

## Angiotensin receptor/neprilysin inhibitor: a novel therapy in the treatment of heart failure

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### ABSTRACT

Recently US Food and Drug Administration (FDA) approved valsartan/sacubitril is the first angiotensin receptor/neprilysin inhibitor (ARNI) that offers a new standard of treatment to physicians for the patients of heart failure with reduced ejection fraction. Sacubitril is a prodrug which gets activated to sacubitrilat and this inhibits the enzyme neprilysin which is a membrane bound endopeptidase and which in turn is responsible for the degradation of various natriuretic peptides. The action of Valsartan which selectively blocks the angiotensin II type-1 receptor is needed in addition to sacubitril because inhibition of neprilysin is accompanied by the activation of renin-angiotensin system. The combination appears to be a suitable alternative for patients of heart failure with persistent symptoms or with recent exacerbation or hospitalization while on standard optimized treatment. The availability of this novel sacubitril/valsartan combination is an important development in the heart failure management.

**Keywords:** Neprilysin, Sacubitril/valsartan, Heart failure, ARNI

### INTRODUCTION

Heart failure, often referred to as congestive heart failure, is a pathophysiologic state in which the heart is unable to pump blood at a rate which commensurate with the requirements of metabolizing tissue, or can do so only from an elevated filling pressure.<sup>1</sup> This results in a clinical syndrome of decreased exercise tolerance with pulmonary and systemic venous congestion.<sup>2</sup> The common causes of heart failure include coronary artery disease, diabetes, obesity and hypertension.<sup>3</sup>

Ejection fraction is a key measurement in assessing the heart's ability to pump out blood and in diagnosing and monitoring heart failure. A substantial number of patients with heart failure have a normal ejection fraction. A preserved ejection fraction (i.e., diastolic heart failure) indicates that the heart muscle contracts normally, but the

ventricles do not relax as they should; a reduced ejection fraction (i.e., systolic heart failure) indicates that the heart muscle does not contract effectively and less oxygen-rich blood is pumped out from the heart.<sup>4</sup>

Heart failure represents a main cause of morbidity and mortality and the first reason for hospital admission in older people, approximately 50% of patients with heart failure die within 5 years of diagnosis.<sup>5,6</sup>

### *Pharmacotherapy of heart failure*

The developments in the treatment of heart failure over the past decades in terms of drug therapy have resulted in a significant improvement in the morbidity pattern of chronic heart failure. The cornerstone of modern drug therapy in chronic heart failure is the inhibition of neuro-humoral activation. More specifically, the drug therapy

aims at inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Both of these systems play a crucial role in the pathophysiology of heart failure development and progression. The drug therapy in heart failure has been proven beneficial for patients with reduced ejection fraction but the same is not true for those with preserved ejection fraction, who roughly represent half of the total heart failure population.<sup>7</sup>

Among the various groups of drugs used in patients with heart failure, angiotensin converting enzyme (ACE) inhibitors prolong survival in patients with reduced ejection fraction (HFrEF) and have served as the backbone of heart failure management for over two decades.<sup>8</sup>

### *Natriuretic peptides*

Natriuretic peptides (NPs) are the hormones responsible for maintaining sodium and fluid homeostasis; their release is triggered by increased myocardial filling pressures. Benefits of NPs include direct vasodilation, increased glomerular filtration rate and reduced release of renin from the kidneys, in addition to natriuresis and diuresis.<sup>9</sup>

### *Nepriylsin inhibition*

Nepriylsin is a membrane-bound endopeptidase found in many tissues, particularly in the kidney.<sup>10,11</sup> It hydrolyses atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (and possibly urodilatin).<sup>12-14</sup> Nepriylsin has been called by many other names, including enkephalinase, neutral endopeptidase, vasopeptidase and atriopeptidase.<sup>10-15</sup> Degradation by nepriylsin is one of the two major means of elimination of natriuretic peptides, the other being through a clearance receptor (the natriuretic peptide clearance receptor; NPRC or NPR3).<sup>16</sup> Inhibition of nepriylsin, therefore, represents a major approach in enhancing endogenous natriuretic peptide levels and activity.

Nepriylsin, which has been described as a 'promiscuous' enzyme, also breaks down angiotensin II.<sup>17</sup> Consequently, by increasing levels of this peptide, nepriylsin inhibition may cause vasoconstriction, offsetting the vasodilator actions of augmented natriuretic peptides. Hence, nepriylsin inhibitor must be combined with an inhibitor of the rennin-angiotensin-aldosterone (RAAS) system. Thus combining a nepriylsin inhibitor and an angiotensin receptor blocker would prolong the survival of patients with heart failure with decreased ejection fraction.

There are three primary issues that must be considered when treating heart failure patients with reduced left ventricular ejection fraction (LVEF):

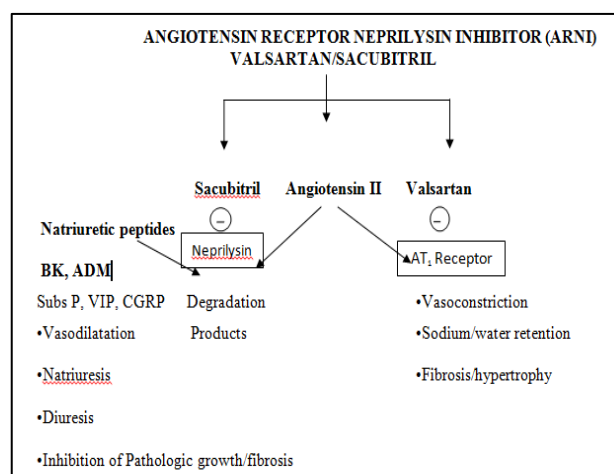
- Improving symptoms and quality of life,

- Slowing the progression or reversing cardiac and peripheral dysfunction, and
- Reducing mortality.

### *Angiotensin receptor/nepriylsin inhibitor (ARNI) in HFrEF*

On July 7, 2015, the US FDA approved nepriylsin inhibitor sacubitril combined with an angiotensin receptor blocker valsartan (brand name Entresto/LCZ696) to reduce the risk for cardiovascular death and hospitalization in patients with chronic heart failure (NYHA class II-IV) associated with reduced ejection fraction.<sup>18</sup> Valsartan was initially approved by the FDA in 1996 for the treatment of hypertension and in 2002 for the treatment of heart failure. In 2005, valsartan received FDA approval to reduce cardiovascular mortality in clinically stable patients with left ventricular (LV) failure or with LV dysfunction after a myocardial infarction.<sup>19</sup>

Sacubitril inhibits nepriylsin and thus helps to improve many of the pathophysiological abnormalities of heart failure.<sup>20</sup> In patients with heart failure, nepriylsin may actually have increased activity, so blocking it with valsartan/sacubitril combination may provide even more favorable results to these patients.<sup>21</sup> Valsartan selectively blocks the angiotensin II type-1 receptor and inhibits the release of angiotensin II-dependent aldosterone.<sup>20</sup> This action is needed in addition to sacubitril because inhibition of nepriylsin is accompanied by the activation of the renin-angiotensin system. This combination of valsartan and sacubitril is described as an angiotensin receptor-nepriylsin inhibitor (ARNI).<sup>21</sup> The mechanism of action of sacubitril/valsartan is shown in Figure 1.



**Figure 1: Mechanism of action of LCZ696 (sacubitril valsartan). ADM, adrenomedullin; AT<sub>1</sub>, angiotensin II type 1; BK, bradykinin; CGRP, calcitonin gene-related peptide; Subs-P, substance P; VIP, vasoactive intestinal (poly)peptide. For possible sacubitril substrates, larger font size indicates greater evidence for such an effect in humans.**

### Adverse effects

The most commonly reported adverse reactions with valsartan/sacubitril combination are hypotension, hyperkalemia, cough, dizziness, and renal failure. valsartan/sacubitril should not be given with ACE inhibitors (e.g., enalapril), renin inhibitor (e.g., aliskiren), or with another angiotensin receptor blocker (ARB). valsartan/sacubitril if given along with ACE inhibitors increase the risk of angioedema. Using valsartan/sacubitril with potassium-sparing diuretics, potassium supplements or with salt substitutes can lead to increase in the serum potassium levels. Combining valsartan/sacubitril with NSAIDs may increase the risk of renal impairment. Concomitant use of valsartan/sacubitril combination with lithium leads to an increased risk of lithium toxicity.<sup>20</sup>

### Contraindications

Valsartan/sacubitril combination is contraindicated in all such patients with a history of angioedema due to previous exposure to ACE inhibitor or ARB and in patients with diabetes. Patients on Valsartan/sacubitril combination should be closely monitored for signs and symptoms of angioedema and hypotension. Renal function and serum potassium levels should be monitored periodically. It is not recommended in patients with severe hepatic impairment.<sup>20</sup>

### Pregnancy and lactation

There is no information on the use of valsartan/sacubitril in lactating women, so presumably it is not recommended. Valsartan/sacubitril can cause fetal harm when administered to pregnant women therefore it is not recommended. The use of drugs that act on the renin-angiotensin system, such as valsartan/sacubitril combination, during the second and third trimesters of pregnancy can reduce fetal renal function and increase fetal and neonatal morbidity and death. If a patient becomes pregnant while taking valsartan/sacubitril, the drug should be discontinued with immediate effect to prevent any teratogenic effect.<sup>20</sup>

### CONCLUSION

Valsartan/sacubitril combination is a new option for the treatment of patients with reduced ejection fraction heart failure. It has been shown to be effective in the treatment of systolic heart failure, preventing one more cardiovascular death or heart failure hospital admission for every 21 patients treated for two years, compared to Enalapril. It has also been shown to decrease the all-cause mortality and reduce the symptoms of heart failure.

Standard heart failure therapy with optimal doses should still be recommended as first-line treatment in most patients with systolic heart failure. If there are persistent symptoms, with recent exacerbations or hospitalization

while on this optimized treatment, consider changing the ACE inhibitor or ARB to valsartan/sacubitril combination. This drug is not indicated for patients with preserved ejection fraction.<sup>22</sup>

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