

The need to apply the best therapy in heart failure – the era after PARADIGM-HF

Malgorzata Lelonek

Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland

Submitted: 28 February 2016

Accepted: 18 April 2016

Arch Med Sci 2017; 13, 5: 1244–1248

DOI: 10.5114/aoms.2016.59711

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Corresponding author:

Prof. Malgorzata Lelonek

MD, PhD

Department of Noninvasive

Cardiology

Medical University of Lodz

113 Zeromski St

90-549 Lodz, Poland

Phone: +48 42 201 43 10

E-mail: mlelonek@poczta.fm

About 26 million adults worldwide suffer from heart failure (HF) [1]. However, general public awareness of HF is poor [2]. Despite the improvement in health care over the past 20 years, mortality in patients with HF remains unacceptably high. About 2–17% of patients admitted to hospital die during hospitalization, 17–45% within 1 year of admission and the majority by 5 years from admission [3]. Despite the use of angiotensin-converting enzyme (ACE) inhibitors, β -blockers, and mineralocorticoid receptor antagonists (MRA), in HF the endogenous neurohormonal system plays an important role.

The molecular complex of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), combines an angiotensin receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril), and represents an important step in the management of HF and reduced ejection fraction. This dual action places this drug at the center of two critically important systems in HF: the renin–angiotensin–aldosterone system (RAAS), and the natriuretic peptide system (NPS). The mechanism of action for valsartan is well known and for sacubitril is prevention of the catabolism of natriuretic peptides (NPs). Neprilysin (NEP), a neutral endopeptidase, diminishes vasorelaxant, natriuretic, and diuretic actions of NPs beneficial in HF.

Natriuretic peptides exert their effects through binding to their receptors and resulting in the generation of cyclic guanosine monophosphate (cGMP). Cyclic guanosine monophosphate mediates natriuresis and inhibition of renin and aldosterone, and induces vasorelaxant, antifibrotic and antihypertrophic effects [4]. The NPs have a short-lived action due to their rapid metabolism by NEP. Therefore, the use of a substance that blocks the action of NEP, such as a NEP inhibitor (sacubitril), will extend their life, increase their blood levels and consequently increase their effectiveness in the treatment of HF [4].

In the recent Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF), chronic administration of sacubitril/valsartan (formerly known as LCZ696) was superior to enalapril in reducing death and hospitalizations in patients with chronic HF and a reduced ejection fraction (HFrEF) [5]. The dose of enalapril was selected based on its effect in reducing the risk of death in the SOLVD-T (Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial). Sacubitril/valsartan at a target dose of 97/103 mg (200 mg of LCZ696) twice daily reduced cardiovascular mortality by 20% compared to an evidence-based dose of the ACE inhibi-

tor enalapril (10 g twice daily), and death from any cause by 16% [5]. The magnitude of the beneficial effects of sacubitril/valsartan, as compared to enalapril, was as great as seen with enalapril compared to placebo but was obtained when sacubitril/valsartan was added to background treatment with a β -blocker and a mineralocorticoid receptor antagonist. The benefit of LCZ696 was consistent across the spectrum of risk, and those at high risk of adverse outcomes obtained a particularly large absolute benefit from sacubitril/valsartan compared with enalapril [6].

The baseline demographics of patients in PARADIGM-HF [5, 7] are similar to those of the population of SOLVD-T. Although the majority of

patients in PARADIGM-HF were in NYHA functional class II or III at the time of randomization, the median NT-proBNP concentration was high (Table I). In PARADIGM-HF [5], patients without a history of HF-hospitalization within 12 months were required to have either BNP \geq 150 pg/ml or NT-proBNP of \geq 600 pg/ml in order to be enrolled. Patients with lower levels of natriuretic peptides (BNP \geq 100 pg/ml or NT-proBNP \geq 400 pg/ml) were eligible if they had been hospitalized for HF within 12 months. Patients enrolled had an ejection fraction of \leq 40% (changed to \leq 35% by amendment). Patients taking any dose of ACE inhibitors or angiotensin receptor blockers (ARBs) were considered for enrollment, but were required to tolerate

Table I. Baseline characteristics of patients in PARADIGM-HF [5, 7]

Parameter	LCZ696 N = 4187	Enalapril N = 4212
Age [years]	63.8 \pm 11.5	63.8 \pm 11.3
Female gender, n (%)	879 (21.0)	953 (22.6)
Systolic blood pressure [mm Hg]	122 \pm 15	121 \pm 15
Heart rate [beats/min]	72 \pm 12	73 \pm 12
Body-mass index	28.1 \pm 5.5	28.2 \pm 5.5
Serum creatinine [mg/dl]	1.13 \pm 0.3	1.12 \pm 0.3
Ischemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction (%)	29.6 \pm 6.1	29.4 \pm 6.3
Median B-type natriuretic peptide (IQR) [pg/ml]	255 (155–474)	251 (153–465)
Median N-terminal pro-B-type natriuretic peptide (IQR) [pg/ml]	1631 (885–3154)	1594 (886–3305)
NYHA functional class I, n (%)	180 (4.3)	209 (5.0)
NYHA functional class II, n (%)	2998 (71.6)	2921 (69.3)
NYHA functional class III, n (%)	969 (23.1)	1049 (24.9)
NYHA functional class IV, n (%)	33 (0.8)	27 (0.6)
Hypertension, n (%)	2969 (70.9)	2971 (70.5)
Diabetes, n (%)	1451 (34.7)	1456 (34.6)
Atrial fibrillation, n (%)	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure, n (%)	2607 (62.3)	2667 (63.3)
Myocardial infarction, n (%)	1818 (43.4)	1816 (43.1)
Stroke, n (%)	355 (8.5)	370 (8.8)
β -Blockers, n (%)	3899 (93.1)	3912 (92.9)
MRA, n (%)	2271 (54.2)	2400 (57.0)
ICD, n (%)	623 (14.9)	620 (14.7)
CRT, n (%)	292 (7.0)	282 (6.7)
Digitalis, n (%)	1223 (29.2)	1316 (31.2)
Diuretics, n (%)	3363 (80.3)	3375 (80.1)

MRA – mineralocorticoid receptor antagonist, CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator.

the equivalent of enalapril 10 mg daily for at least 4 weeks before screening along with stable doses of β -blocker and MRA if indicated. According to the study protocol patients first received enalapril 10 mg twice daily for 2 weeks (single-blind) and then LCZ696 (single-blind) for an additional 4 to 6 weeks, initially at 100 mg twice daily and then 200 mg twice daily. Patients tolerating both drugs at target doses were randomly assigned in a 1 : 1 ratio to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The trial was stopped early, after a median follow-up of 27 months – an overwhelming benefit with LCZ696.

This beneficial effect on mortality was shown in PARADIGM-HF to a parallel 21% reduction in cardiac hospitalization for HF, the other component of the primary composite endpoint in PARADIGM-HF. The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Importantly, the PARADIGM-HF study is one of the few trials demonstrating a reduction in clinical worsening among surviving patients with better health-related quality of life and NYHA class in the sacubitril/valsartan group, compared with the enalapril group [7]. There was also a favorable biomarker response (reductions in NT-proBNP and troponin T) in sacubitril/valsartan-treated patients [8].

The 20% reduction in cardiovascular deaths with LCZ696 relative to enalapril seen during the trial was attributable primarily to reductions in the incidence of both sudden death and death due to progressive HF [9]. Using a putative placebo [10], sacubitril/valsartan showed striking effects on all outcomes examined, with the relative risk reduction for the primary composite endpoint of 39–43% and cardiovascular mortality 32–34%, and also for all-cause mortality (26–28% risk reductions) and even larger effects on HF hospitalization, with relative risk reductions of 46–49%.

LCZ696 was better than enalapril in preventing important clinical outcomes and preventing deterioration in symptoms and functional capacity across the broad spectrum of age studied in PARADIGM-HF [11]. Using actuarial estimates from the PARADIGM-HF trial, and assuming that the protective effects of sacubitril/valsartan remain consistent with long-term use, it has been calculated that treatment with sacubitril/valsartan may result in an additional 1 to 2 years life expectancy (and even greater survival free from HF hospitalization) in patients such as those enrolled in the PARADIGM-HF trial: with chronic HF, NYHA class II–IV symptoms, an elevated plasma BNP or NT-proBNP level, and an LVEF of $\leq 40\%$ [12].

The PARADIGM-HF results suggest that the absolute benefits obtained by switching 1000

patients from an ACE inhibitor/ARB to sacubitril/valsartan over a median treatment period of 27 months would be avoidance of: 47 primary endpoints, 31 cardiovascular deaths, 28 patients hospitalized for HF, 37 patients hospitalized for any reason, 53 admissions for HF and 111 admissions for any reason [4, 8].

Overall, fewer patients in the sacubitril/valsartan group than in the enalapril group had a study drug-related adverse event (particularly elevated serum creatinine, elevated serum potassium or cough) and stopped their study medication [4]. However, after randomization, more patients in the sacubitril/valsartan group had symptomatic hypotension than in the enalapril group, but there was no increase in the rate of discontinuation of the study drug for this adverse event. Importantly, intolerance of sacubitril/valsartan leading to treatment withdrawal did not vary greatly according to age and there was no increased risk of serious angioedema.

Sacubitril/valsartan constitutes the first of a new class of drugs, angiotensin receptor neprilysin inhibitors (ARNIs), designed to replace ACE inhibitors and ARBs in HF.

It is important to explain the NT-proBNP and BNP changes with sacubitril/valsartan. The BNP but not NT-proBNP is a substrate for neprilysin [13]. Levels of BNP will reflect the action of the drug, whereas levels of NT-proBNP reflect the effects of the drug on the heart (e.g. on left ventricular filling pressure and wall stress). Levels of plasma BNP were higher during the treatment with sacubitril/valsartan than with enalapril [6]. In contrast, in comparison with enalapril, patients receiving sacubitril/valsartan had consistently lower levels of NT-proBNP, reflecting reduced cardiac wall stress. LCZ696 led to an early (within 4 weeks) and sustained at 8 months ($p < 0.0001$) reduction in NT-proBNP [8], and the clinical findings are supported by the effects on NT-proBNP measured in surviving patients in PARADIGM-HF. The contrasting effects of sacubitril/valsartan on the 2 types of natriuretic peptides (NT-proBNP and BNP) represent an important finding, because the levels of the 2 peptides are characteristically parallel with each other during the course of HF. So in the era after PARADIGM-HF, the biomarker for monitoring progress and assessing prognosis in HF should be NT-proBNP, not BNP.

There is more news about related biomarkers in HF. Bayés-Genis *et al.* identified a positive association between levels of circulating soluble NEP in HF patients and cardiovascular mortality and morbidity, supporting the importance of NEP inhibition as a therapeutic target [14]. Recently they also found that in a multibiomarker strategy in 797 consecutive ambulatory HF patients, only

Table II. Treatment in heart failure with reduced ejection fraction

Variable	Mortality in heart failure		Hospitalization due to heart failure
	Sudden cardiac death	Pump failure	Pump failure
β-Blockers	Reduction	Reduction	Reduction
ACEI	Reduction	Reduction	Reduction
MRA	Reduction	Reduction	Reduction
Ivabradine	Reduction	Reduction	Reduction
CRT-D	Reduction	Reduction	Reduction
ICD	Reduction	–	–
ARNI	Reduction	Reduction	Reduction

ACEI – angiotensin-converting enzyme inhibitor, ARNI – angiotensin receptor neprilysin inhibitor, MRA – mineralocorticoid receptor antagonist, CRT-D – cardiac resynchronization therapy with defibrillator function, ICD – implantable cardioverter-defibrillator.

soluble NEP remained an independent prognostic marker of the primary composite endpoint of cardiovascular death or HF hospitalization (HR = 1.14; 95% CI: 1.02–1.27; $p = 0.03$) and with cardiovascular death (HR = 1.15; 95% CI: 1.01–1.31; $p = 0.04$), while N-terminal pro-B-type natriuretic peptide lost significance in these analyses [15].

The current HFrEF pharmacotherapy is based on low-cost generic medications. We have no real-world estimates of sacubitril/valsartan cost effectiveness. The only publication, by King *et al.* [16], emphasized the need to make the decision of this intervention based on attempts to determine whether the extra benefit with sacubitril/valsartan is worth the additional costs. Using a Markov model, the authors revealed that sacubitril/valsartan therapy, compared to enalapril, was more costly (\$60,391 vs. \$21,758) and more effective (6.49 vs. 5.74 quality-adjusted life years (QALYs)) over a lifetime. However, it seems the low-cost generic status of angiotensin-converting enzyme inhibitors (ACEIs) and ARBs might be more attractive for payers than the reduction of HF hospitalizations observed in PARADIGM-HF. King *et al.* also reported the relationship between the cost-effectiveness of sacubitril/valsartan and duration of treatment: from \$249,411 per QALY at 3 years to \$50,959 per QALY gained over a lifetime. Finally, as with all new therapies, real-world estimates of sacubitril/valsartan cost effectiveness are needed.

In conclusion, PARADIGM-HF is the first successful active controlled trial with a proven comparator (enalapril) in HF, the largest trial in chronic HF and with the first drug that has proved to be superior to enalapril. The ARNI sacubitril/valsartan combination doubles the effect on cardiovascular death of current inhibitors of the renin-angiotensin system. Therefore, this trial will mark the end of the era of ACE inhibitors/ARBs in HFrEF. The time has come to re-define optimal medical treat-

ment in patients with HFrEF and to update the ESC guidelines published in 2012. Table II summarizes the approach in management in HFrEF to reduce mortality and hospitalization due to HF.

Acknowledgments

I thank Prof. John McMurray (Glasgow) for expert remarks.

Conflict of interest

The author is an investigator in the PARAGON-HF trial.

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