Advances in Cardiac Research

REVİEW

Angiotensin Receptor Neprilysin Inhibition in Heart Failure: Clinical Benefits and Antiarrhythmic Actions

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Abstract

Inhibition of renin–angiotensin–aldosterone system and sympathetic nervous system are crucial for the treatment of HF with reduced ejection fraction (HFrEF). Modulation of the natriuretic system through inhibition of the enzyme that degrades natriuretic peptides, neprilysin, has proven to be successful too. Sacubitril/valsartan (LCZ696) is a first-in-class medicine of angiotensin receptor neprilysin inhibitor (ARNI) that contains a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (valsartan). PARADIGM-HF trial demonstrated that morbidity and mortality can be improved with the use of ARNI. Furthermore, recent studies revealed that ARNI reduces sudden death, implantable cardioverter defibrillator shocks, premature ventricular contractions and cardiovascular mortality. Despite the increase in understanding of how ARNI favorably affects the arrhythmic outcomes, several key aspects are still not fully understood. This review will overview mechanism of action and use of ARNI in HFrEF; summarize data regarding antiarrhythmic action and clinical implications.

Keywords: Angiotensin receptor neprilysin inhibition; ARNI; arrhythmia; heart failure; LCZ696; sacubitril; valsartan.

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Introduction

Heart failure (HF) is a complex clinical and pathophysiological syndrome, characterized by neurohumoral activation. In the pathophysiology of HF, increased activation of the renin–angiotensin–aldosterone system (RAAS) plays an important role[1-4] . Treatment for heart failure with reduced ejection fraction (HFrEF) includes optimal medical therapy with a combination of medications that an inhibitor of the RAAS, such as an angiotensin converting enzyme (ACE) inhibitor or angiotensin II (Ang II) receptor type 1 blocker (ARB), as well as mineralocorticoid antagonists (MRAs), a β-blocker, ivabradine and/or diuretics[1,2]. Although the use of optimal medical therapy improves outcomes for patients with HFrEF, many patients experience recurrent hospitalizations for HF decompensations and mortality remains high[1-7].

Sacubitril/valsartan, which was formerly known as LCZ696, is a first-in-class medicine of angiotensin receptor neprilysin inhibitor (ARNI) that contains a neprilysin (NEP) inhibitor (sacubitril) and valsartan. NEP is an endopeptidase that metabolizes numerous vasoactive peptides including natriuretic peptides (NP), bradykinin and Ang II[8-12]. Inhibition of NEP results in increasing mainly the levels of NP (promoting diuresis, natriuresis and vasodilatation) and Ang II whose effects are blocked by the angiotensin receptor blocker, valsartan (reducing vasoconstriction and aldosterone release)[13-15] . In a double-blind large clinical outcome study, PARADIGM-HF trial, sacubitril-valsartan reduced cardiovascular (CV) mortality and hospitalization for HF as well as all-cause mortality compared with a proven dose of the ACE inhibitor enalapril in patients with HFrEF[9] .

Importantly, the PARADIGM-HF study disclosed that ARNI reduced sudden cardiac death (SCD) in HFrEF patients as compared to ACE inhibition[9,10]. Different mechanisms such as ventricular arrhythmias, asystole, electromechanical dissociation, cardiogenic shock may be implicated in SCD[9,10]. The precise mechanism of SCD reduction remains unclear. Ventricular arrhythmias and appropriate implantable cardioverter defibrillators (ICD) shocks have been showed to be decreased with ARNI in HFrEF patients under home monitoring as compared to angiotensin inhibition in a recent study[16]. Although ARNI decreases SCD, appropriate ICD shocks, premature ventricular contractions (PVCs) and CV mortality; mechanisms by which ARNI

satisfactorily affects cardiac electrophysiology and arrhythmic outcomes are not completely understood[10,16]. Herein, we will overview the mechanism of action and use of ARNI in HFrEF; summarize data regarding antiarrhythmic action and clinical benefits.

Methods

We performed a search of the PubMed database, Scopus, and the Web of Science, using key words, such as “sacubitril”, “valsartan”, “sacubitril/valsartan”, “angiotensin receptor neprilysin inhibitor” and “ARNI” [AND] “arrhythmia”, “heart failure”, “ventricular arrhythmia”, “sudden death” and “sudden cardiac death” (last update: 11 March 2019). There was no date or language restriction for our selection of publication. References of selected studies and all abstracts from cardiology congresses (American College of Cardiology, American Heart Association, European Society of Cardiology) were searched for relevant data.

Mechanism of action

Sacubitril/valsartan is marketed as a fixed-dose combination of valsartan and sacubitril which acts on both the RAAS and the NP system[8,17]. As RAAS blockade has proven efficacy in the reduction of morbidity and mortality in HF, the RAAS has a crucial role in the pathophysiology of HF. In patients with HFrEF, increased production of renin stimulates conversion of angiotensinogen to angiotensin I (Ang I), which is converted to Ang II by ACE. The CV effects of angiotensin II are elicited through interaction with Ang II type 1 (AT1) and Ang II type 2 (AT2) receptors[8,13,17]. Stimulation of the AT1 receptor is primarily responsible from the detrimental effects of Ang II, whereas stimulation of the AT2 receptor has beneficial effects such as vasodilation through increased nitric oxide, bradykinin production, antiproliferative effects and induction of apoptosis. The pathological effects of Ang II are vasoconstriction and stimulation of aldosterone release, which leads to retention of sodium and water. In the long term, RAAS activation leads to progression of HF by deleterious effects on cardiac remodeling, LV hypertrophy and fibrosis. Moreover, reduction in diuresis and natriuresis contributes to volume overload. Valsartan counteracts the effects of Ang II by AT1 receptor blockade, thereby reducing blood pressure and cardiac remodeling, increasing diuresis and natriuresis. In addition, valsartan leaves the AT2

receptor unblocked and receptive to Ang II stimulation[8,17].

The NP system is another compensatory mechanism activated in HFrEF. There are 3 NPs that play important role in HF: atrial NP (ANP), brain or B-type NP (BNP), and C-type NP[2,8]. In HFrEF, volume overload increases intra-atrial pressure, which in turn stimulates the release of ANP from the atria and increased left ventricle (LV) filling pressures stimulate the LV to release BNP. NPs have favorable effects in HFrEF, because they enhance natriuresis and diuresis, prevent cardiac fibrosis and remodeling. In addition, NPs produce vasodilation and exert effects on the RAAS by decreasing renin release, which in turn reduces Ang II and aldosterone, thereby reducing afterload[1,2,8] .

Sacubitril is a prodrug of LBQ657, an active NEP inhibitor. Inhibition of NEP prevents the degradation of NPs, thereby enhancing endogenous NPs and protective mechanisms of these NPs [8,18]. Nesiritide, a recombinant BNP, was shown to produce modest clinical improvements in patients with decompensated HF[19]. However, sacubitril differs from nesiritide by increasing endogenous NPs through inhibition of NEP[8,13]. Because NEP is also responsible for the breakdown of Ang II, inhibition of NEP activates the RAAS, leading harmful effects of RAAS activation. Therefore, this requires the use of a RAAS inhibitor in combination with a NEP inhibitor. Previous attempts at dual ACE/NEP inhibition via omapatrilat were associated with high risk of angioedema, attributed to the inhibition of bradykinin and substance P breakdown[20,21]. Combination of sacubitril and valsartan inhibits the effects of both Ang II and NEP, thereby preventing the hazardous effects of RAAS activation and increasing the endogenous levels of NPs that produce protective cardiac effects without the increased risk of angioedema associated with the combination of ACE and NEP inhibition[8,20,21]. Mechanism of action for sacubitril/valsartan is shown in Figure 1.

Evidence in Heart Failure

The PARADIGM-HF trial is the randomized double-blind clinical outcome study which included 8399 HFrEF [LV ejection fraction (LVEF) 40% or less, which was later reduced to 35% or less] patients with NYHA functional class II, III, or IV to be given either sacubitril/valsartan or enalapril (9). Before randomization, patients were switched to

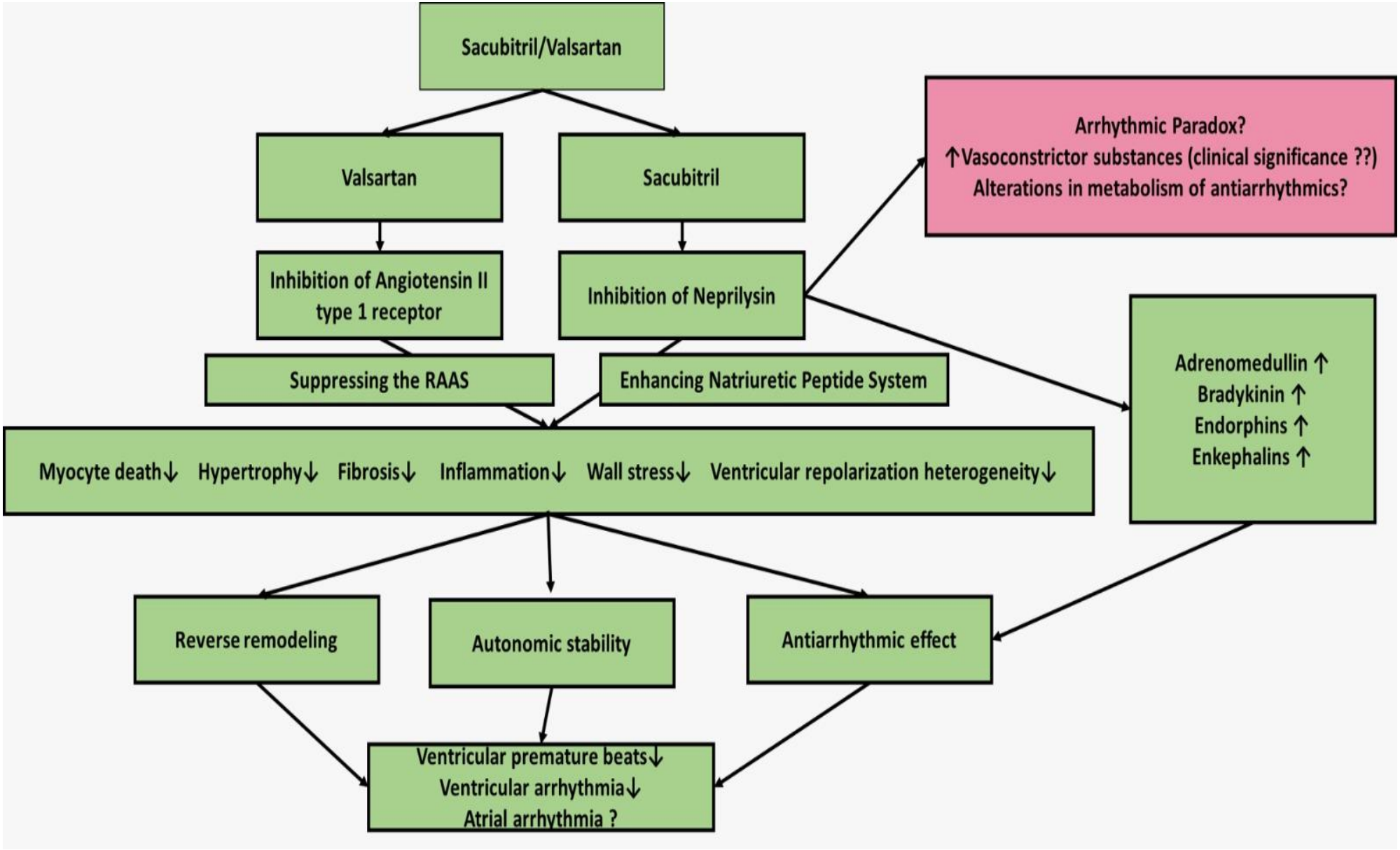

Figure. 1 Mechanism of action for sacubitril/valsartan. RAAS;Renin Angiotensin Aldosterone System

single-blind treatment with 10 mg enalapril twice daily for 2 weeks. This was then followed by single-blind treatment with 100 mg sacubitril/valsartan titrated up to 200 mg for an additional 4–6 weeks. Patients who progressed through the 2 run-in phases were eventually randomized to receive either 200 mg sacubitril/valsartan twice daily or 10 mg enalapril twice daily[9]. After a median follow-up period of 27 months, the primary outcome of CV death or a first HF hospitalization had occurred in 914 (21.8%) patients in the ARNI arm compared with 1117 (26.5%) patients in the enalapril arm ($p < 0.001$). When assessed individually, both CV death and first HF hospitalization occurred in a lower in the ARNI arm in comparison to the enalapril arm ($p < 0.001$ for both outcomes). Death from any cause was also less frequent in the ARNI group (17.0%) than the enalapril arm (19.8%; $p < 0.001$). Furthermore, disease symptoms and physical function, worsened less in the ARNI arm, as evaluated using Kansas City Cardiomyopathy Questionnaire scores. The incidence of atrial fibrillation and renal function decline was similar among the patients in the two groups. Subgroup analyses demonstrated that the risk of the composite primary end point or CV death in the ARNI or enalapril group was not affected by patient-specific risk factors, including age, race, comorbidities and prior use of ACEIs or MRAs[9]. Packer et al[22]. demonstrated that ARNI prevented the clinical progression in surviving HFrEF patients, defined as less need for intensification of medical treatment, intravenous positive inotropes, or intensive care; fewer hospitalizations for worsening HF; and less likely to have implantation of a HF device or cardiac transplant.

Antiarrhythmic action and

clinical considerations

Evidence of favorable effects with ARNI on arrhythmic outcomes has been accumulating[9,10,16]. Major data comes from PARADIGM-HF trial. Twenty percent reduction in CV deaths with ARNI compared to enalapril was seen during the trial and this finding was attributable primarily to reductions in the incidence of both death due to progressive HF and SCD[9,10]. The majority of CV deaths were classified as sudden (44.8%) or HF related (26.5%) in PARADIGM-HF study. Among those who died suddenly, the majority (67.7%) had been last seen alive within the hour prior, and 181 (32.3%) had been last seen alive between 1 and

24 h[10]. Treatment with ARNI significantly reduced the risk for both sudden death and death due to worsening heart failure[9,19]. Ventricular arrhythmias might be expected to play a major role; however no mechanistic information was explained for the cause for SCD reduction in the PARADIGM-HF trial.

NP levels, which reflect myocardial wall stress, were shown in prior studies to be independent strong predictors for sustained ventricular arrhythmias and appropriate implantable cardioverter defibrillator (ICD) shocks[23,24]. As myocardial stretch increases, premature ventricular contractions (PVCs) become more frequent[25]. Although PVCs are the triggers for ventricular arrhythmias, the development of sustained ventricular arrhythmias depends on anatomical substrate and electrophysiological properties such as conduction velocity or repolarization dispersion[26]. Both basic and clinical studies correlated myocardial wall stress to electrophysiological properties, such as repolarization dispersion, involving stretch-activated myocardial membrane channels[27,28]. In addition, NPs enhance vagal input and reduce heart rate. Transgenic mice lacking natriuretic peptide receptors demonstrate elevated heart rates and increased frequency of sinus arrhythmias[29,30]. Cardiac remodeling and fibrosis are well-recognized factors for developing malignant ventricular arrhythmia. Experimental and simulation studies revealed that ARNI causes a greater reduction in cardiac remodeling and fibrosis than RAAS inhibitors[31,32]. In an experimental study of von Lueder et al[31]., attenuation of cardiac remodeling and dysfunction after experimental myocardial infarction (MI) was demonstrated with ARNI. ARNI inhibited cardiac fibrosis and cardiac hypertrophy in vivo after MI, as well as in vitro beyond that achieved by stand-alone ARB[31]. Ishii et al.[33] found that ARNI protected against cardiac rupture and improved the survival rate after MI in another experimental study. This finding was probably because of the suppression of pro-inflammatory cytokines and extracellular matrix degradation in macrophages, by dual regulation of RAAS and NP systems. Similarly, Iborra-Egea et al.[32] disclosed that ARNI reduce cardiomyocyte cell death, hypertrophy, and impaired myocyte contractility by inhibiting phosphatase and tensin homolog (PTEN) protein, thus activating a series of cascades that contribute to myocardial remodeling. Furthermore, ARB improves cardiac remodeling by inhibiting the

guanine nucleotide-binding protein family. More importantly, they found that the combination of sacubitril and valsartan acts synergistically against left ventricular extracellular matrix remodeling and cardiomyocyte cell death[32]. In a study with diabetic rats, Malek et al[34]. showed that combination of telmisartan with a NEP inhibitor thiorphan has protective effect which can be attributed to inhibition of inflammatory, profibrotic and apoptotic cascades.

In a single center study, de Diego et al[16]. showed that ARNI was associated with a significant decrease in ventricular arrhythmias causing a reduction in appropriate ICD shocks as compared to angiotensin inhibition in patients with HFrEF after a follow-up of 9 months. Moreover, as compared to angiotensin inhibition, use of ARNI was correlated with an increase of biventricular pacing in patients with cardiac resynchronization therapy (CRT) owing to a reduction in PVCs. Importantly, there was a correlation between NP levels and PVCs, and ARNI reduced both NP levels and PVCs. In this study, treatment with ARNI caused a significant reduction of heart rate as compared to angiotensin inhibition consistent with a decrease of sympathetic tone[16]. In HFrEF, elevated sympathetic activity contributes to arrhythmias and sudden death. While reducing the catecholamine levels with ARBs, natriuretic peptides may reduce heart rate via enhanced vagal input[29] . According to these data, ARNI may have beneficial effects on arrhythmias by reducing sympathetic activity.

Recently, we evaluated the effects of switching from ACE inhibitor ramipril to ARNI on electrocardiographic indices of ventricular repolarization. Switching from ramipril to ARNI in HFrEF patients favorably changed corrected QT (QTc), T-wave peak to T-wave end interval (Tp-e) and Tp-e/QTc. Reduction in Tp-e and Tp-e/QTc were correlated with clinical improvement in patients with HFrEF. ARNI also reduced symptoms of HFrEF assessed by Minnesota Living with Heart Failure Questionnaire and reduced NT-proBNP levels[34] .

In another study, Martens et al[35]. analyzed 151 HFrEF patients equipped with ICD or CRT with tele-monitoring and found that initiation of sacubitril/valsartan was associated with reduced VT/VF. Also, ARNI significantly reduced the burden of PVCs, which was associated with an improved biventricular pacing in patients with CRT. These beneficial effects on ventricular

arrhythmias were attributed to cardiac reverse remodeling[35] .

According to the data stated above; possible mechanisms of antiarrhythmic benefits with ARNI might include hemodynamic improvements including NP-mediated LV wall stress reduction or improvements in LV function; modification of the substrate for fatal ventricular arrhythmias due to reductions in myocardial fibrosis, reduction in LV hypertrophy, attenuation of progressive LV remodeling and improvement in cardiac autonomic functions[10,16]. However, particular mechanisms by which ARNI leads to reduction in SCD, less ICD shocks, less PVCs, lower CV mortality and favorable modifications in ventricular repolarization are not completely understood and further studies are needed to define probable anti-arrhythmic properties of the ARNI.

Contradictory findings

In recent papers, Vicent et al.[36]and Okutucu et al[37]. presented 7 cases of ventricular arrhythmia that occurred shortly after sacubitril/valsartan initiation that required drug withdrawal. They ruled out other potential triggering factors of electrical storm and, from the arrhythmic perspective, all the patients were stable afterwards. Although, their data are not enough to infer a cause-and-effect relationship, it supplied a question mark about a potential proarrhythmic effect of sacubitril/valsartan in some cases. In another recent paper Weir et al.,[38] reported two cases that raise the possibility of an interaction between sacubitril/valsartan and the class Ib anti-arrhythmic mexiletine resulting in proarrhythmic effects. They suggested careful monitoring for ventricular arrhythmias applied in patients receiving sacubitril/valsartan and mexiletine.

Conclusion

Sacubitril/valsartan, the first-in-class ARNI, blocks both the RAAS and the NEP simultaneously. ARNI reduces SCD, ICD shocks, PVCs and CV mortality. As ARBs and ACE-inhibitors have comparable effects on outcomes in HF patients, the observed benefit is likely to be related to the additional benefits of NEP inhibition in HFrEF. Although our understanding about ARNIs favorably effects on cardiac electrophysiologic properties and arrhythmic outcomes is increasing, several key features are still waiting to be clarified.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. Epub 2016/05/22. doi: 10.1093/eurheartj/ehw128. PubMed PMID: 27206819.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776-803. Epub 2017/05/04. doi: 10.1016/j.jacc.2017.04.025. PubMed PMID: 28461007.

3. Lymperopoulos A, Aukszi B. Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy. World J Cardiol. 2017;9(3):200-6. Epub 2017/04/13. doi: 10.4330/wjc.v9.i3.200. PubMed PMID: 28400916; PubMed Central PMCID: PMCPMC5368669.

4. Zaya M, Phan A, Schwarz ER. Predictors of re-hospitalization in patients with chronic heart failure. World J Cardiol. 2012;4(2):23-30. Epub 2012/03/02. doi: 10.4330/wjc.v4.i2.23. PubMed PMID: 22379534; PubMed Central PMCID: PMCPMC3289890.

5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68(13):1476-88. Epub 2016/05/25. doi: 10.1016/j.jacc.2016.05.011. PubMed PMID: 27216111.

6. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017;33(11):1342-433. Epub 2017/11/08. doi: 10.1016/j.cjca.2017.08.022. PubMed PMID: 29111106.

7. Giannoni A, Mirizzi G, Aimo A, Emdin M, Passino C. Peripheral reflex feedbacks in chronic heart failure: Is it time for a direct treatment? World J Cardiol. 2015;7(12):824-8. Epub 2016/01/06. doi: 10.4330/wjc.v7.i12.824. PubMed PMID: 26730288; PubMed Central PMCID: PMCPMC4691809.

8. Sible AM, Nawarskas JJ, Alajajian D, Anderson JR. Sacubitril/Valsartan: A Novel

Cardiovascular Combination Agent. Cardiol Rev. 2016;24(1):41-7. Epub 2015/10/16. doi: 10.1097/CRD.0000000000000093. PubMed PMID: 26466333.

9. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004. Epub 2014/09/02. doi: 10.1056/NEJMoa1409077. PubMed PMID: 25176015.

10. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, 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;36(30):1990-7. Epub 2015/05/30. doi: 10.1093/eurheartj/ehv186. PubMed PMID: 26022006.

11. Minguet J, Sutton G, Ferrero C, Gomez T, Bramlage P. LCZ696 : a new paradigm for the treatment of heart failure? Expert Opin Pharmacother. 2015;16(3):435-46. Epub 2015/01/20. doi: 10.1517/14656566.2015.1000300. PubMed PMID: 25597387.

12. Bonow RO, ElGuindy AM. PARADIGM-HF: Have we achieved a new paradigm in the treatment of heart failure? Glob Cardiol Sci Pract. 2014;2014(3):224-7. Epub 2014/01/01. doi: 10.5339/gcsp.2014.34. PubMed PMID: 25763372; PubMed Central PMCID: PMCPMC4352673.

13. Hubers SA, Brown NJ. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation. 2016;133(11):1115-24. Epub 2016/03/16. doi: 10.1161/CIRCULATIONAHA.115.018622. PubMed PMID: 26976916; PubMed Central PMCID: PMCPMC4800749.

14. Volterrani M, Iellamo F, Senni M, Piepoli MF. Therapeutic options of Angiotensin Receptor Neprilysin inhibitors (ARNis) in chronic heart failure with reduced ejection fraction: Beyond RAAS and sympathetic nervous system inhibition. Int J Cardiol. 2017;226:132-5. Epub 2016/05/18. doi: 10.1016/j.ijcard.2016.04.180. PubMed PMID: 27184730.

15. Buggey J, Mentz RJ, DeVore AD, Velazquez EJ. Angiotensin receptor neprilysin inhibition in heart failure: mechanistic action and clinical impact. J Card Fail. 2015;21(9):741-50. Epub 2015/07/26. doi: 10.1016/j.cardfail.2015.07.008. PubMed PMID: 26209000.

16. de Diego C, Gonzalez-Torres L, Nunez JM, Centurion Inda R, Martin-Langerwerf DA, Sangio AD, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018;15(3):395-402. Epub 2017/11/18. doi: 10.1016/j.hrthm.2017.11.012. PubMed PMID: 29146274.

17. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond

natriuretic peptides. Heart. 2017;103(20):1569-77. Epub 2017/07/10. doi: 10.1136/heartjnl-2017-311295. PubMed PMID: 28689178.

18. Patel N, Gluck J. Is Entresto good for the brain? World J Cardiol. 2017;9(7):594-9. Epub 2017/08/22. doi: 10.4330/wjc.v9.i7.594. PubMed PMID: 28824789; PubMed Central PMCID: PMCPMC5545143.

19. Fonarow GC. B-type natriuretic peptide: spectrum of application. Nesiritide (recombinant BNP) for heart failure. Heart Fail Rev. 2003;8(4):321-5. Epub 2003/10/24. PubMed PMID: 14574051.

20. Havakuk O, Elkayam U. Angiotensin Receptor-Neprilysin Inhibition. J Cardiovasc Pharmacol Ther. 2017;22(4):356-64. Epub 2017/06/08. doi: 10.1177/1074248416683049. PubMed PMID: 28587583.

21. Prenner SB, Shah SJ, Yancy CW. Role of Angiotensin Receptor-Neprilysin Inhibition in Heart Failure. Curr Atheroscler Rep. 2016;18(8):48. Epub 2016/06/22. doi: 10.1007/s11883-016-0603-4. PubMed PMID: 27324636.

22. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015;131(1):54-61. Epub 2014/11/19. doi: 10.1161/CIRCULATIONAHA.114.013748. PubMed PMID: 25403646.

23. Levine YC, Rosenberg MA, Mittleman M, Samuel M, Methachittiphan N, Link M, et al. B-type natriuretic peptide is a major predictor of ventricular tachyarrhythmias. Heart Rhythm. 2014;11(7):1109-16. Epub 2014/05/20. doi: 10.1016/j.hrthm.2014.04.024. PubMed PMID: 24837348.

24. Seegers J, Bergau L, Exposito PM, Bauer A, Fischer TH, Luthje L, et al. Prediction of Appropriate Shocks Using 24-Hour Holter Variables and T-Wave Alternans After First Implantable Cardioverter-Defibrillator Implantation in Patients With Ischemic or Nonischemic Cardiomyopathy. Am J Cardiol. 2016;118(1):86-94. Epub 2016/05/18. doi: 10.1016/j.amjcard.2016.04.016. PubMed PMID: 27189815.

25. Wang Z, Taylor LK, Denney WD, Hansen DE. Initiation of ventricular extrasystoles by myocardial stretch in chronically dilated and failing canine left ventricle. Circulation. 1994;90(4):2022-31. Epub 1994/10/01. PubMed PMID: 7522991.

26. Weiss JN, Garfinkel A, Karagueuzian HS, Qu Z, Chen PS. Chaos and the transition to ventricular fibrillation: a new approach to antiarrhythmic drug evaluation. Circulation. 1999;99(21):2819-26. Epub 1999/06/03. PubMed PMID: 10351978.

27. Trayanova NA, Constantino J, Gurev V. Models of stretch-activated ventricular arrhythmias. J Electrocardiol. 2010;43(6):479-85. Epub 2010/07/20. doi: 10.1016/j.jelectrocard.2010.05.014. PubMed

PMID: 20638670; PubMed Central PMCID: PMCPMC2970741.

28. Zabel M, Portnoy S, Franz MR. Effect of sustained load on dispersion of ventricular repolarization and conduction time in the isolated intact rabbit heart. J Cardiovasc Electrophysiol. 1996;7(1):9-16. Epub 1996/01/01. PubMed PMID: 8718979.

29. Oatmen KE, Zile MR, Burnett JC, Jr., Spinale FG. Bioactive Signaling in Next-Generation Pharmacotherapies for Heart Failure: A Review. JAMA Cardiol. 2018. doi: 10.1001/jamacardio.2018.3789. PubMed PMID: 30484834.

30. Buttgereit J, Shanks J, Li D, Hao G, Athwal A, Langenickel TH, et al. C-type natriuretic peptide and natriuretic peptide receptor B signalling inhibits cardiac sympathetic neurotransmission and autonomic function. Cardiovasc Res. 2016;112(3):637-44. doi: 10.1093/cvr/cvw184. PubMed PMID: 27496871; PubMed Central PMCID: PMCPMC5157132.

31. von Lueder TG, Wang BH, Kompa AR, Huang L, Webb R, Jordaan P, et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. Circ Heart Fail. 2015;8(1):71-8. Epub 2014/11/02. doi: 10.1161/CIRCHEARTFAILURE.114.001785. PubMed PMID: 25362207.

32. Iborra-Egea O, Galvez-Monton C, Roura S, Perea-Gil I, Prat-Vidal C, Soler-Botija C, et al. Mechanisms of action of sacubitril/valsartan on cardiac remodeling: a systems biology approach. NPJ Syst Biol Appl. 2017;3:12. Epub 2017/06/27. doi: 10.1038/s41540-017-0013-4. PubMed PMID: 28649439; PubMed Central PMCID: PMCPMC5460292.

33. Ishii M, Kaikita K, Sato K, Sueta D, Fujisue K, Arima Y, et al. Cardioprotective Effects of LCZ696 (Sacubitril/Valsartan) After Experimental Acute Myocardial Infarction. JACC Basic Transl Sci. 2017;2(6):655-68. Epub 2018/08/01. doi: 10.1016/j.jacbts.2017.08.001. PubMed PMID: 30062181; PubMed Central PMCID: PMCPMC6059351.

34. Okutucu S, Sabanoglu C, Yetis Sayin B, Aksoy H, Bursa N, Oto A. Switching from ramipril to sacubitril/valsartan favorably alters electrocardiographic indices of ventricular repolarization in heart failure with reduced ejection fraction. Acta Cardiol. 2018:1-6. Epub 2018/12/05. doi: 10.1080/00015385.2018.1535818. PubMed PMID: 30513267.

35. Martens P, Nuyens D, Rivero-Ayerza M, Van Herendael H, Vercammen J, Ceyssens W, et al. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. Clin Res Cardiol. 2019. doi: 10.1007/s00392-019-01440-y. PubMed PMID: 30788621.

36. Vicent L, Juarez M, Martin I, Garcia J, Gonzalez-Saldivar H, Bruna V, et al. Ventricular Arrhythmic Storm after Initiating Sacubitril/Valsartan. Cardiology. 2018;139(2):119-

23. Epub 2018/02/07. doi: 10.1159/000486410. PubMed PMID: 29402859.

37. Okutucu S, Oto A. Electrical Storm after Initiating Sacubitril/Valsartan: Arrhythmic Paradox. Cardiology. 2019;142(1):24-5. doi: 10.1159/000496737.

38. Weir RAP. Sacubitril/Valsartan and Mexiletine: A Proarrhythmic Combination? Cardiology. 2019;142(1):4-6. doi: 10.1159/000497071.