Review On A Novel Dual Acting Angiotensin Receptor-Neprilysin Inhibitor(ARNI): Potential Benefits In Heart Failure And Reduced Ejection Fraction(HFREF).

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Abstract
Objective: To describe the efficacy, superiority and safety profile of the first-in-class angiotensin receptorneprilysin inhibitor "Sacubitril/Valsartan" and angiotensin II receptor blocker (ARB) in heart failure (HF) patients, reviewing data available from both clinical and pre-clinical studies. Evidences on health care utilization outcomes.

Inhibition of neurohumoural pathways such as the renin angiotensin aldosterone and sympathetic nervous systems is central to the understanding and treatment of heart failure (HF). Conversely, until recently, potentially beneficial augmentation of neurohumoural systems such as the natriuretic peptides has had limited therapeutic success. Administration of synthetic natriuretic peptides has not improved outcomes in acute HF but modulation of the natriuretic system through inhibition of the enzyme that degrades natriuretic (and other vasoactive) peptides, neprilysin, has proven to be successful. After initial failures with neprilysin inhibition alone or dual neprilysin-angiotensin converting enzyme (ACE) inhibition, the Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) trial demonstrated that morbidity and mortality can be improved with the angiotensin receptor blocker neprilysin inhibitor sacubitril/valsartan (formerly LCZ696). These findings suggest that sacubitril/valsartan should replace an ACE inhibitor or angiotensin receptor blocker as the foundation of treatment of symptomatic patients (NYHA II–IV) with HF and a reduced ejection fraction.

Key Words: Neprilysin inhibitor, heart failure, ejection fraction.

I. Introduction

Heart failure (HF) is a major and growing health challenge in India and the developing countries. It is one of the most important causes of morbidity and mortality in the industrialized world. The prevalence of HF in India is possibly on the rise as India remains doubly burdened by the rise in the risk factors of traditional cardiovascular (CV) disease and by the persistence of pre-transitional diseases such as rheumatic heart diseases, endomyocardial fibrosis, tuberculosis pericardial disease and anaemia. Burden of HF in India due to hypertension is extrapolated to be 3.5–7 million (estimate of about 4–5 million) and HF due to myocardial infarction is 2.1 million to 8.4 million (estimate of about 4–5 million) while an annual mortality due to HF around 0.1–0.16 million. With resources like cardiac resynchronization therapy and the heart transplant program available on a limited basis, pharmacotherapy still remains the primary treatment option. [1]

Indeed, risk factors, such as hypertension, are common prognostic comorbidities in chronic HF. The impact of HF on patient quality of life and the financial burden imposed on the healthcare system are great, with frequent costly hospitalizations and a 5-year mortality rate of approximately 50%. While survival rates have improved for HF with reduced ejection fraction (HFrEF) due to more widespread use of drugs that block the renin–angiotensin– aldosterone system (RAAS) residual mortality rates remain high. For patients with HF with preserved ejection fraction (HFpEF) no therapy has proven to be effective at reducing morbidity and mortality. Consequently, there is an urgent need for new therapies to prevent and treat HFrEF .[2]

Sacubitril/Valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNi) approved for the treatment of HF. It consists of the angiotensin receptor blocker (ARB) 'valsartan' and the neprilysin inhibitor 'sacubitril', in a 1:1 mixture by molecule count. The combination is thereby marketed as an "Angiotensin

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Receptor-Neprilysin Inhibitor". [3]Currently, sacubitril/valsartan combination has been approved in more than 57 countries including India. The U.S. Food and Drug Administration approved sacubitril/valsartan combination in July 2015 for the treatment of patients with New York Heart Association (NYHA) class II through IV HF symptoms and a reduced ejection fraction (HFrEF) based on the results of the PARADIGM-HF trial. It has now been included as a Class I B recommendation by the 2016 ESC and ACC/AHA/HFSA guidelines.[4]

MECHANISM OF SACUBITRIL/VALSARTAN IN HFrEF

Neprilysin, also known as membrane metallo-endopeptidase (MME), neutral endopeptidase (NEP), cluster of differentiation , and common acute lymphoblastic leukaemia antigen (CALLA), is an enzyme that in humans is encoded by the MME gene. It is found in many tissues, particularly in kidney on the brush border of proximal tubules and on glomerular epithelium. It is the principal enzyme for degradation of multiple vasoactive peptides (VAP) including natriuretic peptides, angiotensin, endothelin 1, adrenomedullin, opioids and amyloid-β peptide (Aβ). It cleaves peptides at the amino side of hydrophobic residues and inactivates several peptide hormones including glucagon, enkephalins, substance P, neurotensin, oxytocin, and bradykinin. Sacubitril (AHU-377), neprilysin inhibitor, is a prodrug that is activated to the active metabolite 'Sacubitril' by deethylation via esterase's. [5]

Sacubitril, thus, increases the levels of these peptides, promoting natriuresis, vasodilation and reduction of ECF volume via sodium excretion; eventually reducing preload and ventricular remodelling. Valsartan inhibits the effects of angiotensin-II by selectively blocking the receptor type-1 (AT1), and concomitantly inhibiting angiotensin-II-dependent aldosterone release. Blockade of AT1 thus reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. In experimental studies, sacubitril/ valsartan have shown to attenuate angiotensin-II-mediated cardio-renal fibrosis and cardiac remodelling and dysfunction after experimental myocardial infarction; attributed to superior inhibition by sacubitril/valsartan on cardiac fibrosis and cardiac hypertrophy than either stand-alone neprilysin inhibitor or ARB. [6]In summary, the CV and renal benefits of sacubitril/valsartan in HF patients are attributed to the increased levels of peptides that are degraded by neprilysin and the simultaneous inhibition of the effects of AT1 receptor by valsartan.

THE NATRIURETIC PEPTIDE SYSTEM

The natriuretic peptide system counter regulates the detrimental effects of the upregulation of RAAS that occurs in HF-REF, inhibits secretion of arginine vasopressin and modulates the autonomic nervous system in ways that are likely to be beneficial in this syndrome. Sodium and water retention and vasoconstriction caused by activation of RAAS and the sympathetic nervous system, and the action of vasopressin, lead to increased ventricular preload and afterload and elevated wall stress which in turn lead to production of pre-pro B-type natriuretic peptide (BNP) which is cleaved to BNP and N-terminal proBNP (NT-proBNP).[7] The release of natriuretic peptides may also be determined by the levels of other neuro-hormones such as angiotensin II and endothelin. The peptide BNP acts to promote natriuresis and vasodilation (NT-proBNP is physiologically inactive).[8] Atrial stretch leads to the production of pre-proatrial or A-type natriuretic peptide and ultimately atrial natriuretic peptide (ANP) which has similar biological properties to BNP. Urodilatin (which is structurally related to ANP), is derived from the same precursor in the kidneys. C-type natriuretic peptide (CNP) is released from endothelial cells and acts in a paracrine fashion but is only found in low concentrations in circulating blood. Two strategies have been employed to try and improve outcomes in HF-REF via modulation of this pathway.[9] The first is the administration of exogenous natriuretic peptides. Nesiritide, a recombinant human BNP, initially showed promising beneficial effects on haemodynamics and natriuresis in patients with HF-REF. However, in a large-scale randomised controlled trial, nesiritide failed to improve outcomes (though it did improve dyspnoea). Although carperitide (recombinant ANP) is used as a treatment for acute HF in Japan, there is no robust evidence supporting this practice. The second strategy is to inhibit the breakdown of natriuretic peptides. ANP, BNP, CNP and urodilatin are cleaved and inactivated by a membrane bound endopeptidase, neprilysin (as well as insulin degrading enzyme). Neprilysin is found in a number of tissues but in especially high concentrations in the kidney. Natriuretic peptides are also cleared via the natriuretic peptide clearance receptor (NPRC and NPRC3).[10]
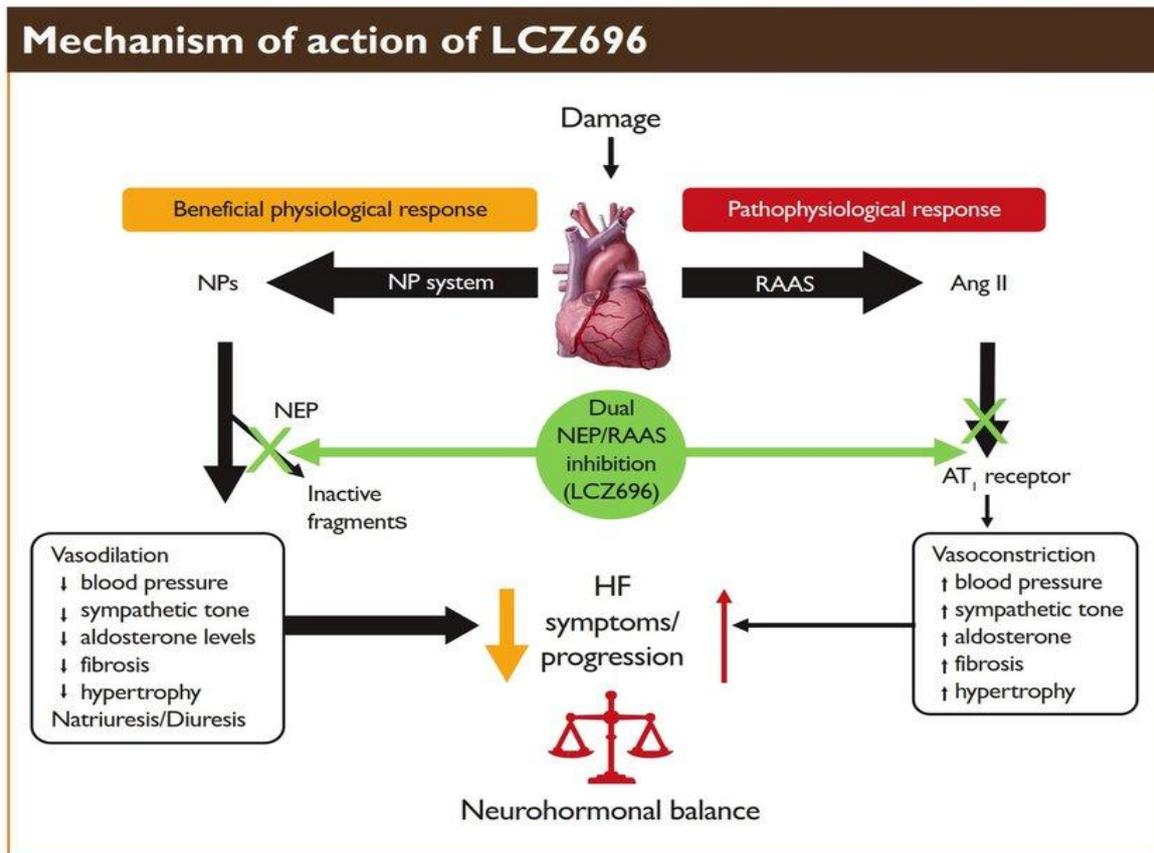
Fig 1 mechanism of LCZ696 in beneficial physiological response and pathophysiological response.

DUAL NEPRILYSIN AND ACE INHIBITION

The solution to the problem of lone neprilysin inhibition appeared to be dual blockade of RAAS and the natriuretic peptide system . As ACE inhibitors are known to improve outcomes it seemed logical to combine an ACE inhibitor with a neprilysin inhibitor. The combined ACE and neprilysin inhibitor omapatrilat was studied in a large randomised controlled trial against enalapril 10 mg twice daily in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial. The primary end point, death from any cause or HF hospitalisations were not reduced by omapatrilat. Although other secondary end points suggested a benefit with omapatrilat (death from any cause or cardiovascular (CV) hospitalisation was 9% lower in the omapatrilat group) the rate of angio-oedema was much higher in the omapatrilat group. Both ACE and neprilysin break down bradykinin and omapatrilat also inhibits aminopeptidase P which also catabolises bradykinin. Therefore, unintended excessive potentiation of bradykinin and resultant high rates of serious angio-oedema led to the discontinuation of the clinical development of this drug.[11]
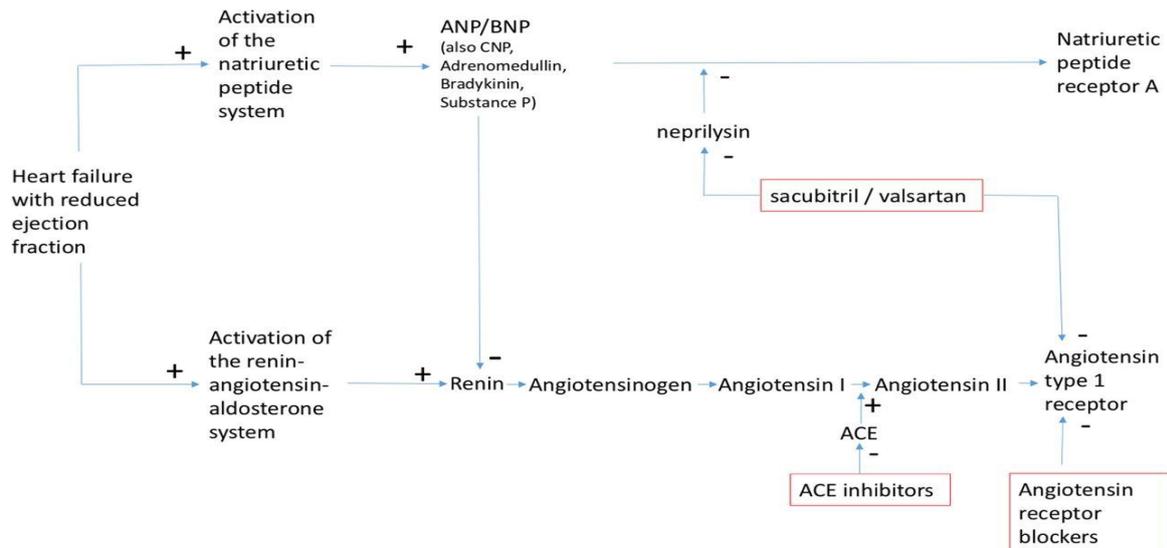
Fig 2 Pathways blocked by ACE inhibitors, angiotensin receptor blockers and neprilysin inhibitors. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, B-type natriuretic peptide.

WHO SHOULD BE PRESCRIBED SACUBITRIL/VALSARTAN?

The only evidence for the use of sacubitril/valsartan is in patients with HF-REF. if we consider the inclusion and exclusion criteria of the PARADIGM-HF trial, sacubitril/valsartan can be given to: adult patients with HF, New York Heart Association (NYHA) II–IV and a reduced ejection fraction (≤40%) on a β-blocker and MRA as recommended by guidelines, with a systolic blood pressure of ≥100 mm Hg and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2 and potassium ≤5.2 mmol/L .

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) prescribing information is consistent with these groups. Although further inclusion criteria were stipulated in the trial (patients had to have a BNP ≥150 pg/mL or if hospitalised with HF a BNP ≥100 pg/mL these are not part of the FDA or EMA prescribing information, presumably because most patients with HF-REF exceed these threshold there was no interaction between baseline natriuretic peptide concentration and the effect of treatment and because there is no biological basis for assuming sacubitril/valsartan would lose its effectiveness below these thresholds.[12]

ADVERSE EFFECTS AND DRUG INTERACTIONS

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of sacubitril/valsartan. Dedicated drug interaction studies demonstrated that co-administration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide, metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, sacubitrilat or valsartan. Use with an ACE inhibitor is contraindicated due to increased risk of angioedema.

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increase in serum potassium concentrations. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible though periodic monitoring of renal function should be performed. Concomitant administration with lithium may result in an increase in serum lithium concentration and lithium toxicity.8–10,13 Clinically significant ADR include hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), orthostasis (2.1%), angioedema(<1%), impaired renal function(reversible).

CONTRAINDICATIONS

Sacubitril/valsartan is contraindicated in:
- pregnancy & lactation
- patients with hypersensitivity to any component
- patients with severe renal (eGFR 7 points score)
- patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- with concomitant use of ACEi
- Do not administer within 36 h of switching from or to an ACEi

✦ with concomitant use of aliskiren in patients with diabetes.

II. Discussion

Dementia and cognition-related adverse effects were not increased by sacubitril/valsartan in PARADIGM-HF, and the beneficial CV actions of angiotensin receptor-neprilysin inhibition might prevent cognitive decline in other ways. Concern has been raised that neprilysin inhibition might lead to accumulation of amyloid-beta peptides in the brain as this enzyme is one of the clearance mechanisms for neurotoxins which are implicated in the development of Alzheimer's disease. It should be noted that as multiple other enzymatic pathways and transport proteins are involved in the clearance of amyloid-beta peptides in the brain, it is not known whether long-term neprilysin inhibition might have a significant effect on accumulation of these peptides. A secondary analysis of the PARADIGM-HF trial revealed that among patients who newly started taking mineralocorticoid receptor antagonists (MRA) during the PARADIGM-HF trial, severe hyperkalemia remained more common in those randomly assigned to enalapril than to those randomly assigned to sacubitril/valsartan. These data suggest that neprilysin inhibition attenuates the risk of hyperkalemia when MRAs are combined with other inhibitors of the renin-angiotensin aldosterone system in patients with HF.

III. Conclusion

The NP system has been shown to play an important cardiac and renal protective role. As a result it has been hypothesized that enhancing NPs may be beneficial in HF. Neprilysin inhibition enhances NP levels by reducing their enzymatic degradation. However, the utility of neprilysin inhibition requires management of the activation of the RAAS, which occurs with neprilysin inhibition alone. LCZ696 improveshemodynamics and cardio-renal biomarkers. On-going studies will determine whetherthese effects translate toimprovements inoutcomesofpatientswithchronic HFwith eitherreduced or preserved LVEF.Additional studies ofthe NPs and of LCZ696 will be needed to further elucidate the mechanisms of its potential cardio-renal protection and the clinical relevance of the metabolic effects of the NPs.

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Conflicts of interest: there is no conflict of interest

S No	Term	Abbreviation
1	NYHA II-IV	NEWYORK HEART ASSOCIATON
2	HFrEF	HEART FAILURE AND REDUCED EJECTION FRACTION
3	VAP	VASOACTIVE PEPTIDES
4	CALLA	COMMON ACUTE LYMPHOCYTIC LEUKEMIA ANTIGEN
5	ARBs	ANGIOTENSIN RECEPTOR BLOCKERS
6	ACEIs	ANGIOTENSIN CONVERTING ENZYME INHIBITORS
7	ANP	ATRIAL NATRIURETIC PEPTIDE
8	BNP	BRAIN NATRIURETIC PEPETIDE
9	CNP	C-TYPE NATRIURETIC PEPETIDE
10	EMA	EUROPEAN MEDICAL AGENCY
11	NPs	NATRIURETIC PEPETIDES