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Arni - A Novel Therapeutic Approach

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ABSTRACT

Over the centuries cardiovascular diseases a warning alarm for the human being. Heart disease mainly heart failure, ischemic heart disease, ischemic stroke, hemorrhagic stroke, peripheral artery disease, myocarditis, hypertensive disorders, rheumatic heart diseases are the main reason for the increased death in the globally. Traditional drugs such as beta-antagonist, Mineralocorticoid receptor blockers, and ACE inhibitors shows a decrease in cardiovascular disease patients mortality. A neutral endopeptidase, natriuretic peptide plays a vital role in degrading many endogenous vasoactive peptides like bradykinin together with RAAS is responsible in developing heart failure. To combine the action of both RAAS and augment natriuretic peptide, a new class of therapy, Angiotensin Receptor Neprilysin Inhibitors updated after clinical trial which is a combination of LCZ696, a Neprilysin inhibitor, sacubitril and valsartan combination. The administration of these drugs had shown a drastic decrease in hospitalization of patients with heart failure and other cardiovascular disease. Finally, we have found that implementing sacubitril/ valsartan combination drug in heart failure patients and other patients with cardiovascular diseases had shown a greater rate of improvement, and a drastic decrease in hospitalization and deaths due to heart failure.

INTRODUCTION

Cardiovascular disease is one of the leading causes of death in the world which. The death caused from cardiovascular disease is drastically alarming and is caused majorly by ischemic heart disease, ischemic stroke, hemorrhagic stroke, atrial fibrillation, peripheral arterial disease (PAD), aortic aneurysm, cardiomyopathy and myocarditis, hypertensive heart disease, endocarditis, rheumatic heart disease, and a category for other CVD conditions.[1] Heart failure (HF) is a clinical syndrome which is caused by structural defect as well as the functional defects in the myocardium of the heart. This will ultimately result in the impairment of ventricular filling or the ejection of blood. Reduction in left ventricular myocardial function, hemodynamic overload, dysfunctions relating to ischemia, ventricular remodeling, and excessive neuro-humoral stimulation, abnormality in myocyte calcium cycling, excessive proliferation of the extracellular matrix, or inadequate proliferation of the extracellular matrix, accelerated apoptosis and genetic mutations are the major causes of heart failure [2] .

Heart failure with preserved ejection fraction and reduced ejection fraction are common among heart failure patients. Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction are two types of classification of heart failure.[3] The major mechanisms involved are myocardial hypertrophy and fibrosis, impairment in diastolic compliance and relaxation, systolic dysfunction, and renal dysfunction altogether lead to elevated intracardiac filling pressures, fluid retention, and exercise intolerance.[4,5] The beta-antagonist and mineralocorticoid-receptor blocker, along with ACE inhibitors, result in drastic decreases in the risk of death of 30 to 35% and 22 to 30% [6].

RAAS and natriuretic peptides play a very important role in developing heart failure.[6] Natriuretic peptide is a neutral endopeptidase that degrades several endogenous vasoactive peptides, like natriuretic peptides, bradykinin, a potent endothelium-dependent vasodilator peptide, which are released at sites of inflammation and also in coagulation.[6,7] When there is an inhibition of neprilysin, endogenous substances level will increase, which will counter the neuro-hormonal over activation and ultimately contribute to vasoconstriction, sodium retention, and maladaptive remodeling [8,9,10,11].

Angiotensin receptor neprilysin inhibitors (ARNI) is a new class of drug which are developed to block both the RAAS and augment natriuretic peptides. These drugs are a combination of

LCZ696, neprilysin inhibitor and valsartan ARBs are present in them. Thus, ARNI process the potential to modulate favorably the neurohormonal imbalance which normally characterizes the heart.[3,6] The angiotensin receptor neprilysin inhibitor sacubitril/valsartan (earlier LCZ696) reduced both death and heart failure (HF) hospitalizations in patients with New York Heart Association (NYHA) functional classes II to IV HF and ejection fraction.[12,13] Sacubitril/valsartan play a very important role in the reduction of cardiovascular and all-cause mortality, as well as HF hospitalizations (HFHs), in patients with HF with reduced ejection fraction (HFrEF) compared with other traditional heart failure drugs [13] but they won't play a very important role in the reduction of hospitalization.[14] The angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696 early) the first ARNI blocks both the RAAS and the endopeptidase neprilysin simultaneously. Sacubitril/valsartan is a crystalline compound composed of both the angiotensin receptor blocker valsartan and the neprilysin(ubiquitous enzymes) inhibitor - sacubitril. Sacubitril is a prodrug. After ingestion ARNI disintegrated into their respective constituents, Further sacubitril esterified to its active form, sacubitril [16,17].

MECHANISM OF ACTION

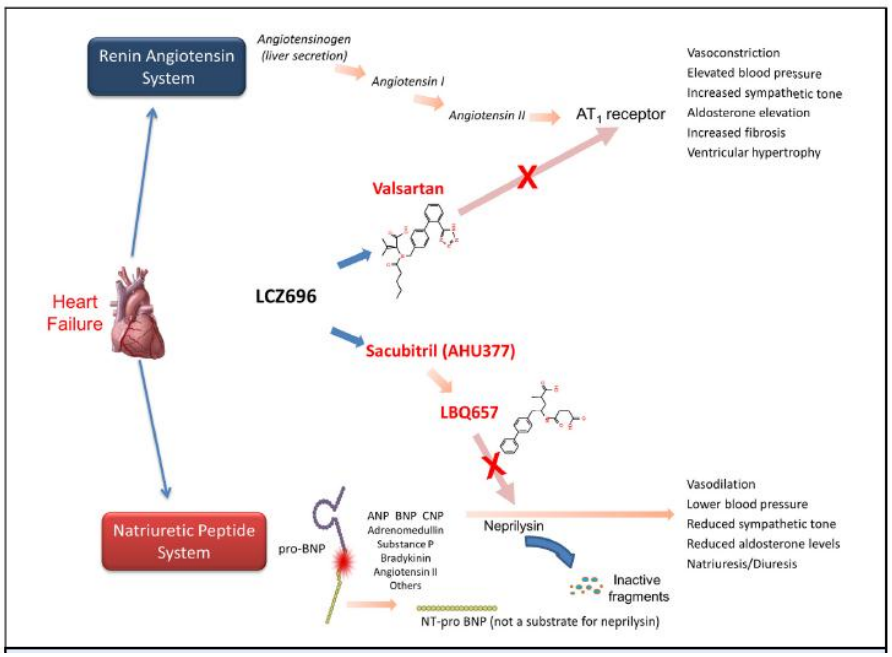

FIG. 1: ARNIs Mechanism of action

The neprylisin inhibition shows beneficial effects by the decrease in the degradation of the natriuretic peptides. These Natriuretic peptides cause vasodilation by stimulating particulate

guanylate cyclase to produce cGMP.[15,18] (but in heart failure patients there occurs an increased expression of phosphodiesterase whose major role is the degradation of Cgmp [23] and produces its beneficial effect. In heart failure, administration of valsartan/sacubitril decreased N-terminal pro-brain natriuretic peptide (NT-proBNP) rather than the effect on BNP [14,15,19] which again contribute to the beneficial effect. The ARNI exerts its role in the kidney in the kidney, by the increase in renal blood flow and glomerular filtration.

The major role of natriuretic peptides is the sodium reabsorption in the proximal convoluted tubule and distal convoluted tubule of nephron present in kidney. They will suppresses the RAAS and sympathetic systems leading to the declining in the secretion of endothelin. The natriuretic peptides also exert anti-inflammatory, antifibrotic, and antihypertrophic effects in cardiomyocytes [20-25]and increase in synthesis of adiponectin. The progression of heart failure result in decreases in responsiveness to natriuretic peptides, in particular (ANP and BNP,).[26,27] This will increases the resistance to natriuretic peptides resulted from down-regulation of natriuretic peptide receptors, increased clearance of BNP by diminished downstream signaling of NPR-C receptor.[28] Decreased degradation of natriuretic peptides with valsartan/sacubitril could overcome natriuretic resistance resulting from any one of these mechanisms. Thus the pharmacological approaches for the augmentation of the activities of natriuretic peptides in humans have discovered exogenous administration of endogenous peptides or degradation-resistant peptides,[20, 21] as well as the development of NEP inhibitors i.e ARNIs.

PHARMACOKINETICS

- After the oral administration of ARNI, is converted to its pro drug valsartan with a median time to reach maximum plasma concentration range from 0.50 to 1.25, 2.00 to 3.00 and 1.50 to 2.50 h, respectively.

- The elimination half-life ranged from 0.89 to 1.35, 8.57 to 9.24 and 5.33 to 7.91 h for sacubitril, sacubitril and valsartan, respectively. The AUC of concentration curve from time zero to the time of the last quantifiable concentration ($AUC_{0–last}$) and C_{max} for sacubitril increased dose proportionally over the entire dose range.

- Neprylisin inhibitor is safe and also well-tolerated at all doses in this study.[16] ARNI can be administered with or without food. Administration of ARBs in combination with ARNIs increases its bioavailability[17].

- The dose of ARNI valsartan is 100 mg (51 mg valsartan), 200 mg (103 mg valsartan). The apparent volume of distribution of valsartan is 75 L and for sacubitril is 103 L. About 94% to 97% of valsartan, sacubitril, and LBQ657 are bound to plasma proteins.

- The surprising fact lies that the ARNi is bioequivalent to 80 and 160 mg than valsartan when administered as its own. Subsequent to oral administration, sacubitril is excreted through the urine and feces. In both of cases, sacubitril at is the excretion form. Valsartan and its metabolites are excreted in feces.

USES OF ARNI (CURRENT AND FUTURE APPLICATIONS)

CVDs are proven to be treated by the blockage or the inhibition of RAAS and the sympathetic nervous system. They are categorised as neurohumoral systems. Recently it's been found that any dysregulation in the natriuretic peptides (NPs) hormonal system can also develop CVDs.To counteract the effects of angiotensin II and to increase the activity of NPs, a new class of therapy, developed. This newer class is angiotensin receptor - neprilysin inhibitor (ARNi). ARNi is currently been used in the therapy of heart failure with reduced ejection fraction (HFrEF). In further years researchers are in the hope to widen the application of this therapy to other CVDs, such as heart failure, with preserved ejection fraction and hypertension[31].

CHANGES IN NATRIURETIC PEPTIDES

BNP concentrations in a study moderately increased throughout the treatment compared with enalapril to the baseline and the group receiving enalapril. Conversely, N- terminal proBNP (NT- proBNP) concentrations decreased in patients receiving sacubitril/valsartan while remaining stable in patients receiving enalapril.[14,15,19] Studies shows that among natriuretic peptides, the useful effects of sacubitril/valsartan occurs in ANP and CNP – rather than BNP [15].

CHANGES IN SOLUBLE NEPRILYSIN ACTIVITY AFTER INVESTIGATION WITH ARNI

Introduction of sacubitril/valsartan was associated with a decrease in serum neprilysin activity which elevated the substrate of neprilysin, fructosamine, ANP[1-28], substance P adrenomedullin, and GLP- 1[15].

CLINICAL APPLICATIONS OF ARNI

HEART FAILURE WITH REDUCED EJECTION FRACTION

The prospective comparison of angiotensin receptor–neprilysin inhibitor with ACEi to determine the impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial was first conducted in sacubitril/valsartan for HFrEF[32]**.** In PARADIGM-HF, sacubitril/valsartan was compared to enalapril in patients having HFrEF who have left ventricular ejection fraction (LVEF) ≤ 35% and an increased BNP level and also the reduction of NT Pro BNP or hospitalized for HF. In many of the PARADIGM-HF shows that ARNI (sacubitril/valsartan) was increasing the effective than enalapril in patients of these patients. These studies also proved that Treatment with sacubitril-valsartan will also result in a 20% relative risk reduction which is considered as the primary endpoint. The reduction in the liability of recurrent hospitalization is another important benefit of the drug[33]**.** PARADIGM-HF data also shows the analysis by using the placebo analysis. Mechanisms of the benefit of ARNI over other drugs are not able to establish from studies**.** It is found that a higher proportion of patients have achieved optimal RAAS inhibition and also additional benefits by neprilysin inhibition with an ARNi [32] help in the reduction of HF with reduced ejection fraction**.** The regulations introduced by America and Europe for the management of HF included sacubitril/valsartan as first-line therapy for outpatients affected by chronic HFrEF [34,35]. It has been established in the study that the Safety and Tolerability of ARNI in Patients with HFrEF also add useful criteria for adding them to the list of traditional heart failure agents. Despite many facts, ARNI had shown the benefits of sacubitril/valsartan which also proved in the subgroup of prediabetic, undiagnosed diabetic, and diagnosed diabetic patients, who are at a higher risk of developing CVDs [40]**.** ARNi also extends its benefit by ensuring nephroprotective effects which proves another reason for its administration in patients[6-39]**.** ARNi also proved a better quality of life by citing the fact that there occurs a reduction in the number of visits to an emergency department for HF, a reduction in the treatment of HF, and a lower need for intensive care, HF devices, or heart transplantation [41]**.** ARNi also reduces the chances of, getting coronary artery associated diseases [42] The combination of sacubitril with valsartan showed an improvement in load-dependent left ventricle contraction and relaxation with a reduction of myocardial collagen content, while the improvement in load-independent left ventricular contractility is due to valsartan [43]**.**

REDUCED CARDIAC FIBROSIS AND REVERSE REMODELLING

Myocardial fibrosis is one of the important factors for the development of heart failure under the influence of various peptides and hormones which are secreted as a result of overlapping hemodynamic, neuro hormonal, and pro-fibrotic triggers.58 Sacubitril-valsartan reduces levels of pro-fibrotic biomarkers i.e., aldosterone, soluble ST2, metalloproteinase tissue inhibitor, galectin-3, and N-terminal propeptide of collagen I, III [44-46] and also inhibits the activity of cardiac fibroblast. [47] Sacubitril-valsartan increases LVEF, and reduces left ventricular and atrial volumes more than angiotensin converting agents or angiotensin receptor blocker [47,48].

DIABETES MELLITUS

Preclinical study on rat models for diabetes showed that the beneficial effects of sacubitril/valsartan depends on an increase in NP levels, bradykinin, glucagon-like peptide 1, and on the decrease in angiotensin II levels that would result in an increased insulin sensitivity **[49,50].** Even though diabetes is not only a comorbidity widely present among HF cases but the invention of ARNi can substantially modify the patient prognosis. Another preclinical data seems to confirm the beneficial effects of sacubitril/valsartan on vascular and neural complications in type 2 diabetes, giving hope about possible wider applications of ARNi in diabetic patients at the future[51]**.** A post hoc analysis done in diabetic patients showed that this treatment leads to a better glycaemic profile (reduction of Hb1Ac and less need to undertake insulin therapy or oral hypoglycaemic agents) for a long duration, independent of the reduction in body weight[52]**.** Similar beneficial effects of sacubitril/valsartan on lipid and glucose metabolism have also been reported in obese patients having hypertension [53]**.**

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Until now, sacubitril/valsartan does not have an evident effect in patients with HFpEF but the most quoted theory is through the blockage of a profibrotic/hypertrophic mechanism by valsartan and stimulation of an antifibrotic/antihypertrophic mechanism by sacubitril was supposed to play a beneficial effect in HFpEF**.** The influence of RAAS may play a vital role in enhancing the inflammation, endothelial dysfunction, and remodeling in patients having HFpEF. By increasing NPs levels sacubitril/valsartan might be beneficial in some major pathways involved in the development of HFpEF. These include cardiac remodeling, such as left ventricular hypertrophy and stiffness, microvascular dysfunction, and oxidative stress [54]**.**

In a phase, II PARAMOUNT trial, which is the prospective comparison of ARNi with ARB on the management of heart failure with preserved ejection fraction, patients affected by HFpEF was tested with Sacubitril/valsartan[55]**.** The trial had shown that the left atrial dimension, which may indicate diastolic function [55], declined more in the sacubitril/valsartan group. Also, the markers of fibrosis was decreased more in sacubitril/valsartan group [56]**.** When New York Heart Association (NYHA) class was considered patient's treated with sacubitril/valsartan had a significant improvement in renal function compared to the valsartan group[57] Phase III PARAGON trial has been designed to determine whether sacubitril/valsartan can reduce CV death or total HF hospitalizations in patients with HFpEF.[58] PARALLAX study had recently proved the superiority of LCZ696 in reducing NTproBNP levels and improving HF symptoms and exercise function in HFpEF patients[59].

HYPERTENSION

In preclinical studies conducted in animal models of hypertension, ARNi favorably exerts antihypertensive and cardioprotective effects**.** They also exert a significant reduction of BP and proteinuria levels and a full prevention from stroke was observed over long-term treatment with sacubitril/valsartan, as compared to valsartan, in the high-salt-fed, stroke-prone, spontaneously hypertensive rat.[60] Furthermore, in a model of spontaneous hypertensive rat, ARNI is proved to be as effective as valsartan alone in improving endothelium-dependent and -independent vasorelaxation [61]**.** Moreover, ARNI has exposed an improvement in the reduction of BP levels compared to valsartan, regardless of the amount of salt intake in the experimental setup. The consequence was linked with a significant augmentation of urinary sodium excretion and suppression of sympathetic activity. Besides, it reduced myocardial inflammation, remodeling, and endothelial dysfunction, also ameliorating coronary circulation [62]**.** A trial enrolling mostly white patients, who are hypertensive established that compare with valsartan or AHU377 alone, sacubitril/valsartan treatment for 2 months provides that additional reduction of blood pressure, systolic, diastolic, pulse pressures, both sitting and ambulatory, without any excess in serious adverse effects [63]**.** In the PARAMETER (prospective comparison of angiotensin receptor–neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly) study, ARNI demonstrated efficacy in reduction of arterial stiffness in the elderly with systolic hypertension and pulse pressure >60 mmHg[11]**.** Compared to olmesartan, ARNI reduced central aortic systolic BP more and reduced mean 24-hour ambulatory brachial and central

aortic systolic BP, at 3 months. Therefore, fewer patients in the sacubitril/valsartan group required add-on antihypertensives [64]. A recent similar study in a cohort-based study of elderly Asiatic patients affected by isolated systolic hypertension showed that ARNI was more effective than olmesartan in reducing mean systolic BP and pulse pressure [66]. But the similarity between both of them is a similarity in drug tolerability. There is another evidence which shows that LCZ696 monotherapy was dose-dependently superior to valsartan monotherapy by clinical and ambulatory blood pressure measurements for all tested doses [65]. Thus, it is proved to be effective for reduction in hypertension.

REDUCTION IN LEVEL OF URIC ACID

Uric acid (UA) produces harmful reactive oxygen species and an increased level of uric acid results in an elevated oxidative stress. ARN I is associated with a reduction in UA levels in PARADIGM-HF). But unfortunately, the proper mechanism is unknown.[33]

ACUTE HEART FAILURE

This is established by studying the Comparison of ARNI versus ACEi on the Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial. The study was completed with the conclusion of the time-averaged proportional change in the NT-proBNP level. The study also found a decline in the level of troponin T and provides benefit for the same. [46]

CONCLUSION

Heart failure had become a major reason behind the increased rate of mortality worldwide. Even though the traditional methods had efficiently managed HF, the deaths have not decreased significantly. The combination of sacubitril/valsartan is found to be an effective option in the management of heart failure. In conclusion, we have found that administration of sacubitril/ valsartan combination drug in heart failure patients and other patients with cardiovascular disease had shown a greater rate of improvement, and a drastic decrease in hospitalization and deaths due to heart failure and other cardiac conditions.

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