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Original Research

Natriuretic peptides and their therapeutic potential in heart failure treatment: An updated review

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Abstract: Brain natriuretic peptide (BNP), also known as a B-type natriuretic peptide, is one of the important biomarkers with a proven role in the diagnosis of congestive heart failure (CHF). Researchers from the different clinical field have researched into the performance features of BNP testing in the acute care set-up to assist and improve in diagnosing CHF and in predicting future morbidity and mortality rates. The potency of BNP has also been researched into in cases like myocardial ischemia and infarction, cor pulmonale, and acute pulmonary embolism (PE). Based on their vaso-dilatory and diuretic properties and ability to inhibit renin–angiotensin–aldosterone system, natriuretic peptides are able to provide an efficient technique and mechanism of action in the pathophysiologic framework for CHF treatment and management. Recent clinical studies reported that ularitide, a synthetic form of urodilatin, secreted by kidney may be effective in managing and treatment of decompensated heart failure. It has also been reported that Nesiritide, a recombinant natriuretic peptide has been proven to improve dyspnea and hemodynamic parameters in heart failure patients. This review provides an update on natriuretic peptides and their therapeutic potential in CHF treatment.

Key words: Natriuretic peptides, nesiritide, BNP, Congestive heart failure, renin–angiotensin–aldosterone system, urodilatin.

Introduction

Chronic Heart Failure (HF) represents a raising health care concern in developed and developing countries, reaching epidemic proportions. About 1 to 2% of adult population in developed countries suffers HF, with $10% prevalence among elderly (>70 years) (1). At least half of HF patients have reduced left ventricular ejection fraction, and coronary artery disease is the leading cause of chronic HF. Although in recent years progresses of pharmacologic and non-pharmacologic therapies led to substantial improvement of survival and rate of hospitalization in HF patients, prognosis remains poor (1,2). Heart failure is a medical condition that outcomes once the heart is incapable to make available adequate blood flow to encounter metabolic necessities or accommodate systemic venous return. These conditions consequence from damage to the myocardium from a diversity of reasons involving diabetes, hypertension, and ischemic heart disease. Less common etiologies consist of myocarditis, infections, systemic toxins, and cardiotoxic drugs, valvular disease, cardiomyopathies. In place of the heart fails, patients develop symptoms comprise peripheral edema and ascites from impaired venous return and dyspnea from pulmonary congestion. Heart failure is triggered by a forfeiture of a dangerous amount of functional myocardial cells after injury to the heart from a number of reasons. The most communal etiologies are diabetes, hypertension, and ischemic heart disease .

Chronic and increased activities of the renin–angiotensin–aldosterone system (RAAS) plays an important role in HF pathophysiology, drugs capable of inhibiting order-stabilizing the important components of the RAAS have become a foundation of new and efficient cardiovascular drug therapy (1,3,4). It has been reported that the biosynthesis of one of the strongest vasoconstrictor and pro-hypertrophic hormone in man, angiotensin-II (Ang-II) is inhibited by the action of angiotensin-converting enzyme inhibitors (ACEi). In addition, ACEi may also be responsible for inhibition of the proteolysis of bradykinin, thus leading to inhibition of vasoconstriction seen in patients with HF (5).

Studies have confirmed that neurohormones play a significant role in the complex cellular and multiorgan adaptations. Natriuretic peptides play a crucial role in this progression, antagonizing the activities of the renin-angiotensin-aldosterone system, thus encouraging natriuresis and vasodilatation. Other significant physiologic characteristics of the natriuretic peptides are antioxidative, anti-inflammatory, anti-ischemic, prolusitropic, antiproliferative, and sympathoinhibitory . The natriuretic peptides (NPs), consisting of atrial NP (ANP), B-type NP (BNP), C-type NP (CNP), and urodilatin, which are mostly generated by organs like heart, vasculature, kidney, and central nervous system in response to several stimuli (Table 1). Figure 1 shows the role of natriuretic peptides in congestive heart failure (CHF).

The NPs, especially ANP and BNP, forms the blood pressure (BP)–lowering system which is responsible for promoting vasodilation, in addition to promoting vasodilation, NPs inhibits pathological growth and dysfunction of vital organs like heart, brain, and kidney. In addition, in some disease states and conditions like left ventricular overload and hypertrophy, conges-

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Table 1. Showing types of NPs and site of production.

Type of NPs	Organ/site of production	Forms	Comments
Atrial NP	Atria in normal adult heart	1	Under pathologic conditions such as chronic heart failure (CHF) or ventricular hypertrophy, the ANP gene is increasingly expressed in the ventricle (11)
Brain-NP	Myocardium of the left ventricle and, in a small fraction, in the brain, kidney, and lung (11)	1	
C-type NP	Primarily produced in vascular endothelial cells, macrophages, and neurones belonging to the central nervous system but is also produced locally in the kidney.	pro-CNP 1–103, a 103-amino-acid pro-hormone prepro-CNP 1– 126, a 126-amino-acid prepro-hormone	CNP is the only NP with the highest concentration in brain (12) and is found at very low levels in the heart
Urodilatin	Kidney, in the distal tubular cells and its secreted into the tubular lumen (11)	1	It binds to a NP type 1 receptors (NPR1) to promote sodium excretion
D-type NP	Several human tissues and plasma		Less is known about the pharmacological properties and (patho)physiological role of DNP (13)

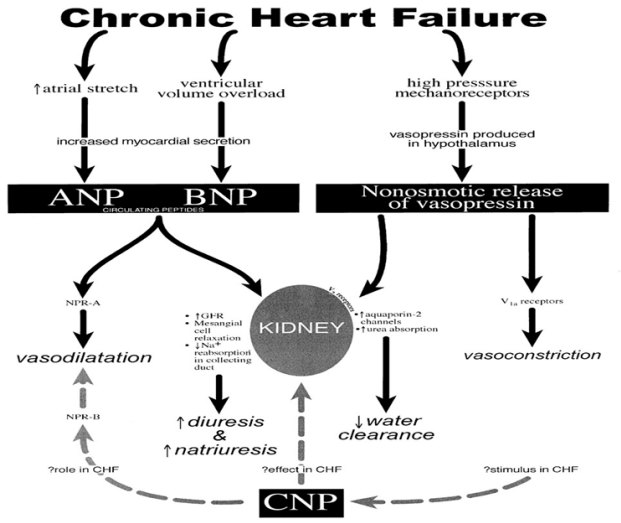

Figure 1. The role of natriuretic peptides in congestive heart failure (CHF).

tive heart failure, and arterial hypertension, there is an increased production of both ANP and BNP. In these above-mentioned cases, the ventricle is responsible for the synthesis of both peptides with BNP levels at 10 - 50-fold higher when compared with ANP. BNP has a more potent natriuretic effect and exerts longer duration of action compared with ANP (6)

The cardiac NPs play a key role in controlling and mediating the arterial blood pressure and intravascular volume via interaction with the ANP receptor, activation of guanylyl cyclase enzyme and increased production of 3 ,5 cyclic guanosine monophosphate (cGMP). NPs can de-activate the activities of RAAS and demonstrate anti-fibrotic and anti-hypertrophic effects (7). Acute administration of ANP has been reported to induce natriuresis, diuresis, and systemic hypotension in lower animals. This hypotensive effect is basically associated with reduced intravascular volume that is continuously maintained by the heart rate via its attenuated autonomic reflex response.

In addition, research studies in animals reported that at high ANP levels after chronic administration there is a decrease in arterial blood pressure sustained basically by lower peripheral resistance (8) unfortunately the results of this research have been linked with the deleterious effects of ANP on the cardiovascular sympathetic tone thereby leading to decrease in peripheral resistance (8). Recent evidence has reported that there is an increase in NPs level in subjects/patients with stage II type of hypertension and above (9) whereas subjects/patients with stage I type of hypertension have been reported to have reduced levels of NT-proBNP1-76 compared with normotensives (9). In another study that was carried out in a large population of adults with history of pre-hypertension and stage I type of hypertension, it was reported that deficiency in BNP is linked with non-activate form of ANP and other types of cardiac NPs leading to an abnormal cardiac endocrine functions at the on-set stages of hypertension (10).

Recent research studies have developed contemporary NP-augmenting techniques that include the design of several synthetic NPs and inhibition of neprilysin, an important enzyme responsible for the chemical breakdown of NP. In addition, Dual-potent angiotensin-receptor neprilysin inhibitors (ARNi) are in the process of been developed for the treatment of hypertension and HF.

Renin-angiotensin aldosterone system (RAAS)

The RAAS is important in the ultimate regulation of cardiovascular homeostasis by regulating vascular tone and blood pressure through vasoconstriction and renal sodium and retention of water via its hormones.

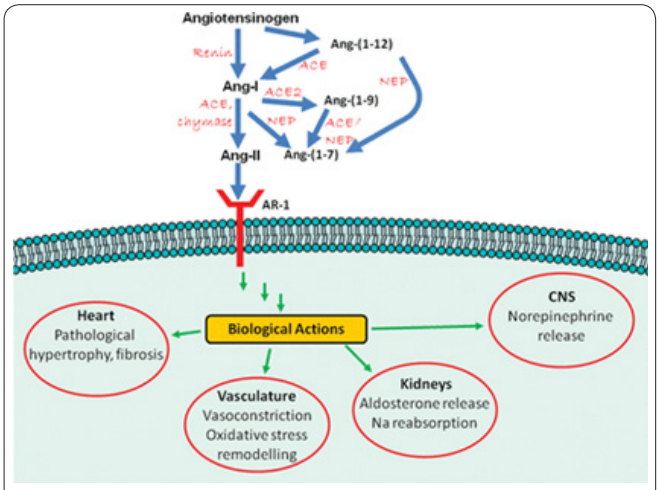

Figure 2. Showing a schematic of the renin–angiotensin–aldosterone system.

Amongst these hormones are angiotensin-II and aldosterone, which are directly important in HF by increasing hypertrophy of cardiac muscle cells and cardiac fibrosis with activation of collagen synthesis and fibroblast proliferation (Figure 2) (14). RAAS has been identified to be involved in the pathophysiology of cardio-renal syndrome in HF, although still with poor prognosis, however a strategy that blocks the activation of RAAS can serve as an efficient therapeutic strategy for HF using RAAS modulating drugs, such as ACEi, angiotensin receptor blockers (ARBs), and mineralcorticoid receptor antagonists (MRA) (1).

Natriuretic peptides in heart failure therapy

The NP system (NPS; Figure 3) has been identified as an important endocrine system linked to particulate guanylyl cyclase (GC) receptors, the cGMP and its effector molecule protein kinase G. It was discovered in 1981, been synthesized by the heart and its responsible for both increasing the process of natriuresis by the kidney and also reducing blood pressure.

An important attribute of natriuretic peptide system (NPS) is the ecto-enzyme neutral endo-peptidase, also known as neprilysin. This membrane-bound enzyme is mostly available in the kidney. Neprilysin is principally responsible for the strategies involved in the enzymatic removal of the native NPs. In addition, neprilysin hydrolyzes Angiotensin-I to Angiotensin-(1–7), given that Angiotensin-(1–7) opposes the activity and action of Angiotensin-II, the hydrolyzes ability of neprilysin has a promising and beneficial CV effects. Inhibition of neprilysin has been developed as a therapeutic option. Intrinsic characteristics like natriuresis, diuresis, RAAS suppressing, inhibition of fibrosis, vasodilatation, and angiogenesis of NPs has made them emerged has a promising candidate for therapeutic use for various type of diseases especially heart failure. Recently the idea of new NPs called designer NPs has emerged as a positive advancement in drug discovery for the treatment and management of several CV diseases.

Therapeutic targeting of the NP system in heart failure

Designer NPs are novel peptides with modified amino acid structures or native NPs, which have been genetically altered. The efficiency of this designer NPs is in their pharmacological and biological potent profiles while reducing undesirable side effects. CD-NP or Cenderitide, a novel hybrid 37 amino acid chain is the most advanced designer NP to date and it was designed by a scientist in the Cardio-renal Research Laboratory at Mayo Clinic in 2008(15). It is a hybrid that consists of a mature form of native human C-type NP integrated with the 15 amino acid C-terminus of dendroaspis NP amino acid, also called cenderitide. Designer NP has efficient characteristics like anti-fibrotic (16) anti-proliferative and anti-hypertrophic of C-type NP, as well as natriuretic and diuretic effects of dendroaspis NP, which are very efficient properties for drugs to treat and manage heart failure.

Based on the successful research findings on cenderitide in designer NP technology, CU-natriuretic peptide (CU-NP) was developed as a humanized form of cenderitide, made up of the 17 amino acid ring of native human CNP bonded to both the Carbon and Nitrogen terminals of urodilatin, which is a 32 amino acid cleavage product of kidney processed pro-ANP. Present researches on experimental studies have reported that intravenous infusion of CU-NP activates Cyclic guanosine monophosphate in canine suffering from heart failure and results into the suppression of RAAS. CU-NP also possess a direct anti-hypertrophic effect via the inhibition of the sodium–hydrogen exchanger 1(NHE-1)/calcineurin pathway (17).

Candoxatril was the first efficient neprilysin inhibitor and it's administered orally and it was responsible for the dose-dependent increase in plasma ANP, natriuresis, and cGMP in humans and also increased circulating Ang-II. Its effect in a human patient with heart failure has been researched and it was reported that it leads to increased ANP and BNP levels, promoted natriuresis, and increased the circulatory time of administered ANP (18). Furthermore, in a canine model of severe heart failure, it was reported that there was an increased level of NP elevation and RAAS activation, candoxatril was natriuretic and suppressed aldosterone.

Dual ACE/Neprilysin (Vasopeptidase) inhibition in heart failure

Another class of therapeutic agent for heart therapy

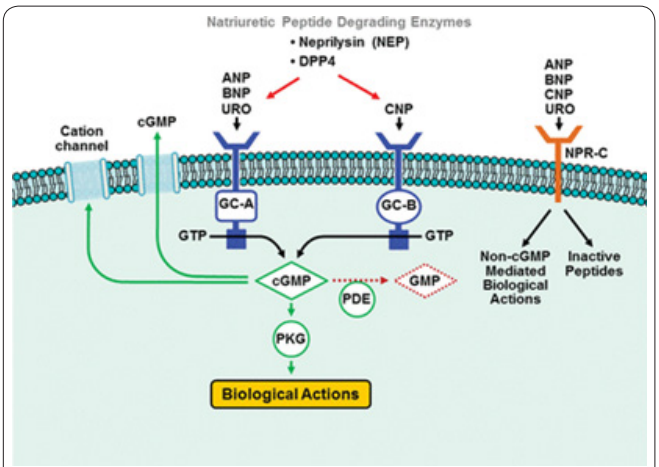

Figure 2. Showing a schematic of the natriuretic peptide system (NPS).

is the combination of the vaso-dilatory and natriuretic effects of the NPs with the vasoconstrictor and anti-natriuretic action of the RAAS suppression agents (19,20), The idea behind this is to overcome the clinical side effects of neprilysin inhibitors as monotherapy with a therapy that involves RAAS blockade. A good example of such drug is omapatrilat (Table 2) with dual neprilysin-ACE inhib ition. Clinical trials like Omapatrilat Cardiovascular Treatment Versus Enalapril (OCTAVE) was the conclusive clinical outcome trial to analyze the positive effects of omapatrilat (versus enalapril) (Table 2) (20) in 25 302 untreated hypertensive patients. OCTAVE showed efficient systolic blood pressure control with omapatrilat and more patients achieved target blood pressure compared with enalapril. There was an increase in the prevalence of angioedema as a side effect in omapatrilat-treated patients, 2.2% versus 0.7% as reported by the OCTAVE trial. The angio-edema is as a result of increased levels of bradykinin achieved with blockade of enzymes like neprilysin, Aminopeptidase-P and dipeptidyl peptidase-4(20). Furthermore, a clinical trial called Phase IIB study (IMPRESS [Inhibition of Metalloprotease by Omapatarilat in a Randomized Exercise and Symptoms Study of Heart Failure]) (21) was carried out on 573 patients to compare omapatrilat 40 mg/d with lisinopril 20 mg/d for 24 weeks (Table 2)

As reported by the clinical trial, Omapatrilat decreased the end point of death, heart failure admission, or stopped the study treatment for aggravated heart failure compared with lisinopril and it leads to a significant improvement in New York Heart Association Class III to IV patients. In addition, there seemed to be a significant improvement of renal function and insignificant angio-edema signal was observed with omapatrilat when compared with lisinopril. The improved outcome of the IMPRESS clinical trial also led to another clinical trial, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) (22), which randomized 5770 patients with New York Heart Association Class II to IV with HF to enalapril 10 mg twice daily or omapatrilat 40 mg once daily for a time period of 14.5 months. The primary end point was insignificantly different when compared with enalapril. A twice-daily dose of omapatrilat may have led to a more improved outcome of smoother pharmacokinetic and pharmacodynamic, and this may have resulted into less major primary end point side effects.

Angiotensin receptor neprilysin inhibitor LCZ696 (Dual-Acting Angiotensin-Receptor/Neprilysin Inhibitors (ARNi))

New and improved therapeutics agents combining neprilysin inhibitor (NEPi) with an angiotensin receptor blocker (ARB) have been developed called an angiotensin receptor neprilysin inhibitor (ARNi). The rationale for these therapeutic agents is that ARBs are less likely to oppose the metabolism of bradykinin and thus reduces their ability to induce cough and angioedema. The first and most clinically effective ARNi is LCZ-696, that is made up of 1:1 ratio of combined valsartan and AHU-377 (NEPi prodrug) called Sacubitril valsatran(24,25). Immediately after ingestion orally, sacubitril valsatran gives off two products namely, sacubitril (AHU-377, which is enzymatically cleaved to the active form, LBQ657) and valsartan (26). There have been few clinical trials of LCZ696 including trials in hypertension, heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Recent research studies have investigated the effect of LCZ696 in patients with heart failure with preserved ejection fraction (HFpEF). Abnormal left ventricular diastolic function with increased ventricular filling pressures, increased vascular stiffness and deterioration of systolic function despite preserved ejection fraction are characteristics of HFpEF(27). HFpEF has been linked with an impaired NP response and renal endocrine response to volume overload (27). As a result, it is hypothesized that LCZ696, by augmenting the effects of NPs in a clinical trial called PARAMOUNT, it was a Phase II, randomized, double-blind multicenter trial in patients with Heart Failure with Preserved Ejection Fraction (HFpEF) (LVEF =45%) (27). The primary endpoint was change from baseline to Week 12 in levels of NT-proBNP (27), the NT-proBNP serves as a marker of left ventricular wall stress that is linked with adverse

Table 2. Showing ACEi+NEPi (vasopeptidase inhibitors).

Drug	Study or model features	Study end results	Key results (NEPi Drugs vs Comparator)
Omapatrilat (23)	Preclinical. Hamsters with heart failure because of dilated cardiomyopathy	Survival, left ventricle remodeling and function at 8 weeks	Reduced mortality and left ventricle remodeling, improved hemodynamics
Omapatrilat (20)	Omapatrilat vs enalapril in patients with hypertension (OCTAVE)	Blood pressure control at 24 weeks	Antihypertensive effect superior to ACEi, but increase of angioedema
Omapatrilat (21)	Omapatrilat vs lisinopril in NYHA class II–IV systolic heart failure (IMPRESS)	Exercise capacity at 12 weeks, heart failure death/ morbidity at 24 weeks	Reduced composite of mortality and heart failure hospitalizations. No angioedema and fewer adverse events than ACEi
Omapatrilat (22)	Omapatrilat vs enalapril in systolic heart failure NYHA 2–4 (OVERTURE)	Composite of mortality and heart failure hospitalizations at 62 weeks	No difference in primary end point

IMPRESS, Inhibition of Metalloprotease by Omapatarilat in a Randomized Exercise and Symptoms Study of Heart Failure; ACEi indicates angiotensin-converting enzyme inhibitor; NYHA, New York Heart Association (functional class; OVERTUNE indicates Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; OCTAVE indicates Omapatrilat Cardiovascular Treatment vs. Enalapril trial.

outcomes in patients with HFpEF (28).

Patients were randomized with LCZ696 or valsartan, 200 mg twice daily or 160mg twice daily respectively for 36 weeks. At 12th weeks, LCZ696 decreased NT-proBNP from baseline by 23% compared with valsartan. PARAMOUNT also showed the effect of LCZ696 on the anatomy of the left atria by measuring parameters like the width, volume and volume index of the left atrial (27), these parameters have been efficient as predictors of signs in chronic HF, with and without reduced LVEF (29,30). After 36 weeks of treatment, the above-mentioned parameters were significantly decreased from baseline with LCZ696 when compared with valsartan. In a recent study, consisting of over 50 years old patient, the administration of LCZ696 led to a constant increase in urinary cGMP that was associated with superior blood pressure control compared with valsartan, without significant increase in natriuresis and diuresis in (31). In another randomized, double-blind, placebo-controlled study, LCZ696 was effective in decreasing SBP and PP levels in the clinic associated with significant reduction in ambulatory blood pressures (32). Compiled results from a double-blind trial made up of 848 patients, most of which are obese, demonstrated that LCZ696 was more potent when compared with valsartan in reducing 24 h ambulatory blood pressure, PP, and office SBP and DBP (33).

In another clinical trial it was reported that 266 Asian patients with systolic hypertension not controlled by amlodipine (34) there was a decrease of 13.9 mmHg in mean 24 h ambulatory SBP in the LCZ696, compared with 0.8 mmHg in the amlodipine arm, this result corroborate the potency of LCZ696 on both the RAAS and sympathetic nervous system. LCZ696 has also been shown to be safe and potent in Asian patients with life-threatening hypertension (35) and has demonstrated superiority against valsartan in hypertensive patients over the age of 65(36). Although the two above clinical trials does-not have large sample area, it is of importance that LCZ696 shown antihypertensive effects among hypertensive populations with no reported cases of angio-edema or other life-threatening side effects.

However, the most concrete evidence of the therapeutic ability of LCZ696 stems from the recent PARADIGM heart failure study (37). In this study, large sample area of 10 521 patients was used with symptomatic heart failure and impaired left ventricular (LV) function (ejection fraction ≤35%) were randomized with either LCZ696 or enalapril for a period of 3 years. Patients had to be on an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker at a stable dose of enalapril 10 mg/day and b-blocker for at least or equivalent of 4 weeks, unless contra-indicated. Patients were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The study showed that LCZ696 was more efficient and potent to enalapril in decreasing death as a result of cardiovascular causes and hospitalization for

Table 3. Showing clinical trials of Sacubitril Valsatran.

First author (Study) (Ref. #)	Sample Size and Patient Population	Study Medications	Study Design	Main Findings
Ruilope et al. (38)	n =1,328 with hypertension	LCZ696 100, 200, and 400 mg vs. valsartan 80, 160, and 320 mg vs. AHU377 200 mg	Randomized controlled dose-ranging study; primary endpoint was reduction in blood pressure between groups at 8 weeks	Significant reductions in systolic and diastolic blood pressure with LCZ696 200 mg vs. valsartan 160 mg and with LCZ696 400 mg vs. valsartan 320 mg; significant reduction in ambulatory blood pressure with LCZ vs.
Kario et al. (32)	n = 309 Asians with hypertension	LCZ696 100, 200, and 400 mg vs. placebo	Randomized controlled dose-ranging study	Significant reductions in systolic and diastolic blood pressures, pulse pressure, and ambulatory pressure with LCZ696
Solomon et al. (PARAMOUNT) (27)	n = 301 with heart failure with preserved ejection fraction.	LCZ696 200 mg twice daily vs. valsartan 160 mg twice daily	Randomized controlled trial; primary endpoint was reduction in N-terminal pro–brain (or B-type) natriuretic peptide at 12 weeks	Significant reduction in N-terminal pro–brain (or B-type) natriuretic peptide at 12 wk with LCZ696, as well as left atrial volume at 36 wk; improvement in New York Heart Association class in patients receiving LCZ696 vs. placebo
McMurray et al. (PARADIGM-HF) (37)	n = 8,442 with heart failure with reduced ejection fraction.	LCZ696 200 mg twice daily vs. enalapril 10 mg twice daily	Randomized controlled trial; primary outcome was cardiovascular death or heart failure hospitalization	Significant reductions in the primary outcome (20%), cardiovascular death (20%), and all-cause mortality (16%) with LCZ696 vs. enalapril

PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAMOUNT = Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction.

heart failure (hazard ratio in the LCZ696 group 0.80; 95% CI 0.73 – 0.87; P, 0.001). It should be noted that LCZ696 exhibited fewer side effects when compared to enalapril (Table 3).

Conclusion

The use of BNP or NT-proBNP as a source of pharmacologic therapy in patients with chronic HF is associated with a significant decreased mortality rate especially in patients below 75 years of age as such there is a need for potent clinical novel therapeutic agents that optimally control HF, hypertension, and coronary artery disease. Any therapeutic strategy targeting the RAAS system and reducing its deleterious effects in HF pathogenesis and progression will optimally and majorly contribute to heart failure pharmacotherapy (39-43).

Angiotensin receptor neprilysin inhibitor (ARNi) and its first in the class molecule, LCZ 696, have been promising in been potent to cure and manage cardiovascular diseases. However, with current research works ARNIs may well soon more efficient angiotensin receptor blockers (ARBs), ushering a new dawn of compound system modulation that will shed more light on the treatment of cardiovascular disease. Finally, extensive studies should be done on the NPs and LCZ696 to further elucidate and clarify its mechanisms of its potential cardio-renal and cardiovascular protection (44-49).

Acknowledgments

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References

1. McMurray JJ V, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J. 2012;33(14):1787–847.
2. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J, et al. Extended heart failure clinic follow-up in low-risk patients: A randomized clinical trial (NorthStar). Eur Heart J. 2013;34(6):432–42.
3. Schroten NF, Gaillard CAJM, Van Veldhuisen DJ, Szymanski MK, Hillege HL, De Boer RA. New roles for renin and prorenin in heart failure and cardiorenal crosstalk. Heart Fail Rev. 2012;17(2):191–201.
4. Von Lueder TG, Krum H. RAAS inhibitors and cardiovascular protection in large scale trials. Vol. 27, Cardiovascular Drugs and Therapy. 2013. p. 171–9.
5. Regoli D, Plante GE, Gobeil F. Impact of kinins in the treatment of cardiovascular diseases. Pharmacol Ther. 2012;135(1):94–111.
6. Jaffe AS, Babuin L, Apple FS. Biomarkers in Acute Cardiac Disease. The Present and the Future. Vol. 48, Journal of the American College of Cardiology. 2006. p. 1–11.
7. Pandey KN. Biology of natriuretic peptides and their receptors. Vol. 26, Peptides. 2005. p. 901–32.
8. Melo LG, Pang SC, Ackermann U. Atrial Natriuretic Peptide: Regulator of Chronic Arterial Blood Pressure. News Physiol Sci An Int J Physiol Prod Jointly by Int Union Physiol Sci Am Physiol Soc. 2000;15:143–9.
9. Belluardo P, Cataliotti A, Bonaiuto L, Giuffrè E, Maugeri E, Noto P, et al. Lack of activation of molecular forms of the BNP system in human grade 1 hypertension and relationship to cardiac hypertrophy. Am J Physiol Heart Circ Physiol. 2006;291:H1529–35.
10. MacHeret F, Heublein D, Costello-Boerrigter LC, Boerrigter G, McKie P, Bellavia D, et al. Human hypertension is characterized by a lack of activation of the antihypertensive cardiac hormones ANP and BNP. J Am Coll Cardiol. 2012;60(16):1558–65.
11. Michels P, Tarnow J. [Natriuretic peptides: physiological, pathophysiological and clinical aspects]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2001;36(7):406–16.
12. Das BB, Solinger R. Role of natriuretic peptide family in cardiovascular medicine. Cardiovasc Hematol Agents Med Chem. 2009;7(1):29–42.
13. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Vol. 27, Endocrine Reviews. 2006. p. 47–72.
14. Zhou J, Xu X, Liu JJ, Lin YX, Gao GD. Angiotensin II receptors subtypes mediate diverse gene expression profile in adult hypertrophic cardiomyocytes. Clin Exp Pharmacol Physiol. 2007;34(11):1191–8.
15. Lisy O, Huntley BK, McCormick DJ, Kurlansky PA, Burnett JC. Design, Synthesis, and Actions of a Novel Chimeric Natriuretic Peptide: CD-NP. J Am Coll Cardiol. 2008;52(1):60–8.
16. Sangaralingham SJ, Huntley BK, Martin FL, McKie PM, Bellavia D, Ichiki T, et al. The aging heart, myocardial fibrosis, and its relationship to circulating C-type natriuretic peptide. Hypertension. 2011;57(2):201–7.
17. Kili?? A, Rajapurohitam V, Sandberg SM, Zeidan A, Hunter JC, Said Faruq N, et al. A novel chimeric natriuretic peptide reduces cardiomyocyte hypertrophy through the NHE-1-calcineurin pathway. Cardiovasc Res. 2010;88(3):434–42.
18. Martin FL, Stevens TL, Cataliotti A, Schirger JA, Borgeson DD, Redfield MM, et al. Natriuretic and antialdosterone actions of chronic oral NEP inhibition during progressive congestive heart failure. Kidney Int. 2005;67(5):1723–30.
19. Nathisuwan S, Talbert RL. A review of vasopeptidase inhibitors: a new modality in the treatment of hypertension and chronic heart failure. Pharmacotherapy. 2002;22(1):27–42.
20. 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(2):103–11.
21. Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, 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(9230):615–20.
22. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, 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(8):920–6.
23. Dalzell JR, Seed A, Berry C, Whelan CJ, Petrie MC, Padmanabhan N, et al. Effects of neutral endopeptidase (Neprilysin) inhibition on the response to other vasoactive peptides in small human resistance arteries: Studies with thiorphan and omapatrilat. Cardiovasc Ther. 2014;32(1):13–8.
24. Langenickel TH, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: A novel approach for the treatment of heart failure. Drug Discov Today Ther Strateg. 2012;9(4).
25. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. Vol. 2, JACC: Heart Failure. 2014. p. 663–70.

26. Feng L, Karpinski PH, Sutton P, Liu Y, Hook DF, Hu B, et al. LCZ696: A dual-acting sodium supramolecular complex. Tetrahedron Lett. 2012;53(3):275–6.
27. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380(9851):1387–95.
28. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Hear Fail. 2011;4:27–35.
29. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation. 2011;124(23):2491–501.
30. Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ, et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2011;58(16):1682–9.
31. Kobalava Z, Kotovskaya Y, Villevalde S, Moiseev V, Albrecht D, Chandra P CL. Blood pressure lowering and natriuretic effects of LCZ696 in pa- tients with hypertension: a randomized, double-blind, controlled, crossover study. J Clin Hypertens. 2013;15(14).
32. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, et al. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in asian patients with hypertension: A randomized, double-blind, placebo-controlled study. Hypertension. 2014;63(4):698–705.
33. Ruilope LM, Izzo JL Jr, Conde LG, Zappe DH, Zhang Y ZI. Efficacy of LCZ696, an angiotensin receptor neprilysin inhibitor (ARNI), in subjects with grade 2 hypertension. Eur Hear J. 2014;(35):65.
34. Wang K, Yukisada A, Sibulo K, Hafeez Y ZJ. Efficacy and safety of LCZ696 add-on to amlodipine in patients with systolic hypertension uncontrolled with am- lodipine monotherapy. Eur Hear J. 2014;35:64.
35. Kario K, Tamaki Y KH. LCZ696, a novel angiotensin receptor neprilysin inhibi- tor: the first trial in patients with severe hypertension. J Hypertens. 2014;32.
36. Izzo JL Jr, Ruilope LM CL. Comparative efficacy of valsartan and LCZ696, an angiotensin receptor neprilysin inhibitor (ARNI), in hypertensive individuals over age 65. J Hypertens. 2014;32.
37. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
38. Ruilope LM, Dukat A, B??hm M, Lacourcire 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(9722):1255–66.
39. Aiyelabegan HT, Zaidi SSZ, Fanuel S, Eatemadi A, Ebadi MTK, Sadroddiny E. Albumin-Based Biomaterial for Lungs Tissue Engineering Applications. Int J Polym Mater Polym Biomater. 2016;(just-accepted).
40. Beiranvand S, Eatemadi A, Karimi A. New Updates Pertaining to Drug Delivery of Local Anesthetics in Particular Bupivacaine Using Lipid Nanoparticles. Nanoscale Res Lett. 2016;11(1):1–10.
41. Daraee H, Eatemadi A, Abbasi E, Fekri Aval S, Kouhi M, Akbarzadeh A. Application of gold nanoparticles in biomedical and drug delivery. Artif cells, nanomedicine, Biotechnol. 2016;44(1):410–22.
42. Daraee H, Etemadi A, Kouhi M, Alimirzalu S, Akbarzadeh A. Application of liposomes in medicine and drug delivery. Artif cells, nanomedicine, Biotechnol. 2016;44(1):381–91.
43. Eatemadi A, Darabi M, Afraidooni L, Zarghami N, Daraee H, Eskandari L, et al. Comparison, synthesis and evaluation of anticancer drug-loaded polymeric nanoparticles on breast cancer cell lines. Artif cells, nanomedicine, Biotechnol. 2016;44(3):1008–17.
44. Eatemadi A, Daraee H, Karimkhanloo H, Kouhi M, Zarghami N, Akbarzadeh A, et al. Carbon nanotubes: properties, synthesis, purification, and medical applications. Nanoscale Res Lett. 2014;9(1):1–13.
45. Eatemadi A, Daraee H, Zarghami N, Melat Yar H, Akbarzadeh A. Nanofiber: synthesis and biomedical applications. Artif cells, nanomedicine, Biotechnol. 2016;44(1):111–21.
46. Ghafarzadeh M, Eatemadi A, Fakhravar Z. Human amniotic fluid derived mesenchymal stem cells cause an anti-cancer effect on breast cancer cell line in vitro. Cell Mol Biol. 2016;2016(6):102–6.
47. Mohammadian F, Eatemadi A. Drug loading and delivery using nanofibers scaffolds. Artif cells, nanomedicine, Biotechnol. 2016;1–8.
48. Mellatyar H, Akbarzadeh A, Rahmati M, Ghalhar MG, Etemadi A, Nejati-Koshki K, et al. Comparison of inhibitory effect of 17-DMAG nanoparticles and free 17-DMAG in HSP90 gene expression in lung cancer. Asian Pac J Cancer Prev. 2014;15(20):8693–8.
49. Seidi K, Eatemadi A, Mansoori B, Jahanban-Esfahlan R, Farajzadeh D. Nanomagnet-based detoxifying machine: an alternative/complementary approach in HIV therapy. J AIDS Clin Res. 2014;2014.