The efficacy of LCZ696 in chronic heart failure

Ting Gong 1,∗, Changlin Lu 2, Jiayao Wang 3 and Yao Ma 4

1 University of Glasgow, UK
2 Beijing Chao-Yang Hospital, China
3 Hebei Yanda Hospital, China
4 Institute of Disaster Prevention, Hangzhou, China

Abstract:
Heart failure (HF) is the abnormality of cardiac structure or function leading to a failure of the heart to deliver enough oxygen required by metabolizing tissues. It is a serious progressive heart disease with high morbidity, mortality and poor prognosis, which is one of the challenges in the cardiovascular field. The new anti-HF drug LCZ696 consists of an angiotensin receptor blocker (valsartan) and a precursor of the enkephalinase inhibitor (AHU377), with the dual ability to block the renin-angiotensin-aldosterone system and to inhibit neprilysin. Many studies have shown that LCZ696 has good application prospects in the treatment of chronic HF. This article reviews the effectiveness and mechanism of LCZ696 in chronic HF.

1. Introduction
Heart failure (HF) is the result of various structural or functional cardiac disease giving rise to ventricular filling, impaired blood drainage and decreased ventricular pumping function, which cannot meet the metabolic needs of body tissues, mainly as the clinical syndrome of dyspnea, fatigue and fluid retentio.[1] At present, the incidence of HF has become one of the major diseases that threaten human health as the increasing of human longevity.[2] Numerous studies have demonstrated that over-activation of the renin-angiotensin-aldosterone system (RAAS) is one of the major pathophysiological mechanisms of chronic HF.[3] So far, the inhibition of RAAS and sympathetic nervous system are the main means of treatment, thus, inhibiting myocardial remodeling.[4] RAAS inhibitors have become the base therapy for chronic HF and could be effectively improving the prognosis of patients with chronic HF. RAAS system inhibitors include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and aldosterone receptor antagonists. Therefore, there is the "golden triangle" treatment in chronic HF formed by three types of drugs: ACEI / ARB, beta blockers and aldosterone receptor antagonists.[5] In addition to blocking RAAS, the inhibition of neprilysin (NEP) enhances the natriuretic peptide system which may also play a role in the treatment of HF. Furthermore, the combination of two mechanisms increases the effect of anti-HF.[6] According to the theory of inhibition of RAAS, but also effectively inhibit the system of NEP, resulting in a new drug of the dual inhibition of angiotensin receptor-neprilysin (LCZ696).

2. The mechanism of LCZ696
LCZ696 is the first dual angiotensin receptor-neprilysin inhibitor (ARNI), which is a compound preparation of 1:1 molar ratio of valsartan and NEP inhibitor precursor AHU377. [7] Valsartan blocks the RAAS system while AHU377 is metabolized to LBQ657, which has the effect of inhibiting NEP and preventing the degradation of natriuretic peptides. More importantly, the combination of two
methods increases the effectiveness of individual method, improving the cardiovascular function of patients with HF. [8]

RAAS is an important fluid regulating system in the human body. It exists both in the circulatory system and in the tissues, such as heart, kidney, brain; and participates in the regulation of target organs. [3] It causes positive inotropic and diastolic dysfunction in the heart at the cellular level, and promotes the secretion of adrenaline, eventually causing arrhythmia. Subsequently, it acts on the coronary artery, which causes the contraction of myocardial ischemia, as well as the expression of the original oncogene, leading to cardiac hypertrophy and remodeling. [3] Angiotensin II is the most important component of RAAS, which is distributed into the heart and blood vessels of angiotensin receptor type 1 (AT1). After being combined with angiotensin II, stimulating the adrenal cortical zone to secrete aldosterone by contracting the arterioles. In addition, angiotensin II stimulates the release of catecholamines and increases sympathetic excitability, thereby promoting cardiac and vascular remodeling. Angiotensin II also stimulates plasminogen activator inhibitor 1 to promote peroxide production.[9] However, valsartan, as a representative drug of ARB, namely RAAS inhibitor, which plays a role in relaxing blood vessels, lowering blood pressure, inhibiting sympathetic neuro-transmitter release and reversing ventricular remodeling. Valsartan is also a clinically widely used angiotensin receptor blocker that acts by blocking the binding of angiotensin II to AT1. Moreover, the increase of angiotensin II also binds to AT2 due to blockage of AT1, resulting in the opposite biological effect to AT1. [10]

Natriuretic peptides are neuroendocrine hormones that maintain sodium balance in the body and play an important role in regulating the homeostasis of the cardiovascular system, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and c-type natriuretic peptide (CNP). ANP is secreted mainly by atrial tissue, BNP is mainly secreted by atria and ventricular tissues and CNP is secreted by vascular endothelial cells. [11] ANP is the most important function in the natriuretic peptide, which secretes less in normal conditions. However, the atrial myocytes secrete a large amount of ANP when the increase of plasma osmotic pressure or atrial pressure. ANP binds to A-type natriuretic peptide receptor (NPR-A) and activates guanylate cyclase to increase intracellular cGMP levels, thus playing an effective role in dilating blood vessels, increasing the output of sodium, antagonizing epinephrine and the retention of sodium and water of RAAS. [12] NEP belongs to a neutral endopeptidase that is a zinc-dependent matrix metalloproteinase including natriuretic peptide, bradykinin, and adrenomedullin, which degrades natriuretic peptide, bradykinin and angiotensin II, containing a variety of peptides. [13,14] However, N-terminal brain natriuretic peptide (NT-proBNP) is not an NEP substrate and does not degrade it, guarantees the physiological function of the peptide when restrained, causing diuresis, vasodilation, and resistance to cell proliferation; thus, significantly reducing the occurrence and development of HF and the function of lowering blood pressure.[15] AHU377 is a prodrug in LCZ696 that can be quickly metabolized to the active product LBQ657, which inhibits NEP, promotes excretion of sodium and water and reverses ventricular remodeling.[7]

3. Drug metabolism of LCZ696

In the human body, about 11% of valsartan is converted into a biologically inactive metabolite (M1) and excreted mainly through feces. AHU377 is further metabolized in vivo to produce LBQ657, which is an active NEP inhibitor. [7] The study has shown that the maximum concentration of valsartan in the blood circulation is earlier in the LCZ696 experimental group, compared with the valsartan and AHU377. In addition, the amount of exposure of the area under the curve and the peak concentration system is about three times than that of the later, while the two groups of LBQ657 levels are almost the same.[7] These findings indicate that LCZ696 is a potent inhibitor that blocks both RAAS and NEP and has similar pharmacokinetic properties as valsartan and LBQ657. [16] In terms of biological effects, the formation of LCZ696 tablets is used to promote the absorption of valsartan. [12]
4. The effectiveness of LCZ696 in Clinical Studies

PARAMOUNT is a randomized, parallel, double-blind, controlled phase II clinical trial involving 65 research centers in 13 countries. The purpose of it is to assess the efficacy, safety, and tolerability of LCZ696 in patients with HF with preserved ejection fraction (HF-PEF) using LCZ696 versus valsartan. [17] In this experiment, 301 HF-PEF patients are enrolled. The criteria for inclusion are as follows: NYHA II to III, left ventricular ejection fraction $\geq 45\%$, NT-proBNP $> 400$ ng/L with at least one of the following symptoms: exertional dyspnea, sitting-in breathing, paroxysmal nocturnal dyspnea, and ankle edema. Patients are randomized into two groups, one group of 149 patients receiving LCZ696 and the other 152 patients receiving valsartan. The results showed that NT-proBNP in LCZ696 group is significantly lower than that in valsartan group at the 4th week, and the reduction of NT-proBNP in LCZ696 group is 23% higher than valsartan group at 12 weeks, the difference is statistically significant.

At the end of the 36 weeks PARAMOUNT study, the reduction in NT-proBNP is still greater in the LCZ696 group than in the valsartan group, but the difference in NT-proBNP is no longer significant between the two groups. However, the left atrial volume, the thickness of left atrium and index of cardiac reconstruction in patients of LCZ696 group are significantly smaller than those in the valsartan group, and the difference is statistically significant. At the same time, the heart function of patients is also improved. Additionally, the incidence of adverse reactions in the LCZ696 group is similar to that in the valsartan group, and the safety of LCZ696 is in an acceptable range and well tolerated.[17] This study shows that LCZ696 is an effective treatment for HF patients with normal left ventricular ejection fraction and improve ventricular remodeling in HF patients, especially in HF-PEF. Renal insufficiency is an independent predictor of poor prognosis in patients with chronic HF. According to the study, compared with valsartan, LCZ696 reduces serum creatinine levels in patients with HF-PEF and improves the estimated glomerular filtration rate.[18] Moreover, a meta-analysis study showed that LCZ696 has a therapeutically beneficial effect on renal function in HF patients compared to other RAAS inhibitors.[19] In general, LCZ696 is effective in patients with HF-PEF but requires further clinical trials to confirm.

PARADIGM-HF is the largest LCZ696 randomized, double-blind phase 3 clinical study with LCZ696 compared to enalapril. ACEI, as the cornerstone of drugs in the past few decades, is used to reduce ejection fraction in HF and achieves good results. Enalapril, as one of the ACEIs, has been proved effective in many trials to reduce the mortality. [20] In order to verify the clinical effect of LCZ696 in reducing HF with reduced ejection fraction (HF-REF) and the replacement of ACEI/ARB drugs, the conduction of PARADIGM-HF trial is used to evaluate the efficacy and safety of LCZ696 in HF patients with reduced ejection fraction. [21] PARADIGM-HF enrolled a total of 8436 patients with HF in NYHA II-IV, BNP $\geq 150$ ng/L or NT-proBNP $\geq 600$ n/L and LVEF $\leq 40\%$. A randomized double-blind trial is divided into two groups: one group with 4187 patients receiving LCZ696 and the other group with 4212 patients receiving enalapril. The endpoint of the study is mainly cardiovascular-related death or HF-induced hospitalizations. The results showed that LCZ696 group has higher survival rate, 20% reduction in sudden death from HF, 21% decrease in hospitalization for HF, 20% reduction in cardiovascular mortality and 16% reduction in all-cause mortality for outpatients with HF compared with the enalapril group. After hospitalization for HF patients, the LCZ696 group has a shorter duration of intensive care (about 18%) and the need for intravenous drug maintenance of cardiac pump function is reduced, although hospitalization duration is similar in the LCZ696 and enalapril group. [21] At the same time, LCZ696 maintains a low level of biomarkers of cardiac load and injury (NT-proBNP and troponin). [22] The above results show that LCZ696 in reducing the mortality of patients with HF and hospitalization rate is significantly better than enalapril.

Furthermore, hypertension is one of the important causes of chronic HF, therefore early control of blood pressure is the key to prevent HF. The new research data shows that LCZ696 also helps to control high blood pressure.[23] KARIO et al study a randomized, double-blind, placebo-controlled trial of the efficacy and safety of LCZ696 in Asian patients with hypertension.[24] The results show
that baseline diastolic blood pressure and pulse pressure baseline are decreased dramatically by using LCZ696. Compared with the placebo-control group, the difference is significant.

5. Security of LCZ696

Previous clinical studies have found that ACEI/NEP improves the morbidity and mortality of patients with HF; however, with the risk of exacerbating angioedema, its withdrawal from the market. [25] This adverse effect is due to the fact that ACEI/NEP inhibits angiotensin convertase and aminopeptidase P, resulting in accumulation of bradykinin and substance P in the body. However, ARB has less effect on bradykinin, the probability of angioedema is significantly lower than that of ACEI. Therefore, compared with ACEI/NEP, LCZ696 does not directly inhibit the action of ACEI and aminopeptidase P; hence, does not reduce the incidence of angioedema[26]. In the PARAMOUNT trial, 22(15%) patients develop severe adverse events in the LCZ696 group compared with 30 (20%) in the valsartan group and no significant differences in adverse reactions such as hypotension, hyperkalemia, and renal failure. [17] The PARADIGM-HF trial shows that LCZ696 does not increase the risk of severe angioedema. [21] However, the incidence of hypotension and mild angioedema in the LCZ696 treatment group is higher than that in the enalapril treatment group; while the incidence of renal dysfunction, hyperkalemia and cough are lower. In addition, there is no significant effect on the basic heart rate and serum creatinine level, therefore does not affect the patient to continue taking medication. [3] Based on these current findings, LCZ696 is safe and well tolerated.

6. Discussion

HF is the terminal stage of a variety of cardiovascular diseases, which could seriously affect the quality of life of patients caused by the rapid progress of clinical condition. [1] New drug LCZ696 is the first ARNI drug to overlap and complement the mechanism of action of valsartan and AHU377, which blocks angiotensin II receptor in RAAS as well as NEP, and avoids the fatal side effects caused by ACEI/NEP in severe angioedema. The incidence of renal damage, hyperkalemia, cough and other adverse reactions in LCZ696 is lower, which is beneficial for patients with HF. It reduces the hospitalization rate and mortality effectively, improves clinical symptoms and enhances the quality of life. [27] Numerous clinical studies have shown that LCZ696 is superior to valsartan and enalapril in the treatment of HF, which leads to a revolution in traditional HF regimens. [17] However, the experimental data of LCZ696 are mostly derived from western populations. It is worth looking forward to the application prospects in the treatment of chronic HF patients in China and further research is needed. Additionally, studies have shown that symptomatic hypotensive adverse re-actions in the LCZ696 treatment group are significantly higher than enalapril treatment group. [28] Therefore, the clinical application of the new drug, LCZ696, need a large amount of experimental research to support the efficacy and safety.

Conflicts of Interest:
The authors declare no conflict of interest.

References


