



PARADIGM-HF trial: will LCZ696 change the current treatment of systolic heart failure?

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1 Introduction

Heart failure (HF) is a global health problem with an estimated prevalence of over 5.8 million in the USA and over 23 million worldwide.^[1] It represents the most common cause of hospitalization in elderly patients (≥ 65 years) and its incidence has a growing trend mainly due to the aging of the population.^[2] Neurohumoral activation plays a major role in the pathophysiology.^[3] So in consequence, the cornerstone of its medical treatment is based on the inhibition of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system.^[2] According to this, all patients with HF and reduced ejection fraction should be treated with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) plus a beta blocker (BB) and if needed, a mineralocorticoid receptor antagonist (MRA).^[2]

2 Natriuretic peptides (NP) and neprilysin inhibition

The NPs are a group of structurally similar peptides that have diverse actions basically affecting cardiovascular and renal homeostasis. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are of myocardial cell origin and C-type natriuretic peptide (CNP) is of endothelial origin.

All of these peptides are compensatory activated in HF promoting basically natriuresis, vasodilation and rennin inhibition (protecting role).^[4] Neutral endopeptidase (NEP) also known as neprilysin, is widely expressed in the kidneys, lungs, and the vascular wall and essentially, is the enzyme that hydrolyses ANP, BNP and CNP.^[4] Therefore, its inhibition represents a way to increase their endogenous concentration and in consequence, their beneficial hemodynamic activity.^[5] NEP also degrades angiotensin II so it

means that neprilysin inhibition may additionally cause vasoconstriction counterbalancing the previous mentioned vasodilator effects.^[6] Taking into account these two diverging effects, an initial clinical approach to the combined inhibition of ACE and NEP was studied in HF patients in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). In this trial, a target dose of enalapril (10 mg, twice daily) was compared with Omapatrilat, a NEP-ACE inhibitor (40 mg, once daily). Omapatrilat was found not superior to enalapril regarding the primary composite endpoint (death from any cause or heart failure hospitalization) but it was associated to a significant increase in angioedema and hypotension.^[7]

3 Angiotensin receptor–neprilysin inhibition (ARNI): LCZ696

LCZ696 is a novel compound that combines the neprilysin inhibitor sacubitril and the ARB valsartan. It was designed to provide a simultaneous blocking of the RAAS and an increase of the NP concentration but minimizing the risk of serious angioedema and hypotension. LCZ696 was also design to be prescribed twice daily in order to guarantee an extended ARNI (24 h); the single dose of 200 mg delivers the equivalent of 160 mg of valsartan.^[5,8]

4 PARADIGM-HF

The Prospective Comparison of ARNI with ACEI to determine Impact on Global Mortality and Morbidity in Heart failure Trial (PARADIGM-HF) is a randomized, double-blind, and event-driven trial which was designed to investigate the effect of LCZ696 compared to enalapril in patients with chronic and symptomatic HF.^[9] The run-in period started in December 2009 and the study was stopped in March 2014 after a median follow-up of 27 months

Table 1. Population at baseline.

Main characteristics	LCZ696 (n = 4187)	Enalapril (n = 4212)
Age (yrs)/Female sex, n (%)	63.8 ± 11.5/879 (21%)	63.8 ± 11.3 /953 (22.6%)
SBP (mmHg)/HR (beats/ min)	122 ± 15/72 ± 12	121 ± 15/73 ± 12
NYHA functional class	I/II/III/IV (4.3%/71.6%/ 23.1%/0.8%)	I/II/III/IV (5.0%/69.3%/ 24.9%/0.6%)
Creatinine (mg/dL) /LVEF (%)	1.13 ± 0.3/29.6 ± 6.1	1.12 ± 0.3/ 29.4 ± 6.3
Median B-type NP*	255 (155-474)	251 (153-465)
Median N-terminal pro-B-type NP*	1631 (8815-3154)	1594 (886-3305)
Ischemic cardiomyopathy, n (%)	2506 (59.9%)	2530 (60.1%)
Atrial fibrillation, n (%)	1517 (36.2%)	1574 (37.4%)
Hypertension/diabetes, n (%)	2969 (70.9%)/1451 (34.7%)	2971 (70.5%)/1456 (34.6%)
HF hospitalization, n (%)	2607 (62.3%)	2667 (63.3%)
Pre-trial use ACEI or ARB	78%/22.2%	77.5%/22.9%
BB/MRA at randomization	93.1%/54.2%	92.9%/57%

In both groups white and black races were 66% and 5.1%, respectively. Body-mass indexes were $28.1 \pm 5.5 \text{ kg/m}^2$ (LCZ696) and $28.2 \pm 5.5 \text{ kg/m}^2$ (enalapril). Pre-use of implantable cardioverter-defibrillators or resynchronization devices were as follow: 14.9%/7% (LCZ696), 14.7%/6.7% (enalapril). Adapted from reference [10]. *Interquartile range, pg/mL. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; HR: heart rate; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NP: natriuretic peptide; NYHA: New York Heart Association; SPB: systolic blood pressure.

Table 2. Clinical endpoints.

Endpoints	LCZ696	Enalapril	Hazard ratio	P value
	(n = 4187)	(n = 4212)	(95% CI)	
Primary composite outcome, n (%)				
Death from CV cause/first HF hospitalization	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	< 0.001
Death from CV cause	558 (1.3)	693 (16.5)	0.80 (0.71–0.89)	< 0.001
First HF hospitalization	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	< 0.001
Secondary outcomes, n (%)				
Death from any cause	711 (17)	835 (19.8)	0.84 (0.76–0.93)	< 0.001
Change in KCCQ	-2.99 ± 0.36	-4.63 ± 0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Renal function deterioration	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

Renal function decline was defined as end stage renal disease or a decrease $\geq 50\%$ in the estimated glomerular filtration rate from the randomization value or a decrease $> 30 \text{ mL/min per } 1.73 \text{ m}^2$, to less than $60 \text{ mL/min per } 1.73 \text{ m}^2$. Adapted from reference [10]. CV: cardiovascular; HF: heart failure; KCCQ: Kansas city cardiomyopathy questionnaire (at 8 months); range from 0–100 with higher scores showing fewer limitations.

due to a very convincing performance with LCZ696. PARADIGM-HF results were announced at the European Society of Cardiology Congress 2014 in Barcelona coinciding with its publication in a September issue of the *New England Journal of Medicine*.^[10]

Study medication LCZ696 (200 mg, BID) was compared with enalapril (10 mg, BID) in patients with systolic HF (NYHA functional class II-IV), previously treated with an ACEI or ARB, left ventricular ejection fraction $\leq 40\%$ and increased levels of BNP or NT-proBNP. The trial randomized 8,442 patients (4,187 in the LCZ696 group and 4,212 in the Enalapril one) and its primary endpoint was a com-

posite of death from cardiovascular causes or first hospitalization for HF. At the time of trial stopping, 21.8% of the LCZ696 group and 26.5% of the enalapril one had reached the primary endpoint (HR: 0.80; 95%CI: 0.73–0.87; $P < 0.001$). Compared with enalapril, LCZ696 reduced the risk of death from any cause by 16% ($P < 0.001$) and the risk of hospitalization from HF by 21% ($P < 0.001$). Overall mortality was also lower in the LCZ696 arm (17.0% vs. 19.8%, HR: 0.84, 95%CI: 0.76–0.93, $P < 0.001$). Symptomatic hypotension and non-serious angioedema were more common in the LCZ696 group but renal deterioration, cough and hyperkalemia occurred more frequently with enalapril. Fewer

patients in the LCZ696 arm needed to stop their medication due to an adverse event (10.7% vs. 12.3%, $P = 0.03$). PARADIGM-HF authors concluded that LCZ696 was superior to enalapril in reducing the risks of death and hospitalization for HF.

5 Considerations

The results of the trial are very positive but unpretentiously, there are some issues to be considered: (1) this study basically involved not very severe patients (about 70% were in NYHA class II) with a quite stable systolic blood pressure (about 120 mmHg). In addition, the enrolled population was in fact not very old (median age was 63.8 years). (2) About 20% of patients were not able to reach the randomization phase, so basically PARADIGM-HF only enrolled subjects that tolerated full doses of both drugs. Administered doses of LCZ696 and enalapril were 375 ± 71 mg and 18.9 ± 3.4 mg, respectively (mean \pm SD). (3) About 10% of patients were dropped out during the single-blinded run-in phase linked with LCZ696 adverse events (not an irrelevant percentage). (4) In the PARADIGM-HF the enalapril target dose was 10 mg (twice daily, 20 mg) which was the same dose used in the SOLVD treatment trial,^[11] but in the case of valsartan, its target dose was 160 mg (twice daily, 320 mg) which was superior to mean doses used in other studies like ValHeft^[12] (254 mg/day) or Valiant trial (247 mg/day).^[13] For that reason, it is not unthinkable the possibility of an additional contribution of this elevated dose in the observed benefit of the study. (5) Baseline medications were reported (about 93% BB and 56% MRA) but doses and types of used BB were not provided (is not known if target doses were reached). (6) Black Americans have an increased risk of angioedema,^[14] but their presence in PARADIGM-HF population was low (5%). So, is LCZ696 really safe in this population?

6 Conclusions

PARADIGM-HF represents an impressive innovation in the therapeutic field of systolic HF because its results imply the replacing of ACEI from its standard treatment. PARADIGM-HF compared LCZ696 with enalapril, which is probably the most used ACEI in HF patients and in this trial, a remarkable reduction in the LCZ696 arm related to risk of death and HF hospitalizations was found. Therefore, the rising “hot” question is if LCZ696 should be quickly incorporated to clinical practice and modestly. I have two considerations in favor: (1) despite modern pharmacological therapy, HF remains as global health problem and it repre-

sents the main cause of morbidity and mortality in older people; and (2) the combined inhibition of the angiotensin receptor and neprilysin seems to be superior to the sole inhibition of the RAAS in this kind of patients.

However, there are some emerging challenges for LCZ696 to be investigated, such as its utilization in unstable scenarios like low blood pressure or acute HF. Undoubtedly, LCZ696 represents a very promising molecule and its potential use in the field of HF and preserved ejection fraction is currently under investigation (PARAGON-HF study/ClinicalTrials.gov Identifier: NCT0192071).

In any case, I truly believe that LCZ696 will significantly change how we are going to treat our patients with HF in the next future and probably and paraphrasing a cinematographic term, PARADIGM-HF could represent a real blockbuster.

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