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NEWER THERAPEUTIC INSIGHTS

Angiotensin Receptor Neprilysin Inhibitor for the Treatment of Cardiovascular Diseases: A New Approach

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ABSTRACT

A new revolution has begun in the management of chronic heart failure with reduced ejection fraction (CHFrEF). The new blockbuster angiotensin receptor neprilysin inhibitor (ARNI/LCZ696) has evoked a new concept of multisystem neurohormonal modulation, and indeed, this has shown an additional decrease in cardiovascular (CV) mortality on top of all standard evidence-based drugs for the treatment of CHFrEF, i.e., angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), beta blockers, and mineralocorticoid receptor antagonists (MRAs) coupled with diuretics. LCZ696 has two drugs, ARB valsartan and neprilysin inhibitor sacubitril, fused in a molecular complex. The combination provides a dual strategy of combating neurohormonal activation in heart failure (HF), i.e., by blocking harmful effect of renin-angiotensin-aldosterone system by valsartan and simultaneously increasing the activation of vasoactive peptides by inhibiting neprilysin. It was evaluated in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, which produced a statistically significant dramatic reduction of 20% in the primary end point of a composite of death from CV cause and hospitalization for HF. The combination is well tolerated, and side effects are minimal. LCZ696 has been approved for clinical use and has been endorsed by the European Society of Cardiology and American College of Cardiology/American Heart Association/Heart Failure Society of America 2016 guidelines. What is very exciting is that it has emerged as a replacement therapy for class I A drug (ACE/ARB) rather than as a mere add-on therapy, which is the usual story with any new drug. The drug is likely to be available in India in the near future.

Keywords: Angiotensin receptor neprilysin inhibitor review, Heart failure with reduced ejection fraction, PARADIGM-HF.

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INTRODUCTION

Angiotensin receptor neprilysin inhibitor (ARNI/LCZ696) is a new blockbuster approved for clinical use in 2015 for chronic heart failure with reduced ejection fraction (CHFrEF). However, it is also being evaluated for a panoply of other conditions like heart failure with preserved ejection fraction (HFpEF), hypertension, postmyocardial infarction, renal impairment, etc. (Table 1). Angiotensin receptor neprilysin inhibitor comprises of two drugs angiotensin receptor blocker valsartan and neprilysin inhibitor sacubitril fused in a molecular complex (Fig. 1). The beauty of this molecule is that it has evoked a new and an exciting concept of multiple neurohormonal modulation.

CHRONIC HEART FAILURE WITH DIMINISHED EJECTION FRACTION

Chronic heart failure with reduced ejection fraction is a common problem encountered in our day-to-day practice.

Table 1: Established and emerging indications of ARNI

Disease	*Trial*
Established indication	
Chronic heart failure with reduced ejection fraction	PARADIGM-HF
Emerging indications	
Heart failure with preserved ejection fraction	PARAMOUNT PARAGON-HF
Hypertension	PARAMETER
Chronic kidney disease	UK HARP-III
Post-MI	Experimental Data

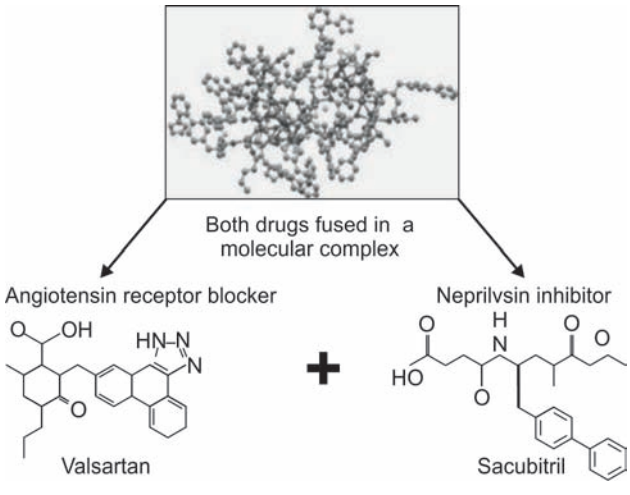


Fig. 1: Chemical structure of ARNI

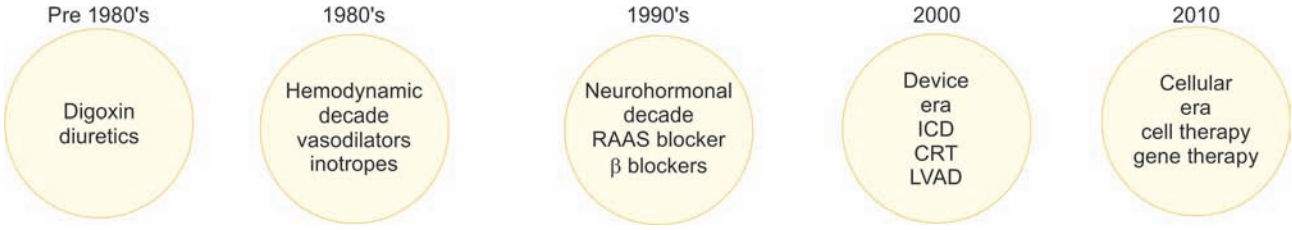
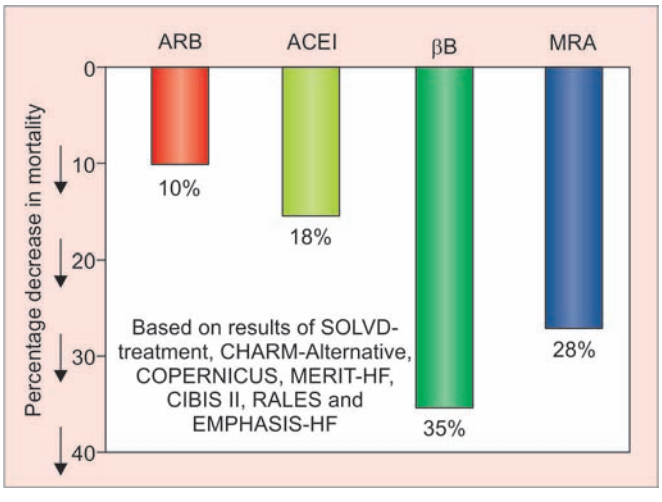


Fig. 2: Therapies for heart failure

When we look at the evolution treatment of CHFrEF (Fig. 2), we find that till the end of 19th century the treatment of this condition was merely restricted to drugs, device came after 2000 and 2010 onwards we are in an era of cell therapy.

By the end of the 19th century, we had three mortality-reducing agents, i.e., angiotensin-converting enzyme inhibitors (ACEI)[1,2]/angiotensin receptor blockers (ARBs),[3] beta blockers,[4,5] and mineralocorticoid receptor antagonists (MRAs)[6,7] (Graph 1). But despite all evidence-based current therapy, patients with CHFrEF continued to have high mortality. The mortality at 1, 2, and 5 years is 5 to 8, 20 and 50% respectively. Because of this, the trialists continued their search for another mortality-reducing agent to further decrease the mortality. But from 2003 to 2013, no new mortality-reducing drug emerged on the scenario of heart failure. However, the year 2014 initiated the dawn of a new era when PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial[8] with ARNI was presented in European Society of Cardiology (ESC) 2014. The drug was approved for clinical use by the US Food and Drug Administration (FDA) in 2015, and the Canadian CV Society Heart Failure guidelines[9] was the first to endorse it in the same year. The American College of Cardiology/American Heart Association Task Force on clinical practice guidelines, and the Heart Failure Society of America (ACC/AHA/HFSA) focused update 2016[10] has also approved it for clinical use in CHFrEF and is recommended as class I (Level of evidence: B-R) to replace ACEI or ARB. The 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure has also approved its use.[11]



Graph 1: Mortality-reducing drugs in CHFrEF

Evolution of ARNI in CHFrEF

After achieving substantial mortality benefit with three neurohormonal blockers,[12] i.e., ACE/ARB, beta blockers and MRAs, further attempts to block the maladaptive neurohormonal system by endothelin, TNF alpha blockers, etc., proved futile, and so attention was focused on the vasoactive natriuretic peptide system.[13-18] This system has several vasoactive peptides like natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide. These peptides counteract the maladaptive mechanisms in heart failure by decreasing neurohormonal activation, vascular tone, cardiac fibrosis and hypertrophy, and sodium retention (Fig. 3). But, this is a weak system because the above peptides are rapidly inactivated by enzyme neprilysin.

The first attempt to boost this system was made by infusing recombinant B-type natriuretic peptide (BNP) in the VMAC (Vasodilation in the Management of Acute CHF)[19] trial, but the drug failed to improve the outcome of heart failure patients. Other trials like PRECEDENT[20] and ASCEND-HF[21] were also negative. This strategy was therefore given up.

The second attempt to activate the system was made by inhibiting the enzyme neprilysin by candoxatril[22] in doses of 200 mg BID. But curiously enough, instead of anticipated decreased in systemic vascular resistance

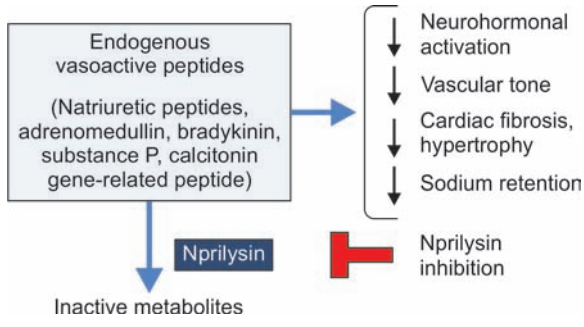


Fig. 3: Vasoactive natriuretic peptide system

and blood pressure, there was a paradoxical increase in blood pressure due to increased levels of angiotensin II. It was later on known that this occurred because neprilysin besides breaking down the natriuretic peptides has several other substrates including enkephalins, oxytocin, gastrin, angiotensin I and II, endothelin-1, substance P, and bradykinin.

The next attempt was made with omapatrilat (sacubitril + enalapril) in trials like OVERTURE[23] and OCTAVE.[24] Sacubitril inhibited neprilysin and enalapril blocked the renin-angiotensin-aldosterone system (RAAS). But to the horror of the trialists, distressing angioedema requiring ventilatory support was seen in the omapatrilat group, and the trial was discarded. This occurred due to marked rise in bradykinin levels because bradykinin is also a substrate for neprilysin and enalapril also increases bradykinin levels.

The next attempt was made by combining neprilysin inhibitor with ARB valsartan, which does not increase bradykinin levels. The combination worked and the result was the PARADIGM-HF trial.

Clinical Evidence of Beneficial Effect of Angiotensin Neprilysin Inhibitor

The PARADIGM-HF[7] trial was designed to test the hypothesis that ARNI could result in reduced morbidity and mortality in patients with chronic heart failure (left ventricular ejection fraction ≤40%).

The inclusion criteria of the trial are outlined in Table 2.

The PARADIGM-HF used a unique study design, with a single-blind active run-in period designed to ensure that patients tolerated both study drugs. Participants who completed run-in were randomly assigned to ARNI 200 mg twice daily or enalapril 10 mg twice daily in a double-blind fashion. The run-in period afforded the data and safety monitoring board early information regarding measures of safety, including hypotension, renal function, and hyperkalemia, because prior experience with this drug in heart failure had been extremely limited. Enalapril 10 mg twice daily was used as the active comparator, as this has been considered both standard of care and the regulatory gold standard in heart failure. Around 8,442 patients were randomized from 947 sites in 47 countries.

The primary endpoint was the composite of CV mortality or hospitalization for heart failure.

The secondary endpoints included

- All-cause mortality.
- Change from baseline in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire at 8 months.
- Time to new onset of atrial fibrillation.
- Time to first occurrence of a protocol-defined decline in the renal function.

The baseline characteristics of the trial are outlined in Table 3.

In late March 2014, the PARADIGM-HF data monitoring committee reviewed the interim safety and efficacy data and recommended early termination of the trial for efficacy, indicating significant reductions in both the primary endpoint (CV death or heart failure hospitalization) and CV death.

The final results confirmed the benefit observed by the data monitoring committee. The mean daily doses of ARNI and enalapril received were 375 and 18.9 mg respectively.

Angiotensin receptor neprilysin inhibitor reduced the primary composite endpoint of CV death or heart failure hospitalization by 20% (hazard ratio [HR]: 0.80;

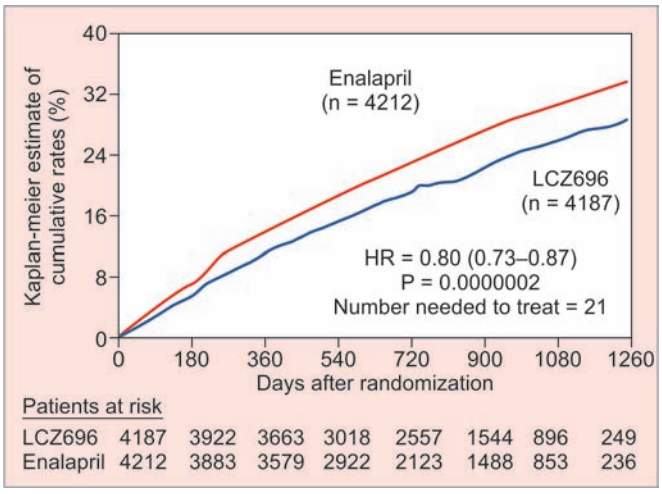
Table 2: PARADIGM-HF: Entry criteria

- New York Heart Association class II to IV heart failure
- Left ventricular ejection fraction ≤40% → 35%
- B-type natriuretic peptide ≥150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months.
- Any use of ACEI or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks.
- Guideline-recommended use of beta blockers and MRAs.
- Systolic blood pressure ≥ 95 mm Hg, estimated GFR ≥ 30 mL/min/1.73 m^2, and serum K ≤ 5.4 mEq/L at randomization.

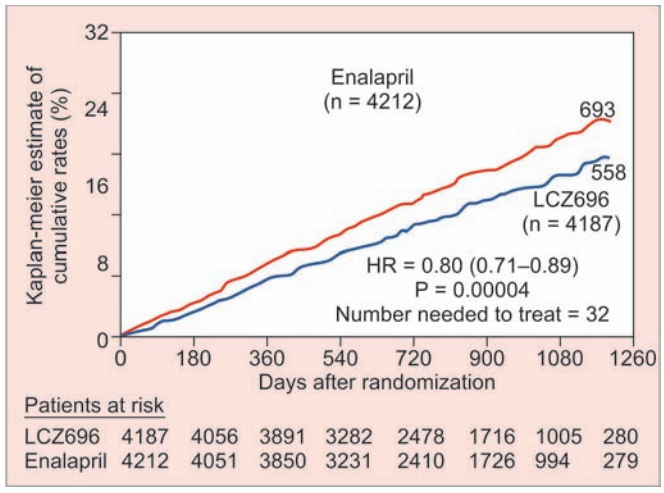
Table 3: PARADIGM-HF: baseline characteristics

Parameter	*LCZ696 (n=4,187)*	*Enalapril (n=4,212)*
Age (years)	63.8±11.5	63.8±11.3
Women (%)	21.0	22.6
NYHA functional class II/III (%)	71.6/23.1	69.4/24.9
LVEF (%)	29.6±6.1	29.4±6.3
N-terminal proBNP (pg/mL)	1631 (885–3154)	1594 (886–3305)
B-type natriuretic peptide (pg/mL)	255 (155–474)	251 (153–465)
Systolic blood pressure (mm Hg)	122±15	121±15
Heart rate (beats/min)	72±12	73±12
History of diabetes	35%	35%
Ischemic cardiomyopathy	59.9%	60.1%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

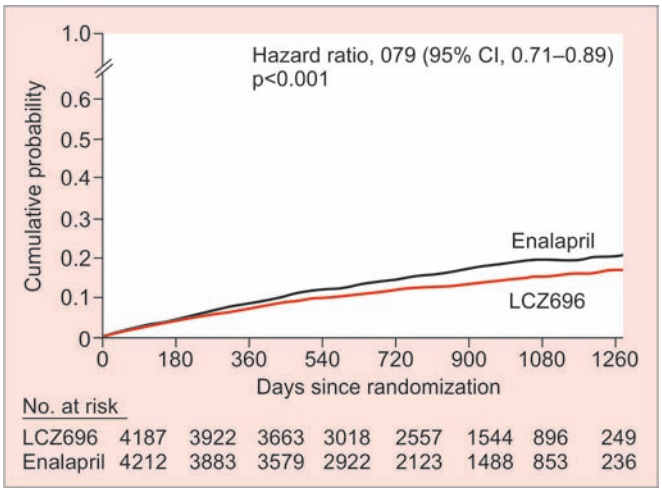
CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association



Graph 2: Primary endpoint of PARADIGM-HF trial



Graph 3: PARADIGM-HF cardiovascular death



Graph 4: PARADIGM-HF hospitalization for heart failure

95% confidence interval [CI]: 0.73 to 0.87; p = 0.0000002) (Graph 2). Similar reduction was observed for CV death (HR 0.80; 95% CI: 0.71 to 0.89; p = 0.00004) (Graph 3) and hospitalization for heart failure (HR: 0.79; 95% CI: 0.71 to 0.89; p = 0.00004 (Graph 4). All-cause mortality was reduced by 16% (HR: 0.84; 95% CI: 0.76 to 0.93; p < 0.001). These findings were consistent across all prespecified subgroups.

After a median duration of follow-up of 27 months, 17.8% of patients in the LCZ696 group and 19.8% of patients in the enalapril group had been discontinued from the study drug.

The important findings of the trials are summarized in Table 4.

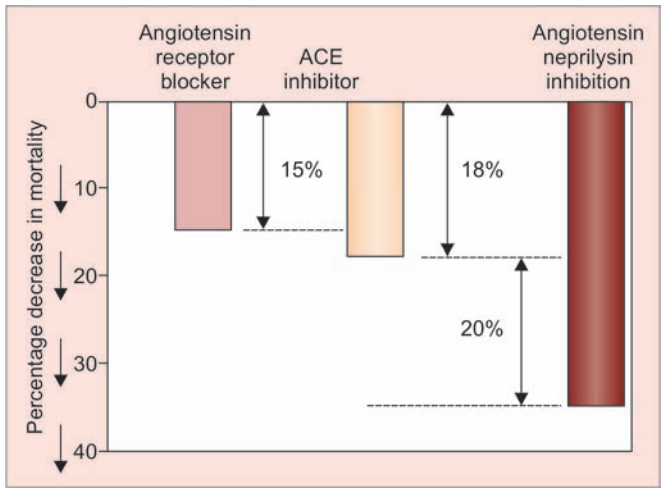
The main point to be noted is that there was an incremental 20% decrease in CV mortality on top of ACE inhibitor therapy (Graph 5).

Side-effect Profile

Hypotension was more common in patients receiving ARNI (p < 0.001), although discontinuation because of hypotension was similar in both arms. Elevations in serum creatinine, potassium, and cough were less frequent in those assigned to ARNI. Serious angioedema was rare and similar between groups, although numerically greater in the ARNI arm (19 *vs* 10), but it did not result in airway compromise.

Table 4: Important findings of PARADIGM-HF trial

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:
LCZ696 was *more* effective then enalapril in…
• Reducing the risk of CV death and HF hospitalization
• Reducing the risk of CV death by incremental 20%
• Reducing the risk of HF hospitalization by incremental 21%
• Reducing all-cause mortality by incremental 16%
• Incrementally improving symptoms and physical limitations
LCZ696 was better tolerated than enalapril…
• Less likely to cause cough, hyperkalemia or renal impairment
• Less likely to be discontinued due to an adverse event
• More hypotension, but no increase in discontinuations
• Not more likely to cause serious angioedema



Graph 5: Incremental benefit of angiotensin neprilysin inhibitors over ACEI and ARB

Diabetic Subset

The diabetic subset in the PARADIGM-HF trial showed that ARNI produced similar beneficial effects compared with enalapril like the overall study, irrespective of glycemic status.[25]

Indian Subset

The results of the Indian data (637 patients) showed similar trends to that of the overall PARADIGM study population in reducing the risk of CV death and heart failure hospitalization. Angiotensin receptor neprilysin inhibitor was well tolerated in Indian patients, with a safety profile comparable to enalapril. The safety data from the Indian patients was consistent with that in the overall study patient population.

Availability in the Indian Market

Although the US FDA and the European Medicines Agency have approved this drug for clinical use in the United States and Europe, the drug is not yet available in India, but it is going to be launched very soon. The drug is being marketed in three strengths; the lowest dose was not tested in the trial. It is proposed that initiating the drug with lowest dose will minimize intolerance to the drug.

- 50 mg (sacubitril 24 mg and valsartan 26 mg)
- 100 mg (sacubitril 49 mg and valsartan 51 mg)
- 200 mg (sacubitril 97 mg and valsartan 103 mg).

Emerging Indications of ARNI

Besides CHFrEF, ARNI is also being evaluated in several others disorders (Table 1).

Heart Failure with Preserved Ejection Fraction

Approximately half of all heart failure patients have normal or nearly normal ejection fraction. While many studies have shown a benefit of pharmacological therapies in heart failure with reduced ejection fraction, no treatment has been shown to reduce mortality or morbidity in HFpEF.

Angiotensin receptor neprilysin inhibitor is being evaluated in this subset of patients of heart failure also. The PARAMOUNT study,[26] a phase II trial conducted in 308 patients in 13 countries, compared the effects of ARNI on the concentrations of natriuretic peptides. The natriuretic peptide investigated in this study, N-terminal pro-BNP (NT-proBNP), is a marker of cardiac wall stress, and levels are increased in patients with HFpEF.

The study showed that ARNI reduced levels of NT-proBNP by 23% when compared with valsartan. Angiotensin receptor neprilysin inhibitor also reduced enlargement of the left atrium, another marker of adverse outcome in heart failure, and improved the symptoms of heart failure. Angiotensin receptor neprilysin inhibitor in the PARAMOUNT study is the first compound to show both reductions in NT-proBNP and left atrial size in HFpEF patients, each powerful predictors of outcome in heart failure.

The PARAGON-HF trial is ongoing and it is the largest trial (4,300) in HFpEF to date. The primary endpoint of the trial is composite of CV death and total heart failure hospitalization. The trial is expected to be completed in 2019. If it comes out to be positive, this drug would be the first evidenced-based therapy in HFpEF.

Hypertension

Angiotensin receptor neprilysin inhibitor is likely to be useful for the treatment of hypertension because of its dual action. The valsartan in ARNI produces RAAS blockade and the neprilysin inhibition with sacubitril results in increased bioavailability of natriuretic peptides, bradykinin, and substance P, which produces natriuretic, vasodilatory, and antiproliferative effects. To evaluate its effect in hypertension, the drug was evaluated in the PARAMETER study.[27]

This 52-week multicenter study randomized 454 patients with hypertension aged ≥60 years with a mean sitting systolic blood pressure (SBP) of ≥150 to <180 and a pulse pressure of >60 mm Hg to once-daily ARNI (200 mg) or olmesartan (20 mg) for 4 weeks, followed by a forced titration to double the initial doses for the next 8 weeks. At 12 to 24 weeks, if the BP target had not been attained, amlodipine (2.5–5 mg) and subsequently hydrochlorothiazide (6.25–25 mg) were added. The primary and secondary endpoints were changes from baseline in central aortic systolic pressure and central aortic pulse pressure at week 12 respectively.

Results showed that after 12 weeks, patients treated with ARNI had a 3.77 mm Hg greater reduction in central aortic systolic pressure and a 2.4 mm Hg greater reduction in central aortic pulse pressure from baseline compared with patients treated with olmesartan. Additionally, the 24-hour ambulatory brachial and central SBPs were significantly reduced from baseline to 12 weeks in both treatment arms, with ARNI lowering brachial SBP by an additional 4.1 mm Hg and central SBP by an additional 3.3 mm Hg compared with olmesartan. This finding was most pronounced during the nighttime.

In other findings, a greater percentage of patients treated with olmesartan (47%) required additional hypertension medication at weeks 12 to 24 compared with patients in the ARNI group (32%). Investigators also noted that an exploratory analysis of the carotid-to-femoral pulse wave velocity indicated a trend toward

greater improvement in a subgroup of ARNI-treated patients with the stiffest arteries at baseline.

PARAMETER is the first randomized study demonstrating the ability of ARNI to significantly reduce central blood pressure and pulse pressure compared with an ARB in high-risk older patients with systolic hypertension and a wide pulse pressure. These data are important because lowering systolic and pulse pressure in older people with stiffened arteries is an unmet need in our endeavor to reduce the risk of CV disease and heart failure in older people. The results suggest that ARNI has been able to achieve more in this regard than existing treatments, and indeed this is an exciting advance.

The holy grail of systolic hypertension therapy is to achieve a "destiffening" effect. The fact that release of BNP was reduced for ARNI provides indirect evidence that this may be occurring. Currently, studies are underway using magnetic resonance imaging to directly measure changes in arterial distensibility following ARNI treatment.

Although ARNI has shown impressive reduction in SBP and diastolic blood pressure, the long-term antihypertensive efficacy of ARNI has not been fully evaluated. Moreover, the effect of ARNI on CV outcomes in patients with hypertension is unknown. It is also to be seen whether ARNI also confers long-term prognostic benefits in patients with hypertension. Further studies need to be conducted to elucidate the role of ARNI in hypertensive patients with (i) diabetes, (ii) chronic kidney disease (CKD), and (iii) resistant hypertension and also the elderly. Since blacks were underrepresented in the published hypertension trials, future trials should also include adequate black population. Most importantly, studies need to be conducted comparing antihypertensive efficacy and outcome of ARNI with other drug classes, such as ARBs, calcium-channel blockers, and diuretics.

Besides PARAMETER trial, several other clinical trials are ongoing (Table 5).

Chronic Kidney Disease

Angiotensin receptor neprilysin inhibitor could benefit patients with CKD by both retarding the progression of CKD (hence delaying the need for renal replacement therapy) and reducing the risk of CVD by controlling hypertension and structural heart disease involving left ventricular hypertrophy and HFpEF.[28]

Table 5: Ongoing trials of LCZ696 in hypertension

Trial number	*Patient population*	*Brief title*	*Comparator*
NCT01785472	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients with Essential Hypertension	Olmesartan
NCT01599104	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients with Essential Hypertension	Olmesartan
NCT01870739	Essential hypertension	A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects with Hypertension	Olmesartan
NCT01615198	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients with Essential Hypertension	Olmesartan
NCT01681576	Salt-sensitive hypertension	Assessment of LCZ696 and Valsartan in Asian Patients with Salt-sensitive Hypertension	Valsartan
NCT01256411	Essential hypertension	A Long-term (12 months) Safety, Tolerability, and Efficacy Study of LCZ696 in Patients with Essential Hypertension	NA
NCT01601470	Mild-to-moderate hypertension	Evaluation of Drug-drug Interaction Between LCZ696 and Sildenafil in Subjects with Mild to Moderate Hypertension	Sildenafil
NCT01353508	Hypertension; heart failure and healthy volunteers	Sodium Excretion of LCZ696 in Patients with Hypertension; Heart Failure and Healthy Volunteers	Valsartan
NCT01692301	Hypertension	Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients with Hypertension	Olmesartan, Amlodipine, Hydrochlorothiazide
NCT01663233	Essential hypertension	Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Comparison with Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine	Amlodipine
NCT01646671	Severe hypertension	Safety and Tolerability and Efficacy of LCZ696 in Japanese Severe Hypertensive Patients	NA
NCT01631864	Hypertension, concurrent obesity	Evaluation of the Metabolic Effects of LCZ696 and Amlodipine in Obese Hypertensive Subjects	Amlodipine
ISRCTN11958993	CKD	Randomized multicenter pilot study of LCZ696 *vs* Irbesartan in Patients with Chronic Kidney Disease: UK Heart And Renal Protection (HARP)-III	Irbesartan

The UK Heart and Renal Protection III (UK HARP-III) trial is ongoing and will compare ARNI against irbesartan in 360 patients with proteinuric CKD (urine albumin/creatinine ratio >20 mg/mmol and estimated glomerular filtration rate (GFR) ≥20 but < 60 mL/min/1.73 m^2). The trial will be the first test of an ARNI in a proteinuric population and will assess the short-term safety and efficacy of ARNI in CKD with a primary outcome of the difference in change in measured GFR from baseline to 6 months between the two arms.

Postmyocardial Infarction Patients

It is hypothesized that ARNI attenuates left ventricular remodeling after experimental myocardial infarction (MI), and that this may be contributed to by inhibition of hypertrophy and fibrosis in cardiac cells.[29] In experimental studies, ARNI attenuated cardiac remodeling and dysfunction after MI. This may be contributed to by superior inhibition of ARNI on cardiac fibrosis and cardiac hypertrophy.

CONCLUSION

Angiotensin receptor neprilysin inhibitor is already available for clinical use in many countries and is poised to be the next wonder drug in CV therapeutics. After its endorsement by the ESC, ACC/AHA/HFSA 2016 guidelines for CHFrEF, it has already started superseding ACEI/ARB in inpatients not intolerant to this drug. It is very rare for a drug to be recommended as a replacement of class 1A drug (ACE/ARB); usually, the endorsement of a new drug is as an add-on therapy. Angiotensin receptor neprilysin inhibitor has the distinction of achieving this rare feat. Its role in several other conditions like HFpEF, hypertension, CKD, post-MI patients is being evaluated. It is heralding a new era of multisystem neurohormonal modulation that may change the way we treat CVD.

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