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**Is Entresto good for the brain?**

Patel N *et al*. Entresto and brain

**Nirav Patel, Jason Gluck**

**Nirav Patel, Jason Gluck,** Department of Cardiology, University of Connecticut, Harford Hospital, Hartford, CT 06102, United States

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**Correspondence to: Nirav Patel, MD,** Department of Cardiology, University of Connecticut, Harford Hospital, 80 Seymour Street, Hartford, CT 06102, United States. nirav.patel@hhchealth.org

**Telephone:** +1-860-9721793

**Fax:** +1-860-5453422

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**Abstract**

The main stay pharmacotherapy for heart failure (HF) is targeted towards rennin-angiotensin-aldosterone (RAAS) and neprilysin pathways (NP). Both therapeutic strategies decreases morbidity and mortality but also carry considerable adverse effects. This review of the literature highlights the new generation of HF drug, sacubitril-valsartan (SV), trade name Entresto (researched as LCZ696, Novartis) which simultaneously blocks RAAS and NP. This dual action of angiotensin receptors blocker and neprilysin inhibitor (NPi) has improved HF prognosis and it is an evolution in the management of HF. Although the initial follow-up of patients treated with SV has yielded promising results, there are concerns regarding potential side effects especially an increase in the risk of Alzheimer’s disease (AD) and young onset of AD. NPi interferes with the breakdown and clearing of beta-amyloid peptides, the plaques seen in AD, raising concern for AD in SV patients. On the other hand, hypertension and cardiovascular diseases are established risk factors for AD which can be decreased by SV therapy. It is therefore essential that SV treated patients are followed up over an extended period of time to detect any adverse cognitive changes.

**Key words:** Heart failure; Sacubitril-valsartan; Entresto; LCZ696; Neprilysin inhibitor; Alzheimer’s disease

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**Core tip:** We are discussing an innovative and exciting new treatment for heart failure (HF). This advance in pharmacotherapy has shown promising results and is rapidly incorporating into standard medical therapy for HF. There is, however, a theoretical concern for cognitive dysfunction and early onset Alzheimer’s disease particularly in the young. This review informs clinicians of the mechanism and potential for cognitive dysfunction, thereby increasing awareness and promoting informed prescribing.

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**INTRODUCTION**

Heart failure (HF) is typified by the reduced ability of the heart to deliver an adequate supply of blood and oxygen to the tissues, and is associated with high morbidity, mortality and cost. Its causes are numerous including ischemic heart disease, diabetes, hypertension, cigarette smoking, obesity and valvular heart disease[1]. Over 5 million individuals worldwide suffer from HF and its incidence is rising with 550000 new diagnoses annually[1,2]. With a steadily aging population, HF incidence is projected to increase to 46% by the year 2030[1,2].

HF occurring due to depressed left ventricular function [ejection fraction (EF) ≤ 40%] is known as HF with reduced EF (HFrEF)[4]. Pharmacological intervention for HF largely depended on angiotensin inhibitors such as angiotensin receptor blockers (ARBs) and angiotensin converter enzyme inhibitors (ACEi). Recently, a new strategy using a Neprilysin inhibition (NIs) and recombinant natriuretic peptides was proven as a therapeutic option to target HF pathophysiology[5]. The new generation of HF pharmacotherapy entails the simultaneous inhibition of both the angiotensin and Neprilysin pathways, the latest version of which is Entresto® – the combination of sacubitril and valsartan (SV) (researched as LCZ696)[6,7]. In this concise review, we highlight the mechanisms of SV activity, the results of the successful clinical trial and the potential adverse effects, highlighting those on cognitive function.

**METHODS**

The search for the relevant articles was conducted on PubMed and Ovid. The following terms *“Entresto”, “neprilysin inhibitors”, “angiotensin inhibitors”, “dementia” and “Alzheimer’s Disease” “cognitive impairment”* were searched in different combinations. The search was limited to articles in English language but no search filters were used for timeline and subjects.

**INCLUSION CRITERIA**

Articles that met our following inclusion criteria were included in this review: (1) Discussed pathophysiology of HF and target pharmacotherapy mechanism, (2) Discussed pathophysiology of development of AD, (3) ongoing trials of Entresto, (4) reported link between neprilysin inhibitors and development of AD, (5) articles that were published full and in English language.

**PATHOPHYSIOLOGY OF HF**

The pathophysiology of HFrEF results mainly from the activation of the renin-angiotensin-aldosterone (RAAS) neuro-hormonal compensatory mechanism. Although the peripheral vasoconstriction initiated by the RAAS mechanism maintains blood pressure and cardiac output for a short time, sustained activation of RAAS leads to ventricular hypertrophy, hypertension and angioedema, ultimately worsening myocardial dysfunction[8,9]. A second compensatory mechanism, the natriuretic peptide (NP) system, counteracts the vasoconstrictive and sodium/water retentive effects of the RAAS system[10].

**GOALS OF PHARMACOTHERAPY**

The initial HF pharmacotherapy targeted the RAAS circuit using ARBs[11], ACEi[12], beta-blockers[13], diuretics[14] and aldosterone inhibitors[15]. All of these drugs have proven to be effective in lowering the morbidity and mortality in HFrEF. The NP system consists of four related peptides (Atrial, Brain, C-Type, and Dendroaspis NP) and a membrane bound peptidase called Neprilysin that degrades these vasoactive peptides[16]. NP system targeting drugs have included a recombinant form of BNP (Nesiritide)[17] as well as Neprilysin inhibitors (NIs), *e.g.*, candoxatril, rececodotril, *etc*[18,19]. HF pharmacotherapy targeting the NP system and the respective clinical trials are summarized in Table 1[20-32]. Although strategies blocking either of these two pathways have reduced mortality and morbidity in HF[12,28,32],the prognosis still remains poor due to long term ineffectiveness of the drugs as well as adverse physiological effects[5].

The newest strategy in HFrEF pharmaco-intervention is the combination of ARB and NI (ARNI) that causes a dual inhibition of the RAAS pathway and Neprilysin: The prototype drug was LCZ696[6,7] which is made up of 1:1 ratio of the ARB valsartan[33] and the NI sacubitril (AHU 377)[34]. The action of SV is multimodal. Sacubitril is a pro-drug which is activates to Sacubitrilat (LBQ657), the active metabolite that inhibits NP while valsartan simultaneously blocks the angiotensin receptor. The dual action of Sacubitril and valsartan augment the beneficial actions of the NPs and inhibits the deleterious effects of the RAAS system[7]. The PARADIGM-HF trial was conducted by McMurray *et al*[31] to determine the efficacy of SV compared to the ACE inhibitor Enalapril[35,36], which improves mortality and morbidity. The median follow-up duration was 27 mo and SV reduced HF related symptoms and overall survival by 20%[31]. Additionally, the ARNI approach avoids the common side-effects of ACEi such as cough and angioedema that result from impaired degradation and elevated levels of bradykinin[37]. In the ONTARGET trial, ARBs were documented to result in a lower rate of cough and angioedema compared to ACEi: Therefore, combination therapy prefers ARBs over ACEi[38].

The US Food and Drug Administration had approved SV for clinical use and at present it is produced under the name of Entresto® by Novartis[39]. The recommended dose of Entresto is 49 mg sacubitril/51 mg valsartan twice daily increased to 97 mg sacubitril/103 mg valsartan after 2-4 wk. It is contraindicated in patients with history of angioedema, hypotension, hyperkalemia or renal dysfunction and in pregnant women due to fetal toxicity[40]. In the PARADIGM-HF trial, 10.7% of the patients reported at least one of the following adverse effects hypotension, renal failure, hyperkalemia, fatigue and dizziness[31].

In clinical practice, approximatley 50% of the HF patients have a preserved left ventricular ejection fraction (HFpEF) and present with similar morbidity and mortality as seen in patients with HFrEF[2-4]. Sacubitril/valsartan is validated in HFrEF but is being evaluated for HFpEF in the PARAMOUNT-HF (The Prospective comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial. Patients who treated with sacubitril/valsartan showed a reduction in NYHA class and left atrial volumes[29]. At present, the PARAGON-HF trial is ongoing compareing the effects of sacubitril/valsartan versus valsartan in the HFpEF patients[32].

**NEPRILYSIN INHIBITORS AND ALZHEIMER’S DISEASE**

An interesting facet of the use of NIs in the treatment of cardiovascular diseases is their potential role in the development or progression of Alzheimer’s disease (AD), as there is considerable overlap between the populations suffering from HF and AD[41]. The hallmark of AD is the accumulation of beta amyloid (βA) peptide in the brain causing neurotoxic plaques that are supposedly responsible for the pathology of AD[42]. Under normal physiological conditions, the βA peptide is degraded by proteases such as ACE, NP and insulin degrading enzyme[43]. NP has a broad range of substrates apart from the NPs such as bradykinin, enkephalins as well as the βA peptide[44]. Additionally, patients with AD have lower expression of NP compared to healthy subjects[45], and NP deficient mice develop the murine form of AD[46]. This possible correlation was further highlighted when intracerebral infusion of NPi lead to the development of AD-like lesions in rabbits[47]. Lastly, certain polymorphisms in the NP gene (NEP) were associated with a higher propensity for AD in a Finnish cohort[48]. Therefore, NP is as much a pharmaceutical target for the treatment of AD as for HF, except that the strategies are opposite for both pathologies (Figure 1). Indeed, NP centered therapies have been developed independently for AD and tested at the pre-clinical levels. CNS targeted recombinant human NP was able to reduce βA peptide toxicity in the mouse model of AD[49,50].

**ENTRESTO® AND ALZHEIMER'S DISEASE**

Clinicians should be aware of the possible inhibitory action of SV in the clearing of βA peptide while considering it for HF treatment. In patients who are at the risk of developing AD, whether due to age or genetic predisposition, the chronic exposure to SV may accelerate the clinical onset of the disease. Critical to this hypothesis is the ability of SV to cross the blood brain barrier (BBB) in order to block brain NP. There is evidence that certain NIs like S-acetlythiorphan can cross the BBB[51]) while some like candoxatril cannot[52]. Both Sacubitril and its active metabolite LBQ657[7] are under the threshold size of 400 kD which makes them fit to cross the BBB[53,54]. It is noteworthy that the PARADIGM-HF trial[31] had excluded patients with AD and did not include any cognitive function tests to evaluate drug safety. McMurray *et al*[55] have confirmed some correlation between EN treatment and βA peptide levels in a recent review article. While cynomolgus monkeys treated with SV had increased levels of βA peptide in the CSF, the healthy volunteers treated with EN for two weeks had no change in βA peptide levels. McMurray *et al*[31] showed that the dementia and cognitive defects were not increased in the EN treated patients during the trial. However, it should be noted that the earliest symptoms of AD can take as long as 8-10 years to manifest[56]. If there is a correlation between EN therapy and AD, one would predict an earlier onset of symptoms.

It is therefore imperative that patients on SV are followed up for cognitive abilities and potentially evaluated for AD. One can consider cerebrospinal fluid (CSF) analysis for βA peptide levels and amyloid plaques through PET scans if early signs of dementia ensue[57]. In the ongoing PARAGON-HF[32] trial, AD patients have not been excluded and serial cognitive tests have also been included as part of initial follow-up.

Another concern is that the proportion of HF patients younger than 40 years old is increasing[58]. Younger patient’s receiving SV have the potential for a longer term exposure and the consequent potential for increased risk of young onset Alzheimer’s disease (YOAD) is noteworthy. YOAD is described in subjects less than 65 years of age and has a more rapid progression than the typical late onset Alzheimer’s[59].

Interestingly, one can also describe SV as having protective effect against AD since hypertension and cardiovascular diseases are established risk factors for AD[60], is decreased by SV therapy. ACEi or ARBs have also been shown to decrease in dementia and other symptoms of AD through reducing hypertension and cardiovascular disease[61]. It will be interesting to follow the neuro-cognitive outcomes from PARAGON-HF trial.

**CONCLUSION**

Clinicians should be aware of the potential adverse effects of SV and make informed decisions in prescribing SV, particularly to patients with existing neurodegenerative diseases or the very young. As there are no definitive answers yet about the long term effects of SV, we await the results from PARAGON-HF and reports to follow with interest. Patients who are currently receiving SV treatment should be well monitored for potential adverse events with particular attention to dementia. A low threshold for testing for AD if/when dementia symptoms occur seems warranted. More study on the implications for young HF patients is warranted.

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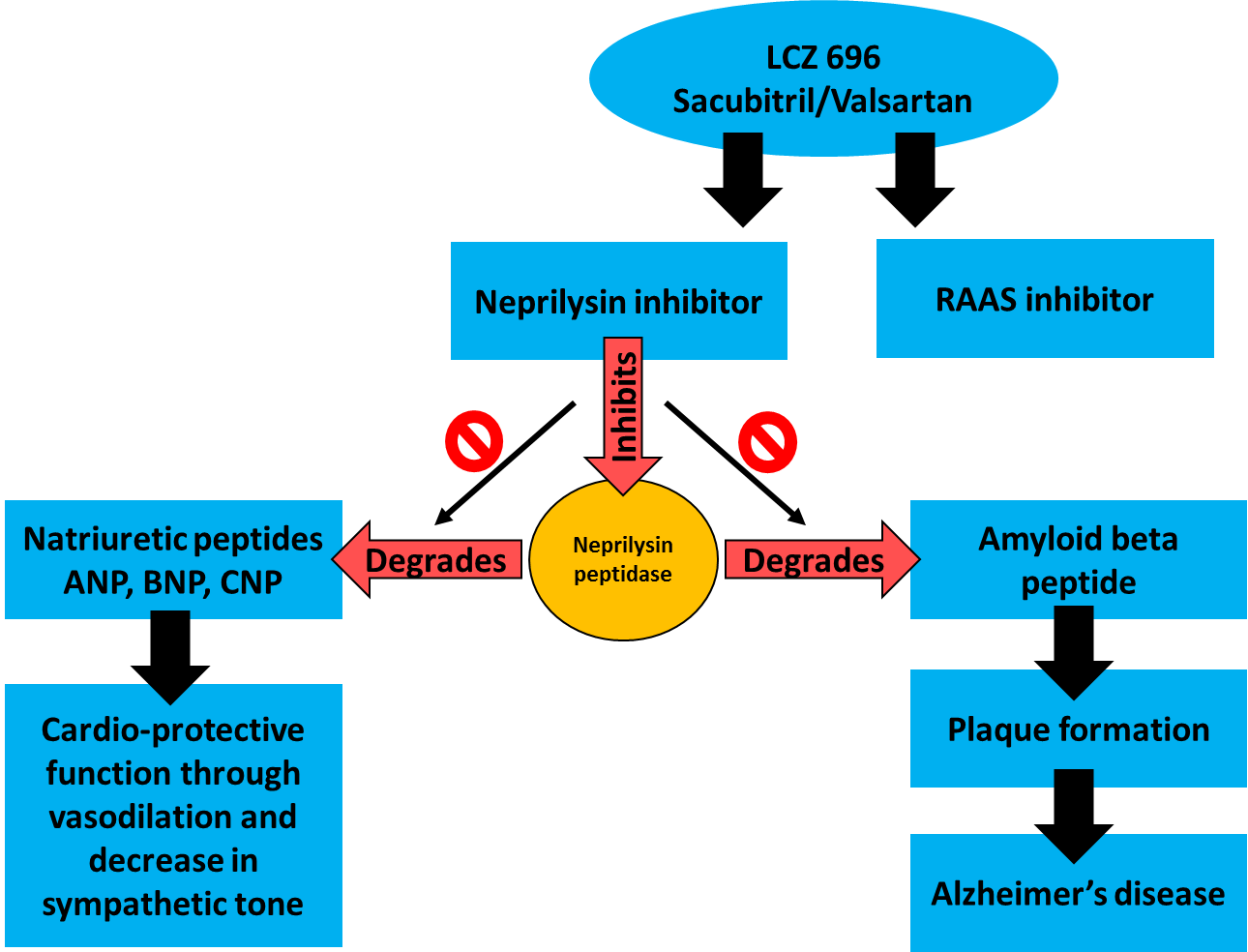
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**Figure 1 Schematic representation of the contradictory effects of angiotensin receptor and neprilysin inhibitors on cerebrovascular disease and Alzheimer’s disease.**



**Table** 1 **Overview of drugs targeting the neprilysin pathways and its pathways**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Mechanism | Clinical Trials and year | Results on HF symptoms |
| Nestiride | Increasing natriuretic peptide activity | VMAC, 2000[20]  PRECEDENT, 2002[21]  ASCENT-HF, 2009[22] | Improved BP and dyspnea  Less cardiac arrhythmias  More hypotension |
| Candoxatril | NPi | Uni-centre investigation with only a limited number of patients[23-25] | More exercise tolerance  Increase in vascular resistance |
| Omapatrilat | NPi | IMPRESS, 2000[26]  OVERTURE, 2002[27]  OCTAVE, 2004[28] | More exercise tolerance  Increase in angioedema  Reduction in BP  Lower mortality |
| LCZ696 | NPi | PARAMOUNT, 2012[29]  PARADIGM, 2014[30,31]  PARAGON, ongoing[32] | Reduction in BP  Improved ejection fraction  Lower mortality  No change in angioedema |

BP: Blood pressure; HF: Heart failure; NPi: Neprilysin inhibitors.