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Review Article
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Critical Questions about PARADIGM-HF and the Future

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Cardiovascular (CV) diseases in general and heart failure (HF) in particular are major contributors to death and morbidity and are also recognized as important drivers of health care expenditure. The PARADIGM-HF trial was a pivotal trial designed to compare the long-term effects of LCZ696 with enalapril in patients with symptomatic HF with reduced ejection fraction (HFrEF). This review article presents an in-depth view of the PARADIGM-HF trial and the implications of the results in the management of patients with HF and is based on peer reviewed manuscripts, editorials, perspectives and opinions written about the PARADIGM-HF trial. The article presents the key safety and efficacy results of the trial with specific emphasis on the clinical implications of these findings. The review highlights the highly statistically significant, 20% reduction in the primary composite endpoint of cardiovascular death or HF hospitalization, and a 16% reduction in the risk of death from any cause. It also provides an overview of the design, clinical findings, limitations and special areas of clinical interest. The review discusses the future of LCZ696 and additional trials that seek to answer questions in other sub-populations of patients with HF. The article reiterates what has been concluded by many experts in the field of HF- the introduction of LCZ696 into routine clinical care, while dependent on the regulatory approvals in various countries as well as acceptance by physicians, payers and patients, will change the treatment landscape for patients with HFrEF.

Key Words: Angiotensin converting enzyme inhibitors • ARB • Entresto • Heart failure • LCZ696 • Neprilysin • PARADIGM-HF • Reduced ejection fraction

INTRODUCTION

Heart failure (HF) continues to be a major public health concern affecting an estimated 23 million patients worldwide and is associated with high rates of morbidity and mortality.[1] In some Asian countries, HF incidence is estimated at 2 million patients in China and 1 million in Japan.[2,3] There is a lack of current epidemiological data on HF in Taiwan; however previous reports have suggested that the annual mortality rate of patients with heart failure could be as high as 40-50% for New York Heart Association (NYHA) functional class III to IV patients who are waiting for cardiac transplantation.[4] The prospective Chin-Shan community cardiovascular cohort (CCCC) study established in 1991 showed an HF prevalence rate of 5.5% after a 10-year follow-up, indicating a high disease burden.[5]

The novel combination drug LCZ696 (Novartis Pharma AG, Basel, Switzerland), a fixed-dose combination of valsartan, an angiotensin receptor blocker (ARB), and sacubitril (AHU-377), a neprilysin inhibitor prodrug, is the most recent significant development in the HF with reduced ejection (HFrEF) arena.

The PARADIGM-HF [Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart

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Failure] trial (NCT01035255) compared the long-term effects of LCZ696 with enalapril in patients with HF with mild-to-moderate symptoms.[6] The trial demonstrated the superiority of LCZ696 over enalapril for both death from any cause and death from cardiovascular causes.[7] This review will summarize some frequently asked questions regarding the PARADIGM-HF trial and highlight why LCZ696 is a potential game changer in the area of cardiovascular disease.

What was the rationale of combining an ARB with a neprilysin inhibitor in LCZ696? Why not combine with ACEI? Why not single use of a neprilysin inhibitor?

Preclinical and clinical studies have shown that blockade of the renin-angiotensin-aldosterone system (RAAS) with an ARB is effective not only in controlling blood pressure but also in preventing end-organ damage.[8] Neprilysin (NEP) is a membrane-bound endopeptidase that hydrolyses atrial, brain, and C-type natriuretic peptides and other endogenous vasodilator peptides such as adrenomedullin and bradykinin, and is a major means of elimination of these peptides.[9] NEP inhibition increases the levels of natriuretic peptides and other vasodilator peptides, which have potent favorable natriuretic and vasodilatory properties. Dual RAAS and NEP inhibition translates into decreased angiotensin II-mediated cardiac hypertrophy and fibrosis, as well as beneficial natriuretic peptide-induced antiproliferative and antihypertrophic effects.[10]

Natriuretic peptides (NPs) oppose most of the known biological effects of angiotensin II. They antagonize angiotensin II inducing aldosterone production.[11] By regulating fluid homeostasis, NPs are secreted in response to excess plasma volume and left ventricular filling pressures, commonly found in patients with heart failure. NPs contribute to the regulation of sodium and water balance, blood volume, arterial pressure, and sympathetic inhibition through their effects on the venous system, kidneys, and brain. NPs also cause direct vasodilation, which results in decreased ventricular preload, systemic vascular resistance, and arterial pressure. Additionally, NPs increase glomerular filtration rate, resulting in natriuresis and diuresis, thus decreasing total body sodium and fluid. Finally, the NPs also reduce renin release from renal juxtaglomerular cells, thereby reducing plasma angiotensin II (and subsequent secretion of aldosterone), resulting in vasodilation.

In HF, the natural increases in NPs are ineffective at alleviating fluid overload. Neprilysin inhibition represents a potential alternative strategy to exogenous BNP administration by preventing the breakdown of endogenous NPs. Heart failure stimulates both the renin-angiotensin system and the natriuretic peptide system. The solution to this was thought to be the combination of NEP inhibition with an ACEI or an ARB.[6,10,12] The combined inhibition of angiotensin converting enzyme (ACE) and NEP was explored with a series of compounds, the lead example of which was omapatrilat.[13,14] However, omapatrilat treatment was associated with angioedema that was quite common and life threatening and was relatively more frequent in patients with hypertension. This led to the termination of the clinical development of this drug and related compounds in the class. LCZ696 (Figure 1) was designed to provide the benefits of simultaneously blocking RAAS and augmenting the levels of endogenous natriuretic peptides without a consequent increase in bradykinin, thereby minimizing the risk of serious angioedema.[12,15,16] LCZ696 is composed of 2 molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril (AHU377). Valsartan blocks the angiotensin type I (AT1) receptor. Sacubitril is converted enzymatically to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, an enzyme that breaks down the breakdown of atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), as well as other vasoactive substances.

LCZ696 blocked the angiotensin II type 1 receptor rather than ACE, and because LBQ657, the active metabolite of sacubitril, did not inhibit aminopeptidase P, the risk of angioedema was considered to be less than that with omapatrilat.[15-17] These initial successes led to the phase III PARADIGM-HF trial that demonstrated the striking benefits of LCZ696 over enalapril, and provided convincing proof that NEP inhibition is of benefit in HFrEF.

In July 2015, LCZ696 (Entresto™) was approved by the US Food and Drug Administration for the treatment of HF.[18] Entresto will be available by prescription for patients with NYHA class II-IV HF and is indicated to reduce the risk of cardiovascular death and heart failure hospi-

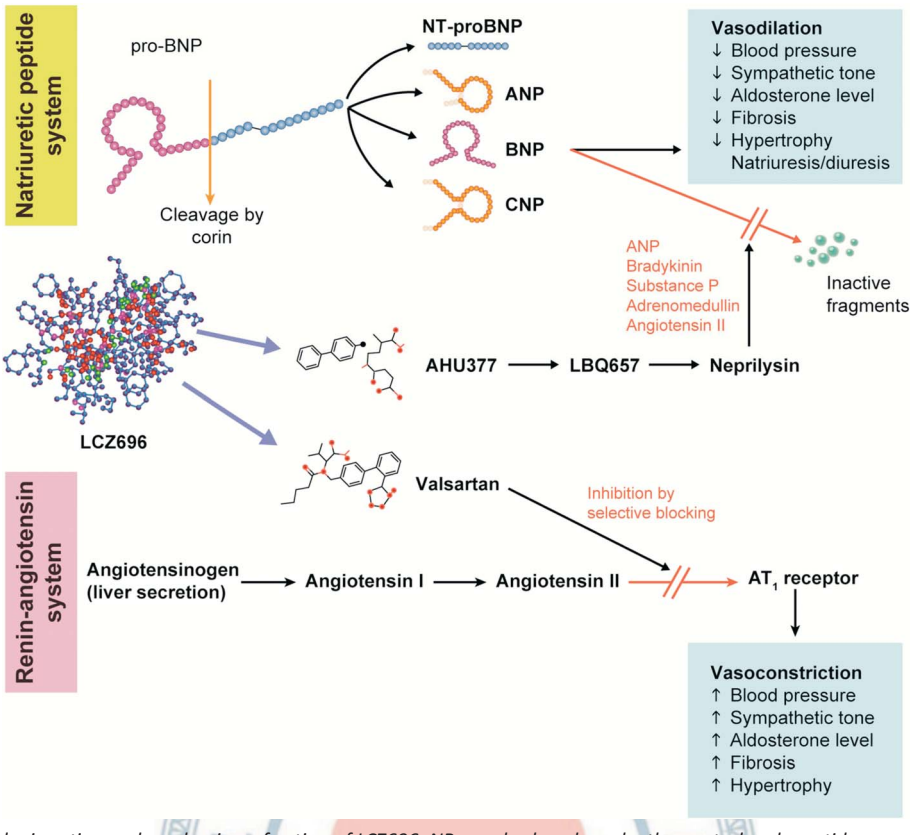


Figure 1. *Pharmacologic action and mechanism of action of LCZ696. NPs are broken down by the neutral endopeptidase neprilysin, also known as membrane metalloendopeptidase. Neprilysin is expressed in several tissues but most commonly in the kidney. It catalyzes the degradation of numerous endogenous peptides, such as ANP, BNP, CNP, bradykinin, substance P, adrenomedullin, glucagon, and vasoactive intestinal peptide, and also contributes to the breakdown of angiotensin II. Other proteases, such as insulin-degrading enzyme, may play a role in NP degradation as well, and the absence of significant physiologic alterations in mice that lack neprilysin suggests that other degradation pathways may compensate when neprilysin is absent or inhibited.*

talization. It will be administered in conjunction with other heart failure therapies, in place of an ACEI or other ARB.

What is the PARADIGM-HF study design?

PARADIGM-HF was a randomized, double-blind, parallel-group, active controlled, two-arm, event-driven clinical trial that enrolled 8442 adults with chronic HFrEF (Figure 2).[7,19]

For at least 4 weeks prior to screening, all patients were receiving stable doses of an ACEI or an ARB at a dose level equivalent to the evidence-based dose of enalapril of 10 mg/day, as well as a β-blocker unless contraindicated or intolerable. Patients with more serious HF could receive a mineralocorticoid receptor antagonist (MRA). Patients with a history of angioedema were excluded.

During randomized, double-blind treatment, patients were followed-up over a median of 27 months. The composite primary outcome was the occurrence of cardiovascular death or a first hospitalization for HF, but the trial was powered to detect a significant difference between 2 arms in cardiovascular death as a sole outcome. The specified event rate for the co-primary end point was 2410 patients, at which point the trial could be halted.[6,7,19]

Why was the enalapril dose in PARADIGM-HF lower than the highest recommended dose?

The PARADIGM-HF trial was designed with enalapril 10 mg b.i.d. as the active comparator because enalapril has been considered both the standard of care and the regulatory gold standard in HF, and is the only ACEI shown to reduce mortality in a broad spectrum of pa-

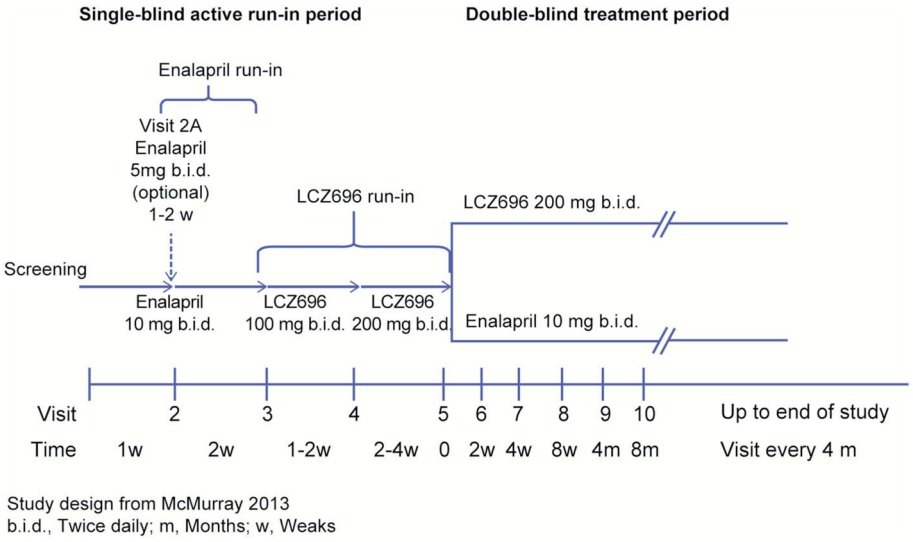


Figure 2. *Study design of PARADIGM-HF.*

tients with HFrEF.[20] Although the target dose of enalapril in the CONSENSUS trial may have been 40 mg daily, the actual dose achieved was 18.4 mg. In the SOLVD trial, the pivotal trial that proved enalapril reduced mortality, the mean dose achieved was 17 mg.[20] This was also true of the SOLVD prevention trial where the dose achieved was 17 mg.[21] In the V-HeFT II trial, which was not placebo-controlled, the average daily dose of enalapril was 15 mg.[22] The average dose of 18.9 mg enalapril achieved in the PARADIGM-HF trial is thus the highest dose of the drug ever used in a clinical trial of HF (Table 1).

Did the baseline patient characteristics have an impact on efficacy?

NYHA class: In PARADIGM-HF, nearly 70% patients were categorized as NYHA class II, and 24% patients were NYHA class III.

Before enrollment, 77% of patients in PARADIGM-HF were treated with an ACEI and 22% with an ARB; thus, almost all patients had received either ACEI or ARB treatment. According to the trial's subgroup analyses, in ACEI-naïve patients LCZ696 led to a higher incidence of symptomatic hypotension compared to enalapril, which, however, did not result in a higher treatment discontinuation.[19] It is not possible to comment on treatment benefits between subgroups of prior use of ACEi or ACEI-naïve patients without conducting additional studies to answer that question.

The patients most likely to benefit from LCZ696 are those similar to patients in the PARADIGM-HF trial. A recent analysis of a large database of HF patients in ambulatory care suggested that 80% of patients would be eligible based on natriuretic peptide criteria, and 90% would be eligible based on blood pressure criteria.

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score was used to determine the benefit of the ARNI LCZ696 (sacubitril-valsartan) across the spectrum of HF severity. We can also examine the effect of LCZ696, compared with enalapril, according to the baseline risk calculated using these scores. Although most patients in PARADIGM-HF had mild symptoms, many were at high risk of adverse outcomes and obtained a substantial benefit from LCZ696 compared with enalapril. And the results show that the benefits derived from LCZ696 were consistent across the spectrum of risk.[23]

The other analyses showed that LCZ696 was better than enalapril in preventing important clinical outcomes and preventing deterioration in symptoms and functional capacity across the broad age spectrum studied in PARADIGM-HF. Older patients may have a higher probability for treatment intolerance, and age-related safety profile data in the PARADIGM-HF study still needs further elucidation. However, the significant benefits on CV mortality and HF hospitalization of patients receiving LCZ696 compared with patients receiving enalapril were not different between patients < 75 and ≧ 75 years old.

Table 1. Target enalapril doses vs achieved doses in HF trials

Name of trial (Year of publication)	Primary outcome	Comparator arm	Patient population	Dose of enalapril in trial protocol	Dose administered to patients	Reference
CONSENSUS (1987)	Effect of enalapril versus placebo on mortality	Placebo	NYHA class IV	40 mg/day (20 mg b.i.d.)	18 mg/day	38
SOLVD-treatment trial (1991)	Reduction in mortality due to enalapril in patients with low ejection fraction (≤ 0.35)	Placebo	NYHA class II-IV	20 mg/day (10 mg b.i.d.)	17 mg/day	20
SOLVD-prevention trial (1992)	Would the use of enalapril reduce mortality, the incidence of HF, and the rate of related hospitalizations in patients with ejection fraction ≤ 35% who were not receiving therapy for HF	Placebo	LVEF ≤ 35%, the patients had to be asymptomatic (however, 33% were in NYHA class II)	20 mg/day	17 mg/day	21
V-HeFT II (1991)	To compare the effects of enalapril with those of hydralazine and isosorbide dinitrate in a population of patients similar to that in V-HeFT I and also treated with digoxin and diuretics	No placebo, hydralazine and isosorbide dinitrate	NYHA class II (51%) or III (43%)	20 mg/day	15 mg/day	22
PARADIGM-HF (2014)	The effect of LCZ696 on the occurrence of cardiovascular death or a first hospitalization for HF	Enalapril	HFrEF (all NYHA classes)	20 mg/day (10 mg b.i.d.)	18.9 mg/day	19

HF, heart failure; HFREF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Importantly, intolerance of LCZ696 leading to treatment withdrawal did not differ according to age.[24]

What are the key efficacy and safety data from the PARAIDGM study?

EFFICACY

PARADIGM-HF demonstrated the striking benefits of LCZ696 over enalapril and proof that NEP inhibition is of benefit in HFrEF.[19,25] As compared to enalapril 10 mg b.i.d., LCZ696 200 mg b.i.d. led to a highly statistically significant 20% reduction in the primary composite endpoint of cardiovascular death or HF hospitalization, and a 16% reduction in the risk of death from any cause.[19,25,26] Sub-analyses demonstrated that the risk of the composite primary endpoint or cardiovascular death occurring in the LCZ696 or enalapril arms was not affected by patient-specific risk factors, including age, race, comorbidities, and prior use of ACEIs or MRAs.[19]

Other significant outcomes that indicated the advantages of LCZ696 over enalapril were worsening of outpatient treatments, visits to the emergency department for HF, hospitalization due to cardiovascular events as well as for any other cause, and ICU admissions.[19,25]

The patients in the LCZ696 group had 23% fewer hospitalizations for worsening heart failure; they were also less likely to require intensive care, to receive intravenous positive inotropic agents, and to have implantation of a HF device or cardiac transplantation.

SAFETY

The most frequent reasons for permanent treatment discontinuation were similar in the 2 groups: hypotension, renal impairment, and hyperkalemia. Overall, a lower proportion of patients in the LCZ696 arm

discontinued treatment because of an adverse event (10.7% vs. 12.3%; p = 0.03). Hypotensive episodes, defined as asymptomatic and symptomatic with systolic blood pressure < 90 mmHg, were more common in LCZ696-treated patients (14.0% and 2.7%, respectively) than in enalapril-treated subjects (9.2% and 1.4%, respectively; p < 0.001 for both types of hypotensive episodes). Elevated serum creatinine (≥ 2.5 mg/dL) was observed in a lower proportion of patients in the LCZ696 arm than in the enalapril arm (3.3% vs. 4.5%; p = 0.007), while the proportion of patients with elevated serum potassium levels (> 5.5 mmol/L) was similar. Angioedema which was evaluated in a blinded manner by an expert committee and classified into 4 categories of severity, was reported in 19 (0.45%) and 10 (0.24%) patients in the LCZ696 and enalapril arms, respectively. No cases of angioedema causing airway compromise were reported in either arm, and no differences were observed when analyzing according to the severity of angioedema.

An analysis of patients who required dose reduction in the PARADIGM-HF trial showed better outcomes in patients treated with LCZ696 than in those treated with enalapril. LCZ696 is contraindicated in patients with a history of angioedema, and standard contraindications related to ARB should also be considered. In patients developing hypotension while on LCZ696 treatment, the use of medications for comorbid conditions, e.g., alpha-blockers for benign prostatic hyperplasia, or oral nitrates should be reviewed. Diuretic dose should be reduced in these patients followed by a reduction in LCZ696 dose.

Is LCZ696 efficacious in all types of HF?

Over two-thirds of patients with HFrEF in PARADIGM-HF were NYHA class II, which is similar to other HF trials.[27-31] A subgroup analysis showed interaction between NYHA class and effect of treatment on the primary endpoint (p = 0.03 without adjustment for multiple comparisons), but this interaction was not seen for death from cardiovascular causes.[31] Patients with higher scores in the Meta-Analysis Global Group in Chronic (MAGGIC) risk score analysis were more likely to be in NYHA functional class III/IV than I/II, have worse Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and have an ischemic etiology.[32]

The mean change from baseline to month 8 in the KCCQ clinical summary score was a reduction of 2.99 points in the LCZ696 group and a reduction of 4.63 points in the enalapril group (between-group difference, 1.64 points; 95% CI, 0.63 to 2.65; p = 0.001). When zero values were not imputed for patients who died, the score improved in the LCZ696 group and declined in the enalapril group, and the between-group difference (0.95 points; 95% CI 0.31 to 1.59) remained significant (p = 0.004).

Although there were many fewer functional class III and IV patients than class I and II enrolled in PARADIGM-HF, with comparatively mild symptoms, many patients included in the trial were at high risk of adverse outcomes and obtained a large absolute benefit from LCZ696 compared with enalapril. Furthermore, the benefit of LCZ696 was consistent across the spectrum of risk.

In summary, patients on LCZ696 were less likely to show symptomatic deterioration, to need intensification of oral therapy or addition of intravenous therapy, to visit the emergency department, to be admitted to the hospital and when admitted, were less likely to go to the ICU and less likely to need iv inotropic therapy, or to die prematurely (either suddenly or from worsening HF).

What is the effect of changes in blood pressure on LCZ696 treatment?

A key issue in PARADIGM-HF was if blood pressure control was a determinant of outcome measures. Blood pressure decreased in the LCZ696 and enalapril groups, respectively, over 27 months of treatment. The mean systolic blood pressure at 8 months was 3.2 ± 0.4 mm Hg lower in the LCZ696 group than in the enalapril group (p < 0.001) as compared to the value measured at randomization. However, when the between-group difference in blood pressure was analyzed with time as a dependent covariate, there was no incremental benefit associated with LCZ696 treatment.[19] A criticism has been levied that the reduced blood pressure of patients in the LCZ arm could lead to hypotensive episodes and thus may be a potential area of concern. Because of greater vasodilator effects, treatment with LCZ696 was associated with a higher rate of symptomatic hypotension, but there was no increase in the rate of discontinuation because of possible hypotension-related ad-

verse effects.[27] Furthermore, a sub analysis revealed that low systolic blood pressure was not associated with an impairment of improved quality of life on LCZ696.[33] Doses of the study drugs were increased to target levels during the run-in phase, primarily to ensure that patients in the enalapril group received doses that have been shown to reduce mortality. Hence, the results are applicable to a broad spectrum of patients with heart failure, including those who are currently taking an ACE-I or ARB or who are likely to be able to take such an agent without having unacceptable side effects. However, physicians should exercise clinical judgment while performing dose titrations based on the patients' clinical condition.

What is the effect of LCZ696 on renal impairment?

The effects of LCZ696 on patients with renal impairment are of interest because NEP inhibition is expected to improve kidney function.[34] This idea is supported by data from the PARADIGM-HF trial where elevated serum creatinine levels (≥ 2.5 mg/dl) were found in fewer patients in the LCZ696 arm in comparison to the enalapril arm, although no significant difference in proportions of patients with a decline in renal function [based on estimated glomerular filtration rate (GFR)] were found.[19] Although it can be hypothesized that a greater hypotensive effect of LCZ696 might impair renal perfusion, clinically important increases in the serum creatinine level and discontinuation of the study drug because of renal impairment were less frequent in the LCZ696 group than in the enalapril group.[26]

Patients in PARADIGM-HF had a lower risk of hyperkalemia. Natriuretic peptides are known to have an impact on electrolyte/fluid balance by increasing renal blood flow and GFR, further optimizing renal function.[35] The increase in permeability co-efficient of the glomerular basement membrane reflected by the increase in the filtration fraction and altered pore size alters the flow of serum and plasma into the renal tubule. The PARADIGM-HF trial had strict criteria for the inclusion of patients based on GFR. Patients with an estimated GFR < 30 mL/min were not included in the trial. However, the PARAGON-HF trial has more relaxed criteria where patients with an estimated GFR as low as 25 mL/min will be allowed to continue on LCZ696 in the active run-in period. However, in the absence of specific guidelines, physicians without extensive experience in treating patients with HF and renal impairment should prescribe LCZ696 only to patients who have an estimated GFR ≥ 30 mL/min.

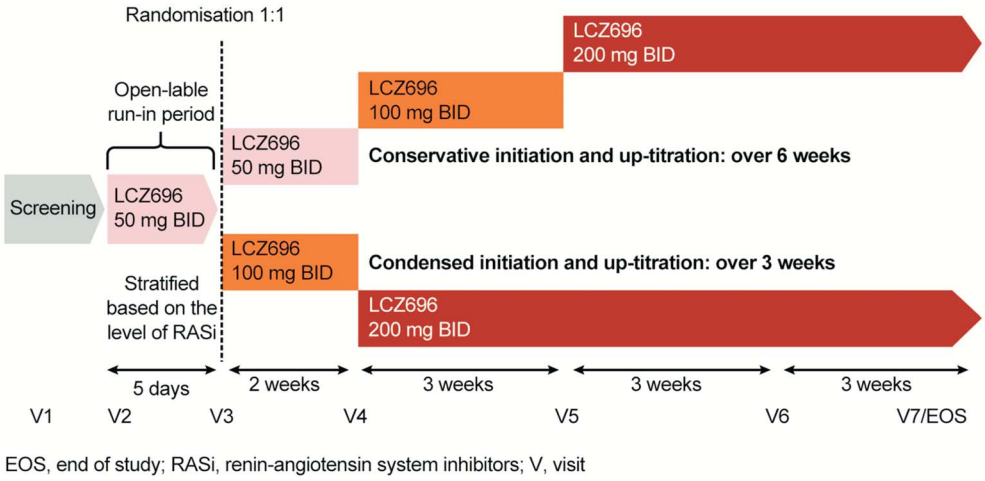
CLINICAL IMPLICATIONS

What are the limitations of the PARADIGM-HF study?

A single-blind run-in period during which all patients received enalapril was followed by a single-blind run-in period during which all patients received LCZ696, to ensure an acceptable side-effect profile of the study drugs at target doses. Doses of the study drugs were increased to target levels during the run-in phase, primarily to ensure that patients in the enalapril group received doses that have been shown to reduce mortality. Only 12% of patients did not complete the run-in period because of adverse events, and the rates of adverse events were higher for patients receiving enalapril than for those receiving LCZ696.[19]

Although a run-in phase limits the possibility of treatment discontinuation and enhances a trial's internal validity, it can also limit the inference of the results to the general HF population, thus affecting its external validity. In addition, 2 short washout periods of 36 hours were applied between the enalapril and LCZ696 run-in periods and at the end of the run-in phase, to decrease the risk of angioedema due to the overlap of ACEI and LCZ696. Another key issue is the ability of the physician to mimic the dose titration described in the PARADIGM-HF trial, in order to counter the potential for hypotension seen in these patients. Treatment guidance will be needed for patients who are already on other blood pressure lowering agents. It is unclear how this would translate into real-world clinical practice.

The TITRATION study, designed to provide additional supportive information regarding the initiation and up-titration of LCZ696, comprised an open-label run-in (LCZ696 50 mg bid for 5 days) followed by an 11-week, double-blind randomized period (Figure 3). The primary objective was to assess the safety and tolerability of initiating and up-titrating LCZ696 from 50 mg bid to a target dose of 200 mg bid over a 3-(Condensed) versus 6-week (Conservative) period in patients with HFrEF. The results show that LCZ696 demonstrated an acceptable safety



EOS, end of study; RASi, renin-angiotensin system inhibitors; V, visit

Figure 3. *Study design of TITRATION study.*

and tolerability profile regardless of the up-titration regimen. After excluding non-adverse event or death-related discontinuations, > 76% of patients achieved and maintained the target dose of LCZ696 200 mg bid for 12 weeks. Achievement of target dose was possible even in patients who required dose interruption or down-titration during the study period. Also, the rate of adverse events was lower than in the PARADIGM-HF trial.[36]

Another potential limitation is patients without elevated NP levels were not enrolled in this study, so we cannot confirm if this patient population would still benefit as much as those who have elevated NP levels.

THE FUTURE OF LCZ696

Are there any new trials ongoing to answer additional questions about LCZ696?

The challenges posed by multiple sub-classes of HF and the lack of adequate evidence in patients with HF with preserved ejection fraction (HFpEF) led to the design of the ongoing PARAGON-HF trial (NCT01920711). The purpose of this study was to evaluate the effect of LCZ696 compared to valsartan in the reduction of cardiovascular death and HF hospitalizations in patients with HFpEF.

LCZ696 has demonstrated its ability in reducing central BP and PP in high-risk older patients with systolic hypertension and an increased pulse pressure as compared to olmesartan. PARAMETER is a multicenter, randomized, double-blind, active-controlled, 52-week study to evaluate the safety and efficacy of an LCZ696 regimen on central aortic pressures and arterial stiffness in elderly hypertensive patients.

Will PARADIGM-HF change the treatment paradigm for patients with heart failure?

Despite the fact that ACEIs (and when not tolerated, ARBs) are the standard of care in pharmacological therapy for HfrEF,[37] the benefits of LCZ696 over enalapril in PARADIGM-HF were statistically and clinically compelling. Enalapril is the only ACEI shown to reduce mortality in chronic HFrEF, and the average dose achieved in PARADIGM-HF was greater than that used in either the CONSENSUS or SOLVD trials, yet LCZ696 was significantly beneficial.[20,38]

LCZ696 was also superior to enalapril in reducing the risk of a first emergency department visit or hospitalization for heart failure. Furthermore, the drug was also more effective than ACE inhibition alone in decreasing the need for repeated emergency visits and hospitalizations for heart failure. Despite the criticisms levied against the trial design, the PARADIGMHF-trial highlights the fact that LCZ696 was superior to enalapril in reducing the risk of symptom progression as well as exerting a favorable effect on the clinical progression of patients with mild-to-moderate HFrEF.

As Dr. John McMurray states in a recent commentary on LCZ696 "The P-value for the primary endpoint (4×10^{-7}) in PARADIGM-HF is equivalent to having 4-5 trials each with $p < 0.05$ (for all-cause mortality, the equivalent number is 2-3 trials). Clearly, the regulatory authorities, guideline committees, payers, and the clinical

community have to decide what they make of the efficacy, safety, and cost-effectiveness of LCZ696, but it may be that ultimately ARNIs replace ACEIs/ARBs as one of the cornerstones of drug treatment for HFrEF."[39]

Is LCZ696 cost effective as compared to other medications for chronic heart failure?

Recently, the Institute for Clinical and Economic Review (ICER) released a new report that evaluates the long-term cost-effectiveness of LCZ696 use.[40] The analysis states that there is a "moderate certainty that LCZ696 provides a small to substantial net health benefit compared to the current standard of care in patients with chronic HF". Additional studies are ongoing to evaluate this question.

CONCLUSIONS

The approval of LCZ696 for the management of patients with HFREF will lead to increased survival rates and reductions in the rate of hospitalizations. The introduction of LCZ696 into routine clinical care, while dependent on the regulatory approvals in various countries as well as acceptance by physicians, payers and patients, still heralds a new era in the treatment of patients with HFrEF.

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REFERENCES

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;8:30-41.
2. Shengshou H, Lingzhi K (eds). Report on cardiovascular diseases in China, 2009. National Centre of Cardiovascular diseases Encyclopedia of China Publishing House.
3. Okura Y, Ramadan MM, Ohno Y. Impending epidemic future projection of heart failure in Japan to the year 2055. *Circ J* 2008;72:489-91.
4. Chen H, Chen M, Tang W. Improving care for patients with heart failure: what can Taiwan accomplish? *Acta Cardiol Sin* 2007;23: 211-24.
5. Huang C, Chien K, Chen W, et al. Impact of heart failure and left ventricular function on long-term survival — report of a community-based cohort study in Taiwan. *Eur J Heart Fail* 2007;9:587-93.
6. McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Committees and Investigators. 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;15:1062-73.
7. McMurray JJ, Packer M, Desai AS, et al. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014;16: 817-25.
8. Schmieder RE. Mechanisms for the clinical benefits of angiotensin II receptor blockers. *Am J Hypertens* 2005;18(5 Pt 1):720-30.
9. Vanneste Y, Michel A, Dimaline R, et al. Hydrolysis of alpha-human atrial natriuretic peptide in vitro by human kidney membranes and purified endopeptidase - 24.11. Evidence for a novel cleavage site. *Biochem J* 1988; 254:531-7.
10. von Lueder TG, Sangaralingham SJ, Wang BH, et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. *Circulation* 2013; 6:594-605.
11. Richards AM, Wittert GA, Espiner EA, et al. Effect of inhibition of endopeptidase 24.11 on responses to angiotensin II in human volunteers. *Circ Res* 1992;71:1501-7.
12. Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. *Clin Pharmacol Ther* 2013;94:445-8.
13. McClean DR, Ikram H, Garlick AH, et al. The clinical, cardiac, renal, arterial and neurohormonal effects of omapatrilat, a vasopeptidase inhibitor, in patients with chronic heart failure. *J Am Coll Cardiol* 2000;36:479-86.39.
14. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000;356:615-20.
15. 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;50:401-14.
16. Hegde LG, Yu C, Renner T, et al. Concomitant angiotensin AT1 receptor antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. *J Cardiovasc Pharmacol* 2011; 57:495-504.
17. Ruilope LM, Dukat A, Böhm M, et al. 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;375:1255-66.
18. FDA News Release 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm. Last accessed July 22, 2015.
19. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371:993-1004
20. SOLVD Investigators (a). Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325: 293-302.
21. SOLVD Investigators (b). Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327: 685-91.
22. Cohn JN, Johnson G, Ziesche S. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of congestive heart failure. *N Engl J Med* 1991;325:303-10.
23. Simpson J, Squire I, Martinez F, et al. Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril according to baseline risk in PARADIGM-HF. European Society of Cardiology Congress, 23rd to 26th May 2015, Sevilla, Spain.
24. McMurray J, Jhund PS, Fu M, et al. Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril according to age in PARADIGM-HF. European Society of Cardiology Congress, 23rd to 26th May 2015, Sevilla, Spain.
25. Packer M, McMurray JJ, Desai AS, et al. PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015;131:54-61.
26. Jessup M, Fox K, Komajda M, McMurray J, Packer Milton. PARADIGM-HF — the experts' discussion. *N Engl J Med* 2014;371:e15
27. Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. 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;362:767-71.
28. Konstam MA, Neaton JD, Dickstein K, et al.; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;374:1840-8.
29. Swedberg K, Komajda M, Böhm M, et al.; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
30. Tang AS, Wells GA, Talajic M, et al.; Resynchronization – Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385-95.
31. Zannad F, McMurray JJ, Krum H, et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
32. Pocock SJ, Ariti CA, McMurray JJ, et al.; Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies. *Eur Heart J* 2013;34:1404-13.
33. Bohm M, Refsgaard J, Ramires FJA, et al. Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared to enalapril according to systolic blood pressure in PARADIGM-HF.
34. Judge P, Haynes R, Landray MJ, et al. Neprilysin inhibition in chronic kidney disease. *Nephrol Dial Transplant* 2015;30(5): 738-43.
35. Boerrigter G, Burnett JC. Recent advances in natriuretic peptides in congestive heart failure. *Expert Opin Investig Drugs* 2004;13: 643-52.
36. Senni M, Reyes A, Majercak I, et al. Results of the TITRATION STUDY: a 12-week multicenter, randomised, double-blind, safety evaluation of a 3- versus 6-week up-titration regimen of LCZ696 in patients with HFrEF. European Society of Cardiology Congress, 23rd to 26th May 2015, Sevilla, Spain.
37. 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 2012of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14:803-69.
38. CONSENSUS: effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429-35.
39. McMurray J. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. *Eur J Heart Fail* 2015; 17:242-7.
40. Institute for Clinical and Economic Review. CardioMEMS HF System (St Jude Medical) and sacubitril/valsartan (Entresto, Novartis) for management of congestive heart failure: effectiveness, value, and value-based price benchmarks. September 11, 2015. http://www.icer-review.org/chf-draft-report-posted/ Last accessed 27th October 2015.