are reached 2.5 to 3 hours after LCZ696 administration.[44] Mean half-lives for valsartan and LBQ657 are 13 hours and 10 hours, respectively.[44] On bioequivalence assessment, LCZ696 400 mg resulted in a valsartan systemic exposure equivalent to 320 mg of the parent drug.[44] This dose is found to deliver approximately 90% of its maximal NEP inhibition.[45] The 200-mg, twice-daily dosing selected for clinical trials ensured target dosing of valsartan, consistent neprilysin inhibition over a 24-hour period, and minimization of hypotension experienced with its predecessors.[45]

In preclinical trials, patients with stable HFrEF given LCZ696 achieved biomarker evidence of effective angiotensin receptor and neprilysin blockade. LCZ696, 200 mg, twice daily, increased plasma renin concentrations and activity, suggesting adequate AT1 blockade.[44] Patients developed increased plasma cGMP and urinary ANP concentrations consistent with neprilysin inhibition.[44] Although LCZ696's appropriate biomarker responses and theoretical cardiorenal improvements were intriguing, reduced mortality is the standard set by previous neurohormonal modulators. Without demonstrating a clear improvement in mortality, LCZ696's place in the HFrEF treatment would be limited. The PARADIGM HF trial set out to determine if dual angiotensin receptor and neprilysin inhibition improved clinical outcomes in HFrEF over standard of care.

PARADIGM HF: The Landmark Clinical Trial

PARADIGM-HF was a randomized, double-blind, active-controlled trial comparing the long-term efficacy and safety of LCZ696 compared with the ACE inhibitor enalapril in patients with chronic HFrEF.[7] The study was conducted in 1043 centers in 47 countries. The primary end point included a composite of death from cardiovascular causes or first hospitalization for heart failure. Key secondary outcomes included all-cause mortality, change in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to a new onset of atrial fibrillation, and time to the first decline in renal function.

Study Protocol

The study protocol consisted of a screening period, an active treatment run-in period, and ultimately the randomized trial.[7] The screening period assessed patient eligibility according to the study inclusion/exclusion criteria. Screening was followed by a run-in period to determine if eligible patients could tolerate target doses of both treatment options. All patients received enalapril titrated to 10 mg twice daily over 2 to 4 weeks, followed by a period of LCZ696 treatment titrated to a dose of 200 mg twice daily over 4 to 6 weeks. Patients tolerating a period of both enalapril 10 mg twice daily and LCZ696 200 mg twice daily were randomized in a 1:1 ratio to either treatment arm for the clinical trial.

Patient Population

A total of 10 521 patients met inclusion/exclusion criteria for the trial.[7] After the active run-in phases, 2079 patients were ineligible for randomization. Of the remaining patients, 4187 patients were randomized to LCZ696 and 4212 patients to enalapril. Baseline characteristics were similar between the groups, and the median duration of follow-up was 27 months. Prior to the scheduled completion of the study, the

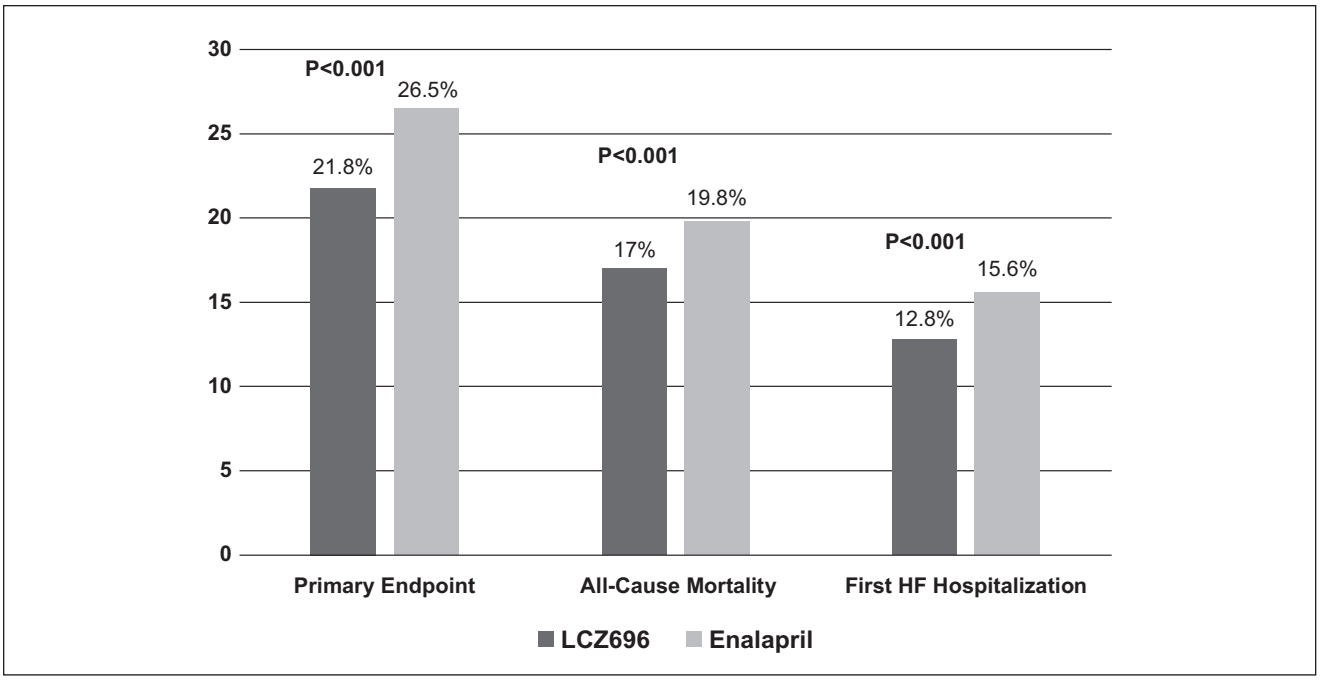

Figure 1. PARADIGM heart failure (HF) clinical outcomes[7]: Prevalence of the primary end point (death from cardiovascular causes or first hospitalization for heart failure), death from any cause, and first hospitalization for heart failure with LCZ696 and enalapril in the PARADIGM HF trial.

prespecified boundary for overwhelming benefit was met for the primary end point and death from cardiovascular causes; therefore, the study was ended early.

Efficacy Outcomes

The primary end point of death from cardiovascular causes or hospitalization for heart failure was reduced by 20% with LCZ696 compared with enalapril ($P < 0.001$; Figure 1).[7] The difference was seen early in the treatment period and maintained throughout. Individually, death from cardiovascular causes was reduced by 20% ($P < 0.001$), and hospitalization for heart failure was reduced by 21% ($P < 0.001$). All-cause mortality was significantly reduced by 16% with LCZ696 ($P < 0.001$). The effect of LCZ696 was fairly consistent across prespecified subgroups. KCCQ clinical summary scores improved to a greater degree with LCZ696 ($P = 0.001$), indicating more improvement in symptoms and fewer physical limitations associated with heart failure. The incidence of new-onset atrial fibrillation and protocol-defined decline in renal function were similar between the 2 treatment groups ($P = 0.83$ and $P = 0.28$, respectively).

A subsequent exploratory analysis of patients who survived the duration of the PARADIGM study found that fewer patients treated with LCZ696 demonstrated signs of clinical deterioration.[39] LCZ696 improved multiple prespecified measures of nonfatal clinical deterioration, including less need for outpatient treatment intensification, less emergency department visits for worsening heart failure, hospitalized patients were less likely to require intensive care or intravenous inotropic support, and fewer patients progressed to heart failure mechanical device implantation or cardiac transplantation.[46]

Safety Outcomes

The study drug was discontinued in 17.8% of patients receiving LCZ696 compared with 19.8% of those receiving enalapril ($P = 0.02$).[7] Fewer patients receiving LCZ696 stopped their study medication because of an adverse event when compared with those taking enalapril (10.7% vs 12.3%, $P = 0.03$). Symptomatic hypotension with or without a systolic blood pressure less than 90 mm Hg occurred more frequently with LCZ696: 14% versus 9.2% ($P < 0.001$) and 2.7% versus 1.4% ($P < 0.001$), respectively.[7] Elevated serum creatinine ≥2.5 mg/dL (4.5% vs 3.3%, $P = 0.007$), elevated serum potassium >6 mmol/L (5.6% vs 4.3%, $P = 0.007$), and cough (14.3% vs 11.3%, $P < 0.001$) occurred more frequently with enalapril. Most notably, there was no statistically significant difference in angioedema (19 patients in the LCZ696 group vs 10 patients in the enalapril group, $P = 0.13$). No patient with angioedema in either group experienced airway compromise.

New PARADIGM or Pipe Dream?

As new evidence emerges, it is important to assess the quality and reproducibility of the outcomes in real life clinical practice. PARADIGM HF was an appropriately sized, randomized, prospective clinical trial that is consistent with the gold standard for clinical research. The trial was adequately powered for both cardiovascular mortality and the composite primary end point. Statistical analysis included data from all patients who had undergone randomization according to the intention-to-treat principle. Overall, the PARADIGM patient population represents a common, well-managed population with relatively mild heart failure. At baseline, patients were managed with HFrEF standard of care, with >90% treated with β-blockers and >50% on mineralocorticoid receptor antagonists.[7] The mean EF was approximately 30%, and >70% of patients had NYHA class II functional capacity or better.[7] Blood pressure, heart rate, and renal function were well preserved. The randomized patient population was consistent with patients commonly encountered in clinical practice, though self-described blacks and women were underrepresented, as is often seen in clinical trials.

Clinical Significance

LCZ696 significantly improved both cardiovascular and all-cause morbidity and mortality in a compelling fashion against a worthy comparator in a very stable HFrEF population on good background medical therapy. Furthermore, surviving patients experienced an improved clinical status, requiring less-intensive HFrEF management and resource use.[46] All-cause mortality reduction is a benchmark set by ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists over the past several decades. In present-day HFrEF management, novel therapies unable to achieve mortality reduction have limited roles for use in treatment. In PARADIGM HF, the number needed to treat (NNT) with LCZ696 to prevent 1 primary end point was 21 and to prevent 1 cardiovascular death was 32, both over 2 years.[7] The NNT attained in PARADIGM HF is similar to that achieved with the addition of mineralocorticoid receptor antagonism in HFrEF with mild symptoms (Figure 2). Given the severity of the outcomes and the prevalence of HFrEF, the NNT attained in PARADIGM HF represents clinical significance. At this time, it has not been reported whether LCZ69 prevents sudden cardiac death, death from heart failure progression, or both. Traditional RAAS therapies have primarily prevented death from heart failure progression but not sudden cardiac death.[19,30]

The mortality reduction achieved with LCZ696 over enalapril was similar to the extent of benefit seen with enalapril over placebo in SOLVD.[19] It is worth noting that in SOLVD, very few patients received HFrEF standard of care as we know it today. History has shown that incremental improvements in mortality become more difficult as the risk is reduced with good medical therapy (Figure 2), yet

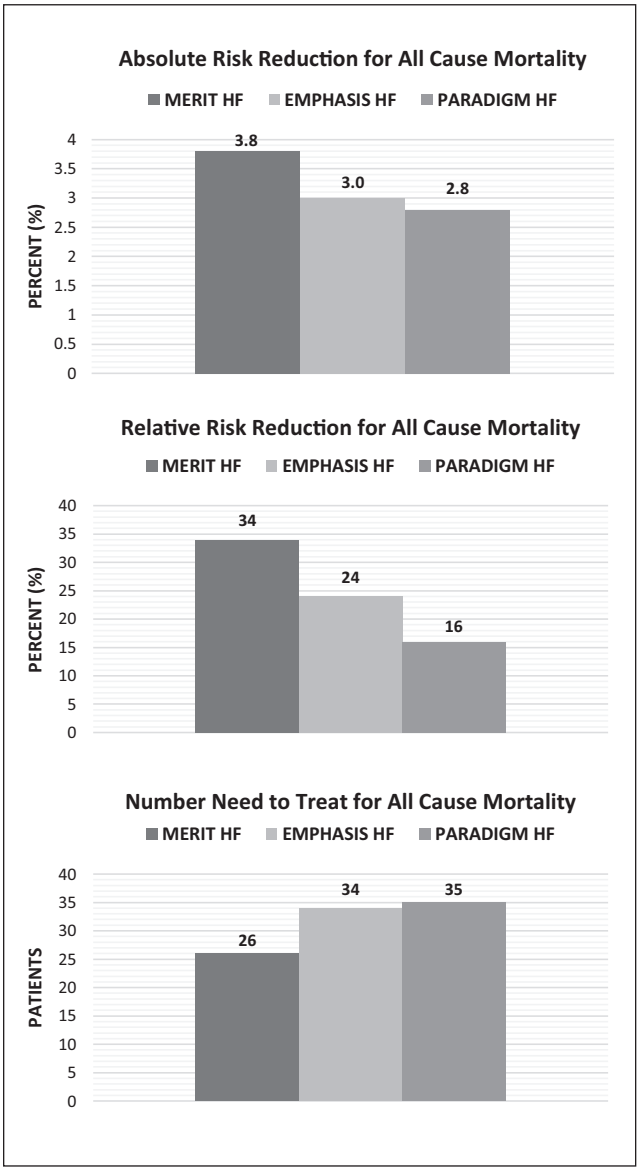

Figure 2. Mortality reduction with each additional medication added to HFrEF standard of care[7,26,30]: comparison of absolute risk reduction, relative risk reduction, and number needed to treat for all-cause mortality for each medication added to the heart failure with reduced ejection fraction standard of care. MERIT HF represents the addition of β-adrenergic receptor antagonists to ACE inhibitors. EMPHASIS HF represents the addition of mineralocorticoid receptor antagonists to ACE inhibitors and β-adrenergic receptor antagonists. PARADIGM HF represents the addition of dual angiotensin receptor and neprilysin inhibition to β-adrenergic receptor antagonists and mineralocorticoid receptor antagonists. The addition of each medication class adds further risk reduction for all-cause mortality, but the incremental benefit decreases with each medication.

LCZ696 improved mortality on top of strong background pharmacotherapy in PARADIGM HF.

Enalapril as a Comparator

PARADIGM HF compared the benefits of LCZ696 to the ACE inhibitor enalapril, the first medication to achieve mortality benefit in HFrEF with a neurohormonal target integral to the management of HFrEF. The use of enalapril as a comparator to LCZ696 in PARADIGM HF, instead of valsartan, can raise the question of how much neprilysin inhibition contributed to the achieved mortality reduction as opposed to greater RAAS blockade with the valsartan component of LCZ696 over ACE inhibition. As discussed previously, the hopes that RAAS inhibition with angiotensin receptor blockade improves outcomes over ACE inhibition never came to fruition. Available clinical trials comparing ACE inhibitors to ARBs in HFrEF are limited (Table 1), but all in all, ARBs have demonstrated either noninferiority or near inferiority, but never superiority, to ACE inhibitors for improving clinical outcomes in HFrEF. In PARADIGM HF, the average patient was treated with either nearly 95% of the well-established target enalapril dose or 93% of the well-accepted target valsartan dose, suggesting adequate and clinically equivalent RAAS blockade for both treatment arms.[7] The evidence supporting the benefits of ACE inhibition established it as a standard against which novel HFrEF treatments should be measured.

Enalapril Dosing

Among patients taking the study medication, the mean daily doses in the enalapril and LCZ696 groups were 18.9 and 375 mg, respectively.[7] The recognized target dose of enalapril is 20 mg daily based on doses targeted and achieved in previous placebo controlled trials.[10,19] The enalapril dose achieved in SOLVD was 16.6 mg and in the CONSENSUS trial was 18.4 mg.[10,19] Therefore, LCZ696 was compared against a dose of enalapril that had previously been shown to reduce mortality in HFrEF and was the highest median enalapril dose achieved in a clinical trial of HFrEF.

Blood Pressure Reduction and Outcomes

Greater blood pressure reduction with LCZ696 compared with enalapril may be considered a confounding factor contributing to the mortality benefit of LCZ696. Blood pressure reduction in HFrEF is complicated to interpret because it may correlate with afterload reduction but is also associated with disease progression and worsening myocardial failure.[6] The use of antihypertensives, particularly those that provide arterial vasodilation, have been shown to improve cardiac function secondary to afterload reduction.[8] In contrast, numerous potent antihypertensives with arterial dilating properties, including dihydropyridine calcium channel blockers and α-antagonists, have lowered blood pressure without improving morbidity and mortality.[8,47-49] The neurohormonal model of HFrEF has shown that hemodynamic targets have less influence on mortality than neurohormone-specific targets. PARADIGM HF compared LCZ696, a modulator of 2 important neurohormonal systems in HFrEF, with enalapril, a modulator of one such system with LCZ696 demonstrating superiority. An analysis of PARADIGM HF found that blood pressure reduction was not a determinant of its incremental benefit over enalapril.[7]

Tolerability

Overall, LCZ696 was well tolerated during its clinical trial, with a higher frequency of symptomatic hypotension but a lower frequency of elevated serum creatinine, hyperkalemia, and cough. Most notably, the difference in angioedema risk was not statistically different between the 2 treatment arms.[7] Numerically, the incidence of angioedema with LCZ696 was nearly double that of enalapril (19 with LCZ696 vs 10 with enalapril), and the trial was significantly underpowered to detect a statistical difference, given its low event rate.[7] The lack of power and underrepresentation of those at risk for angioedema (blacks, history of idiopathic angioedema, etc) warrants thorough patient education and close postmarketing follow-up.

PARADIGM had an extensive run-in period that spanned up to 10 weeks to ensure that patients could tolerate target doses of both LCZ696 and enalapril.[7] Roughly 20% of the cohort was excluded prior to randomization despite meeting inclusion/exclusion criteria, presumably because of intolerable side effects associated with either agent. This left a randomized study population destined for acceptable tolerability. Although a run-in period is not uncommon in clinical trials, it leaves interpretation of the tolerability profile difficult to apply to a general population.

Practical Considerations and Clinical Approach

PARADIGM HF represents an advancement in the chronic management of HFrEF. Neprilysin inhibition is the first novel mechanism of action to reduce all-cause mortality in HFrEF since mineralocorticoid receptor antagonists were introduced with the RALES trial in 1999.[29] Similarly, PARADIGM HF is the first contemporary trial since V HeFT II in 1991 to propose substituting a novel medication to replace HFrEF standard of care, as opposed to the add-on strategy traditionally used in chronic heart failure.[11] It is important to understand that targeting angiotensin II, through ACE inhibition or angiotensin receptor blockade, was not omitted with the use of LCZ696, given its valsartan component. Angiotensin II remains an integral target for HFrEF pharmacotherapy.

Widespread clinical success with LCZ696 will depend on the proper application of PARADIGM HF to real-world HFrEF populations. The selection of patients most likely to benefit from, and not be harmed by, LCZ696 can be guided by the inclusion and exclusion criteria of the trial as well as considering the baseline characteristics of the patients enrolled.

Baseline Treatment Considerations

In PARADIGM HF, patients were required to have demonstrated tolerability to ACE inhibitors and ARBs without any history of any serious side effects. A history of RAAS inhibitor–related, idiopathic, or other angioedema etiology can be considered a firm contraindication even if the patient is actively tolerating an ARB. To be considered for enrollment in PARADIGM HF, patients had to be on ≥50% of the target dose of an ACE inhibitor or ARB.[45] Patients unable to tolerate these doses may find it difficult to tolerate LCZ696. At the present time, there is a paucity of data on the use of LCZ696 in patients with newly diagnosed HFrEF who are naïve to ACE inhibitors or ARBs. Only 20 patients in PARADIGM HF had no prior ACE inhibitor or ARB use.[7] Although it is not certain, it would be unlikely that ACE inhibitor or ARB exposure prior to LCZ696 initiation could significantly influence the benefits achieved in the clinical trial. To be considered for LCZ696 in alignment with the PARADIGM HF trial, patients should be ACE inhibitor/ARB candidates, without history of angioedema, and able to tolerate near target dosing of ACE inhibitors/ARBs.

In PARADIGM HF, patients were on strong-evidence medical therapy, with nearly 93% of patients on β-blockers and 54% of patients on a mineralocorticoid receptor antagonist.[7] Unlike β-blocker therapy, mineralocorticoid receptor antagonist use was not mandatory in the trial, although it was encouraged. Prespecified subgroup analyses did not demonstrate an effect of mineralocorticoid receptor antagonist use on the benefits of LCZ696 over enalapril.[7] In accordance with PARADIGM HF and good clinical practice, LCZ696 should be utilized with β-blocker pharmacotherapy. Although concomitant mineralocorticoid receptor antagonist use is preferred, it should not necessarily prohibit the initiation of LCZ696.

Functional Status Considerations

Overall, the PARADIGM HF trial involved a population of patients with stable, mildly symptomatic heart failure on excellent medical therapy. Patients were excluded if they were in acute decompensated heart failure manifested by signs and symptoms that may require intravenous therapy.[45] At randomization, symptoms were well managed, with the vast majority of patients having NYHA class II limitations. A prespecified subgroup analysis suggested that patients less symptomatic at baseline derived more benefit than those with NYHA class III or IV heart failure symptoms, although this should be interpreted as hypothesis generating.[7] Baseline hemodynamics correlated well with symptoms, given that stable mean heart rates (72 beats per minute) and systolic blood pressure (121 mm Hg) were well within normal limits and not indicative of advanced disease.[7] The hemodynamics are consistent with adequate cardiac output and the modestly reduced mean ejection fraction. Patients most likely to benefit from LCZ696 are stable outpatients with minimal HFrEF symptoms on strong medical therapy. Often patients and providers prefer to continue a seemingly successful medication regimen. The practice of making a medication adjustment in stable patients will be a paradigm shift in and of itself.

Baseline NP Considerations

A potential indicator for a need to intensify HFrEF treatment was the requirement for significantly elevated NPs at randomization in PARADIGM HF. Inclusion criteria stipulated elevated BNP or NT proBNP levels at baseline to attain a higher-risk patient population for the clinical trial.[45] Regardless of symptom severity, stable patients with HFrEF can live with a wide range of plasma NP levels, including reports of up to 21% of patients having levels below what is often considered diagnostic.[50] Whether low NP levels are secondary to a patient's response to good medical management, a sign of less-progressed disease, or secondary to patient-specific factors that artificially lower NP levels, such as obesity, remains to be determined.[50,51] It could be assumed that patients without elevated natriuretic levels may not benefit from NP augmentation with a neprilysin inhibitor to the same extent as those with a highly activated NP system.

This would not be consistent with the prespecified subgroup analysis suggesting similar outcomes for patients above and below the median NT proBNP levels. Because of significant interpatient variability, NP levels should not limit the use of LCZ696.

Age Considerations

As with many medications, patient age can significantly affect efficacy, safety, and tolerability. The incidence of heart failure rises with age and approaches 1 per 100 people and higher after 65 years of age.[1] All patients ≥18 years old were eligible for randomization and the average age of the PARADIGM HF was relatively low, at 64 years old, albeit consistent with that in other HFrEF trials.[19,26,30] Although only hypothesis forming, a prespecified subgroup analysis suggests that patients >75 years old did not fare as well as their counterparts in PARADIGM HF.[7] It is not clear if safety concerns negated the benefits of LCZ696, if prognosis at this age was too poor to provide benefit, or if this was an incidental finding that would not be upheld with a

prospective trial. Advancing age should not be considered a contraindication to LCZ696, but particularly close care and follow-up would be indicated to assess for clinical failure and tolerability.

Blood Pressure Considerations

One of the biggest obstacles in HFrEF is the need to reach high target doses of multiple potent antihypertensives in a patient population that often experiences low blood pressure secondary to myocardial dysfunction. LCZ696 has demonstrated potent antihypertensive effects in clinical trials. Compared with valsartan 160 mg twice a day, LCZ696 reduces systolic blood pressure by nearly 6 mm Hg and diastolic blood pressure by nearly 3 mm Hg in patients with hypertension.[52] In PARADIGM HF, baseline hemodynamics were stable, with mean heart rates and blood pressure well within normal limits. Whereas inclusion criteria included a systolic blood pressure ≥95 mm Hg, the mean baseline blood pressure of patients randomized was 121 mm Hg on target dose enalapril or LCZ696 at randomization.[7] Despite the robust blood pressure, patients treated with LCZ696 still had a greater incidence of symptomatic hypotension with or without a systolic blood pressure ≤90 mm Hg during the trial.[7] In the trial, mean systolic blood pressure at 8 months was roughly 3 mm Hg lower in the LCZ696 group than in the enalapril group.[7] The study did not find an increased rate of discontinuation resulting from hypotension-related adverse effects with LCZ696. Notwithstanding, blood pressure and symptomatic hypotension may be a major obstacle for the use of LCZ696 and should be considered prior to switching from an ACE inhibitor or ARB.

Renal Function Considerations

Renal dysfunction is strong prognostic indicator in HFrEF, independently associated with an increased risk for all-cause mortality secondary to an increased risk of heart failure progression.[53] Early, modest worsening of renal function in the setting of RAAS initiation has not been associated with a loss of benefit from ACE inhibitor treatment and is often reversible over time.[54] Unfortunately for some, permanent renal dysfunction or failure remains a risk.[55] NPs have been shown to increase glomerular filtration rate (GFR); therefore, progressive decline in renal function while treated with neprilysin inhibition is of interest.[32] Long-term renal preservation was no different compared with enalapril in PARADIGM HF.[7] In PARADIGM HF, the incidence of elevated serum creatinine ≥2.5 mg/dL was significantly less with LCZ696.[7] Prior to randomization, patients had to demonstrate renal tolerance of both LCZ696 and enalapril. Additionally, whereas exclusion criteria allowed patients with a GFR ≥30 mL/min/1.73 m^2 to enroll, the mean GFR was 68 mL/min/1.73 m^2.[7]

The long-term renal benefits of ARB therapy in chronic kidney disease supports the use of LCZ96 in patients with a GFR ≥30 mL/min/1.73 m^2 at screening, with the understanding that renal tolerability may be more difficult with a GFR of 30 to 60 mL/min/1.73 m^2. Fewer patients treated with LCZ696 stopped treatment because of renal impairment (0.7% vs 1.4%, $P = 0.002$), suggesting that LCZ696 may be considered in those previously renal intolerant to ACE inhibitors or ARBs as long as the renal function is not secondary to hypotension.[7]

Initiation and Titration

In addition to careful patient selection, the proper initiation and titration of LCZ696 is critical to successful use, particularly with an unfamiliar medication. To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, enalapril was withheld a day before the initiation of treatment with LCZ696 during the run-in period for PARADIGM HF.[7] LCZ696 was initiated at 100 mg twice daily. After 1 to 2 weeks of tolerance, the dose was increased to 200 mg twice daily for an additional 2 to 4 weeks before randomization to ensure tolerability of the target dose.[7]

The intent of the run-in period was to ensure that the maximum benefit from LCZ696 could be achieved by selecting for patients most likely to tolerate target doses of both medications. Patients who did not tolerate a drug were not maintained on it and not randomized. The dose-response profile differs significantly between HFrEF therapeutics. β-Blockers have demonstrated a clear dose-dependent reduction in mortality and morbidity at increasing dose, with the maximal benefit at target doses.[56] In contrast, ACE inhibitors have predominantly shown only morbidity improvement at increasing doses, with maximum mortality reduction achieved at lower doses.[57] At this time, the dose-response profile for LCZ696 is not known; therefore, a conservative approach would assume that target doses are needed to achieve optimal mortality and morbidity reduction compared with ACE inhibition. The vast majority of patients in PARADIGM HF achieved target doses of LCZ696. If the target dose of LCZ696 cannot be achieved, a transition back to the patient's previous ACE inhibitor or ARB should be considered until dose response is delineated.

Clinical Monitoring

Clinical monitoring is particularly important for the safe and effective use of a novel medication with limited clinical experience. Historically, the RALES trial demonstrated a mortality benefit of spironolactone in HFrEF with an acceptably modest increased risk of hyperkalemia.[29] In Ontario, Canada, the publication of RALES results was associated with abrupt increases in the rate of prescriptions

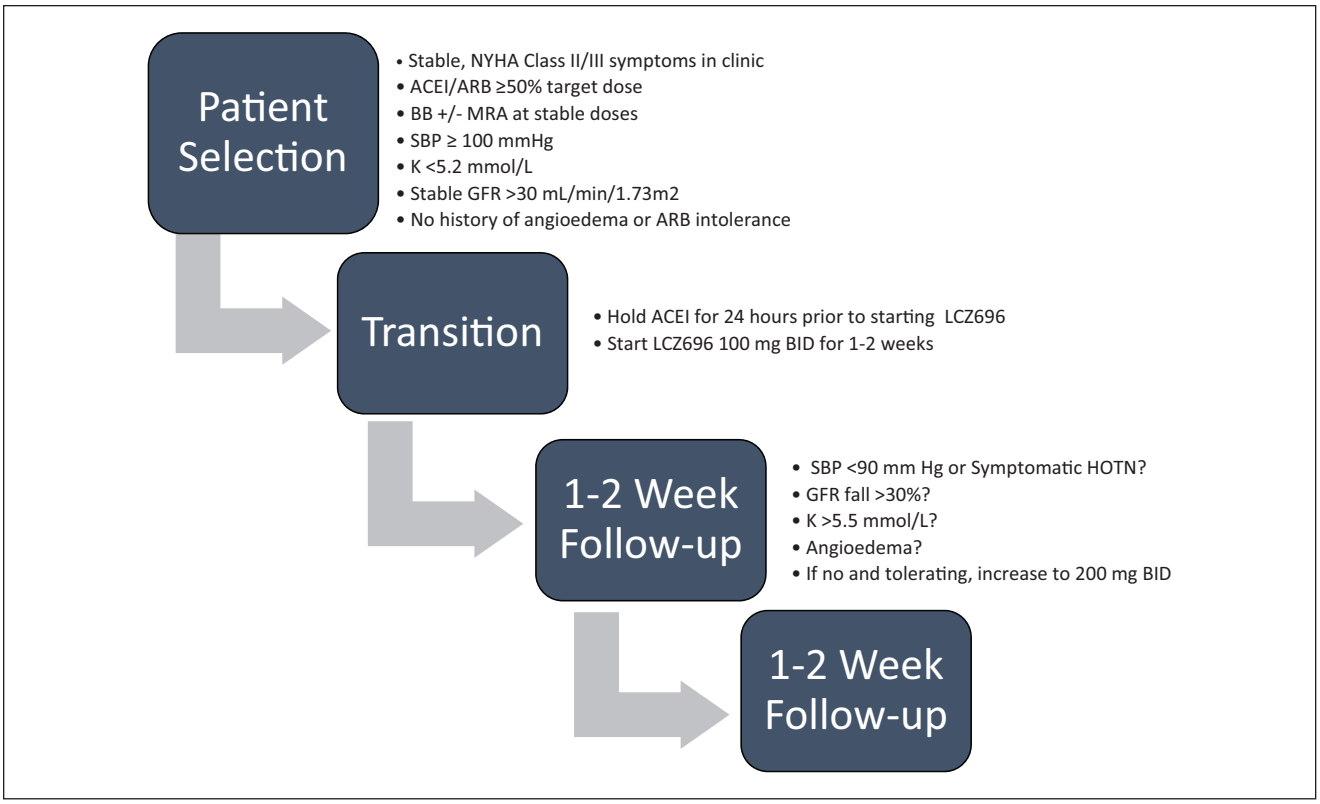

Figure 3. Approach to patient selection and initiation of LCZ696 in HFrEF: proposed approach to patient selection, transition from ACE inhibitor, and follow-up for LCZ696. Duration of follow-up should be tailored to patient-specific concerns for tolerance but should not exceed 2 weeks until tolerance of target dose LCZ696 is confirmed. Follow-up after achievement of target dose LCZ696 should consist of the same monitoring parameters (BP, GFR, K, and angioedema) as earlier follow-up. If a patient experiences angioedema then LCZ696 should be discontinued immediately. If LCZ696 is not tolerated for reasons other than angioedema, consider temporary dose reduction of LCZ696, with attempts to retitrate or resumption of previously tolerated ACE inhibitor or ARB.
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; BNP, brain natriuretic peptide; BP, blood pressure; GFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HOTN, hypotension; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of BNP; NYHA, New York Heart Association; SBP, systolic blood pressure.

for spironolactone and in hyperkalemia-associated morbidity and mortality.[58] Often the acceptable safety profile of a medication in clinical trials can reflect unusually close monitoring and restriction of other drugs or conditions that may compromise efficacy and safety.

During PARADIGM HF, fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an adverse event ($P = 0.03$). At a minimum, patients were evaluated every 2 to 8 weeks for the first 4 months of the trial; then, patients returned every 4 months thereafter.[7] In clinical practice, it is not practical for the patient or provider to execute follow-up as intensive as a clinical trial. To ensure that the safety profile is maintained, a systematic approach to patient selection, treatment initiation, and follow-up is important for safe introduction into an unselected HFrEF patient population (Figure 3). Monitoring for safety and tolerability should include blood pressure and symptoms of symptomatic hypotension, angioedema, serum creatinine, potassium, and any other potential adverse reactions not already documented as a result of limited clinical experience. If a patient cannot tolerate the target dose of LCZ696 because of hypotension, reduction or discontinuation of non–disease-modifying antihypertensives should be strongly considered. A reduction in doses of HFrEF standard of care, particularly β-blockers, should be avoided if possible and never discontinued because this was not done in the clinical trial and may result in a net negative outcome.

Conclusion

Despite substantial advances in our understanding of HFrEF pharmacotherapy, morbidity and mortality remains high. For the past 30 years, neurohormonal inhibition of

RAAS and β-adrenergic receptors have been the cornerstone of HFrEF pharmacotherapy. New therapeutic targets and strategies for HFrEF are important to continue to minimize the medical, social, and economic impacts of the disease. NP augmentation represents the next step in HFrEF neurohormonal pharmacotherapy. LCZ696 provided significant improvements in both morbidity and mortality over enalapril in the PARADIGM HF population. LCZ696 may not be optimal for everyone with HFrEF; therefore, careful patient selection and monitoring is important to maximize benefit and minimize risk. In addition, cost utility and patient affordability are presently unknown but important to consider as information becomes available. In appropriate patients, LCZ696 should be considered in place of ACE inhibition within the pharmacotherapeutic backbone of HFrEF.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240-e327.
2. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005;111:2837-2849.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-e322.
4. Stevenson LW, Pande R. Witness to progress. *Circ Heart Fail*. 2011;4:390-392.
5. Askoxylakis V, Thieke C, Pleger ST, et al. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. *BMC Cancer*. 2010;10:105.
6. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive heart failure practice guideline. *J Card Fail*. 2010;16:e1-e194.
7. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
8. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314:1547-1552.
9. Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent drug trials. *Br Med J (Clin Res Ed)*. 1985;291:993-996.
10. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429-1435.
11. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-310.
12. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol*. 1992;20:248-254.
13. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm*. 2007;(8, suppl B):9-20.
14. Benedict CR, Johnstone DE, Weiner DH, et al. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the Registry of Studies of Left Ventricular Dysfunction. SOLVD Investigators. *J Am Coll Cardiol*. 1994;6:1410-1420.
15. Fuchs F, Smith SH. Calcium, cross-bridges, and the Frank-Starling Relationship. *News Physiol Sci*. 2001;16:5-10.
16. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
17. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362:772-776.
18. Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol*. 2002;40:1414-1421.
19. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
20. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747-752.
21. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial: the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355:1582-1587.
22. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767-771.
23. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-1675.
24. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-1847.
25. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349-1355.
26. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
27. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.

28. Borghi C, Boschi S, Ambrosioni E, et al. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. *J Clin Pharmacol*. 1993;33:40-45.
29. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717.
30. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.
31. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. *Endocr Rev*. 2006;27:47-72.
32. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med*. 1998;339:321-328.
33. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, vonScheidt W. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *J Am Coll Cardiol*. 2001;38:1934-1941.
34. Inagami T. Atrial natriuretic factor as a volume regulator. *J Clin Pharmacol*. 1994;34:424-426.
35. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart*. 1996;76:36-44.
36. Miller WL, Phelps MA, Wood CM, et al. Comparison of mass spectrometry and clinical assay measurements of circulating fragments of B-type natriuretic peptide in patients with chronic heart failure. *Circ Heart Fail*. 2011;4:355-360.
37. Stephenson SL, Kenny AJ. Metabolism of neuropeptides: hydrolysis of the angiotensins, bradykinin, substance P and oxytocin by pig kidney microvillar membranes. *Biochem J*. 1987;241:237-247.
38. McDowell G, Nicholls DP. The therapeutic potential of candoxatril, a neutral endopeptidase inhibitor, in humans. *Cardiovasc Drug Rev*. 2000;18:259-270.
39. McClean DR, Ikram H, Mehta S, et al. Vasopeptidase inhibition with omapatrilat in chronic heart failure: acute and long-term hemodynamic and neurohumoral effects. *J Am Coll Cardiol*. 2002;39:2034-2041.
40. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*. 2002;106:920-926.
41. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111.
42. Fryer RM, Segreti J, Banfor PN, et al. Effect of bradykinin metabolism inhibitors on evoked hypotension in rats: rank efficacy of enzymes associated with bradykinin-mediated angioedema. *Br J Pharmacol*. 2008;153:947-955.
43. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med*. 2012;172:1582-1589.
44. Gu J, Noe A, Chandra P, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. 2010;50:401-414.
45. McMurray JJ, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062-1073.
46. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61.
47. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation*. 1997;96:856-863.
48. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med*. 1996;335:1107-1114.
49. Rouleau JL, Warnica JW, Burgess JH. Prazosin and congestive heart failure: short- and long-term therapy. *Am J Med*. 1981;71:147-152.
50. Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation*. 2003;108:2964-2966.
51. Clerico A, Giannoni A, Vittorini S, Emdin M. The paradox of low BNP levels in obesity. *Heart Fail Rev*. 2012;17:81-96.
52. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-1266.
53. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:681-689.
54. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011;4:685-691.
55. Devoy MA, Tomson CR, Edmunds ME, Feehally J, Walls J. Deterioration in renal function associated with angiotensin converting enzyme inhibitor therapy is not always reversible. *J Intern Med*. 1992;232:493-498.
56. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807-2816.
57. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312-2318.
58. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543-551.