

Dual blockade angiotensin-receptor neprilysin-inhibitor (ARNI) - A new era for heart failure treatment

Oana Tautu *, Maria Manea, Maria Dorobantu

Carol Davila University of Medicine and Pharmacy, Cardiology Department,
Clinical Emergency Hospital, Bucharest, Romania

Received: October 17, 2017, Accepted: December 11, 2017

Abstract

Blockade of neurohormonal over-activation through beta-blockers, angiotensin - converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and mineralocorticoid- receptor antagonists (MRA) represents the core-stone of the medical treatment in chronic heart failure. Since their use into the daily clinical practice recommended by the guidelines, the overall survival of heart failure patients has significantly increased. But yet, there is still room for improvement, since on the long term these patients remain at an increased risk of acute worsening episodes requiring hospitalization and mortality. This „residual” morbidity could be explained by a persistent inadequate response of the endogenous adaptive mechanisms in chronic heart failure that is not target by sympathetic nervous system (SNS) - renin angiotensin aldosterone system (RAAS) inhibition strategy. The dual angiotensin-receptor neprilysin - inhibitor has proven a superior efficacy in decreasing the morbi-mortality of chronic heart failure patients that the standard of care treatment, and is widely recommended by all the guidelines for treatment in patients with heart failure with reduced ejection fraction, being the first heart failure drug that gets into the guidelines after the completion of only one (but the largest) clinical trial. Also there are several issues that await a response regarding the use of ARNI as first-line treatment instead of ACEIS and ARBs, that for sure will come in the next years, we can neither the less say that ARNI sacubitril-valsartan has the traits of a revolutionary drug that has definitely changed the paradigm of the HF treatment.

Keywords: heart failure, ARNI, neprilysin inhibitor, ARB, valsartan, LCZ696, sacubitril

Blockade of neurohormonal over-activation through beta-blockers, angiotensin - converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs)

and mineralocorticoid- receptor antagonists (MRA) represents the core-stone of the medical treatment in chronic heart failure. Since their use into the daily clinical practice recommended by the guidelines, the overall survival of heart failure patients has significantly increased. But yet, there is still room for improvement, since on the long term these patients remain at an increased risk of acute worsening episodes requiring hospitalization and mortality. This „residual” morbidity

* Correspondence to: Oana TAUTU, MD, PhD
Clinical Emergency Hospital Bucharest, Calea Floreasca no.8,
sector 1, postal code 014461, Bucharest, Romania.
Tel./fax: 004021-3170108; e-mail: dr.tautu@yahoo.com

could be explained by a persistent inadequate response of the endogenous adaptive mechanisms in chronic heart failure that is not target by sympathetic nervous system (SNS) – renin angiotensin aldosterone system (RAAS) inhibition strategy.

Natriuretic peptides system, bradykinin or adrenomedulin are peptides produced to suppress the negative effects of RAAS and SNS, promoting vasodilation and natriuresis, inhibit the abnormal growth and cardiac and vascular remodelling [1]. Their effects include, also, increase of the glomerular filtration, renin and aldosterone inhibition and they have, also, antihypertrophic and antifibrotic actions, vascular regeneration, arterial and venodilatation [2].

The natriuretic peptide system consists of atrial natriuretic peptide (ANP) that is secreted in response to atrial dilation, B-type natriuretic peptide (BNP), secreted in response to the increased ventricle wall stress and C-type (CNP) which is derived from endothelial and renal cells[3]. CNP and BNP are released in response to increased stress of the cardiac wall in the context of volume or pressure overload. Their levels are higher in patients with heart failure [4].

Since natriuretic peptide have the potential of counteracting the overstimulation of SNS and RAAS, when their plasmatic circulation levels are increased secondary to volume-pressure overload they should balance and prevent the decompensation episode. But this does not happen in real life. In fact, levels of BNP and NT-proBNP are well known markers used for detecting episodes of decompensations in heart failure: the higher the BNP/ NT-proBNP levels the worst the episode. And why these increased levels of natriuretic peptides fail to prevent the acute episode in a heart failure patient? The response comes for studies on mass spectrometry and measurements of circulating natriuretic peptides that proved that in patients with acute decompensating episodes, the increased plasmatic levels of natriuretic peptides are in fact of increased levels of inactive fragments of natriuretic peptides that do no longer have the same beneficial biological effects on SNS/RAAS as the mature peptides.

Increasing the natriuretic peptides circulating levels is therefore considered an optimal strategy in the treatment for heart failure [5,6]. So far, oral administration of these peptide has been proven to be ineffective, so the option to increase natriuretic peptides is to develop an alternative approach.

Neprilysine (NEP) is a metallopeptidase enzymes which brake-down the natriuretic peptides into inactive circulating fragments.

Having an optimal endogen counteracting natriuretic peptide system could be the necessary step for eliminating the residual mortality in heart-failure patients. And for that is required not only the increase in circulating levels of natriuretic peptides but also to protect them from inactivation by the use of neprilysin inhibitors. Never the less, keeping in mind that, besides inactivation of natriuretic peptides, neprilysin also inhibits several other peptides such as bradykinin, endothelin, angiotensin I and II, the use of an neprilysin inhibitor will result in a supplementary activation of RAAS, an agent who blocks simultaneously neutral endopeptidase and RASS is necessary [1].

Neprilysin inhibitor. From Candoxatril to sacubitril/valsartan

Candoxatril was the first neutral endopeptidase inhibitor, but this drug could not adjust the blood pressure in hypertensive patients and vascular resistances in patients with heart failure [6].

Omapatrilat was the first inhibitor of neutral endopeptidase and the angiotensin-converting enzyme, with a better profile than candoxatril regarding the blood pressure and the vascular resistances, but his use was stopped because of a high risk of angioedema [7].

Angiotensin receptor neprilysin inhibitors (ARNIs) is a new class of heart failure drug whose effect is to block RAAS and increase the natriuretic peptides [3, 8].

The US Food and Drug administration (FDA) approved on July 2015 sacubitril/valsartan to reduce the risk of death and hospitalization in patients diagnosed with heart failure, NYHA class II-IV and associated with reduced ejection fraction.

Sacubitril/valsartan is a combination of angiotensin receptor neutral endopeptidase inhibitor (ARNI) with the angiotensin II receptor antagonist valsartan. Angiotensin receptor neprilysin inhibitor is a new class of drug used to block the RAAS and increase natriuretic peptides [9,10]. So, sacubitril has the potential to reduce the negative effects of the neurohormonal activity in heart failure.

Sacubitril/valsartan: Mechanism of action

Sacubitril is a neutral endopeptidase inhibitor (a neprilysin inhibitor). Valsartan is an angiotensin receptor blocker. LCZ696 (sacubitril/valsartan) is the main one in his category of ARNI [1].

After oral administration of the sacubitril/valsartan, the drug dissociates into valsartan, an ARB, and AHU377, which is neprilysin inhibitor prodrug which is further metabolised to LBQ657, this being the active form. LCZ696 increases plasma and urinary levels of cGMP, by activating the NPRA-receptor and, also, blocks the angiotensin type I receptor [9,10].

The peak levels of those two drugs are reached at the same time. The steady-state of valsartan and sacubitril (LBQ657) appears in 3 days [9]. So, the combination between sacubitril (LBQ657 active metabolite of sacubitril) and valsartan inhibits neprilysin (neutral endopeptidase) via LBQ657 and is associated with blockade of angiotensin II type I receptor via valsartan. Valsartan selectively blocks the angiotensin 1 receptor, so it inhibits the angiotensin II effects. Also, valsartan inhibits the aldosterone release.

The effects of sacubitril/valsartan are the consequences of NEP and RAAS inhibition. The effects of sacubitril/valsartan were evaluated in a 7 day controlled study in which were noted an increase in natriuresis and the increased levels of cGMP in urine [8]. Also, in a 21 day study, the levels of cGMP in plasma and urine were high. In PARAMOUNT study, a phase II, randomised, double-blind trial (were included patients with NYHA II-III, with left ventricular ejection fraction over 45% and with NT-proBNP levels over 400 pg/m), the levels of NT-proBNP were reduced after administration of sacubitril/valsartan [11].

Dosing and administration

The recommended dose at initiation of treatment is 49 mg sacubitril with 51 mg of valsartan twice daily [12], the dose being doubled after 2 weeks. A 24 mg sacubitril with 26 mg valsartan starting dose is recommended for patients who are not receiving ACEI or an angiotensin receptor blocker and, also, for patients with renal or hepatic dysfunction [3].

The combination of sacubitril/valsartan is available in tablets with the following concentrations: 24

mg of sacubitril and 26 mg valsartan, 49 mg of sacubitril and 51 mg valsartan, 97 mg sacubitril and 103 mg valsartan [13].

Adverse effects and contraindications

Hypotension is the most frequently encountered adverse effect of administration sacubitril/valsartan, with an incidence over 5%. Also, most common adverse effects are hyperkalaemia, cough, dizziness and renal failure (for patients who were already with renal dysfunction) [14].

This drug is contraindicated for patients with history of angioedema at previous administration of an ACEI. It is also contraindicated to use this drug in combination with an ACEI or an angiotensin receptor blocker, because valsartan is an angiotensin receptor blocker, with cumulative side effects [11]. Also, concomitant administration of sacubitril/valsartan with potassium-sparing diuretics or potassium supplements [13]. The concomitant use of sacubitril/valsartan with nonsteroidal anti-inflammatory drugs can lead to worsening the renal function in patients with renal dysfunction, elderly [15].

The combination of valsartan with sacubitril should be administered with precaution in patients with history of angioedema, hypotension, impaired renal function or hyperkalaemia. Also, the use of this drug should be discontinued when pregnancy is detected because can be toxic for the foetus [12].

Sacubitril/valsartan in clinical trials

PARADIGM-HF (The Prospective Comparison of ARNI with ACE inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) is a randomised, double-blind and event-driven trial whose purpose was to compare the effects of sacubitril/valsartan and enalapril in patients diagnosed with chronic and symptomatic heart failure. This study started in December 2004 and was stopped in March 2014 [16]. Sacubitril/valsartan in dose of 200 mg twice daily was compared with a dose of 10 mg twice daily of enalapril, administered in patients with heart failure, with NYHA class II-IV, with left ventricular ejection fraction of under 40%, with NT-proBNP over 400

pg/ml and previously treated with an ACEI or ARB. A total of 8399 patients were included in this study, aged 18-96 years. Patients with intolerance at ACEI or ARB, hypotension, eGFR under 30 ml/min/1,73 m², hyperkalaemia or history of angioedema were excluded [17].

This study had the purpose to compare sacubitril/valsartan (LCZ696), having the following exploratory objective: cardiovascular death, hospitalization for heart failure, the number of patients hospitalized, time to treatment (the need of a new drug, intravenous treatment or an increase in treatment dose for worsening heart failure), NYHA classification after 8 months of therapy, the incidence of coronary revascularization procedures, the profile of biomarkers [17]. Conclusions were that sacubitril/valsartan (LCZ696) is superior to enalapril regarding reducing the risk of death of cardiovascular cause and overall death and for hospitalization for heart failure [1, 17].

In this study, it was shown that sacubitril/valsartan reduced the risk of death from any cause by 16% and the risk of hospitalisation from heart failure by 21%, compared with enalapril. Also, sacubitril/valsartan has lower any cause mortality compared with enalapril (17% vs 19%). 537 (12,8%) of patients from sacubitril/valsartan group were hospitalized for heart failure, compared with those who received enalapril (658; 15%) [7, 18].

Deaths from cardiovascular causes were in number of 914 for sacubitril/valsartan group and 1117 for enalapril [2].

The renal function has worsened in the group of enalapril during the study (108 in the group of enalapril vs 94 for sacubitril/valsartan) [3].

During this study, 12% of patients presented adverse effects, especially in the enalapril group. Hypotension and non-severe angioedema were more frequently in the sacubitril/valsartan group, but renal dysfunction and hyperkalaemia were more common in enalapril group [4].

In the group of sacubitril/valsartan were fewer patients with worsened heart failure, the number of hospitalization for heart failure was lower (537 vs 658 in enalapril), the need for intravenous positive inotropes (161 in sacubitril/valsartan vs 229 in enalapril) was lower [19] and recommendation for implantation of a ventricular assist device or for heart transplantation was fewer (94 in sacubitril/valsartan vs 119 for enalapril)

[7]. In this trial, the need to prevent cardiovascular events or death was 21 in group of sacubitril/valsartan and 32 in the group of enalapril.

Sacubitril/valsartan reduces biomarkers like troponin and NT-proBNP and increases the levels of cGMP in urine as a result of NEP inhibition [20].

During the study, 1546 of patients died, 711 in sacubitril/valsartan group (558 CV causes) and 833 in the enalapril group (693 CV causes) [9].

The deaths in the context of pump-failure were reduced in the group of sacubitril/valsartan [8].

PARADIGM-HF shown that sacubitril/valsartan is superior in preventing clinical progression of heart failure than enalapril. There is strong evidence that the combination of angiotensin receptor inhibitor and neprilysin is superior to inhibiting RAAS alone in patients with chronic heart failure. Sacubitril/valsartan is strongly recommended to be used for patients with chronic heart failure, left ventricular ejection fraction under 40%, instead of an ACEI or ARB alone. So, the combination was approved with the purpose to reduce the risk of cardiovascular death for patients with chronic heart failure and reduced ejection fraction [17]25.

Sacubitril/valsartan has been included in many other studies.

TITRATION is a double-blind, randomised study, which compare two regimens of up titrating the dose of sacubitril/valsartan. It is a 5 day open-label run-in (sacubitril/valsartan 50 mg twice daily), preceded by 11 weeks double-blind, randomised period (100 mg twice daily for 2 weeks followed by 200 mg twice daily) vs 50 mg twice daily for 2 weeks, 100 mg twice daily for 3 weeks, followed by 200 mg twice daily. In TITRATION study, the purpose was to assess the tolerability of increased dose (from 50 to 200) of sacubitril/valsartan in patients with heart failure [21]. This study compared two regimens of increasing the dose of sacubitril/valsartan, and the results showed an acceptable tolerability [10]. The most common adverse effects were non-serious hypotension and hyperkalaemia, but these not lead to the discontinuation of the treatment. Also, were reported two cases of non-serious angioedema. The tolerability of up titrating dose of sacubitril/valsartan is acceptable [22]. Previously treated patients with ACEI/ARB were tolerated at sacubitril/valsartan target dose. The TITRATION study showed that up titrating dose of sacubitril/valsartan progressively, no serious ad-

verse effects occur and this will increase the therapeutic success [17].

PARAMOUNT is a randomised study, double blind trial, with patients diagnosed with heart failure and preserved ejection fraction. After 12 weeks of treatment, it was observed that the levels of NT-proBNP have decreased. The study evaluated, also, the effect of sacubitril/valsartan on the left atrial structure. After 6 weeks of treatment, left atrial volume was reduced significantly. It was shown that sacubitril/valsartan have positive renal effects, than valsartan alone [23].

PIONEER investigates the effect of sacubitril/valsartan on NT-proBNP. This study will be done in 2018 [24].

PARAGON-HF is a study on patients with heart failure and preserved ejection fraction. Will be completed in 2019 [25].

PARABLE-HF is a study whose purpose is to determine if combination sacubitril/valsartan is safe and to determine the positive effects on the heart and blood vessels in asymptomatic patients, with elevated natriuretic peptide and elevated left atrial volume index, with hypertension, diabetes. Patients will be treated with sacubitril/valsartan for 18 months to evaluate the impact on left ventricular diastolic function [26].

PARASAIL is an interventional study, whose purpose is to describe the tolerability in patients with heart failure with reduced ejection fraction, treated over 6 months with optimal dose of sacubitril/valsartan. This study will describe tolerability, effectiveness and safety of sacubitril/valsartan [27].

TRANSITION study is a randomized study which purpose is to compare in-hospital initiation of sacubitril/valsartan and initiation after hospital discharge in patients with heart failure and reduced ejection fraction who have recently been hospitalised for acute decompensation. This study will be complete in 2018 [28].

Sacubitril/valsartan in guidelines

Sacubitril/valsartan is included in the standard therapy for heart failure as an alternative for ACEI or ARB [23]

Sacubitril/valsartan got recommendations from European Society of Cardiology (ESC) and in American College of Cardiology (ACC) / American Heart Association guidelines (AHA). In ACC/AHA Guideline for

the management of Heart Failure (2016), the combination got I-BR which means strong and moderate quality. So, the recommendation is that an ARNI should be used in patients with chronic heart failure [23].

Sacubitril/valsartan has got class IB recommendation in the 2016 ESC Guideline for the Diagnosis and Treatment of Acute and Chronic Heart Failure, which means that is recommended and data derived from one single trial [13]. So, this drug is recommended to replace ACEIs / ARBs in patients with heart failure, to reduce the risk of death in hospitalisation for heart failure [13].

Conclusions

The dual angiotensin-receptor neprilysin – inhibitor has proven a superior efficacy in decreasing the morbidity of chronic heart failure patients that the standard of care treatment, and is widely recommended by all the guidelines for treatment in patients with heart failure with reduced ejection fraction, being the first heart failure drug that gets into the guidelines after the completion of only one (but the largest) clinical trial.

Since PARADIGM-HF trial, an increased interest led to the initiation of several other clinical-trial meant to extend the use of ARNI to heart failure patients with preserved ejection fraction and for its early initiation after an acute episode of decompensating HF.

Also there are several issues that await a response regarding the use of ARNI as first-line treatment instead of ACEIs and ARBs, what is the optimal up-titrating strategy, how to use it in patients that are not similar to those enrolled in PARADIGM trial and also about how this drug really works.

Although these questions await responses that for sure will come in the next years, we can neither the less say that ARNI sacubitril-valsartan has the traits of a revolutionary drug that has definitely changed the paradigm of the HF treatment.

References

1. Edgardo Kaplinsky. Sacubitril/valsartan in heart failure: latest evidence and place in therapy. *Ther Adv Chronic Dis*. 2016 Nov; 7(6): 278–290
2. Kobalava Z, Averkov O, Meray I. Natriuretic peptide inhibition in the presence of angiotensin receptor blockade following

- short term treatment with LCZ696 in heart failure patients: effect on ANP, BNP, NT-proBNP and cGMP. *Eur Heart J* 32 (Suppl.): 784 - 785
3. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M et.al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. 2010 Apr;50(4):401-14
 4. Hegde LG, Yu C, Renner T, Thibodeaux H, Armstrong SR et.al. Concomitant angiotensin AT1 receptor antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. *J Cardiovasc Pharmacol*. 2011 Apr;57(4):495-504
 5. McMurray JJ. CONSENSUS to EMPHASIS: the overwhelming evidence which makes blockade of the renin-angiotensin-aldosterone system the cornerstone of therapy for systolic heart failure. *Eur J Heart Fail*. 2011 Sep;13(9):929-36
 6. McMurray J, Struthers AD. Significance of atrial natriuretic factor in chronic heart failure. *Br J Hosp Med*. 1988 Jul;40(1):55-7.
 7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP et.al. 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 Sep;15(9):1062-73
 8. Ruilope LM1, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010 Apr 10;375(9722):1255-66
 9. Thomas H, Langenickel T.H., Dole W.P. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today Ther Strateg* 2012;9:e131-e139
 10. Mangiafico S1, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC Jr. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J*. 2013 Mar;34(12):886-893c
 11. Northridge DB, Jardine AG, Alabaster CT, Barclay PL, Connell JM et al. Effects of UK 69 578: a novel atriopetidase inhibitor. *Lancet*. 1989 Sep 9;2(8663):591-3.
 12. Packer M., Califf R.M., Konstam M.A., Henry Krum H., McMurray J.J et al. 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
 13. Ponikowski P., Voors A.A., Anker S.D., Bueno H., Cleland J.G.F et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal* (2016) 37, 2129–2200.
 14. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J*. 2015 Aug 7;36(30):1990-7.
 15. Fala L. Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure. *Am Health Drug Benefits*. 2015 Sep; 8(6): 330-334.
 16. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990 Nov;82(5):1724-9.
 17. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail*. 2016 Sep;18(9):1193-202
 18. Solomon SD, Claggett B, Desai AS, Packer M, Zile M et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. *Circ Heart Fail*. 2016 Mar;9(3):e002744; doi: 10.1161/CIRCHEARTFAILURE.115.002744.
 19. Solomon SD, Zile M, Pieske B, Voors A, Shah A et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012 Oct 20;380(9851):1387-95
 20. Krupi ka J., Janota T., Kasalová Z., Hradec J. Natriuretic Peptides - Physiology, Pathophysiology and Clinical Use in Heart Failure. *Physiol. Res*. 58: 171-177, 2009
 21. Von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Atar D et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. *Circ Heart Fail*. 2013 May;6(3):594-605
 22. Yancy C. W., Jessup M., Bozkurt B., Hollenberg S.M., Butler J., et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Circulation*. 2016;134:000–000; DOI: 10.1161/CIR.0000000000000435
 23. Solomon SD, Zile M, Pieske B, Voors A, Shah A et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012 Oct 20;380(9851):1387-95
 24. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail*. 2014 Dec;2(6):663-70

25. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail.* 2017 Jul;5(7):471-482
26. ARNI in Asymptomatic Patients With Elevated Natriuretic Peptide and Elevated Left Atrial Volume Index eLEVation (PARABLE). Available at: <https://clinicaltrials.gov/ct2/show/NCT02682719>
27. N Bastien, H Haddad, S Bergeron, A Ignaszewski, G Searles. THE PARASAIL STUDY: patient reported outcomes from the canadian real world experience use of sacubitril/valsartan in patients with heart failure and reduced ejection fraction. *Canadian Journal of Cardiology* Volume 33. 2017. S162-S163.
28. Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION). Available at: <https://clinicaltrials.gov/ct2/show/NCT02661217>.