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## Is Entresto good for the brain?

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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. Its causes are numerous including ischemic heart disease, diabetes, hypertension, cigarette smoking, obesity and valvular heart disease<sup>[1]</sup>. Over 5 million individuals worldwide suffer from HF and its incidence is rising with 550000 new diagnoses annually<sup>[1,2]</sup>. With a steadily aging population, HF incidence is projected to increase to 46% by the year 2030<sup>[1,2]</sup>. HF is associated with increased morbidity, mortality and cost<sup>[1,3]</sup>.

HF occurring due to depressed left ventricular function [ejection fraction (EF)  $\leq$  40%] is known as HF with reduced EF (HFrEF)<sup>[4]</sup>. 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<sup>[5]</sup>. 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)<sup>[6,7]</sup>. 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 Medline. 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; and (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<sup>[8,9]</sup>. A second compensatory mechanism, the natriuretic peptide (NP) system, counteracts the vasoconstrictive and sodium/water retentive effects of the RAAS system<sup>[10]</sup>.

## GOALS OF PHARMACOTHERAPY

The initial HF pharmacotherapy targeted the RAAS circuit using ARBs<sup>[11]</sup>, ACEi<sup>[12]</sup>, beta-blockers<sup>[13]</sup>, diuretics<sup>[14]</sup> and aldosterone inhibitors<sup>[15]</sup>. 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<sup>[16]</sup>. NP system targeting drugs have included a recombinant form of BNP (Nesiritide)<sup>[17]</sup> as well as NIs, *e.g.*, candoxatril, recedodotril, *etc*<sup>[18,19]</sup>. HF pharmacotherapy targeting the NP system and the respective clinical trials are summarized in Table 1<sup>[20-32]</sup>. Although strategies blocking either of these two pathways have reduced mortality and morbidity in HF<sup>[12,28,32]</sup>, the prognosis still remains poor due to long term ineffectiveness of the drugs as well as adverse physiological effects<sup>[5]</sup>.

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<sup>[6,7]</sup> which is made up of 1:1 ratio of the ARB valsartan<sup>[33]</sup> and the NI sacubitril (AHU 377)<sup>[34]</sup>. The action of SV is multimodal. Sacubitril is a pro-drug which is activated 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<sup>[7]</sup>. The PARADIGM-HF trial was conducted by McMurray *et al*<sup>[31]</sup> to determine the efficacy of SV compared to the ACE inhibitor Enalapril<sup>[35,36]</sup>, which improves mortality and morbidity. The median follow-up duration was 27 mo and SV reduced HF related symptoms and overall survival by 20%<sup>[31]</sup>. 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<sup>[37]</sup>. 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<sup>[38]</sup>.

The United States Food and Drug Administration had approved SV for clinical use and at present it is produced under the name of Entresto® by Novartis<sup>[39]</sup>. 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<sup>[40]</sup>. In the

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

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

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

PARADIGM-HF trial, 10.7% of the patients reported at least one of the following adverse effects hypotension, renal failure, hyperkalemia, fatigue and dizziness<sup>[31]</sup>.

In clinical practice, approximately 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<sup>[2-4]</sup>. 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<sup>[29]</sup>. At present, the PARAGON-HF trial is ongoing comparing the effects of sacubitril/valsartan versus valsartan in the HFpEF patients<sup>[32]</sup>.

## NEPRILYSIN INHIBITORS AND ALZHEIMER'S DISEASE

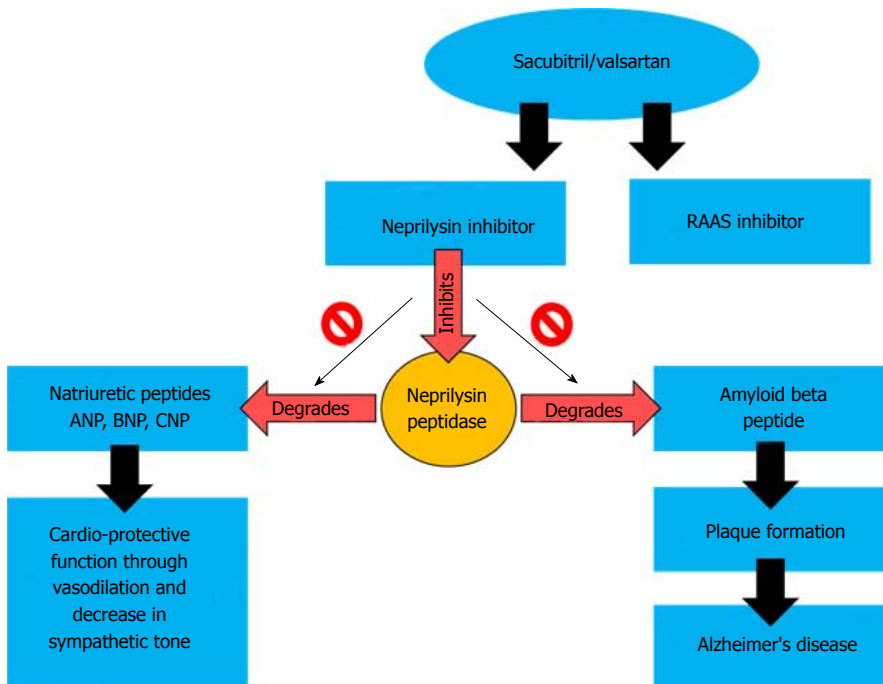
An interesting facet of the use of NIs in the treatment of cardiovascular diseases is their potential role in the development or progression of Alzheimer's disease (AD), as there is considerable overlap between the populations suffering from HF and AD<sup>[41]</sup>. The hallmark of AD is the accumulation of beta amyloid ( $\beta$ A) peptide in the brain causing neurotoxic plaques that are supposedly responsible for the pathology of AD<sup>[42]</sup>. Under normal physiological conditions, the  $\beta$ A peptide is degraded by proteases such as ACE, NP and insulin degrading enzyme<sup>[43]</sup>. NP has a broad range of substrates apart from the NPs such as bradykinin, enkephalins as well as the  $\beta$ A peptide<sup>[44]</sup>. Additionally, patients with AD have lower expression of NP compared to healthy subjects<sup>[45]</sup>, and NP deficient mice develop the murine form of AD<sup>[46]</sup>. This possible correlation was further highlighted when intracerebral infusion of NPi lead to the development of AD-like lesions in rabbits<sup>[47]</sup>. Lastly, certain polymorphisms in the NP gene (NEP) were associated with a higher propensity

for AD in a Finnish cohort<sup>[48]</sup>. 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  $\beta$ A peptide toxicity in the mouse model of AD<sup>[49,50]</sup>.

## ENTRESTO® AND ALZHEIMER'S DISEASE

Clinicians should be aware of the possible inhibitory action of SV in the clearing of  $\beta$ A 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-acetylthiorphan can cross the BBB<sup>[51]</sup> while some like candoxatril cannot<sup>[52]</sup>. Both Sacubitril and its active metabolite LBQ657<sup>[7]</sup> are under the threshold size of 400 kD which makes them fit to cross the BBB<sup>[53,54]</sup>. It is noteworthy that the PARADIGM-HF trial<sup>[31]</sup> had excluded patients with AD and did not include any cognitive function tests to evaluate drug safety. McMurray *et al.*<sup>[55]</sup> have confirmed some correlation between EN treatment and  $\beta$ A peptide levels in a recent review article. While cynomolgus monkeys treated with SV had increased levels of  $\beta$ A peptide in the CSF, the healthy volunteers treated with EN for two weeks had no change in  $\beta$ A peptide levels. McMurray *et al.*<sup>[31]</sup> 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<sup>[56]</sup>. 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



**Figure 1** Schematic representation of the contradictory effects of angiotensin receptor and neprilysin inhibitors on cerebrovascular disease and Alzheimer's disease. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide.

evaluated for AD. One can consider cerebrospinal fluid (CSF) analysis for  $\beta$ A peptide levels and amyloid plaques through PET scans if early signs of dementia ensue<sup>[57]</sup>. In the ongoing PARAGON-HF<sup>[32]</sup> 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<sup>[58]</sup>. Younger patients 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<sup>[59]</sup>.

Interestingly, one can also describe SV as having protective effect against AD since hypertension and cardiovascular diseases are established risk factors for AD<sup>[60]</sup>, 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<sup>[61]</sup>. 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 neuro-degenerative 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.

## REFERENCES

- 1 **American Heart Association.** Classes of heart failure. [updated 2015 Apr 23]. Available from: URL: [http:// www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure\\_UCM\\_306328\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp)
- 2 **Mozaffarian D,** Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation* 2015; **131**: e29-322 [PMID: 25520374 DOI: 10.1161/CIR.000000000000152]
- 3 **Mayo Clinic staff.** Diseases and conditions: heart failure. [accessed 2015 Jan 17]. Available from: URL: [http:// www.mayoclinic.org/diseases/conditions/heart-failure/basics/definition/con-20029801](http://www.mayoclinic.org/diseases/conditions/heart-failure/basics/definition/con-20029801)
- 4 **Yancy CW,** Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: 1810-1852 [PMID: 23741057 DOI: 10.1161/CIR.0b013e31829e8807]
- 5 **Singh JS,** Lang CC. Angiotensin receptor-neprilysin inhibitors: clinical potential in heart failure and beyond. *Vasc Health Risk*

- Manag* 2015; **11**: 283-295 [PMID: 26082640 DOI: 10.2147/VHRM.S55630]
- 6 **Gu J**, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol* 2010; **50**: 401-414 [PMID: 19934029 DOI: 10.1177/0091270009343932]
  - 7 **Langenickel TH**, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today Ther Strateg* 2012; **9**: e131-e139 [DOI: 10.1016/j.ddstr.2013.11.002]
  - 8 **Crowley SD**, Gurley SB, Herrera MJ, Ruiz P, Griffiths R, Kumar AP, Kim HS, Smithies O, Le TH, Coffman TM. Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. *Proc Natl Acad Sci USA* 2006; **103**: 17985-17990 [PMID: 17090678 DOI: 10.1073/pnas.0605545103]
  - 9 **Holtz J**. Pathophysiology of heart failure and the renin-angiotensin-system. *Basic Res Cardiol* 1993; **88 Suppl 1**: 183-201 [PMID: 8357333]
  - 10 **Bayes-Genis A**, Morant-Talamante N, Lupón J. Neprilysin and Natriuretic Peptide Regulation in Heart Failure. *Curr Heart Fail Rep* 2016; **13**: 151-157 [PMID: 27260315 DOI: 10.1007/s11897-016-0292-x]
  - 11 **Karnik SS**, Unal H, Kemp JR, Tirupula KC, Eguchi S, Vanderheyden PM, Thomas WG. International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli [corrected]. *Pharmacol Rev* 2015; **67**: 754-819 [PMID: 26315714 DOI: 10.1124/pr.114.010454]
  - 12 **Pilote L**, Abrahamowicz M, Eisenberg M, Humphries K, Behloul H, Tu JV. Effect of different angiotensin-converting-enzyme inhibitors on mortality among elderly patients with congestive heart failure. *CMAJ* 2008; **178**: 1303-1311 [PMID: 18458262 DOI: 10.1503/cmaj.060068]
  - 13 **Rienstra M**, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. *JACC Heart Fail* 2013; **1**: 21-28 [PMID: 24621795 DOI: 10.1016/j.jchf.2012.09.002]
  - 14 **Brandimarte F**, Mureddu GF, Boccanelli A, Cacciatore G, Brandimarte C, Fedele F, Gheorghade M. Diuretic therapy in heart failure: current controversies and new approaches for fluid removal. *J Cardiovasc Med (Hagerstown)* 2010; **11**: 563-570 [PMID: 20186069 DOI: 10.2459/JCM.0b013e3283376bfa]
  - 15 **Nappi JM**, Sieg A. Aldosterone and aldosterone receptor antagonists in patients with chronic heart failure. *Vasc Health Risk Manag* 2011; **7**: 353-363 [PMID: 21731887 DOI: 10.2147/VHRM.S13779]
  - 16 **Jhund PS**, McMurray JJ. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. *Heart* 2016; **102**: 1342-1347 [PMID: 27207980 DOI: 10.1136/heartjnl-2014-306775]
  - 17 **Colucci WS**, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 2000; **343**: 246-253 [PMID: 10911006 DOI: 10.1056/NEJM200007273430403]
  - 18 **Gros C**, Souque A, Schwartz JC, Duchier J, Cournot A, Baumer P, Lecomte JM. Protection of atrial natriuretic factor against degradation: diuretic and natriuretic responses after in vivo inhibition of enkephalinase (EC 3.4.24.11) by acetorphan. *Proc Natl Acad Sci USA* 1989; **86**: 7580-7584 [PMID: 2529543]
  - 19 **Northridge DB**, Jardine AG, Alabaster CT, Barclay PL, Connell JM, Dargie HJ, Dilly SG, Findlay IN, Lever AF, Samuels GM. Effects of UK 69 578: a novel atriopeptidase inhibitor. *Lancet* 1989; **2**: 591-593 [PMID: 2570286]
  - 20 **Young JB**, Abraham WT, Stevenson LW, Horton DP. Results of the VMAC trial: vasodilation in the management of acute congestive heart failure. *Circulation* 2000; **102**: 2794 [DOI: 10.1161/01.CIR.102.22.2794-a]
  - 21 **Burger AJ**, Horton DP, LeJemtel T, Ghali JK, Torre G, Dennish G, Koren M, Dinerman J, Silver M, Cheng ML, Elkayam U; Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. *Am Heart J* 2002; **144**: 1102-1108 [PMID: 12486437 DOI: 10.1067/mhj.2002.125620]
  - 22 **Hernandez AF**, O'Connor CM, Starling RC, Reist CJ, Armstrong PW, Dickstein K, Lorenz TJ, Gibler WB, Hasselblad V, Komajda M, Massie B, McMurray JJ, Nieminen M, Rouleau JL, Swedberg K, Califf RM. Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF). *Am Heart J* 2009; **157**: 271-277 [PMID: 19185633 DOI: 10.1016/j.ahj.2008.07.031]
  - 23 **Northridge DB**, Currie PF, Newby DE, McMurray JJ, Ford M, Boon NA, Dargie HJ. Placebo-controlled comparison of candoxatril, an orally active neutral endopeptidase inhibitor, and captopril in patients with chronic heart failure. *Eur J Heart Fail* 1999; **1**: 67-72 [PMID: 10937982 DOI: 10.1016/S1388-9842(98)00003-8]
  - 24 **Westheim AS**, Bostrom P, Christensen CC, Parikka H, Rykke EO, Toivonen L. Hemodynamic and neuroendocrine effects for candoxatril and frusemide in mild stable chronic heart failure. *J Am Coll Cardiol* 1999; **34**: 1794-1801 [PMID: 10577572]
  - 25 **Kentsch M**, Otter W, Drummer C, Nötges A, Gerzer R, Müller-Esch G. Neutral endopeptidase 24.11 inhibition may not exhibit beneficial haemodynamic effects in patients with congestive heart failure. *Eur J Clin Pharmacol* 1996; **51**: 269-272 [PMID: 9010697]
  - 26 **Rouleau JL**, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, Porter CB, Proulx G, Qian C, Block AJ. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000; **356**: 615-620 [PMID: 10968433]
  - 27 **Packer M**, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; **106**: 920-926 [PMID: 12186794]
  - 28 **Kostis JB**, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17**: 103-111 [PMID: 14751650]
  - 29 **Solomon SD**, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectionN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380**: 1387-1395 [PMID: 22932717 DOI: 10.1016/S0140-6736(12)61227-6]
  - 30 **McMurray JJ**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; **15**: 1062-1073 [PMID: 23563576 DOI: 10.1093/eurjhf/hft052]
  - 31 **McMurray JJ**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; **15**: 1062-1073 [PMID: 23563576 DOI: 10.1093/eurjhf/hft052]
  - 32 **Novartis**. Novartis Announces Enormous Clinical Trial Program For Heart Failure Drug. Press release. [released 2016 May 9].



- Available from: URL: <http://cardiobrief.org/2016/05/19/novartis-announces-enormous-clinical-trial-program-for-heart-failure-drug/>
- 33 **Mistry NB**, Westheim AS, Kjeldsen SE. The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7**: 575-581 [PMID: 16553573]
  - 34 **Ksander GM**, Ghai RD, deJesus R, Diefenbacher CG, Yuan A, Berry C, Sakane Y, Trapani A. Dicarboxylic acid dipeptide neutral endopeptidase inhibitors. *J Med Chem* 1995; **38**: 1689-1700 [PMID: 7752193]
  - 35 **CONSENSUS Trial Study Group**. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**: 1429-1435 [PMID: 2883575 DOI: 10.1056/NEJM198706043162301]
  - 36 **Yusuf S**, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293-302 [PMID: 2057034 DOI: 10.1056/NEJM199108013250501]
  - 37 **Byrd JB**, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006; **26**: 725-737 [PMID: 17085287 DOI: 10.1016/j.jiac.2006.08.001]
  - 38 **Yusuf S**, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**: 1547-1559 [PMID: 18378520 DOI: 10.1056/NEJMoa0801317]
  - 39 **Novartis**. Novartis' new heart failure medicine LCZ696, now called Entresto, approved by FDA to reduce risk of cardiovascular death and heart failure hospitalization. Press release. [released 2015 July 8]. Available from: URL: <http://www.novartis.com/news/media-releases/novartis-new-heart-failure-medicine-lcz696-now-called-entrestotm-approvedfda>.
  - 40 Entresto (sacubitril and valsartan) tablets [prescribing information]. East Hanover, NJ: Novartis; July 2015. Available from: URL: <https://www.entrestotm.com/dosing>
  - 41 **Cermakova P**, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med* 2015; **277**: 406-425 [PMID: 25041352 DOI: 10.1111/joim.12287]
  - 42 **Ghiso J**, Frangione B. Amyloidosis and Alzheimer's disease. *Adv Drug Deliv Rev* 2002; **54**: 1539-1551 [PMID: 12453671]
  - 43 **Iwata N**, Higuchi M, Saido TC. Metabolism of amyloid-beta peptide and Alzheimer's disease. *Pharmacol Ther* 2005; **108**: 129-148 [PMID: 16112736 DOI: 10.1016/j.pharmthera.2005.03.010]
  - 44 **Webster CI**, Burrell M, Olsson LL, Fowler SB, Digby S, Sandercock A, Snijder A, Tebbe J, Haupts U, Grudzinska J, Jermutus L, Andersson C. Engineering neprilysin activity and specificity to create a novel therapeutic for Alzheimer's disease. *PLoS One* 2014; **9**: e104001 [PMID: 25089527 DOI: 10.1371/journal.pone.0104001]
  - 45 **Yasojima K**, Akiyama H, McGeer EG, McGeer PL. Reduced neprilysin in high plaque areas of Alzheimer brain: a possible relationship to deficient degradation of beta-amyloid peptide. *Neurosci Lett* 2001; **297**: 97-100 [PMID: 11121879]
  - 46 **Iwata N**, Tsubuki S, Takaki Y, Shirohara K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saido TC. Metabolic regulation of brain Abeta by neprilysin. *Science* 2001; **292**: 1550-1552 [PMID: 11375493 DOI: 10.1126/science.1059946]
  - 47 **Newell AJ**, Sue LI, Scott S, Rauschkolb PK, Walker DG, Potter PE, Beach TG. Thiorphan-induced neprilysin inhibition raises amyloid beta levels in rabbit cortex and cerebrospinal fluid. *Neurosci Lett* 2003; **350**: 178-180 [PMID: 14550923]
  - 48 **Vepsäläinen S**, Helisalmi S, Mannermaa A, Pirttilä T, Soininen H, Hiltunen M. Combined risk effects of IDE and NEP gene variants on Alzheimer disease. *J Neurol Neurosurg Psychiatry* 2009; **80**: 1268-1270 [PMID: 19864659 DOI: 10.1136/jnnp.2008.160002]
  - 49 **Marr RA**, Rockenstein E, Mukherjee A, Kindy MS, Hersh LB, Gage FH, Verma IM, Masliah E. Neprilysin gene transfer reduces human amyloid pathology in transgenic mice. *J Neurosci* 2003; **23**: 1992-1996 [PMID: 12657655]
  - 50 **Spencer B**, Marr RA, Gindi R, Potkar R, Michael S, Adame A, Rockenstein E, Verma IM, Masliah E. Peripheral delivery of a CNS targeted, metallo-protease reduces Aβ toxicity in a mouse model of Alzheimer's disease. *PLoS One* 2011; **6**: e16575 [PMID: 21304989 DOI: 10.1371/journal.pone.0016575]
  - 51 **Lecomte JM**, Costentin J, Vlaiculescu A, Chaillet P, Marçais-Collado H, Llorens-Cortes C, Leboyer M, Schwartz JC. Pharmacological properties of acetorphan, a parenterally active "enkephalinase" inhibitor. *J Pharmacol Exp Ther* 1986; **237**: 937-944 [PMID: 3519939]
  - 52 **Becker M**, Siems WE, Kluge R, Gembardt F, Schultheiss HP, Schirner M, Walther T. New function for an old enzyme: NEP deficient mice develop late-onset obesity. *PLoS One* 2010; **5**: pii: e12793 [PMID: 20862277 DOI: 10.1371/journal.pone.0012793]
  - 53 **Pardridge WM**. Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab* 2012; **32**: 1959-1972 [PMID: 22929442 DOI: 10.1038/jcbfm.2012.126]
  - 54 **Bell RD**, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol* 2009; **118**: 103-113 [PMID: 19319544 DOI: 10.1007/s00401-009-0522-3]
  - 55 **McMurray JJ**, Packer M, Solomon SD. Neprilysin inhibition for heart failure. *N Engl J Med* 2014; **371**: 2336-2337 [PMID: 25494275 DOI: 10.1056/NEJMc1412654]
  - 56 **Bäckman L**, Jones S, Berger AK, Laukka EJ, Small BJ. Multiple cognitive deficits during the transition to Alzheimer's disease. *J Intern Med* 2004; **256**: 195-204 [PMID: 15324363 DOI: 10.1111/j.1365-2796.2004.01386.x]
  - 57 **Vodovar N**, Paquet C, Mebazaa A, Launay JM, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? *Eur Heart J* 2015; **36**: 902-905 [PMID: 25636748 DOI: 10.1093/eurheartj/ehv015]
  - 58 **Wong CM**, Hawkins NM, Petrie MC, Jhund PS, Gardner RS, Ariti CA, Poppe KK, Earle N, Whalley GA, Squire IB, Doughty RN, McMurray JJ. Heart failure in younger patients: the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). *Eur Heart J* 2014; **35**: 2714-2721 [PMID: 24944329 DOI: 10.1093/eurheartj/ehu216]
  - 59 **Stanley K**, Walker Z. Do patients with young onset Alzheimer's disease deteriorate faster than those with late onset Alzheimer's disease? A review of the literature. *Int Psychogeriatr* 2014; **26**: 1945-1953 [PMID: 24989902 DOI: 10.1017/S1041610214001173]
  - 60 **Thorin E**. Hypertension and Alzheimer disease: another brick in the wall of awareness. *Hypertension* 2015; **65**: 36-38 [PMID: 25331847 DOI: 10.1161/HYPERTENSIONAHA.114.04257]
  - 61 **Villapol S**, Saavedra JM. Neuroprotective effects of angiotensin receptor blockers. *Am J Hypertens* 2015; **28**: 289-299 [PMID: 25362113 DOI: 10.1093/ajh/hpu19]

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