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Review Article

# SACUBITRIL/VALSARTAN: A NEW PARADIGM IN HEART FAILURE

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**ABSTRACT**

Heart failure (HF) is a syndrome whose cardinal symptoms are dyspnea and fatigue leading to a progressive decrease in exercise capacity. Drugs currently used include angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers (ARB), diuretics, alone or in combination, and in the cases where indicated, digoxin. Sacubitril/valsartan represents a new approach to treatment since the drug complex is made up of moieties of sacubitril, a neprilysin inhibitor and valsartan, an ARB. Since sacubitril and valsartan, inhibit neprilysin and block the angiotensin receptor, respectively, the drug molecule can be considered to play a central role by causing a dual inhibition of both the pathways that play an important role in the pathogenesis of HF. It was approved in July 2015 by the US Food and Drug Administration to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction. Symptomatic hypotension and angioedema were the major side effects reported from clinical trials. The trials are currently being done to study its effects in HF preserved ejection fraction, chronic kidney disease, and aortic stiffness; the results of which are awaited.

**Keywords:** Sacubitril/valsartan, Neprilysin inhibitor, Dual neutral endopeptidaseneprilysin renin-angiotensin system Inhibition.

## INTRODUCTION

Heart failure (HF) is a syndrome rather than a disease, the cause of which may be structural or functional, or more often than not, both. Whatever be the underlying cause, the cardinal symptoms are dyspnea and fatigue leading to a progressive decrease in exercise capacity; peripheral edema, and/or pulmonary/splanchnic congestion due to a fluid retention can occur. Ejection fraction (EF) is an important parameter based on which patients with HF can be classified into HF with reduced EF (HFrEF; EF ≤40%), HF with preserved EF (HFpEF; EF ≥50%), and an intermediate/borderline group of patients [1]. Once HF is diagnosed, the treatment is for life. However, even with regular treatment, the death rate can be high-up to 50% patients after being diagnosed with HF, do not survive for more than 5 years [2].

## CURRENT APPROACH TO MANAGEMENT

Currently, the following drugs are used for the treatment of symptomatic HFrEF as a single agent or in combinations of two or more drugs as indicated: Angiotensin-converting enzyme inhibitors (ACEi), Beta-adrenergic receptor blockers (such as bisoprolol, carvedilol, and sustained-release metoprolol succinate), and aldosterone receptor antagonists (ARB). Diuretics are recommended in patients who have evidence of fluid retention. Digoxin is reserved for specific circumstances to decrease hospitalizations for HF [1].

## NATRIURETIC PEPTIDES (NPS) AND NEPRILYSIN

NPs, a family of peptide hormones that work to maintain the sodium and fluid balance and thereby protect the cardiovascular system from the harmful effects of fluid overload, mainly originate from the atria of the heart whenever the atrial pressure rises. So far, three distinct NPs have been identified: Atrial NP (ANP), brain (or B-type) NP (BNP), and C-type NP. The major effects include vasodilation, diuresis, and natriuresis, brought about by the intracellular increase of cyclic guanosine monophosphate, which in turn plays a very important role in the cardiovascular system. NPs are also considered an important diagnostic marker of the severity of HF since their levels are increased in response to fluid overload. The clearance of NPs takes place by a number of different processes such as receptor-mediated degradation, breakdown by extracellular proteases, particularly by the action of neutral endopeptidase neprilysin (NEP) also referred to as membrane metalloendopeptidase. The expression of NEP occurs throughout the body, but majorly in the kidneys. It also contributes to the breakdown of other substances such as angiotensin II, bradykinin, substance P, vasoactive intestinal peptide, and glucagon [3].

## THE PATH TREADED SO FAR

Once the fact that NPs work to maintain homeostasis in HF started to gain acceptance, this came to be considered a novel pathway to target in the management of HF. However, it came to be noted that though the levels of NPs were raised in HF, it was not adequate to completely reduce the fluid retention. Therefore, it was hypothesized that administering exogenous NPs could be helpful in HF. Moreover, thus began the spate of research in this area, to try and identify various ways to modulate this pathway [3,4].

The vasodilation in the management of acute congestive HF study compared the efficacy and safety of a recombinant BNP called nesiritide given intravenously, intravenous nitroglycerin, and placebo, in addition to standard medications. It was observed that addition of nesiritide improved the hemodynamic function and some self-reported symptoms more than intravenous nitroglycerin or placebo, in acute decompensated HF [4]. However, on comparing, the safety of nesiritide to that of non-inotrope based therapy, it was noted that nesiritide was associated with an increased risk of death, after the acute decompensated stage was treated [5].

Another trial referred to as the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF trial studied the effect of nesiritide when added to the standard method of management; neither an increase nor a decrease in the rate of re-hospitalization or death was seen. A small effect on dyspnea though observed and was not significant. Furthermore, the rate of hypotension was higher with nesiritide. Hence, it was concluded that these results were not promising enough to warrant routine use of nesiritide in acute HF [6].

In continuation with the previous hypothesis, it was proposed that the levels of NPs could be increased by suppressing the activity of neutral endopeptidase. On comparing, the effects of candoxatril, a drug causing endopeptidase inhibition to the effects of atrial natriuretic factor, on systemic and forearm hemodynamics, and muscle sympathetic nerve activity in healthy young men, it was observed that both the

interventions reduced the central venous pressure with no reflex increase in sympathetic activity. However, a rise in epinephrine was seen, suggesting that there could be specific inhibition of sympathetic nerve traffic to muscle at the physiologic plasma atrial natriuretic factor concentrations [7]. Yet, it failed to demonstrate a reduction in blood pressure (BP) in hypertensive patients, and also a reduction in systemic pulmonary/vascular resistance in patients with HF, because of which the development of the drug was discontinued [8]. Ecadotril, a drug with a similar mechanism of action was also tried; a safety and tolerability study at doses ranging from 50 to 400 mg showed no symptomatic benefit, and also, an unfavorable adverse event profile was seen. Hence, the clinical development was not continued [9].

Further on, a dual inhibition of NEP and renin-angiotensin system (RAAS) was suggested. The omapatrilat cardiovascular treatment versus enalapril trial studied the safety and efficacy of omapatrilat to enalapril, an ACEi. It was observed that the antihypertensive effect of omapatrilat was relatively better. Furthermore, angioedema, albeit not life-threatening, was higher with enalapril. Hence, it was concluded that if the risk-benefit profile of omapatrilat was considered, it seemed favorable for use in appropriate patients [10]. The Inhibition of metalloprotease by BMS-186716 in a randomized exercise and symptoms study in subjects with HF trial was done to compare the effect of omapatrilat to that of lisinopril (an ACEi), on exercise tolerance and morbidity in HF. It was observed that the advantages with omapatrilat were more than that with lisinopril, suggesting that this could be an effective treatment option in the management of patients with HF [11]. Another trial comparing omapatrilat with enalapril called omapatrilat versus enalapril randomized trial of utility in reducing events found that both hospitalization and mortality were reduced by omapatrilat; however, this effect was not more than what was seen with using ACEi alone, which resulted in the drug falling out of the drug developmental pathway and its route to US Food and Drug Administration's approval [12].

## SACUBITRIL/VALSARTAN

### What is it?

Sacubitril/valsartan (LCZ696) is a dual acting complex containing both sacubitril, a neprilysin inhibitor (NEPi) and valsartan, an angiotensin receptor blocker (ARB) moieties in its structure. Six moieties each of sacubitril and valsartan in their anionic form, along with 18 sodium cations and 15 water molecules constitute one molecule of the drug complex [13]. It was approved in July 2015 by the US Food and Drug Administration to reduce the risk of cardiovascular death and hospitalization for HF in patients with a chronic HF (NYHA Class II-IV) and reduced EF [14]; the approval from the European Medicines Agency came forth in September 2015 [15].

### How does it act?

Since sacubitril and valsartan inhibit neprilysin and block the angiotensin receptor, respectively, the drug molecule can be considered to play a central role by causing a dual inhibition of both the pathways. In patients with HF, an activation of both RAAS and of sympathetic nervous system is seen, which together increase the renin release. This, in turn, activates the cascade, and the end result is increase in the levels of circulating angiotensin II, the final step being catalyzed by the ACE. Angiotensin II by acting via the AT-1 receptor brings about its biological effects, and this is blocked by valsartan, by blocking the AT-1 receptor.

HFrEF is associated with a gradual increase in vessel wall stress, which is responsible for the activation of the neprilysin system causing the release of ANP and BNP, whose aforementioned biological actions try and maintain homeostasis in HF. In addition, renin release is also blocked by ANP. Sacubitril, a drug that inhibits NEP which is responsible for the breakdown of these peptides, preserves ANP levels by preventing its breakdown.

Therefore, the two-component complex blocks RAAS activation, and enhances the actions of ANP [16].

## THROUGH THE DEVELOPMENTAL PIPELINE

### Preclinical studies

A study done in Sprague-Dawley rats which involved the oral administration of sacubitril/valsartan demonstrated a dose-dependent raise in the levels of ANP owing to the NEPi. A dose-dependent reduction in BP was also observed in hypertensive double-transgenic rats [17].

### Clinical studies

#### *Phase 1*

A pharmacokinetic study with a randomized, double-blind, placebo-controlled design, with sacubitril/valsartan given either as a single-dose (200-1200 mg) or in multiple doses (50-900 mg once daily for 14 days) was conducted in 80 healthy participants. The peak concentrations of sacubitril and valsartan were reached in 0.5-1.1 hrs and 1.6-4.9 hrs, respectively; the peak concentration of the active moiety of sacubitril was seen at 1.8-3.5 hrs. Similar effects were also observed in another randomized, open-label crossover study. In addition, proof of inhibition of NEP and blockade of the AT-1 receptor was observed in the form of an increase in plasma cGMP, renin concentration and activity, and angiotensin II [17].

#### *Phase 2*

This was a randomized, double-blind, placebo-controlled study done to compare the BP lowering effects of sacubitril/valsartan versus valsartan alone, involving 1328 patients, divided into eight groups that received treatment intervention for an 8-week period. Of these, three groups received three different doses of the drug complex (100 mg, 200 mg, and 400 mg), three groups received valsartan alone in three different doses (80 mg, 160 mg and 320 mg), one group received sacubitril alone (200 mg), and the last group received a placebo. It was observed that the drug complex produced an additional decrease in BP compared to valsartan alone [18].

Another randomized, double-blind, placebo-controlled trial conducted across five Asian countries to study the effects of the drug complex on BP included 389 adult patients. They were divided into four groups of which three received the study drug complex in three doses used in the previous study, and the fourth group received placebo for 8 weeks. A significantly higher reduction in BP (systolic BP (SBP), diastolic BP, pulse pressure, 24 hrs ambulatory BP) was seen with all doses of the study drug [19].

The PARAMOUNT trial (Prospective comparison of ARNi with ARB on Management of HFpEF) was a randomized, double-blind, active-comparator, parallel-group trial done to assess the efficacy and safety of the drug complex in patients with HFpEF (New York Heart Association Classes II and III, with EF ≥45%). Randomly divided into treatment groups, the patients received either sacubitril/valsartan titrated to 200 mg or valsartan titrated to 160 mg, both twice a day, for a period of 36-week. A change in NT-proBNP at 12 weeks from baseline was taken as the primary endpoint. It was observed that the study drug produced a larger reduction in the NT-proBNP levels than did valsartan alone [20].

#### *Phase 3*

This was a double-blind study that compared sacubitril/valsartan (200 mg twice daily) to enalapril (10 mg twice daily) in addition to the routine drugs prescribed, in patients with HFrEF (New York Heart Association Classes II, III, or IV; EF ≤40%). An attempt was made to study the difference in the mortality rate from cardiovascular causes. As the trial progressed, on overwhelming benefit was seen with the study drug during a median follow-up of 27 months, and the trial was stopped since this complied with rules laid down before the trial had been started. When the study was closed, the primary outcome which was either hospitalization for HF or death from cardiovascular causes, had occurred in 13.3% patients receiving sacubitril/valsartan, and 16.5% patients receiving enalapril (hazard ratio:0.80). Although cases of non-serious angioedema and hypotension were higher in the study

group, cases of hyperkalemia and renal impairment were higher with enalapril as was a cough [21]. This was the study following which sacubitril/valsartan was approved for the clinical use.

## SACUBITRIL/VALSARTAN: CURRICULUM VITAE

### Adverse effects

The most common adverse effects observed were symptomatic hypotension, hyperkalemia, renal dysfunction, and angioedema; acute hepatitis was observed in a patient in a phase 2 study for which the causality to the study drug could not be ruled out. However, the test drug was well tolerated across studies, compared either to a placebo or an active comparator, and rarely required discontinuation of the treatment [17-21].

### Use in special groups

Any drug acting on the renin-angiotensin system can cause fetal damage (reduction in renal function) and even death; hence, sacubitril/valsartan is contra-indicated in pregnancy. Furthermore, this drug should be discontinued during lactation and in patients with severe hepatic impairment [22].

### Drug interactions

Since dual inhibition of RAAS has fallen out of favor, this drug should not be used with ACEi and an ARB. The risk of hyperkalemia maybe increased if used concomitantly with a potassium-sparing diuretic, potassium supplements, or salt substitutes containing potassium, and hence, must be avoided. There could be worsening of renal function if used along with non-steroidal anti-inflammatory drugs, especially in the elderly, volume-depleted patients, and those with compromised renal function. Concomitant use with lithium should be avoided as lithium toxicity can occur [22].

### Dosage and administration

Sacubitril/valsartan is available as unscored film-coated tablets in strengths of 24/26 mg, 49/51 mg, and 97/103 mg. The recommended starting dose of sacubitril/valsartan is 49/51 mg twice a day. The dose has to be doubled after a period of 2-4 weeks, until the target maintenance dose of 97/103 mg twice a day is reached, as tolerated by the patient. The starting dose is reduced to 24/26 mg twice a day in patients not currently taking an ACEi or an ARB, in patients who previously have been taking a low dose of ACEi or ARBs, patients with severe renal impairment and patients with moderate hepatic impairment; dose adjustment as required and tolerated by the patients has to be done in 2-4 weeks [22].

## SACUBITRIL/VALSARTAN: LOOKING AHEAD

### HFpEF

A randomized, double-blind, active-comparator, parallel-group trial named PARAGON (Prospective Comparison of LCZ696 with ARB Global Outcome in HFpEF; NCT01920711) done to compare the effects of sacubitril/valsartan and valsartan alone in reducing hospitalizations and cardiovascular death in patients with the HFpEF has been completed, and the results of which are awaited [16].

### Chronic kidney disease

The UK Heart and Renal Protection-III trial is a randomized, double-blind, active-comparator, parallel-group trial that is being carried in patients with chronic kidney disease assigned to receive either irbesartan or sacubitril/valsartan; the change in the glomerular filtration rate from baseline to the 6$^{th}$ month time point is being studied here. A completion is expected at the end of January 2016 [16].

### Aortic stiffness

A randomized, double-blind, active-comparator, parallel-group trial named PARAMETER (Prospective comparison of angiotensin receptor NEPi with ARB measuring arterial stiffness in the elderly; NCT01692301) is being done to compare the efficacy of sacubitril/valsartan versus olmesartan in the elderly patients with a raised SBP and widened PP; the parameters being assessed are central aortic SBP and other suitable measures that denote central hemodynamics [16].

## SACUBITRIL/VALSARTAN: SO WHERE DOES IT CURRENTLY STAND?

This drug complex looks to be a promising agent in the management of patients with HF. Dual inhibition of the RAAS and NEP represents a novel approach to therapy since it targets one of the central mechanisms involved in the pathogenesis and progression of HF. Trials like PARADIGM-HF have shown significant reductions in both cardiovascular deaths and all-cause mortality in the patients with HFrEF who received sacubitril/valsartan against those who received only enalapril. Hence, it can be considered over an ACEi or an ARB for the first-line management of patients of HFrEF [21]. Symptomatic hypotension and angioedema could be causes of concern, and need to be dealt with. Results from studies that are being conducted for its use in HFpEF and other conditions mentioned earlier, will provide answers to many unanswered questions, and could pave the way for its use for other indications.

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