Rev. Fac. Med. Hum. 2023; 23(3):140-147.
DOI: 10.25176/RFMH.v23i3.5089
REVIEW ARTICLES

ISSN Versión Online: 2308-0531
Facultad de Medicina Humana URP
RFMH

THE DIFFICULT PATHWAY OF NATRIURETIC PEPTIDES IN HEART FAILURE

EL DIFICIL CAMINO DE LOS PÉPTIDOS NATRIURÉTICOS EN LA INSUFICIENCIA CARDIACA

Omar Díaz-Cucho [1,a,b]

REVIEW ARTICLES

ABSTRACT

This review is carried out on the role of natriuretic peptides and attempts to use them properly, as a treatment, their functioning in the pathophysiology of heart failure with depressed systolic function was better understood. It is recounts its journey through multiple failed studies and explains the reasons for its failures, until it achieved the desired success with the combination of sacubitril/valsartan. This produced a paradigm shift in the management of heart failure.

Keywords: Heart failure; Natriuretic peptides; Sacubitril-valsartan; Neprilysin. (Source: MESH-NLM)

RESUMEN

Esta es una revisión sobre el papel de los péptidos natriuréticos y los intentos de utilizarlos como diana terapéutica a medida que se iba comprendiendo mejor su papel en la fisiopatología de la insuficiencia cardíaca con función sistólica deprimida. Se hace un recuento de su participación en sucesivos estudios fallidos y se explican los motivos de sus fracasos, hasta lograr el éxito deseado con la combinación del sacubitrilo/valsartan, lo que produjo un cambio de paradigma en el manejo de la insuficiencia cardíaca.

Palabras clave: Insuficiencia cardíaca, Péptidos natriuréticos, Neprilisina. (Fuente: DeCS- BIREME)

[1] Hospital Alberto Barton Thompson, Callao, Peru.
[a] Cardiologist.
[b] Master's in Heart Failure.

Cite as: Díaz-Cucho O. The difficult pathway of natriuretic peptides in heart failure. Rev Fac Med Hum. 2023;23(3):140-147.
doi 10.25176/RFMH.v23i3.5089

Journal home page: http://revistas.urp.edu.pe/index.php/RFMH

REVIEW ARTICLE

INTRODUCTION

In the pathophysiology of chronic heart failure with reduced ejection fraction, neurohormonal regulation plays a fundamental role. The treatment of heart failure has been centered for decades on the inhibition of vasoconstrictive substances (renin-angiotensin-aldosterone system and sympathetic nervous system) [1-3]. , yielding good results in terms of reducing morbidity and mortality [4-8].

However, the prognosis of heart failure remains poor, with persistently elevated rates of mortality and hospitalizations[9-11]. Therefore, it has been important to explore the other side of the neurohormonal model, focusing on vasodilatory substances (natriuretic peptide system) and their potential benefit in the treatment of heart failure [12,13].

The objective of this work is to review the main clinical studies focused on modulating the natriuretic peptide system as a treatment for chronic heart failure with reduced ejection fraction and its evolution over time, explaining the reasons for successive failures until the arrival of LCZ696.

SEARCH STRATEGY

From January to March 2021, a literature review was conducted on Pubmed, ScienceDirect, and Clinical Key. The search terms used were: heart failure, neprilysin, LCZ 696, and natriuretic peptides. Boolean operators AND and OR were employed. The review included narrative reviews, books, and clinical trials. There was no time limit imposed, as a historical review was necessary. Articles not focused on heart failure with reduced ejection fraction or its pathophysiology, as well as those not available in Spanish or English, were excluded. Titles and abstracts were reviewed, and a secondary search was performed using the bibliographic references of the included articles.

NEUROHORMONAL REGULATION IN HEART FAILURE

In the early stages of the pathophysiology of heart failure with reduced left ventricular systolic function, the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system play a fundamental, compensatory, and beneficial role. These mechanisms, through vasoconstriction, lead to an increase in systemic vascular resistance, ensuring adequate perfusion to important organs despite the decrease in cardiac output. Additionally, they cause sodium and water retention, increasing preload and enhancing stroke volume through the Frank-Starling mechanism. However, prolonged vasoconstriction leads to well-known harmful effects, particularly at the level of the heart, kidneys, and vasculature, contributing to disease progression and a poor prognosis [1-3].

THE NATRIURETIC PEPTIDE SYSTEM

In contrast to the adverse effects of these two systems, there is a third system, known as the natriuretic peptide system, which is composed of substances with predominantly vasodilatory function. These substances produce favorable effects such as increased natriuresis and diuresis, reduced sympathetic tone, decreased vasopressin and aldosterone activation, and decreased cardiac remodeling [2,3,12-14]. (Figure 1)

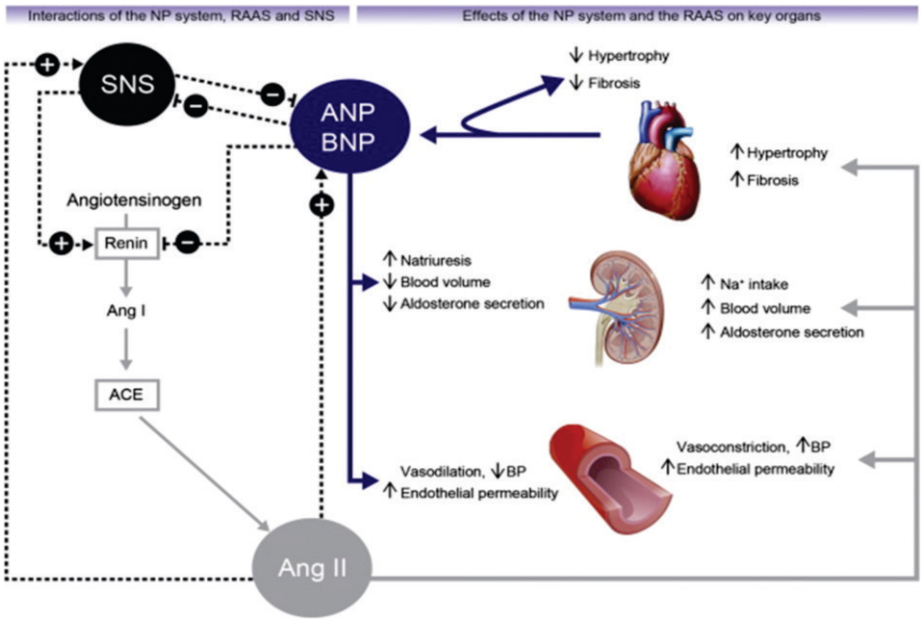

Figure 1. Interaction of the natriuretic peptide system with the sympathetic nervous system and the renin-angiotensin-aldosteronesystem, and its counterregulatory effects on key organs.

ACE = angiotensin converting enzyme; Ang = angiotensin; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; BP = blood pressure; NP = natriuretic peptide; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system (tomado de Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiol. 2014;176(3):630-9.

The most important ones are atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). ANP is stored in the atrium and is released in response to atrial distension. BNP, on the other hand, is only produced in abnormal states of ventricular hemodynamic stress, as seen in heart failure. In the endothelium, C-type natriuretic peptide (CNP) is produced, which has a limited natriuretic effect but plays a significant role in vasodilation [2]. Additionally, there are three types of natriuretic peptide receptors. ANP and BNP bind to the type A natriuretic peptide receptor, leading to its activation via guanylate cyclase. CNP is activated upon binding to the natriuretic peptide receptor type B. Natriuretic peptide receptor type C degrades peptides [14]. (Figure 2)

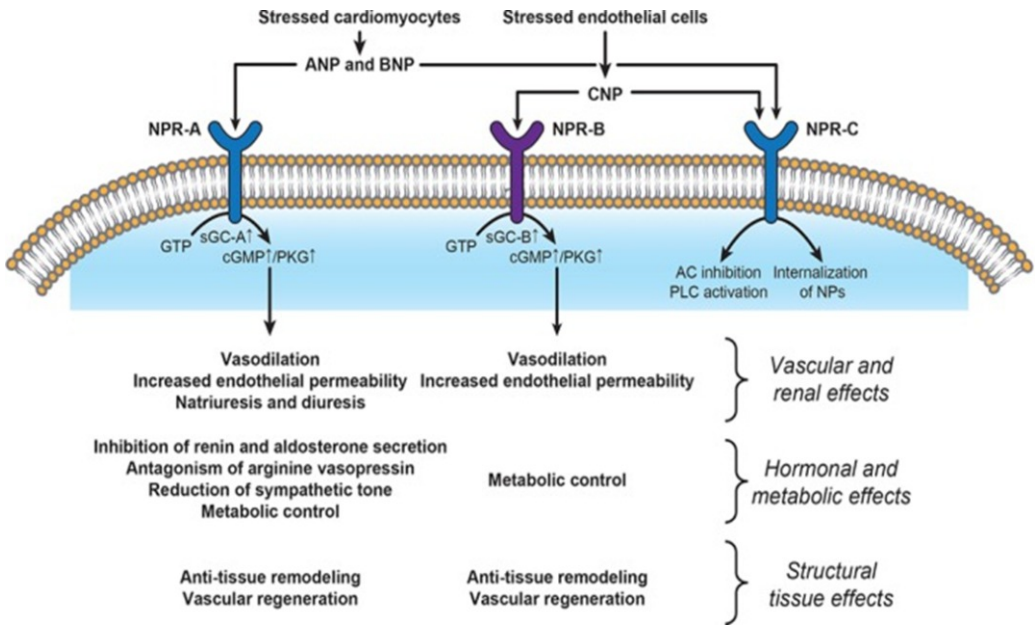

Figure 2. Interaction of natriuretic peptides with their receptors and their effects.

AC, adenylyl cyclase; ANP, atrial natriuretic peptide; AVP, arginine–vasopressin; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; GTP, guanosine triphosphate; NPR, natriuretic peptide receptor; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylate cyclase" (tomado de Díez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. Eur J Heart Fail. 2017;19(2):167-76.)

FIRST FAILED ATTEMPT: USE OF SYNTHETIC NATRIURETIC PEPTIDES

Once the beneficial effects of natriuretic peptides were known, it seemed reasonable to synthesize exogenous peptides to enhance the effects of endogenous peptides. The main one was nesiritide, a recombinant type B natriuretic peptide, approved by the FDA in 2001 for the treatment of acute decompensated heart failure, as it reduced dyspnea and fatigue compared to placebo [15]. However, its safety came into question when an increased risk of renal failure and death was reported with its use [16]. In the ASCEND-HF study, nesiritide was not associated with worsening renal function but showed no beneficial impact on mortality or hospitalization for heart failure, nor significant improvement in dyspnea at 30 days [17]. Carperitide, a recombinant type A peptide, was used in Japan with some benefits for acute heart failure, but it did not consistently improve long-term mortality or morbidity [18].

Therefore, the strategy of using synthetic peptides proved to be ineffective in the management of chronic heart failure.

WHY DID THE USE OF SYNTHETIC NATRIURETIC PEPTIDES FAIL? THE ROLE OF NEPRILYSIN

We must remember that natriuretic peptide levels are already elevated in heart failure, and their levels increase as the disease progresses [14]. In fact, elevated levels of natriuretic peptides are associated with worse functional class [19] and correlate directly with a worse prognosis, being associated with higher all-cause mortality, heart failure mortality, sudden death, and higher rates of hospitalizations [20]. So, why do elevated natriuretic peptide levels associate with higher morbidity and mortality when they have been described to have beneficial effects in heart failure? The answer is simple: these large amounts of natriuretic peptides do not have adequate effectiveness; they represent quantity, but not quality.

The reduced effectiveness of natriuretic peptides is mainly due to excessive activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, which counterregulate and mitigate their effects, even at the renal and vascular levels. Therefore, in heart failure, the effects of vasoconstrictive substances prevail over vasodilators (14) (Figure 3).

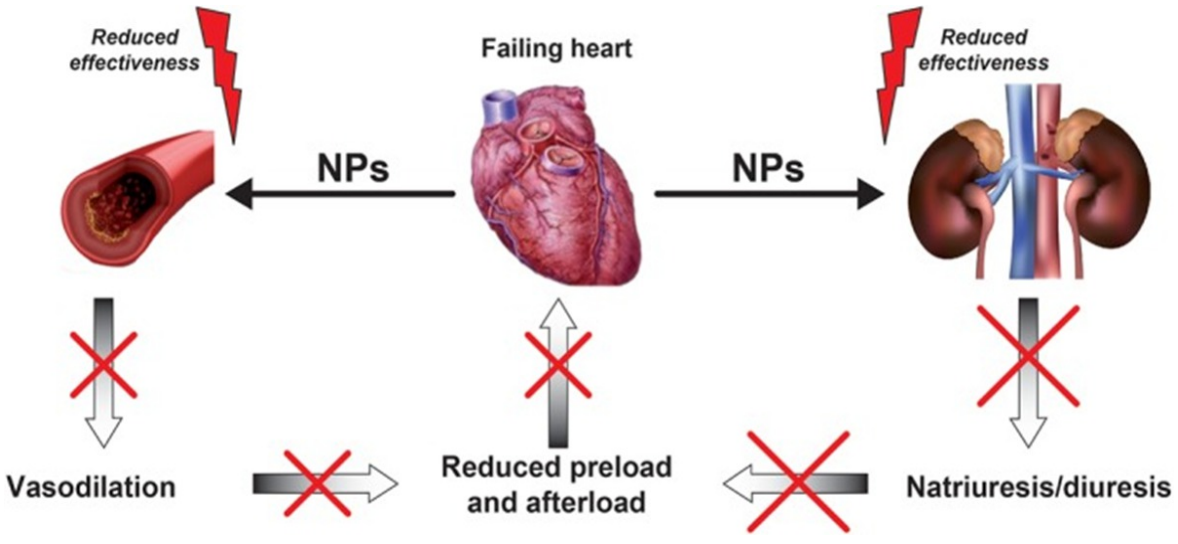

Figure 3. Consequences of the reduced effectiveness of natriuretic peptides in heart failure.

(Adapted from Díez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. Eur J Heart Fail. 2017;19(2):167-76.)

But why did the use of drugs that block the renin-angiotensin-aldosterone system and the sympathetic system not imply greater effectiveness of natriuretic peptides? This is because, in heart failure, in addition to having elevated levels of natriuretic peptides, there is also an increase in the enzyme responsible for degrading natriuretic peptides through a mechanism different from the type C natriuretic peptide receptor [21-23]. This enzyme, called neprilysin, is a zinc-dependent metalloproteinase. It is widely distributed in the body, mainly in the kidney at the level of the proximal convoluted tubule but also in the brain, lung, endothelium, cardiomyocytes, fibroblasts, adipocytes, and neutrophils[24,25].

In summary, despite having increased levels of natriuretic peptides, they were not effective because they were degraded by neprilysin before reaching their target site.

SECOND FAILED ATTEMPT: ISOLATED NEPRILYSIN INHIBITION

The next reasonable step was to use neprilysin inhibitors to decrease the degradation of natriuretic peptides. Phosphoramidon was shown to prevent the elimination of ANP in the renal tissue of mice at the level of the proximal convoluted tubule and glomerulus[21].

Oral candoxatril, used in humans, was expected to lower blood pressure by increasing the bioavailability of natriuretic peptides. However, in a study in hypertensive patients, despite increasing ANP levels, the reduction in blood pressure was not sustained[26]. In a later study, also conducted in hypertensive patients, candoxatril significantly increased angiotensin II levels, leading to greater vasoconstriction. It was concluded that its effects on arterial hypertension were unpredictable, as it could increase, decrease, or have no effect on blood pressure, depending on the balance of its vasoconstrictive and vasodilatory effects [27].

WHY DID THE USE OF NEPRILYSIN INHIBITORS FAIL? NEPRILYSIN, A "VERY PROMISCUOUS" ENZYME

In the scientific literature, neprilysin behaves like a "promiscuous" enzyme because it has many substrates. It not only degrades vasodilatory peptides, such as natriuretic peptides, adrenomedullin, and bradykinin, but also vasoconstrictive peptides, such as angiotensin I and II, and endothelin-1. Therefore, the use of neprilysin inhibitors functions as a double-edged sword, as it increases the level of natriuretic peptides on one hand, but also raises the levels of angiotensin II, potentially mitigating the beneficial effects of natriuretic peptides [28-32].

THIRD FAILED ATTEMPT: USE OF VASOPEPTIDASES, DUAL INHIBITION OF NEPRILYSIN AND ANGIOTENSIN-CONVERTING ENZYME

In response to this new failure, a solution was proposed to enhance the effect of neprilysin inhibition by using an angiotensin-converting enzyme inhibitor to block the effects of the renin-angiotensin-aldosterone system. This dual combination was named vasopeptidase [33]. The most widely used was omapatrilat, which showed a decrease in cardiac remodeling in rats[34].

The OCTAVE study demonstrated better blood pressure control compared to enalapril in untreated hypertensive patients, but it also reported a higher rate of angioedema [35]. On the other hand, the OVERTURE clinical trial compared omapatrilat with enalapril in patients with systolic heart failure and showed a decrease in all-cause mortality and cardiovascular hospitalization. However, it was also associated with high rates of angioedema, leading to the abandonment of this strategy[36].

THE FAILURE OF DUAL NEPRILYSIN AND ANGIOTENSIN-CONVERTING ENZYME INHIBITION: WHY DID VASOPEPTIDASES LEAD TO A HIGHER RATE OF ANGIOEDEMA?

Angioedema has been described to be primarily associated with an increase in bradykinin levels[37]. Both angiotensin-converting enzyme and neprilysin degrade bradykinins. Moreover, omapatrilat also inhibits aminopeptidase P, which in turn metabolizes bradykinin [38]. Consequently, the excessive increase in bradykinin levels led to the high rate of angioedema and resulted in the failure of this drug[39].

FOURTH ATTEMPT: ARNI AND THE EMERGENCE OF A NEW PARADIGM

With the goal of overcoming this new failure and reducing the potentiation of bradykinin, a new drug was designed, initially known as LCZ696. Currently called sacubitril/valsartan, it is a unique drug as it is an inhibitor of both neprilysin and the angiotensin receptor (ARNI, angiotensin receptor-neprilysin inhibitor). Sacubitril, its active metabolite, does not inhibit aminopeptidase P, which implies that there is no increased risk of angioedema, as seen with omapatrilat[40,41]. When tested in hypertensive patients, sacubitril/valsartan showed greater reduction in blood pressure compared to valsartan[42]. Its effects are summarized in figure 4.

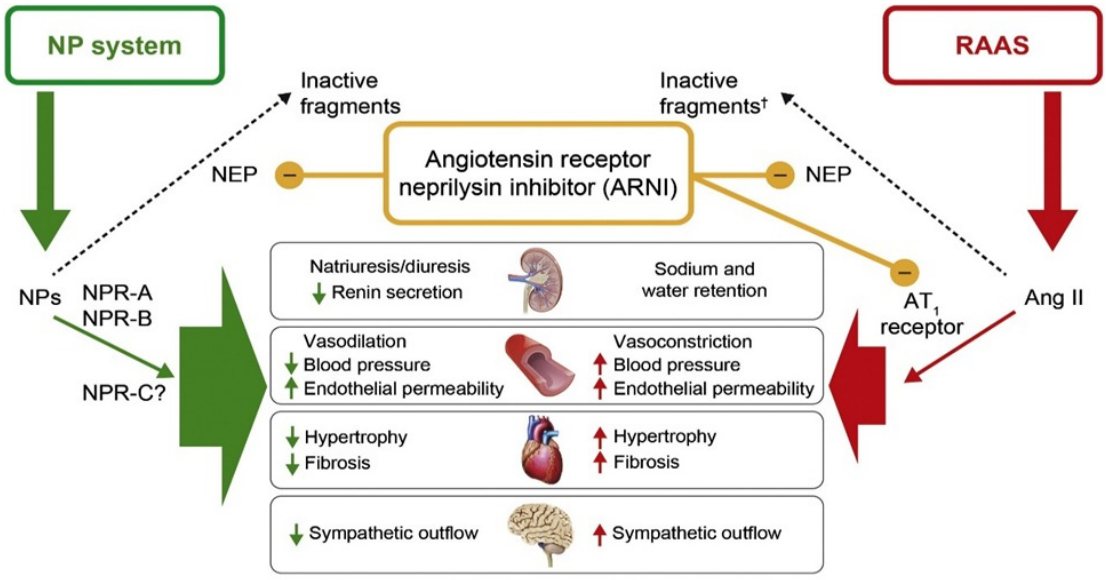

Figure 4. Mechanism of action of ARNI. Sacubitril inhibits neprilysin, improving the levels of natriuretic peptides, which are beneficial in heart failure. On the other hand, valsartan, by blocking the AT receptor, inhibits the renin-angiotensin-aldosterone system, counteracting the harmful effects of elevated angiotensin II.

Ang II = angiotensin II; ARNI = angiotensin receptor neprilysin inhibitor; AT1 = angiotensin type 1 receptor; CV = cardiovascular; NEP = neprilysin; NP = natriuretic peptide; NPR = natriuretic peptide receptor; RAAS = renin–angiotensin–aldosterone system" (tomado de Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiol. 2014;176(3):630-9.

The expectations of success for this new medication were greatly exceeded. In 2014, the results of the PARADIGM-HF study were published, a double-blind trial that involved 8,442 patients with chronic heart failure and a reduced ejection fraction of less than 40%, with functional class II to IV and optimal medical treatment.

The study had to be terminated early because sacubitril/valsartan, as compared to enalapril, demonstrated a 20% reduction in the primary end point of cardiovascular death and hospitalization for heart failure; it also resulted in a 16% reduction in all-cause mortality, a 20% reduction in sudden death, a 21% reduction in death due to worsening heart failure, a 23% reduction in the risk of hospitalization for heart failure, an 18% reduction in intensive care unit admissions, and an improvement in quality of life. There were no significant differences in the rate of angioedema[43].

The results of this trial are so consistent (p <0.00125.29) that they would be equivalent to at least four clinical trials with the same results [13]. Undoubtedly, these findings led to a paradigm shift in the management of heart failure, resulting in strong recommendations in the latest versions of the heart failure guidelines[44,45].

CONCLUSION

Heart failure is a complex syndrome with significant residual morbidity and mortality rates, despite the use of optimal medical treatment aimed at inhibiting the effects of vasoconstrictor substances. After years of research and numerous failures, we have reached a paradigm shift in the modulation of the neurohormonal system, led by a new class of drug, the ARNI sacubitril/valsartan, which enhances the effects of vasodilator substances and mitigates the effects of vasoconstrictor substances. In this way, the results obtained are compelling in reducing morbidity and mortality in patients with heart failure and reduced ejection fraction.

Authorship Contribution: ODC has participated as the sole author in the conception of the article, information search, writing, and approval of the final version.

Funding: Self-funded.

Conflict of Interest: The author declares no conflict of interest.

Received: August 28, 2022.
Approved: August 02, 2023.

Correspondence: *Omar Díaz Cucho.*
Address: *Jr. Río Chira 552, San Luis, Lima.*
Telephone number: *(+51) 990011235*
E-mail: *omardiazcucho@hotmail.com*

REVIEW ARTICLE

REFERENCES

1. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14(1):30-8.

2. Miranda D, O´Gara P, Lilly L. Insuficiencia cardiaca. En: Cardiología Bases Fisiopatológicas De Las Cardiopatías. 6°. Wolters Kluwer; 2015. p. 220-48.

3. Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiol. 2014;176(3):630-9.

4. SOLVD Investigators, 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(5):293-302.

5. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet Lond Engl. 2003;362(9386):772-6.

6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet Lond Engl. 1999;353(9146):9-13.

7. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.

8. Sacks CA, Jarcho JA, Curfman GD. Paradigm shifts in heart-failure therapy--a timeline. N Engl J Med. 2014;371(11):989-91.

9. Mosterd A, Hoes A. Clinical epidemiology of heart failure. Heart 2007. 2007;93(9):1137-41.

10. Jaagosild P, Dawson NV, Thomas C, Wenger NS, Tsevat J, Knaus WA, et al. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. SUPPORT Investigators. The Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments. Arch Intern Med. 1998;158(10):1081-9.

11. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6-245.

12. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clin Sci. 2016;130(2):57-77.

13. Jhund PS, McMurray JJV. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. Heart Br Card Soc. 2016;102(17):1342-7.

14. Díez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. Eur J Heart Fail. 2017;19(2):167-76.

15. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med. 2000;343(4):246-53.

16. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293(15):1900-5.

17. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32-43.

18. Hata N, Seino Y, Tsutamoto T, Hiramitsu S, Kaneko N, Yoshikawa T, et al. Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. Circ J Off J Jpn Circ Soc. 2008;72(11):1787-93.

19. Rademaker MT, Richards AM. Cardiac natriuretic peptides for cardiac health. Clin Sci Lond Engl 1979. 2005;108(1):23-36.

20. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. Clin Chem. 2006;52(8):1528-38.

21. Shima M, Seino Y, Torikai S, Imai M. Intrarenal localization of degradation of atrial natriuretic peptide in isolated glomeruli and cortical nephron segments. Life Sci. 1988;43(4):357-63.

22. Potter LR. Natriuretic Peptide Metabolism, Clearance and Degradation. FEBS J. 2011;278(11):1808-17.

23. Fielitz J, Dendorfer A, Pregla R, Ehler E, Zurbrügg HR, Bartunek J, et al. Neutral endopeptidase is activated in cardiomyocytes in human aortic valve stenosis and heart failure. Circulation. 2002;105(3):286-9.

24. Bayes-Genis A, Lupón J. Neprilisina: indicaciones, expectativas y retos. Rev Esp Cardiol. 2016;69(7):647-9.

25. Wills B, Prada LP, Rincón A, Buitrago AF. Inhibición dual de la neprilisina y del receptor de la angiotensina (ARNI): una alternativa en los pacientes con falla cardiaca. Rev Colomb Cardiol. 2016;23(2):120-7.

26. Bevan EG, Connell JM, Doyle J, Carmichael HA, Davies DL, Lorimer AR, et al. Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. J Hypertens. 1992;10(7):607-13.

27. Richards AM, Wittert GA, Crozier IG, Espiner EA, Yandle TG, Ikram H, et al. Chronic inhibition of endopeptidase 24.11 in essential hypertension: evidence for enhanced atrial natriuretic peptide and angiotensin II. J Hypertens. 1993;11(4):407-16.

28. Von Lueder TG, Atar D, Krum H. Current role of neprilysin inhibitors in hypertension and heart failure. Pharmacol Ther. 2014;144(1):41-9.

29. Abassi Z, Golomb E, Keiser HR. Neutral endopeptidase inhibition increases the urinary excretion and plasma levels of endothelin. Metabolism. 1992;41(7):683-5.

30. Erdös EG, Skidgel RA. Neutral endopeptidase 24.11 (enkephalinase) and related regulators of peptide hormones. FASEB J Off Publ Fed Am Soc Exp Biol. 1989;3(2):145-51.

31. Skidgel RA, Engelbrecht S, Johnson AR, Erdös EG. Hydrolysis of substance P and neurotensin by converting enzyme and neutral endopeptidase. Peptides. 1984;5(4):769-76.

32. Stephenson SL, Kenny AJ. Metabolism of neuropeptides. Hydrolysis of the angiotensins, bradykinin, substance P and oxytocin by pig kidney microvillar membranes. Biochem J. 1987;241(1):237-47.

33. Von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Atar D, Burnett JC, et al. Renin-Angiotensin Blockade Combined With Natriuretic Peptide System Augmentation: Novel Therapeutic Concepts to Combat Heart Failure. Circ Heart Fail. 2013;6(3):594-605.

34. Trippodo NC, Fox M, Monticello TM, Panchal BC, Asaad MM. Vasopeptidase inhibition with omapatrilat improves cardiac geometry and survival in cardiomyopathic hamsters more than does ACE inhibition with captopril. J Cardiovasc Pharmacol. 1999;34(6):782-90.

35. 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(2):103-11.

36. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau J-L, 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(8):920-6.

37. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet Lond Engl. 1998;351(9117):1693-7.

38. Richards AM, Wittert GA, Espiner EA, Yandle TG, Ikram H, Frampton C. Effect of inhibition of endopeptidase 24.11 on responses to angiotensin II in human volunteers. Circ Res. 1992;71(6):1501-7.

39. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clin Sci (Lond). 2016;130(2):57-77.

40. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). J Clin Pharmacol. 2010;50(4):401-14.

41. Bloch MJ, Basile JN. Combination angiotensin receptor blocker-neutral endopeptidase inhibitor provides additive blood pressure reduction over angiotensin receptor blocker alone. J Clin Hypertens Greenwich Conn. 2010;12(10):809-12.

42. Ruilope LM, 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 Lond Engl. 2010;375(9722):1255-66.

43. McMurray JJV, 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.

44. 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 J Heart Fail. 2016;18(8):891-975.

45. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, 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. Circulation. 2017;136(6):e137-61.