

Neprilysin Inhibitors: History, Pharmacology, Pharmacological-Clinical Evidence, and Clinical Practice, from the Risk of Angioedema to a Pillar of Therapy in Heart Failure

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Abstract

The recognition that alterations in the regulation of the neurohormonal axis are the main factor behind the development and progression of heart failure was fundamental to constructing the pillars of therapy currently available for the treatment of this syndrome.

The main objective of this review is to understand the entire historical and pharmacological process that has led neprilysin inhibition to become one of the pillars of heart failure treatment.

For years, there was a gap in drug therapy for heart failure with reduced ejection fraction, and it took years to understand neprilysin inhibition, establish its safety, and confirm its effects, in order to achieve the beneficial results we have today.

Introduction

Heart failure (HF) is a complex clinical syndrome, characterized by structural and hemodynamic changes, often leading to ventricular remodeling; its main mechanism is disturbances in the neurohormonal axis.¹ The recognition that alterations in the regulation of the neurohormonal axis are the main factor behind the development and progression of HF was fundamental to constructing the pillars of therapy currently available for the treatment of this syndrome. Three main systems are notable in this panorama: the autonomic nervous system, the renin-angiotensin-aldosterone system, and the natriuretic peptide system.²

For many years, different pharmacological approaches have been used in the attempt to regulate these systems, mainly the autonomic nervous system and the renin-angiotensin-aldosterone system, including the following: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists.

Keywords

Neprilysin; Heart Failure; Angioedema.

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A new class emerged with the aim of regulating the hitherto unmodulated system, the natriuretic peptide system. The study of natriuretic peptides, however, is not new; since 1981, when Bold et al.³ demonstrated that this atrial extract is capable of stimulating natriuresis in rats, this molecule became the target of studies, and its therapeutic potential garnered the interest of the entire scientific community.

Subsequently, there were multiple attempts to demonstrate that the deregulation of natriuretic peptides could play an important role in the development of HF and that, by modulating them, it would be possible to attenuate this syndrome, finally arriving at a safe combination, as demonstrated in the PARADIGM-HF⁴ study in 2014, which combined sacubitril (an inhibitor of the enzyme that cleaves the natriuretic peptide, namely, neprilysin) with valsartan (an angiotensin receptor blocker).

The main objective of this review is to understand the entire historical and pharmacological process that has led neprilysin inhibition to become one of the pillars of HF treatment.

Natriuretic peptides

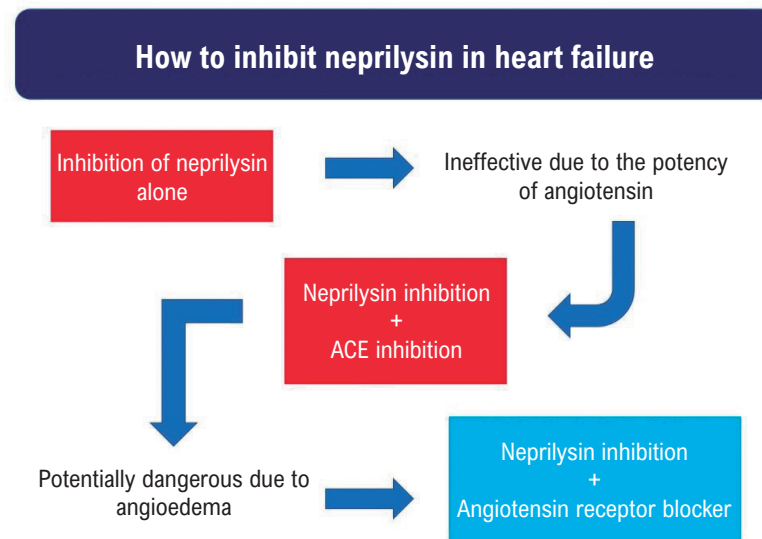
There are 3 types of natriuretic peptides: atrial (ANP), cerebral or type B (BNP), and type C (CNP). ANP was the first to be discovered, as previously mentioned. This molecule is derived from pre-proANP and is expressed and stored mainly in the atria when there is tension in the wall, although lower concentrations can be found in the ventricles and kidneys. Human BNP is similarly synthesized as a prehormone, pre-proBNP, a peptide of 134 amino acids and cleaved into proBNP, which is 108 amino acids long. ProBNP is further cleaved into the 32 biologically active amino acids of BNP, in addition to the 76 amino acids of NT-proBNP. Although low levels of BNP are found in the atria, a higher concentration of BNP is stored in the ventricles, and it is released in response to cardiac stress, such as volume overload.⁵ CNP is the natriuretic peptide most expressed in the brain, but it is also produced in chondrocytes and endothelial cells. After a vascular insult or endothelial injury, neointimal CNP expression increases.⁶

These peptides have functions that go beyond simple natriuresis, including inhibiting renin and aldosterone secretion, increasing myocardial relaxation, in addition to inhibiting ventricular remodeling.⁷⁻¹⁰ Thus, a new possibility arose: if we increase the serum levels of these peptides, it could offer benefits in the treatment of HF. With this rationale, a recombinant form of ANP called carperitide was

Central Illustration: Neprilysin Inhibitors: History, Pharmacology, Pharmacological-Clinical Evidence, and Clinical Practice, from the Risk of Angioedema to a Pillar of Therapy in Heart Failure



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ACE: angiotensin-converting enzyme.

developed and approved for use in acute decompensated HF, but to date no large trials have produced robust evidence to support this practice.^{11,12} Recombinant human BNP has also been developed and approved under the name nesiritide.¹¹ Although nesiritide has favorable hemodynamic, neurohumoral, and renal actions and led to a slight reduction in dyspnea in a large randomized trial, this treatment did not reduce death or hospitalization.^{13,14}

Neprilysin inhibition

Neprilysin is a neutral endopeptidase, also known as enkephalinase, vasopeptidase, or atriopeptidase,¹⁵ which binds to the membrane surface of many tissues, such as endothelial cells, smooth muscle cells, cardiomyocytes, fibroblasts, and especially renal epithelial cells. It is also found in the lungs, intestines, adrenal glands, brain, and heart. Its main function is to catalyze the degradation of natriuretic peptides, including not only ANP, BNP, and CNP, but also bradykinin, substance P, and adrenomedullin, to varying degrees.¹⁶⁻¹⁹

Therefore, inhibiting the enzyme that accelerates the degradation process of natriuretic peptides would be one means of enhancing the effect of these peptides, and this was demonstrated with oral racecadotril and intravenous infusion of candoxatrilat, which led to an increase in circulating levels of ANP and urinary sodium excretion.^{20,21}

These results generated great expectations in this class as a new alternative for the treatment of HF; however, studies with these drugs were aimed at the treatment of hypertension, and the results obtained were discouraging. Unfortunately, continued use of candoxatrilat (the orally active prodrug of

candoxatrilat) did not cause a sustained reduction in blood pressure,²² leading the development of this agent to be terminated, with the emergence of a new paradox: why can neprilysin inhibitors not maintain a sustained hypotensive action? The most convincing explanation is that neprilysin inhibition leads to an increase in vasoconstrictor molecules, such as endothelin 1 and angiotensin 2 itself, to compensate for the vasodilatory action generated by the increase in natriuretic peptides.²³⁻²⁵

Since the increase in natriuretic peptides leads to beneficial hemodynamic effects in HF and, paradoxically, the activation of the renin-angiotensin-aldosterone system in a compensatory manner, it became clear what the most logical next step would be for the success of a new therapy.

Neprilysin and angiotensin-converting enzyme inhibition

Simultaneous neprilysin and ACE inhibition demonstrated a reduction in blood pressure levels,^{26,27} and it also produced greater short- and long-term benefits in experimental models of HF compared to ACE inhibition alone.^{28,29}

In 2002, the OVERTURE study demonstrated that the combination of the neprilysin and ACE inhibitor omapatrilat was noninferior to the ACE inhibitor with respect to reducing mortality in patients with heart failure with reduced ejection fraction (HFrEF). However, although it was not superior to enalapril with regard to the primary composite endpoint of all-cause mortality or hospitalization for HF, the main secondary endpoint of all-cause mortality or cardiovascular hospitalization was reduced by 9% in the omapatrilat group ($p = 0.024$).³⁰

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In the OVERTURE study, once-daily administration of a large dose of omapatrilat led to excessive initial hypotension, without promoting sustained ACE and neprilysin inhibition over 24 hours; this left hope that, perhaps, a dose adjustment would be able to achieve the desired outcome in HFrEF.³¹ Nonetheless, one of the main concerns would be the risk of angioedema, since both neprilysin and ACE inhibition increase bradykinin levels.

This concern was confirmed in 2004 by the OCTAVE study of omapatrilat versus enalapril in patients with hypertension, which demonstrated a 3-fold higher risk of angioedema with omapatrilat when compared to enalapril, especially in African American patients, although it was not life-threatening.³² As a result, omapatrilat never received approval from the United States Food and Drug Administration, which led the clinical development of this agent to be terminated.

Although both ACE and neprilysin metabolize bradykinin, inhibition of both enzymes was not expected to lead to enough accumulation of bradykinin to cause the observed problem of angioedema. Omapatrilat also inhibited aminopeptidase P, a third key enzyme involved in bradykinin metabolism.³³

Angiotensin receptor and neprilysin inhibition (ARNI)

To overcome this problem of increased angioedema risk, the combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan was used in the new drug LCZ696. LCZ696 blocked the angiotensin II type 1 receptor, rather than ACE, and LBQ657, the active metabolite of sacubitril (AHU377), did not inhibit aminopeptidase P; thus, the risk of angioedema was considered lower than with omapatrilat.^{34–36} Other means of minimizing this risk were related to the pharmacology of this new compound. The twice-daily dosage ensured sustained inhibition of neprilysin and the renin-angiotensin system during a 24-hour period.³⁷

The reference study that tested LCZ696 in the setting of HFrEF, PARADIGM-HF, was also designed to minimize possible risks related to this new class. All randomized patients underwent a run-in period, where they were first required to tolerate enalapril 10 mg twice daily for 2 weeks and then LCZ696 200 mg twice daily for an initial period before randomization. This period identified patients who were particularly susceptible to hypotension and angioedema, although both problems rarely led to treatment discontinuation. Two brief wash-out periods were also included to avoid overlap between neprilysin inhibition with LCZ696 and ACE inhibition with enalapril.⁴

INRA and heart failure with reduced ejection fraction

In the PARADIGM-HF study, sacubitril-valsartan 200 mg twice daily compared with enalapril 10 mg twice daily led to a statistically significant reduction of 20% in the primary composite endpoint of cardiovascular death or hospitalization for HF and a reduction of 16% in the risk of all-cause mortality.

It was a multicenter, double-blind study that randomized 8,442 patients with New York Heart Association (NYHA) class II to IV HF and left ventricular ejection fraction < 35% to receive sacubitril-valsartan or enalapril, in addition to optimized

therapy. The study was stopped early, after 27 months, on account of the benefits achieved by this new class.

After this emblematic study, this new drug combination gained strength and rapidly began to change guidelines in the treatment of HFrEF worldwide.

ARNI and decompensated heart failure

After these results, sacubitril-valsartan began to be tested in several different scenarios, including acute decompensated HF. The PIONEER-HF study aimed to evaluate the efficacy and safety of the sacubitril-valsartan combination in patients with acute decompensated HF. It was a multicenter, randomized, double-blind, 8-week study that included 881 patients with symptomatic HF, left ventricular ejection fraction < 35%, and NT-proBNP $\geq$ 1600 pg/ml or BNP $\geq$ 400 pg/ml after clinical stabilization.

The time-averaged reduction in NT-proBNP concentrations (primary outcome) compared to baseline was significantly greater in the sacubitril-valsartan group than in the enalapril group (reduction of -46.7% versus -25.3% ; $p < 0.001$). This decrease was observed from the first week.

The authors concluded that, in patients with HFrEF hospitalized due to acute decompensation, the initiation of therapy with sacubitril-valsartan was associated with a greater reduction in NT-proBNP than therapy with enalapril.³⁸

The reduction of a combination of rehospitalization for HF or cardiovascular death was also shown to be significant in patients treated with sacubitril-valsartan in an exploratory analysis of the PIONEER-HF trial.³⁹ The exploratory composite endpoint of all-cause death, rehospitalization for HF, implantation of a ventricular assist device, or indication for heart transplantation was 42% lower in the sacubitril-valsartan group than in the enalapril group ($p = 0.005$). There was also a 42% reduction in the risk of cardiovascular death or rehospitalization due to HF in the sacubitril-valsartan group versus enalapril ($p = 0.007$). It is worth emphasizing that these were exploratory outcomes.

Patients with HF who were discharged after hospitalization for decompensated HF had a higher risk of readmission in the first 30 days post-discharge. A subanalysis of the PARADIGM-HF study demonstrated that there were 1,076 (45.2%) hospitalizations for HF in the sacubitril-valsartan group and 1,307 (54.8%) in the enalapril group. All-cause readmission rates within 30 days were lower in the sacubitril-valsartan group than in the enalapril group (17.8% versus 21.0%; $p = 0.031$). Likewise, readmission rates for HF were lower with sacubitril-valsartan versus enalapril (9.7% versus 13.4%; $p = 0.006$).⁴⁰

A common question after HF decompensation regards the best time to start this new class. The objective of the TRANSITION study⁴¹ was to answer this question: is it better to start sacubitril-valsartan in the hospital or immediately after discharge? For this purpose, the study included 1,002 patients who started using sacubitril-valsartan $\geq$ 12 hours before hospital discharge or 1 to 14 days after discharge. The initial dose was 24/26 mg or 49/51 mg, twice daily, titrated based on tolerability. The primary outcome was the proportion of patients attaining the target dose of 97/103 mg twice daily after 10 weeks.

The proportion of patients who attained the target dose was similar in both groups (45.4% versus 50.7%). The proportions of patients who achieved and maintained the dose for 2 weeks leading to week 10 (49/51 or 97/103 mg, twice a day) were 62.1% in pre-discharge versus 68.5% in post-discharge (risk ratio 0.91; 95% confidence interval 0.83 to 0.99).

With the results of these studies, sacubitril-valsartan began to be considered for patients with HFrEF in the beginning of treatment as the first option, as well as for patients hospitalized for decompensated HF, according to the latest update of the Brazilian Heart Failure Guidelines.⁴²

ARNI and decreased fibrosis and remodeling

Initially, experimental studies with rats demonstrated that ANP can protect the heart from remodeling induced by angiotensin II, attenuating inflammation, at least partially, through the endothelin-1/endothelin receptor A cascade.⁴³ Another study also experimentally demonstrated in rats that the LCZ696 molecule attenuated cardiac remodeling and ventricular dysfunction after myocardial infarction, reducing fibrosis and hypertrophy.⁴⁴

Following the results of PARADIGM-HF,⁴ mechanistic studies were developed to elucidate the role of ARNI in cardiac remodeling. The PROVE-HF study aimed to evaluate whether changes in NT-proBNP levels are associated with changes in cardiac volumes and function. It was a multicenter, open, prospective study, with 12 months of follow-up, including 794 patients with HFrEF.

After 12 months of treatment, NT-proBNP reduced from 816 pg/ml to 455 pg/ml ($p < 0.001$). Changes in NT-proBNP levels were associated with a significant increase in ejection fraction from 28.2% to 37.8% ($p < 0.001$), in addition to considerable reductions in left ventricular end-diastolic volume index and end-systolic volume index ($p < 0.001$), left atrial volume index, and E/e' ratio.⁴⁵

During the same period, the EVALUATE-HF study was conducted to determine whether sacubitril-valsartan improves aortic stiffness and cardiac remodeling. This was also a randomized, double-blind study, which included 464 patients with HF and ejection fraction $\leq 40\%$, who received sacubitril-valsartan or enalapril. After 12 weeks, a reduction in aortic characteristic impedance (primary outcome) was observed in the sacubitril-valsartan group, while there was an increase in the enalapril group; however, there was no statistically significant difference ($p = 0.78$). Nonetheless, secondary outcomes demonstrated a more pronounced improvement in echocardiographic parameters associated with cardiac remodeling, such as decreased left atrial volume and increased left ventricular diastolic and systolic volumes, in the group that received the ARNI.⁴⁶

ARNI and sudden cardiac death

A subanalysis that evaluated causes of death among patients included in the PARADIGM-HF concluded that the risk of cardiovascular death was significantly reduced by ARNI treatment (hazard ratio 0.80; 95% confidence interval 0.72 to 0.89; $p < 0.001$). Among cardiovascular deaths, both sudden cardiac death (hazard ratio 0.80; 95% confidence

interval 0.68 to 0.94; $p = 0.008$) and death due to worsening HF (hazard ratio 0.79; 95% confidence interval 95% 0.64 to 0.98; $p = 0.034$) were reduced by treatment with ARNI compared to enalapril.⁴⁷

Another more recent subanalysis of the PARADIGM-HF trial aimed to investigate the effect of sacubitril-valsartan therapy on sudden cardiac death according to implantable cardioverter defibrillator (ICD) use and eligibility, stratified by cause of HF. At baseline, of the 7,145 (85%) patients eligible for ICD implantation, only 1,243 (15%) had an ICD. In this scenario, sacubitril-valsartan reduced the risk of sudden cardiac death regardless of ICD use or eligibility, particularly in ICD users and patients with non-ischemic cardiomyopathy.⁴⁸

ARNI and terminal heart failure

When we stratify patients who participated in the PARADIGM study by HFrEF and NYHA functional class, we observe that less than 1% belonged to functional class IV. Thus, the LIFE study was designed, with the objective of evaluating the use of sacubitril-valsartan in patients with HFrEF ($\leq 35\%$) with more limiting symptoms.⁴⁹ It was a multicenter, double-blind, prospective study with 24 weeks of follow-up, comparing sacubitril-valsartan with valsartan. The study included 335 patients with NYHA IV, BNP ≥ 250 , and NT-proBNP ≥ 800 pg/mL. These patients underwent a run-in period of 3 to 7 days on sacubitril-valsartan 24/26 mg twice daily. After this period, they would use sacubitril-valsartan with a target dose of 97/103 mg twice daily or valsartan 160 mg twice daily. Due to the COVID-19 pandemic, patient recruitment was stopped earlier than expected.

The primary outcome was proportional change in the area under the curve of NT-proBNP levels assessed at 24 weeks. Neither group showed an improvement in BNP levels. There were no differences in hospitalization or cardiovascular death, or in hospitalization alone, although there was not enough power to show a significant difference.

These results corroborate previous observations, which suggest that, as HF progresses, excessive and chronic activation of the renin-angiotensin aldosterone system may diminish the effect of natriuretic peptides on the heart, vasculature, or kidneys. Unlike what we observed in patients with HF in functional class II or III, this population might not benefit from this medication.

ARNI and acute myocardial infarction

The PARADISE-MI study was designed to evaluate the possible benefits of ARNI in the post-acute myocardial infarction (AMI) setting.⁵⁰ It was a randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of using sacubitril-valsartan compared with ramipril in high-risk patients after AMI. They included 5,669 patients from 41 countries (178 from Brazil) with AMI, after 12 hours and before 7 days of the index event, with ventricular dysfunction (ejection fraction $\leq 40\%$) and/or pulmonary congestion, requiring treatment (diuretics, vasodilators, vasopressors, and/or inotropes). Included patients had at least 1 of the following 8 risk factors: age > 70 years, estimated glomerular filtration rate < 60 ml/min/1.73 m², type 1 or 2 diabetes, previous AMI,

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atrial fibrillation, ejection fraction < 30% associated with the index AMI, Killip class III or IV, and AMI with ST-segment elevation without reperfusion within the first 24 hours. The primary outcome was time to occurrence of cardiovascular death, hospitalization for HF, or outpatient diagnosis of HF, and there was no statistical difference between the two groups (hazard ratio 0.90; $p = 0.17$).

Recently, Berwanger et al. published a post-hoc analysis of the PARADISE-MI study using the win ratio and including investigator-identified events without confirmation of clinical event classification, where sacubitril-valsartan was superior to ramipril among high-risk survivors of AMI.⁵¹

Another subanalysis of the same study, the PARADISE Echo Substudy, proposed evaluation of the effects on left ventricular ejection fraction and adverse remodeling after high-risk AMI.⁵² Treatment with sacubitril-valsartan compared to ramipril after AMI did not result in changes in left ventricular ejection fraction or left atrial volume at 8 months. However, patients randomized to sacubitril-valsartan had less left ventricular enlargement and greater improvement in filling pressure.

ARNI and heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) is associated with substantial morbidity and mortality, but effective treatments are lacking. The emergence of ARNI brought hope that this new class would be able to reduce this morbidity. Initially, studies indicated this trend. The PARAMOUNT study was a phase 2, randomized, parallel-group, double-blind multicenter trial including patients with NYHA class II or III HF, left ventricular ejection fraction of 45% or greater, and NT-proBNP greater than 400 pg/mL. Initially, 301 patients were randomized to receive LCZ696, titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. The primary endpoint was change in NT-proBNP from baseline to 12 weeks; LCZ696 reduced NT-proBNP to a greater extent than valsartan at 12 weeks and was well tolerated.⁵³

With this in mind, the PARAGON-HF study was designed to answer the following question: would ARNI be capable of reducing mortality in the setting of HFpEF? With the primary composite outcome evaluating the total number of hospitalizations for HF and death from cardiovascular causes, the study included 4,822 patients with NYHA class II to IV HF, ejection fraction of 45% or higher, elevated natriuretic peptides levels, and structural heart disease to receive sacubitril-valsartan (target dose of 97 mg sacubitril with 103 mg valsartan twice daily) or valsartan (target dose of 160 mg twice daily).

After 34 months, the difference in the primary outcome between the groups was not statistically significant (with a relative risk reduction of 13% in favor of sacubitril-valsartan, but with $p = 0.059$). However, exploratory analysis of secondary outcomes provided some interesting data; in the group that received the ARNI, there was an improvement in functional class, quality of life, and renal function. On the other hand, they also had a higher incidence of hypotension and angioedema. In relation to the group with left ventricular ejection fraction < 57%, the PARAGON-HF

findings reinforce the suspicion that patients with HF with slightly reduced ejection fraction may benefit from the same treatments indicated in the management of HFrEF.⁵⁴

Also in the setting of HFpEF, the PARALLAX study had a very similar design and population to the PARAMOUNT study. It was innovative in the comparison treatment (ACE inhibitor, angiotensin receptor blocker, or placebo), and its main outcome included the change in NT-proBNP and distance in the 6-minute walk test among subjects with left ventricular ejection fraction > 40%. Even though sacubitril-valsartan reduced NT-proBNP, it was not superior in relation to functional class, improved quality of life, or distance covered on the walk test.⁵⁵

To evaluate the management of HFpEF after decompensation, the PARAGLIDE-HF study evaluated sacubitril-valsartan versus valsartan in ejection fraction > 40% after a recent HF decompensation event. The primary endpoint was the time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8. Among patients with ejection fraction > 40% stabilized after HF, sacubitril-valsartan led to a greater reduction in plasma NT-proBNP levels, and it was associated with clinical benefit compared to valsartan alone, despite more symptomatic hypotension.⁵⁶

Safety: angioedema, hypotension, renal function, hyperkalemia, and cognitive impairment

Angioedema was independently evaluated in the PARADIGM-HF study by a blinded committee with a small number of confirmed cases, with no major imbalance between treatment arms. Consistent with previous reports that African American patients are at an increased risk of treatment-related angioedema, Black patients in the PARADIGM-HF study were at a higher risk of sacubitril-valsartan-related angioedema than non-Black patients.

In the PARADIGM-HF study, symptomatic hypotension occurred more frequently in the sacubitril-valsartan group than in the group receiving enalapril, although this did not lead to a difference in discontinuation between treatment arms. It is worth highlighting that there was no interaction between the occurrence of hypotension, either during the initial phase or after randomization, and the beneficial effect of treatment with sacubitril-valsartan. In addition to these results, patients who received subdoses of sacubitril-valsartan due to intolerance to higher doses were observed to achieve benefits similar to those who tolerated higher doses.

In the same landmark study, both renal dysfunction and severe hyperkalemia occurred less frequently with sacubitril-valsartan than with enalapril.⁴ Furthermore, the decline in glomerular filtration rate over time was attenuated with sacubitril-valsartan compared to enalapril, despite a small increase in the urinary albumin-to-creatinine ratio with neprilysin inhibition.⁵⁷

The combination of a mineralocorticoid receptor antagonist with a renin-angiotensin system blocker increases the risk of hyperkalemia. Patients who received a mineralocorticoid receptor antagonist at baseline in the PARADIGM-HF trial randomized to enalapril were more likely to experience severe hyperkalemia than those

randomized to sacubitril-valsartan, suggesting that the addition of neprilysin inhibition to dual renin-angiotensin system blockade may reduce the risk of hyperkalemia associated with this combination.⁵⁸

As neprilysin is partially responsible for clearing certain amyloid beta peptides from the brain, an ARNI could theoretically increase brain deposition of these peptides and, in the long term, have a potentially adverse impact on cognition. Two weeks of treatment with sacubitril-valsartan compared with placebo increased concentrations of amyloid- β 1-38 in the cerebrospinal fluid of healthy volunteers, although concentrations of amyloid- β 1-40 and the toxic amyloid- β 1-42 were unchanged.⁵⁹

In this setting, the PERSPECTIVE study was the first randomized trial to evaluate the long-term effects of sacubitril-valsartan compared to valsartan on the cognitive function of patients with HF and ejection fraction > 40%. In that study, 592 patients from 137 centers in 20 countries were randomized 1:1. The primary outcome was change in cognitive function over 3 years, as assessed by the CogState score (GCCS), and there were no significant differences in this outcome when compared with patients treated with valsartan.⁶⁰

Conclusion

Sacubitril-valsartan has shown to be an extremely safe and effective therapy in the treatment of HFrEF, with respect to reduced mortality, remodeling, quality of life, and hospitalization. This has made this class a solid pillar in the treatment of this syndrome. When we discuss HFpEF, this

benefit seems to be smaller. Nonetheless, in patients with HF with slightly reduced ejection fraction, there is an important trend for this medication class to be useful as well.

Author Contributions

Conception and design of the research: Souza PVR, Madrini Junior V, Fernandes F, Fernandes FD, Ramires FJA; Acquisition of data: Souza PVR, Fernandes FD, Ramires FJA; Analysis and interpretation of the data and Writing of the manuscript: Souza PVR; Statistical analysis: Ramires FJA; Critical revision of the manuscript for content: Madrini Junior V, Fernandes F, Ramires FJA.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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