

ARNI in cardiovascular disease: current evidence and future perspectives

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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the mainstay of therapy for cardiovascular disease and heart failure (HF). The angiotensin receptor II blocker – neprilysin inhibitor (ARNI), sacubitril-valsartan has an established role in treatment of patients with HF with reduced ejection fraction (HFrEF) based on the results of PARADIGM-HF trial. This trial has provided a strong evidence base for treatment of HFrEF in various subsets of patients. Several studies are done using ARNI in various indications such as HFrEF, HFpEF, patients hospitalized with acute decompensated HF, HF with preserved EF, AMI with LVEF <40%, hypertension, chronic kidney disease, pulmonary hypertension, obstructive sleep apnea, so on and so forth. This review provides an update of current literature and future perspective on ARNI in various cardiovascular disorders.

First draft submitted: 12 December 2019; Accepted for publication: 16 March 2020; Published online: 22 April 2020

Keywords: angiotensin receptor – neprilysin inhibitor • arterial hypertension • cardiovascular disease • chronic kidney disease • heart failure • HFpEF • HFrEF • natriuretic peptides • renin–angiotensin system • sacubitril-valsartan

Heart failure (HF) is an important clinical syndrome associated with emergency admissions, morbidity, readmissions and mortality. Pathophysiology of HF includes structural and functional alterations of cardiac muscle, activation of renin-angiotensin system (RAS). Stimulation of RAS initially helps to augment blood pressure and cardiac contractility, but overtime becomes counterproductive and causes worsening of HF by fluid retention. The management of HF is based on our understanding of these mechanisms and the mainstay of pharmacotherapy includes diuretics, β blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB). The latter drugs have been the cornerstone of therapy of HF over the last two decades. Apart from RAS, other neurohormonal substances are also implicated in the pathophysiology of HF.

De Bold *et al.* have reported that intravenous injection of atrial muscle extract produced a rapid; 30-fold natriuretic response in rats [1]. This led to the discovery of natriuretic peptides (NPs), small peptide hormones predominantly secreted by the cardiac myocytes in response to stretching forces. Currently there are six NPs – atrial NP, brain NP (BNP), C-type NP, dendroaspis NP, ventricular NP and urodilatin [2].

NPs cause natriuresis, vasodilation, possess antiproliferative effects, cause vascular remodeling and modulation of renin–angiotensin–aldosterone systems thus benefiting in treatment of HF. These NPs are degraded majorly by neprilysin, a membrane bound endopeptidase and through a clearance receptor (the NP clearance receptor) [3]. Therapeutically beneficial effects of NPs may be derived by one of the two methods:

1. Exogenous administration of NPs; or
2. Inhibition of their degradation by neprilysin inhibitors.

While exogenous administration is the best possible way to acutely augment NPs action, requirement of intravenous infusion, lack of clinical efficacy and durable effect are shortcomings of this approach. Two agents nesiritide, a recombinant BNP and carperitide, recombinant atrial NP are examples of this approach.

The second method of augmenting NPs action is by inhibiting neprilysin – in contrast with parenteral administration, three oral drugs – racecadotril, ecdotril [4] and candoxatril were tested. However, these drugs failed

to provide sustained hemodynamic benefit. The reason being neprilysin also breaks down angiotensin II and by inhibiting neprilysin, increase in angiotensin II levels occurs. Angiotensin II is a potent vasoconstrictor and offsets the beneficial effects of vasodilation provided by neprilysin. Addition of ACE inhibitors to neprilysin inhibitors helps to balance these opposing effects. One important side effect of ACE inhibitors is increased angio edema due to excess of bradykinin. To overcome this unwanted adverse effect of angio edema, instead of ACE inhibitors, angiotensin receptor blockers were added to neprilysin inhibitors with favorable results, thus ushering in the concept of angiotensin receptor – neprilysin inhibitor (ARNI).

Neprilysin inhibition with ACE inhibition

The first combined angiotensin converting enzyme inhibitor (ACEI) and neprilysin inhibitor developed was omapatrilat, an orally active, long acting, selective, competitive inhibitor of neutral endopeptidase and angiotensin converting enzyme.

Initial clinical study involving 573 patients comparing omapatrilat 40 mg (n = 289) with lisinopril 20 mg (n = 284) in patients with HF suggested a trend toward benefit on the combined end point of death or admission for worsening HF (p = 0.052; hazard ratio [HR]: 0.53 [95% CI: 0.27–1.02]) [5]. Further strength to this drug was gained by another large, randomized clinical study involving 5770 patients with moderate-to-severe HF randomized to omapatrilat 40 mg daily (n = 2886) and enalapril 10 mg twice daily (n = 2884), in OVERTURE trial [6], showed omapatrilat-reduced morbidity and mortality but was not more effective than ACE inhibition alone in reducing the risk of the combined risk of death or hospitalization for HF requiring intravenous treatment. However, Omapatrilat inhibits aminopeptidase that catabolizes bradykinin, thereby resulting in excess bradykinin, which in turn causes more angioedema [7]. A study assessing the safety and efficacy of omapatrilat in comparison with enalapril in hypertensive patients also showed excess incidence of angioedema with omapatrilat (2.17 vs 0.68%) [8].

Neprilysin inhibition with ARBs

The major shortcoming of omapatrilat, namely the risk of angioedema was surmounted by development of an ARNI, sacubitril-valsartan, known as LCZ696. Soon after oral ingestion, LCZ696 dissociates into sacubitril (a neprilysin inhibitor prodrug, AHU-377, which is enzymatically cleaved to the active form, LBQ657 and valsartan). Valsartan blocks angiotensin II Type 1 receptor, and LBQ657, the active metabolite of sacubitril (AHU377), does not inhibit aminopeptidase P, the risk of angioedema is considered to be less than with omapatrilat. Sacubitril-valsartan is administered twice daily therefore providing sustained Neprilysin and RAAS inhibition over a 24-h period addressing one limitation of the OVERTURE trial in which omapatrilat was given as a single large dose once daily [9].

Dose & availability

The dose of sacubitril-valsartan (LCZ696) is 49/51 mg (i.e., 100 mg LCZ696) taken per orally twice daily and uptitrated to a target dose of 97/103 mg (i.e., 200 mg) twice daily. Lower starting dose of sacubitril-valsartan (24/26 mg) may be used in selected patients and uptitrated every 3–4 weeks [10]. With the publication of PARADIGM HF trial (vide infra), ARNI has become an important advance in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF). Encouraged by results of this trial, several other indications in cardiovascular disease (CVD) are being explored. The following table (Table 1) summarizes the new frontiers being explored with ARNI.

HF & sacubitril-valsartan

As mentioned in the introduction, HF is a clinical syndrome characterized by symptoms of fluid overload such as dyspnea and edema, and signs such as elevated jugular venous pulse, basal crepitations in the lungs caused by decreased cardiac contractility and elevated intra cardiac pressures. This definition does not identify patients with asymptomatic structural or functional cardiac abnormalities (systolic or diastolic left ventricular (LV) dysfunction), which are precursors of HF. The ESC definition of HF comprises of patients with normal LVEF (typically considered as $\geq 50\%$; HF with preserved EF [HFpEF]) and those with reduced LVEF (typically considered as, $< 40\%$; HFrEF) [11].

There are several demographic and cardiac structural differences between patients with HFrEF and HFpEF, as well as therapeutic response to medications. Patients with HFpEF are older, hypertensive, more likely to be women, less likely to have ischemia. In HFrEF, the LV is dilated with eccentric remodeling and in HFpEF LV size is normal

Table 1. List of studies with sacubitril-valsartan in various cardiovascular disorders.

Cardiovascular disorder	Study
Heart failure with reduced ejection fraction	PARADIGM HF (NCT01035255) LIFE (NCT02816736) EVALUATE HF (NCT02874794)
Acute heart failure with reduced ejection fraction	PIONEER HF (NCT02554890) TRANSITION (NCT02661217)
Heart failure with preserved ejection fraction	PARAGON HF (NCT01920711) PARAMOUNT HF (NCT00887588) PARALLAX (NCT03066804)
Acute coronary syndrome	PARADISE AMI (NCT02924727)
Left ventricular remodeling	PARABLE (NCT02682719) PROVE HF (NCT02887183)
Functional mitral regurgitation	PRIME (NCT02687932)
Hypertension	PARAMETER (NCT01692301)
Chronic kidney disease	UK HARP III (ISRCTN11958993)
Pulmonary hypertension	PARENT (NCT02788656)
Cognitive function	PERSPECTIVE (NCT02884206)
Obstructive sleep apnea	ENTRESTO SAS (NCT02916160)

with concentric remodeling. The therapies proven to improve outcome in HFrEF, which are associated with reversal of LV dilation, have not been demonstrated to be effective in patients with HFpEF [12].

HFrEF

PARADIGM-HF [13] trial was a ‘game-changer’ for the concept of ARNI in treatment of HFrEF. In this large double-blind trial, 8442 patients with class II, III or IV HF and an ejection fraction of 40% or less were randomly assigned to receive LCZ696 at a dose of 200 mg twice daily ($n = 4187$) or enalapril at a dose of 10 mg twice daily ($n = 4212$), in addition to recommended therapy. After a median follow-up of 27 months, the trial was stopped due to overwhelming benefit of LCZ696 over enalapril. The study drug LCZ696 proved superior to enalapril in:

- The primary outcome of composite of death from CV causes or hospitalization for HF (21.8 vs 26.5%; $p = 0.001$);
- Difference in the rates of death from CV causes 13.3 vs 16.5% ($p = 0.001$);
- Risk of hospitalization for HF by 21% ($p = 0.001$) and decreasing the risk of hospitalization for HF by 21% ($p = 0.001$).

Apart from these hard end points, the drug also proved to significantly reduce the clinical worsening of patients evidenced by reduction in intensification of medical treatment for HF (520 vs 604; HR: 0.84; 95% CI: 0.74–0.94; $p = 0.003$) or an emergency department visit for worsening HF (HR: 0.66; 95% CI: 0.52–0.85; $p = 0.001$) [14]. The beneficial effects were evident as early as 30 days.

The superiority of LCZ696 over enalapril was not accompanied by important safety concerns. Fewer patients stopped their study medication overall or because of an adverse event such as symptomatic hypotension or worsening of serum creatinine in the LCZ696 group than in the enalapril group. It helped to establish the safety and efficacy of sacubitril-valsartan over ACE inhibitors.

PARADIGM-HF trial was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with LCZ696 in the management of chronic HF and was successful in the same as the 2017 ACC/AHA/HFSA Heart Failure Focused Update recommends in patients with chronic symptomatic HFrEF New York Heart Association class II or III who tolerate an ACE inhibitor or ARB, replacement with an ARNI to further reduce morbidity and mortality is indicated as COR I, LOE – BR [15].

While PARADIGM-HF trial has shown superiority of sacubitril-valsartan in chronic HF, data in patients with acute decompensated HF (ADHF) are wanting. PIONEER-HF study randomized 881 patients with HFrEF who were hospitalized for ADHF and stabilized to receive sacubitril-valsartan ($n = 440$) or enalapril ($n = 441$). The medication was started at a lower dose of sacubitril/valsartan (24/26 or 49/51 mg), and for enalapril (2.5 or 5 mg), both given orally twice daily and uptitrated to maximum dose of 97/103 mg twice daily and enalapril to 10 mg twice daily. Eight weeks after discharge, the sacubitril/valsartan group had a 29% greater reduction in NT-proBNP

and a 42% lower rate of the composite clinical end point of CV death or HF rehospitalization than the enalapril group [16]. Open label treatment of both groups of PIONEER-HF patients with sacubitril-valsartan to additional 4 weeks, provided additional 36% reduction in NT-proBNP in enalapril-treated patients while maintaining 18.5% reduction in sacubitril-valsartan group. More importantly the relative risk of the composite end point of CV death, HF rehospitalization or LV assist device implantation during the 4-week extension phase was 33% lower in the continuous sacubitril/valsartan group than in the switchers. These points highlight the safety of initiating sacubitril-valsartan in stabilized ADHF patients.

The safety and tolerability of initiating and uptitrating to maximum dose of ARNi was assessed in HFrEF patients after they have been stabilized following an ADHF episode in TRANSITION study that randomized 991 patients after stabilization to initiate sacubitril/valsartan either ≥ 12 -h predischage ($n = 495$) or between days 1–14 postdischarge ($n = 496$) [17]. The proportion of patients who achieved and maintained for ≥ 2 weeks leading to week 10, either 49/51 or 97/103 mg bid was 62.1 versus 68.5% ($p = 0.034$); or any dose was 86.0 versus 89.6% (0.089). More than 80% of patients with SBP ≥ 100 mmHg achieved and maintained the target dose of sacubitril/valsartan if the treatment was titrated gradually; underscoring the need for care in this high risk condition. The incidence of adverse events and discontinuations of ARNi due to adverse events was similar in both groups.

HFpEF

In contradistinction to successful evidence-based therapy for HFrEF, no therapies have been shown to definitively improve mortality or hospitalization in HFpEF possibly due to the fact that most of the hospitalizations and deaths in patients with HFpEF are likely to be non-CV. Therefore, current practice favors only symptomatic treatment with diuretics in patients with fluid overload and management of risk factors and comorbidities. There is evidence for role for ARB candesartan in symptomatic improvement and reduce HF hospitalizations in patients with HFpEF [18]. Trials of ACEIs, ARBs, β -blockers and mineralocorticoid receptor antagonists (MRAs) have all failed to reduce mortality in patients with HFpEF.

NT-pro BNP is a marker for diagnosis and prognosis of HF. Reduction in NT-pro BNP levels in patients with LV ejection fraction $\geq 45\%$ with sacubitril-valsartan was studied in PARAMOUNT trial. 301 patients were randomized to sacubitril-valsartan ($n = 149$) or valsartan alone ($n = 152$) and it was found that NT-pro BNP levels significantly decreased in former group ([783 pg/ml at baseline and 605 pg/ml] compared with the latter group [862 pg/ml at baseline and 835 pg/ml] at 12 weeks.) [19]. There was 7% reduction of LA volume ($p = 0.003$) indicating reverse left atrial remodeling, 9% improvement in New York Heart Association class ($p = 0.051$).

While PARAMOUNT trial assessed the efficacy of sacubitril-valsartan on the biomarker NT-proBNP, PARAGON-HF trial assessed the clinical primary end point of composite of total hospitalizations for HF and death from CV causes in patients with HFpEF. In this study, 4822 patients with HFpEF were randomized to sacubitril-valsartan ($n = 2407$) and valsartan alone ($n = 2389$). The study failed to show significant beneficial effect with sacubitril-valsartan [20].

The authors observed greater benefit in patients with ejection fraction below the median of 57%, with a 22% reduction (rate ratio: 0.78; 95% CI: 0.64–0.95) and in women, with a 28% reduction (rate ratio: 0.73; 95% CI: 0.59–0.90) in the primary end point. Sacubitril/valsartan was associated with more hypotension, but less hyperkalemia and less renal dysfunction compared with valsartan, findings similar to those seen in the PARADIGM-HF trial. An important observation is made by O'Connor that in PARAGON-HF trial, the baseline NTProBNP levels were much lower as compared with those in PARADIGM-HF trial and reduction of adverse cardiac remodeling reflected by reduction in NP levels might be a less important mechanism of benefit in this group of patients [21].

Another ongoing study in 2547 patients with HFpEF sponsored by Novartis is examining the superiority of sacubitril-valsartan therapy over individualized medical therapy for comorbidities in reducing NT-proBNP and improving exercise capacity and HF symptoms over 24 week in 3 strata – ACEi (sacubitril-valsartan vs enalapril), ARB (sacubitril-valsartan vs valsartan) or no RASi (sacubitril-valsartan vs placebo) [22].

Sacubitril-valsartan in acute coronary syndrome & post-MI HF

Angiotensin II, a potent vasoconstrictor, a key component of RAS, acting via AT 1 receptors, promotes atherothrombosis, through inflammation, endothelial dysfunction, inhibition of urinalysis and LDL oxidation [23]. ACE inhibition demonstrated to decrease the risk of coronary events and death in patients with HF and LV dysfunction (with enalapril, lisinopril, ramipril and trandolapril), in high risk patients (ramipril) and in low risk patients (perindopril)

without LV dysfunction and HF. The cardiovascular (CV) benefit provided by ARBs is controversial and is explained by the selective antagonism of AT1 receptor and therefore increasing AT II levels by 200–300% [24].

A *post hoc* analysis of PARADIGM-HF study reported significant reduction in the coronary composite of CV-death, nonfatal MI, angina hospitalization or coronary revascularization (HR: 0.83 [0.75–0.92]; $p < .001$) among patients receiving sacubitril-valsartan compared with enalapril [25]. It might be that sacubitril, by augmenting the effects of NP system, overcomes the ATII effects induced by valsartan. Ongoing PARADISE-AMI trial is evaluating the safety and efficacy of sacubitril-valsartan compared with ramipril in addition to standard post-myocardial infarction pharmacotherapy [26]. The primary end point is time to the first occurrence of a composite end point of CV death, HF hospitalization, or outpatient HF. The secondary outcomes include time to the first occurrence of a confirmed composite of CV death or HF hospitalization; composite of HF hospitalization or outpatient HF; composite of CV death, nonfatal spontaneous myocardial infarction or nonfatal stroke; and time to all-cause mortality.

Sacubitril-valsartan in cardiac remodeling

Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury [27].

Remodeling after injury either by myocardial infarction or following myocarditis occurs to the myocardial mass, geometry and shape. Early in the post-myocardial infarction phase, there is a repair of the necrotic area by fibrosis, scarring and subsequently the noninfarcted zone becomes hypertrophied elongated and assumes spherical shape. These changes lead to decline in ventricular performance. Cardiac remodeling is detected clinically, by echocardiography, radionuclide ventriculography or cardiac magnetic resonance imaging. Echocardiography is by far the most used and easy method for assessment of cardiac remodeling indices which include LV end-diastolic volume index (LVEDV; normal $<76 \text{ ml/m}^2$), LV end-systolic volume index (LVESV; normal $<30 \text{ ml/m}^2$), left atrial volume index (a value $\geq 34 \text{ ml/m}^2$), LV mass index (normal $<89 \text{ g/m}^2$ in women and $<103 \text{ g/m}^2$ in men) and doppler derived early diastolic filling velocity (E wave) and early diastolic mitral annular velocity (e'); an E/e' ratio. These indices have independent prognostic utility for predicting clinical outcomes in patients with LV dilation and/or decreased LVEF.

Numerous studies have shown favorable effects on parameters of LV remodeling for drugs that improve clinical outcomes in patients with decreased LVEF and LV dilation, notably ACE inhibitors, β -blockers and ARBs. Earliest study of ARNI on cardiac remodeling in HFrEF was published by Martens *et al.*, who prospectively evaluated 125 patients switched from RAS blockers to sacubitril-valsartan [28]. During a median follow-up of 4 months significant improvement in LVEF ($29.6 \pm 6\%$ vs $34.8 \pm 6\%$; $p < .001$) and decrease in LVESV ($147 \pm 57 \text{ ml}$ vs $129 \pm 55 \text{ ml}$; $p < .001$) and LVEDV ($206 \pm 71 \text{ ml}$ vs $197 \pm 72 \text{ ml}$; $p = .027$) was observed. Diastolic function also improved with decrease in E/A -wave ratio (1.75 ± 1.13 vs 1.38 ± 0.88 ; $p = .002$) and drop in the percent of patients with a restrictive mitral filling pattern from 47 to 23% ($p = .004$). PROVE-HF study assessed the correlation of reduction in NT-pro BNP levels with cardiac remodeling indices [28]. Sacubitril-valsartan-treated patients have shown a significant mean 9.4% increase in LVEF, and mean reductions in LVEDV -11.32 ml/m^2 , LVESV -14.15 ml/m^2 , left atrial volume index -7.06 ml/m^2 and $E/e' -0.93$. These indices started to improve by 6 months but more pronounced at 1 year and underscore the potential benefit of reduction in NT-pro BNP levels and associated improvement in diastolic dysfunction.

Sacubitril-valsartan in functional mitral regurgitation

Secondary or functional mitral regurgitation (MR) is commonly seen in HFrEF patients and is a poor prognostic marker. Despite guideline-directed maximal medical treatment, 2-year mortality is of the patients admitted with HF is almost 50%. Interventional therapies to improve outcomes in this population include cardiac resynchronization therapy, LV assist devices, cardiac transplantation and transcatheter mitral valve repair. Although β -blockers, ACE inhibitors and ARBs could partially attenuate LV dilation and remodeling after myocardial injury, their effects on LV remodeling are insufficient for reducing the severity of MR.

The effect of sacubitril-valsartan on functional mitral regurgitation is noted in two studies. In their study Martens *et al.* have shown that volumetric remodeling was associated with a reduction in the degree of mitral regurgitation (1.59 ± 1.0 vs 1.11 ± 0.8 ; $p < .001$; [scale from 0–4]) apart from the improvement in EF and other metrics mentioned above [29]. In PRIME trial (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation), Kang *et al.*, assessed the therapeutic impact of ARNI on functional MR by randomizing 118 patients with HF with

chronic functional MR secondary to LV dysfunction to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for HF. Over 12 months follow-up, there was a significant 30% decrease in effective regurgitant orifice area and 33% decrease in regurgitant volume in the sacubitril/valsartan group compared with valsartan group (-0.058 ± 0.095 vs -0.018 ± 0.105 cm²; $p = 0.032$; mean difference, -7.3 ml; 95% CI: -12.6 to -1.9 ; $p = 0.009$) [30]. Though small in numbers, these studies again provide mechanistic explanation for the benefit of sacubitril-valsartan therapy in patients with HFrEF including functional MR.

ARNI & antiarrhythmic effect

Sudden cardiac death occurs in up to 50% of patients with HF most commonly due to ventricular tachycardia, ventricular fibrillation and less commonly due to bradycardia and pulseless electrical activity. In PARADIGM-HF trial, a total of 80.9% deaths were attributed to CV deaths, 14.8% to non-CV and 4.3% to unknown causes. Among the CV deaths, 44.8% were sudden cardiac deaths and 26.5% were related to HF. Patients randomized to sacubitril-valsartan had 20% reduction in sudden deaths compared with those in enalapril group (HR: 0.80; LCZ696 vs enalapril, 95% CI: 0.68–0.94; $p = 0.008$) [31]. De Diego *et al.* have reported the impact of sacubitril-valsartan treatment compared with ACEI/ARB in 120 patients with home monitored ICD over 18 months and found that sacubitril-valsartan reduced PVCs, nonsustained ventricular tachycardia (VT), ventricular arrhythmias and appropriate shocks [32]. These findings may suggest an important role for sacubitril-valsartan in reduction of sudden cardiac death in patients with HFrEF. The possible mechanisms of this benefit may be related to the effect of sacubitril-valsartan on improvement in hemodynamics, improvement in LV function, reduction in myocardial fibrosis and reduction in sympathetic nervous system tone. It is not yet known whether sacubitril-valsartan has direct antiarrhythmic effects.

ARNI & glycemic control

Diabetes is an important risk factor for patients with HF and control of diabetes is very important in these patients to prevent further complications. In an interesting *post hoc* analysis of PARADIGM HF study, Seferovic *et al.* reported findings that patients receiving sacubitril-valsartan had a great glycemic control evidenced by HbA1C reduction compared with those on enalapril. The authors reported a total of 3778 (45%) patients were found to be having diabetes and assessed their glycemic control by HbA1c measurements yearly upto 3 years. Patients in sacubitril-valsartan arm ($n = 1904$) had greater reduction in HbA1c levels, lesser need for initiation of new insulin therapy compared with those on enalapril ($n = 1874$) [33]. These findings could be explained by the neprilysin inhibition by sacubitril-valsartan. Neprilysin inhibition is associated with increase in bradykinin that causes increase in insulin sensitivity and an increase in GLP-1 that causes increased insulin release and decreased glucagon secretion.

Expanding indications for ARNI

ARNI is approved for HFrEF at present. However, several other indications are being explored based on experimental and clinical studies.

Sacubitril-valsartan in systemic hypertension

Sacubitril/valsartan results in systemic vasodilation and increased diuresis and natriuresis, leading to reduction of peripheral vascular resistance and volume contraction thereby lowering systemic blood pressure.

Early studies using LCZ696 as antihypertensive drug were reported by Ruilope *et al.* [34]. A total of 1328 patients with mild-to-moderate hypertension were randomized to LCZ696 or valsartan at varying single daily dosages of drugs, and placebo. The authors compared the effect of LCZ696 with valsartan on the mean sitting diastolic blood pressure at three incremental doses.

It was observed that LCZ696 effectively reduced mean sitting diastolic and systolic blood pressure compared with valsartan. p 24 hour mean ambulatory systolic BP decreased with 200 mg and 400 mg LCZ696.

Kario *et al.* reported in a similar study, but in Asian patients and against placebo. LCZ696 at all doses tested significantly reduced 24-h, daytime and night-time ambulatory systolic, diastolic and pulse pressures [35]. Several trials are under way comparing the efficacy and safety of LCZ696 with comparators such as olmesartan, valsartan, amlodipine, sildenafil and irbesartan [36].

One important study comparing sacubitril-valsartan to olmesartan is the PARAMETER study, which aimed to study the effects on central aortic blood pressure. The study included 454 elderly hypertensive patients and found that sacubitril-valsartan-reduced central aortic pressure more than olmesartan and demonstrated less need

for additional antihypertensive medications in this elderly cohort [37]. As several safe and effective options with large trial data and long term follow-up and established CV benefits are available, LCZ696 may not be a drug indicated for treatment of hypertension.

While the above studies looked at patients with primary hypertension, in the HF trials utilizing sacubitril-valsartan also there was significant reduction in blood pressure compared with valsartan in PARAMOUNT trial and enalapril in PARADIGM trial. A sub study of the latter trial addressed the concerns about significant lowering of blood pressure in patients with HFrEF might produce decline in cardiac and renal function and showed that even in patients with a persistently low SBP after treatment, sacubitril/valsartan was superior to enalapril in reducing mortality and morbidity [38].

Sacubitril-valsartan in chronic kidney disease

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m² for 3 months or more, irrespective of cause [39]. Kidney damage can be ascertained by albuminuria defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, and GFR calculated from serum creatinine is used as a guide to stage the CKD. The two principal outcomes of CKD are the progressive loss of kidney function over time, and development and progression of CVD. CVD in patients with CKD poses higher mortality and morbidity risk and hence it is imperative to control the progression of CKD. Several randomized controlled trials have shown that RAS inhibitors slow the progression of CKD in proteinuric patients with and without diabetes.

There is yet no data with ARNI in this condition. By providing angiotensin receptor blockade and by promoting NP effects, ARNI might be useful to reduce blood pressure effectively and retard progression of CKD and reduce CV events.

The UK HARP-III trial randomized 414 patients with CKD to sacubitril/valsartan 97/103 mg twice daily (n = 217) versus irbesartan 300 mg once daily (n = 217). After 1 year follow-up, there was no difference in GFR and urine albumin-creatinine ratio. Sacubitril/valsartan was found to reduce blood pressure and biomarkers of CV risk (troponin I and NT-proBNP) compared with irbesartan [40].

PARADIGM-HF study excluded patients with an estimated GFR below 30 ml/min per 1.73 m² of BSA at screening, which is a common subset in real world practice. Chang *et al.* included 10.9% of patients with eGFR = 10 ml/min/1.73 m² of BSA in their study of 932 patients with HFrEF randomized to sacubitril-valsartan (n = 466) and no sacubitril-valsartan (n = 466). Over a follow up period of 15 months, significantly less incidence of death from CV causes or hospitalization was observed in sacubitril-valsartan group compared to those not on sacubitril-valsartan; 33.4 vs. 56.6%; p = 0.001 [41].

Sacubitril-valsartan in pulmonary hypertension & chronic obstructive pulmonary disease

Pulmonary hypertension, defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise, is often characterized by a progressive and sustained increase in pulmonary vascular resistance that eventually may lead to right ventricular failure. Of the five groups of pulmonary arterial hypertension (PAH) classified by WHO, group 2 occurs secondary to left heart disease and group 3 due to lung disease. Sacubitril-valsartan could be considered in the treatment of both these groups of pulmonary hypertension owing to its effect both at postcapillary level, acting on natriuresis, and at precapillary level, generating vasodilation.

Encouraging case report was published by Simone *et al.*, wherein they treated two patients with group 2 PAH with sacubitril-valsartan and demonstrated reduction in pulmonary hypertension, improvement in filling pressures and decrease in the dose of furosemide [42]. Reduction in pulmonary artery pressure in this group of patients is demonstrated by Desai *et al.*, who published 30 days outcomes of 96 of the 117 patients that were initiated on sacubitril-valsartan from among 637 subjects with HF included in CardioMEMS post-approval study. Baseline mPAP was 32.8 ± 10.5 mm Hg prior to start of sacubitril/valsartan and decreased to 29.9 ± 9.4 mm Hg after 30 days (difference -2.9 mmHg, 95% CI: -0.1 to -5.8 mmHg; p = 1.001) [43]. Ongoing PARENT trial that is ongoing will provide more insights into this therapy in patients with HFrEF on hemodynamic monitoring with implanted CardioMEMS device randomized to sacubitril-valsartan or ACEI/ARB [44]. Considering these initial reports and also foregoing discussion of safety of sacubitril-valsartan in patients with HFrEF and low blood pressure and even renal impairment, the drug may be considered in these high risk patients.

In patients with HFrEF, Chronic obstructive pulmonary disease (COPD) and CV disease frequently occur together and their coexistence is associated with worse outcomes than either condition alone. One major concern

for the physicians taking care of this group of patients is the use of β -blockers. Ehteshami-Afshar *et al.* analyzed a subgroup of 8399 PARADIGM-HF patients with COPD ($n = 1080$, 12.9%) and reported that this group of patients had significantly higher baseline NT-proBNP levels, worse functional class, more frequent CV risk factors and disease, including atrial fibrillation, angina, previous myocardial infarction and percutaneous coronary intervention compared with those without COPD. Sacubitril-valsartan therapy in this group was associated with similar composite end point of hospitalization for HF and death compared with enalapril-treated patients [45].

Sacubitril-valsartan & cognitive function

Although sacubitril-valsartan has demonstrated excellent outcomes, there are concerns regarding the long term use of ARNI. Chronic neprilysin inhibition might have an effect on angio-oedema, bronchial reactivity, inflammation and cancer, and might predispose to polyneuropathy. Additionally, inhibition of neprilysin metabolism of amyloid- β peptides might have an effect on Alzheimer's disease, age-related macular degeneration and cerebral amyloid angiopathy [46]. However, it is reassuring to know that In PARADIGM-HF study, over a follow-up period of up to 4.3 years there was no evidence of increased dementia-related adverse events (AEs). The narrow standardized medDRA queries (SMQ) search identified 0.36% AEs on enalapril and 0.29% on sacubitril/valsartan (HR: 0.73; 95% CI: 0.33–1.59), while broad search identified 2.30 and 2.48% AEs (HR: 1.01; 95% CI: 0.75–1.37) [47]. It is interesting to know that dementia might be related to other comorbidities and hospitalizations for HF. Sacubitril-valsartan might be in fact useful in the long term therapy by improving hospitalization for HF.

An ongoing PERSPECTIVE trial is examining the effect of LCZ696 compared with valsartan on cognitive function in patients with chronic HF and preserved ejection fraction. Cognitive function will be assessed using a comprehensive battery of tests with an evaluation of longitudinal change of cognitive domains including memory, executive function and attention [48].

Sacubitril-valsartan in sleep apnea syndrome

Sleep apnea syndrome is frequently associated with HF in 20–75% of cases. The presence of an apnea syndrome is associated with a greater morbidity and mortality. A three months real life observational trial is performed. A measure of the apnea hypopnea index is realized before and after 3 months of SACUBITRIL-VALSARTAN treatment [49].

Conclusion

Neprilysin inhibitors have become successful therapeutic agents for treatment of HFrEF and gained US FDA approval for the same. Further studies have provided insights into several mechanisms of HF, hypertension which are important contributors for CV disease. Clinical studies that have been published so far support a role for these drugs in expanding indications in CV diseases. Ongoing research and development of NPs and clinical trials involving these molecules will continue to evolve with the promise of exciting therapeutics for CV disease and beyond [50].

Future perspective

ARB-neprilysin inhibitors have transformed the management of HFrEF. In view of the mortality benefit conferred by this class of drug, regulatory approval is accorded in preference to existing class of drugs such as ACE inhibitors and ARBs. Encouraging results are seen for other CV indications such as HFpEF, HF and acute myocardial infarction and LV dysfunction; reverse remodeling, sudden cardiac death, functional mitral regurgitation, CKD, obstructive sleep apnea and pulmonary hypertension. There is an expanding understanding of NPs and their modulation is going to usher in a new era of treatment of CV diseases. Newer concepts of neprilysin inhibition with non renal elimination and clinical studies of other NPs such as synthetic agents are likely to change the landscape.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Natriuretic peptides (NP) have several beneficial effects in cardiovascular disease such as natriuresis, vasodilation, possess antiproliferative effects, cause vascular remodeling and modulation of renin–angiotensin–aldosterone systems.
- Neprilysin degrades these NPs and neprilysin inhibition is associated with augmenting NPs actions. Combining neprilysin inhibition with angiotensin receptor blocker helps to overcome the adverse effect of angioedema.
- Sacubitril-valsartan, the first angiotensin receptor II blocker – neprilysin inhibitor agent has shown significant mortality benefit in heart failure with reduced ejection fraction compared with ACE inhibitor, thus paving way for a new class of therapeutics.
- Encouraged by the results of PARADIGM-HF study, sacubitril-valsartan is tested in other cardio vascular indications with promising results.
- Further understanding of NP and their analogs is likely to change the future of cardiovascular disease therapy.

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