Review Article

Angiotensin receptor / neprilysin inhibitors (ARNIs) : the new hope in the management of heart failure

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Heart failure (HF) represents major challenges in cardiovascular disease and despite newer therapeutic advances, mortality still remains high. Inhibition of neurohumoural pathways such as the renin angiotensin aldosterone and sympathetic nervous systems is central in the management of heart failure. LCZ696 (sacubutril/valsartan), a first-in-class angiotensin II AT1 receptor neprilysin inhibitor (ARNI), has a unique mode of action that targets both pathways. The Prospective comparison of ARNI with angiotensin convertase enzyme inhibitor (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 ARNI. This trial suggests that sacubitril/valsartan should replace an ACE inhibitor or angiotensin receptor blocker for the treatment of symptomatic patients (NYHA II–IV) with HF with reduced ejection fraction. This review will explore the background of neprilysin inhibition in management of HF, the results of the PARADIGM-HF trial and also guide how to use sacubitril/valsartan in clinical practice.

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Heart failure (HF) is defined as a complex clinicalsyndrome, and can result from any structural or functionalcardiac disorders which impair the ability of ventriclesto fill with or eject blood[1]. The renin angiotensin aldosterone system (RAAS)system is main contributing agent in the pathophysiology of HF and its modulation is central to modify the disease process in HF with reducedejection fraction (HFrEF)[2]. Successive randomisedcontrolled trials (RCT) have proved that blockadeof RAAS improves morbidity and mortality inpatients with HFrEF[3]. Though the prognosis ofHFrEF has been improved over the years, still there is high mortality and morbidity as it remains a complexsyndrome involving a various neurohormonalpathways[4]. Therefore, further therapies need to develop to improveoutcomes in these patients.

The Natriuretic Peptide System :

The natriuretic peptide system counter regulates those detrimental effects of the upregulation of RAAS that occurs in HFrEF. It inhibits secretion of arginine vasopressin and modulates the autonomic nervous system in the favour of our body[5].

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 leads to production of pre-pro B-type natriuretic peptide (BNP) which is cleaved to BNP and N-terminal proBNP (NT-proBNP)[6]. The BNP acts to promote natriuresis and vasodilation. Whereas, atrial stretch leads to the production of pre-proatrial or A-type natriuretic peptide and ultimately atrial natriuretic peptide (ANP) which also has similar biological properties to BNP. 6C-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[6]. Though Nesiritide, a recombinant human BNP, initially showed promising beneficial effects on haemodynamics and natriuresis in patients with HFrEF, but it failed in to improve outcomes in large-scale randomised controlled trial[7]. So another strategy was to inhibit the breakdown of natriuretic peptides by inhibiting a membrane bound endopeptidase, neprilysin[8]. Neprilysin is found in a number of tissues but in especially high concentrations in the kidney. Initial Neprilysin Inhibitors like oral (racecodotril) and intravenous (candoxatrilat) formulation were successful in promoting natriuresis and increasing urinary excretion of ANP but failed to show any clinical benefits in HFrEF[9].

Dual Neprilysin and ACE Inhibition :

Dual blockade of RAAS and the natriuretic peptide system came as a solution to the problem of lone neprilysin

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inhibition. 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 (OVERTURE) trial. Omapatrilat failed to reduce primary end point (death from any cause or HF hospitalisations). The rate of angio-oedema was much higher in the omapatrilat group as 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.10

Angiotensin Receptor Blocker and Neprilysin Inhibitors :

Combining an angiotensin receptor blocker (ARB) and a neprilysin inhibitor was the next logical step and potential solution to the problem encountered with omapatrilat. The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (formerly known as LCZ696) was designed with the aim of inhibiting neprilysin while blocking the adverse effects of RAAS and reducing bradykinin potentiation.The drug LCZ696 is made of the ARB valsartan and neprilysin inhibitor prodrug sacubitril. As the active metabolite of sacubitril, sacubitrilat (LBQ657) does not inhibit aminopeptidase P, the risk of angio-oedema was expected to be lower than with omapatrilat. The systemic exposure delivered by sacubitril/valsartan 97 mg/ 103 mg (200 mg LCZ696) is equivalent to 160 mg of valsartan and neprilysin is almost completely inhibited for up to 12 h. The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) was conducted to test whether 97 mg/103 mg twice daily of sacubitril/valsartan was superior to enalapril 10 mg twice daily in reducing the primary end point of CV death or HF hospitalisation.The trial was terminated early, on the recommendation of the Data Monitoring Committee, due to a sustained and highly significant reduction in the risk of the primary composite end point (CV death or HF hospitalisation) and in CV mortality in the sacubitril/ valsartan group compared with the enalapril group. At the end of the trial, there was a 20% relative risk reduction in the primary end point as well as a 16% reduction in all-cause mortality. The two major modes of CV death, sudden death and death from worsening HF were equally and significantly reduced.Both first hospitalisations for HF and total (including repeat) hospitalisations were also reduced by 21% and 23%, respectively. Therefore, for every 1000 patients switched from enalapril to sacubitril/valsartan, over a median of 27 months, there would be: 47 less primary end points (CV death or HF hospitalisations), 33 less CV deaths, 28 less first hospitalisations for HF (53 less total hospitalisations for HF) and 32 less deaths from any cause.No interactions were observed between any of the subgroups and study outcomes.There was no statistically significant difference in the rate of angio-oedema with sacubitril/valsartan although numerically more cases were observed than in the enalapril group. Hypotension was significantly more common with sacubitril/valsartan than with enalapril (14% *versus* 9% in the in the sacubitril/valsartan and enalapril groups respectively, $p<0.001$), although this rarely led to study drug discontinuation (0.9% and 0.7% in the sacubitril/valsartan and enalapril groups respectively, $p=0.38$). Conversely, renal dysfunction, hyperkalaemia and cough were less common with sacubitril/valsartan than with enalapril. Subsequent analyses of PARADIGM-HF have confirmed that the relative reductions in morbidity and mortality and differential rates of adverse events were similar across all agesand baseline risk of death as determined by risk-scoring systems[11-14].

With the result of PARADIGM-HF trial, both American College of Cardiology and European Society of Cardiology included ARNI as class IB recommendation of using it in HFrEF. It can be used either as de novo or in place of ACEI/ ARB.

How should ARNI be Prescribed ?

ARNI should not be given in conjunction with another ARB or renin inhibitor (because of the risk of renal impairment and hyperkalaemia) or an ACE inhibitor (risk of renal impairment, hyperkalaemia and angio-oedema). Due to the potential risk of angio-oedema when used concurrently with an ACE inhibitor, sacubitril/valsartan must not be started for at least 36 h after discontinuing an ACE inhibitor[15]. The starting dose of sacubitril/valsartan is 49 mg/ 51 mg twice daily. The dose should be doubled every 2–4 weeks as tolerated by the patient to the maximum dose of 97 mg/103 mg twice daily. Patients should also be prescribed other evidence-based drugs (ß-blocker, mineralocorticoid receptor antagonist, ivabradine and digoxin) and devices (cardiac resynchronisation therapy (CRT), implantable cardioverter defibrillator (ICD)), as appropriate.

Side Effects and Cautions :

Renal function, potassium and blood pressure should be monitored as for any other RAAS blocker. The drug is not started in those with a systolic blood pressure of <100 mm Hg. In the event of the development of hypotension, renal impairment or hyperkalaemia, evaluation of the potential causes should be searched and appropriate measures like reducing the dose of other non-essential blood pressure-lowering drugs, adjusting the dose of diuretics, discontinuing other drugs such as non-steroidal anti-in-

flammatory drugs must be done. The development of angio-oedema should lead to immediate discontinuation and treatment with appropriate therapy until it has resolved. Rates of discontinuation for renal impairment were lower in the sacubitril/valsartan group compared with the enalapril group (0.7% vs 1.4% respectively, p=0.002). As sacubitril/valsartan increases levels of circulating BNP therefore BNP is not useful for monitoring the prognosis of these patients.16NT-proBNP still be used as a marker for HF.

Heart Failure with Preserved Ejection Fraction (HFpEF) :

Currently there is also experience with sacubitril/valsartan in HFpEF. In the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejectioN fracTion (PARAMOUNT) trial, 301 patients with HF-PEF were randomised to valsartan or sacubitril/ valsartan.17NT-proBNP fell in the latter group along with reductions in NYHA class and left atrial volumes. On the basis of these findings and the favourable effects seen in PARADIGM-HF a large multicentre randomised outcomes trial of sacubitril/valsartan versus valsartan, PARAGON-HF, is currently recruiting.

Summary :

With the result of PARADIGM-HF, ARNI brings new era of hope in the management of HFrEF. ARNI should replace ACE inhibitor/ ARB in all symptomatic patients with HF as it reduces mortality, morbidity and repeat HF admission more than the age old drugs. It is also reflected in the latest HF guidelines. Still we need more data before prescribing in HFpEF.

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References

1 Yancy CW, Jessup M, Bozkurt B — ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am CollCardiol* 2013; **62:** e147–239.

2 McMurray JJ, Adamopoulos S, Anker SD — ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; **33:** 1787-847.

3 Cohn JN, Tognoni G — A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667-75.

4 Jhund PS, MacIntyre K, Simpson CR — Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009; 119: 515-23.

5 Daniels LB, Maisel AS — Natriuretic peptides. *J Am Coll Cardiol* 2007; **50:** 2357-68.

6 Schulz-Knappe P, Forssmann K, Herbst F — Isolation and structural analysis of “urodilatin”, a new peptide of the cardiodilatin-(ANP)-family, extracted from human urine. *Klin Wochenschr* 1988; **66:** 752-9.

7 O’Connor CM, Starling RC, Hernandez AF — Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; **365:** 32-43.

8 Hata N, Seino Y, Tsutamoto T — Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. *Circ J* 2008; **72:** 1787-93.

9 Bevan EG, Connell JMC, Doyle J — Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. *J Hypertens* 1992; **10:** 607-13.

10 Packer M, Califf RM, Konstam MA — 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:** 920-6.

11 Ruilope LM, Dukat A, Böhm M — 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:** 1255–66.

12 McMurray JJV, Packer M, Desai AS — on behalf of the PARADIGM-HF Committees, Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact. *Eur J Heart Fail* 2013; **15:** 1062-73.

13 McMurray JJV, Packer M, Desai AS —. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014; **16:** 817-25.

14 Jhund PS, Fu M, Bayram E — PARADIGM-HF Investigators and Committees. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J* 2015; **36:** 2576-84.

15 Simpson J, Jhund PS, Silva Cardoso J — Effect of LCZ696, compared with enalapril, according to baseline risk in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *J Am Coll Cardiol* 2015; **66:** 2059-71.

16 US Food and Drug Administration. ENTRESTO (sacubitril and valsartan). Highlights of prescribing information. (cited 30 September 2015). http://www.accessdata.fda. gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf

17 Solomon SD, Zile M, Pieske B — The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380:** 1387-95.