REVIEW ARTICLE

Neprilysin: A Potential Therapeutic Target of Arterial Hypertension?

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Abstract: Arterial hypertension is the most prevalent chronic disease in the adult population of developed countries and it constitutes a significant risk factor in the development of cardiovascular disease, contributing to the emergence of many comorbidities, among which heart failure excels, a clinical syndrome that nowadays represents a major health problem with uncountable hospitalizations and the indolent course of which progressively worsens until quality of life decreases and lastly death occurs prematurely. In the light of this growing menace, each day more efforts are invested in the field of cardiovascular pharmacology, searching for new therapeutic options that allow us to modulate the physiological systems that appear among these pathologies. Therefore, in the later years, the study of natriuretic peptides has become so relevant, which mediate beneficial effects at the cardiovascular level such as diuresis, natriuresis, and decreasing cardiac remodeling; their metabolism is mediated by neprilysin, a metalloproteinase, widely expressed in the human and capable of catalyzing many substrates. The modulation of these functions has been studied by decades, giving room to Sacubitril, the first neprilysin inhibitor, which in conjunction with an angiotensin receptor blocker has provided a high efficacy and tolerability among patients with heart failure, for whom it has already been approved and recommended. Nonetheless, in the matter of arterial hypertension, significant findings have arisen that demonstrate the potential role that it will play among the pharmacological alternatives in the upcoming years.

Keywords: Arterial hypertension, heart failure, neprilysin, natriuretic peptides, sacubitril, pharmacology.

1. INTRODUCTION

Arterial hypertension (HT) is the most prevalent chronic disease in the adult population of developed countries, contributing substantially to a high morbidity and mortality rate [1]. It represents a severe risk factor in the development of cardiovascular disease (CVD), and its prevalence ranges between 10% and 73% at a global level [2]. In Latin America, it is estimated that 40% of the adult population suffers from HT, noticing considerable variations between ethnic groups, socioeconomic condition, sex and between the different countries of the region [3].

Heart failure (HF) is a condition characterized by a failed cardiac output, which does not meet the metabolic requirements of tissues and cannot restore the venous return. This condition is usually silent and progressive, resulting in high morbidity, and lastly, premature death [4]. There are more than 22 million subjects diagnosed with HF all around the world, and right now, it represents a serious public health issue, with uncountable hospitalizations, worsening of life quality and decreased survival rates. The economic burden is estimated to be between 10 to 38 billion dollars annually in the United States alone [5]. As time goes by, one of the leading restrictions in the treatment of both clinical entities has been the inability to maintain the control of blood pressure in the long term, due to the heterogeneity of its physiopathology, and the presence of other comorbidities such as obesity, diabetes mellitus and metabolic syndrome [6-8]. Currently pharmacological efforts are being conducted to find new therapeutic agents and clinical strategies that allow optimal management of HT and HF [1].

Novel therapeutic options are still in experimental or preclinical phase [9]. Among these options, neprilysin stands out. This enzyme is a neutral endopeptidase that degrades endogenous vasoactive peptides such as natriuretic peptides (NP), bradykinin (BK), and adrenomedullin (ADM) [10], rendering it a potential therapeutic target in Renin-

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Angiotensin-Aldosterone System dysfunction (RAAS) [10]. This review aims to describe the molecular mechanisms of endogenous endopeptidase as a therapeutic target for HT, taking into consideration the most recent results in patients with HF [4].

1.1. Natriuretic Peptides

Natriuretic peptides (NP) constitute a family of three hormones and paracrine factors that are genetically different but structurally and functionally related. These are the atrial natriuretic peptide (ANP), the B-type natriuretic peptide (BNP) and the C-type natriuretic peptide (CNP) [11-13]. ANP is derived from pre-proANP, a 151 amino acids precursor, whose first 25 amino acids form an amino-terminal signal sequence that is cleaved to make a 126 amino acids peptide named proANP, stored in secretory granules in the auricle [14]. Once secreted, proANP is degraded by a transmembrane serine-protease highly expressed in the extracellular surface of auricle myocytes, into a 28 amino acids peptide; this being its biologically active form named ANP [15]. ANP is mainly stored and expressed in the auricles, although to a lesser extent, it can also be found in the ventricles and kidneys [16]. The leading stimulus to trigger ANP secretion lies in the enlargement of the auricle walls, as a consequence of an increased intravascular volume or transmural pressure, which promotes biosynthesis and secretion of ANP by the ventricles, especially in the context of HF [17, 18].

BNP, formerly known as "Brain natriuretic peptide", is synthesized as a 134 amino acids pre-proBNP peptide, later cleaved into proBNP (108 amino acids). The proBNP is cleaved to form its biologically active 32 amino acid and a 76 amino acids molecule known as NT-proBNP [19]. The latter is stored in secretory granules in conjunction with ANP at the auricle level. When the ventricle is under stress, due to increased transmural pressure and intravascular volume, BNP is released by the ventricles towards the bloodstream, which explains high BNP levels in subjects with left ventricular failure [20]. Lastly, CNP is the most abundant natriuretic peptide in the brain, although it is also expressed in kidneys, chondrocytes and endothelial cells [21]. Its neointimal expression is increased in the presence of endothelial dysfunction [11].

There are three known NP receptors [11]. They have a 450 amino acids extracellular ligand binding domain and a transmembrane domain of approximately 20 amino acids [22]. The natriuretic peptide receptor-A (NPR-A) and B (NPR-B) contain an equally large intracellular domain consisting of a kinase homology domain, dimerization domain and carboxyl-terminal guanylyl cyclase domain [22]. Therefore, this grant signalling property, when it binds the bioactive form of natriuretic peptides through activation of G proteins, is coupled to the transmembrane domain, and cyclic guanosine monophosphate (cGMP) synthesis [23]. NPR-A is activated through binding with ANP and BNP. NPR-B is activated by CNP binding. The natriuretic peptide receptor-C (NPR-C), the third member of this family, varies structurally in comparison with the former two by not having guanylyl cyclase activity but, in turn, mediating the elimination of NP, through lysosomal ligand hydrolysis [20].

The NP system is an endogenous regulator of arterial blood pressure homeostasis, *via* sodium and water homeostasis control [20]. The NP accomplishes a considerable number of biological functions (Fig. **1**), being essential in physiological cardiac development as well as many anti-inflammatory and anti-proliferative effects in various tissues [24].

1.2. Atrial Natriuretic Peptide Functions

1.2.1. Renal Effects

ANP induces diuresis and natriuresis by inhibiting sodium reabsorption at the level of internal medullary collecting tubules. This absorption is controlled by the amiloride-sensitive sodium channel located on the luminal membrane of the cells, aided by the concentration gradient created by the sodium-potassium ATPase located on the basal membrane [25]. ANP blocks the sodium channel promoting phosphorylation mediated by protein kinase G (PKG) which is activated by cGMP, and decreasing reabsorption of sodium by the renal tubules [25].

ANP favors natriuresis by inhibiting renin release from the juxtaglomerular apparatus through cGMP action independently of intracellular $Ca2^{+}$. It also decreases aldosterone synthesis, which in turn, reduces sodium reabsorption in the collecting tubules promoting even more urinary sodium excretion [26]. It also increases glomerular filtration rate by vasodilating the afferent arterioles directly and by inhibiting their vasoconstriction produced by noradrenaline [27].

1.2.2. Cardiovascular Effects

ANP significantly reduces arterial blood pressure by lowering circulating plasma volume and increasing hematocrit levels due to increased vascular permeability and fluid extravasation from the extracellular space to the interstitium [28]. It also induces systemic vasodilation *via* endothelial nitric oxide release [29, 30]. Moreover, ANP reduces arterial blood pressure due to a combination between inhibiting RAAS and sympathetic nervous system (SNS) by modulating the activity of baroreceptors and stimulating vagal afferent fibers, thereby decreasing peripheral vascular resistance [31].

1.2.3. Cardiac Remodeling Effects

ANP has a direct impact on the cardiac tissue by inhibiting cardiac hypertrophy and fibrosis [25]. Reduced ventricular remodeling occurs due to cardiomyocytes apoptosis induction and inhibition of fibroblast growth [25], through inactivation of angiotensin II, aldosterone and endothelin-1, the culprits in cardiac remodeling in HF [20].

1.3. B-type and C-type Natriuretic Peptide Functions

BNP shows similar physiological effects as those of ANP when it attaches to NPR-A, through induction of cGMP dependent PKG phosphorylation [32]. In addition to the previous, it is also associated with direct cardiovascular effects such as cardiomyocyte apoptosis and necrosis inhibition, decreasing hypertrophy and cardiac fibrosis [33, 34]. This is achieved by inhibition of fibroblast proliferation through attenuation of TGFβ1, collagen 1 marker genes, fibronectin,

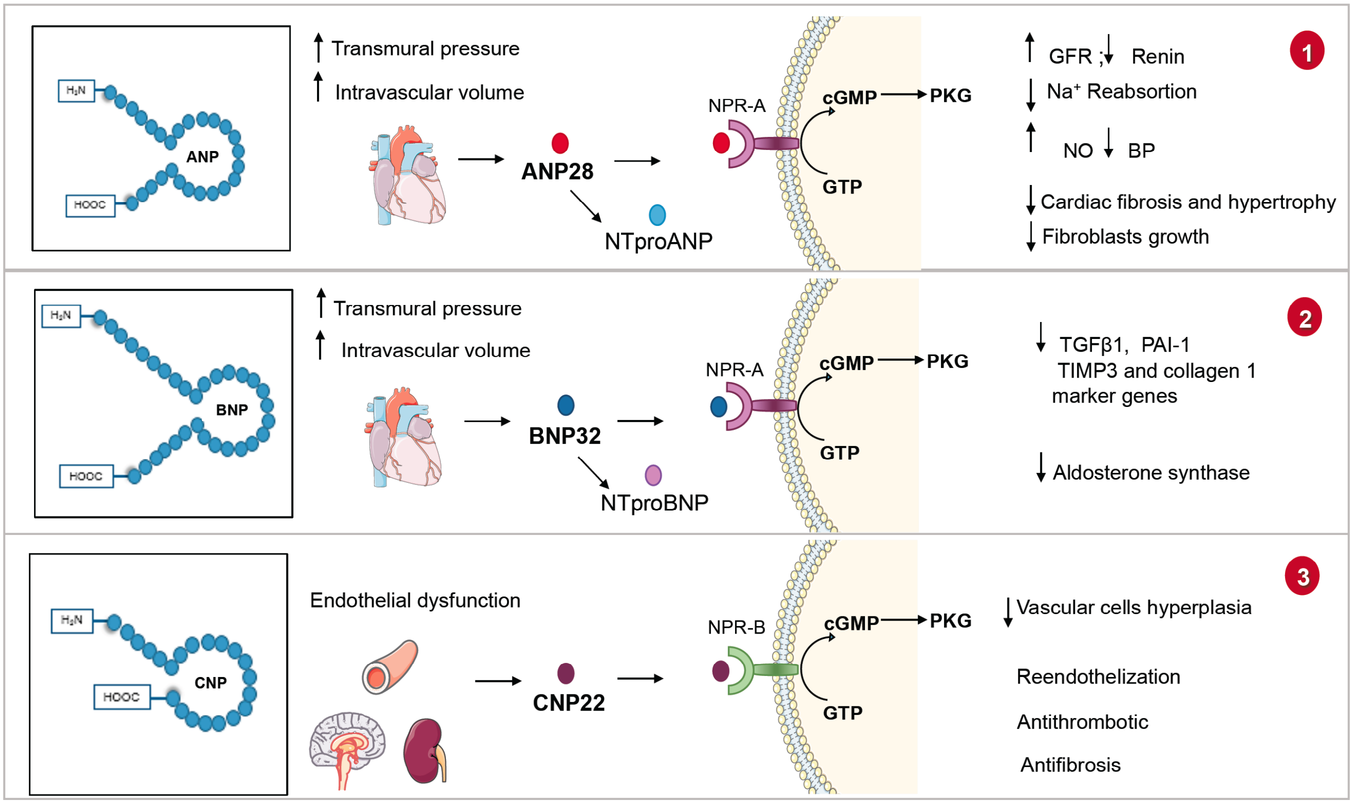

Fig. (1). Natriuretic peptides. Functions against an increase in transmural pressure and/or intravascular volume an auricular wall stretching occurs, which promotes the enhanced **ANP** biosynthesis and secretion, which is then divided into his biologically active form of 28 amino acids, that activates its receptor **NPR-A** which increases **GFR** and **NO** synthesis, while diminishing renin excretion, Na^+ reabsorption and fibroblasts growth, facilitating diuresis, natriuresis and reduction of both **BP** and cardiac remodeling. **BNP** is also secreted by the ventricles, with the increment of transmural pressure and/or intravascular volume, with posterior binding to its receptor **NPR-A**, showing similar effects to those of **ANP**, additionally acting over cardiac remodeling by modulating the expression of **TGFβ1**, **PAI-1**, **TIMP3** and collagen 1 marker genes and suppressing activity of RAAS by blocking aldosterone synthase expression. **CNP** is expressed in the brain, kidneys, and endothelial cells, it is secreted in the presence of endothelial dysfunction and then binding its receptors **NPR-B,** whose principal effects are seen in the blood vessels such as promoting reendothelization, antithrombotic and decreasing vascular cells hyperplasia.
Abbreviations: ANP: Atrial natriuretic peptides; **BNP:** Type-B natriuretic peptide; **CNP:** Type-C natriuretic peptide; **NPR-A:** Natriuretic peptide receptor A; **NPR-B:** Natriuretic peptide receptor B; **GFR:** Glomerular filtration rate; **NO:** Nitric oxide; **BP:** Blood pressure; **TGFβ1:** transforming growth factor beta 1; **PAI-1:** Plasminogen activator inhibitor 1; **TIMP3:** tissue inhibitor of metalloproteinases-3; **RAAS:** Renin-angiotensin-aldosterone system. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

plasminogen activator inhibitor 1(PAI-1) and tissue inhibitor metalloproteinase 3 (TIMP3) expression. The mechanism depends on the extracellular signal-regulated kinases (ERK) mechanism, the increased activity of which is associated with ventricular hypertrophy and also through inhibition of the aldosterone synthase expression which consecutively suppresses the activity of RAAS [35, 36]. BNP has a longer mean lifetime, approximately 22 minutes in contrast with ANP, which is about 4 - 5 minutes [37].

CNP works through NPR-B, and it is not mainly secreted at the cardiac level. It is fundamental for vasomotion, it opposes to vascular cells hyperplasia, and promotes other cardiovascular effects such as reendothelization, hyperpolarization, antithrombosis, and antifibrosis [38].

1.4. Neprilysin: A Molecular Perspective

Neprilysin was discovered in 1970. It has been reported with other names such as neutral endopeptidase (NEP), enkephalinase or common acute lymphoblastic leukemia antigen. Neprilysin is a member of the M13 family of peptidases, being a zinc-dependent type II integral membrane metallopeptidase, found in chromosome 3q25.2 [39, 40]. It has 749 amino acids residues and a number of protein domains: a) short amino-terminal cytoplasmic domain, b) single transmembrane helix, and c) carboxyl-terminal extracellular domain bound to a zinc atom on its active site, which work as a cofactor of it in order to catalyze substrates once they are attached to the extracellular domain [41]. Neprilysin hydrolyzes peptides' hydrophobic residues in the amino-terminal site with a preference for phenylalanine and leucine. The extracellular domain of neprilysin has two helicoidal structures that form a cleft which contains the catalytic site of the enzyme (Fig. **2**) [42]. This catalytic cleft presents a certain amount of specificity, allowing the catalysis of peptides with a molecular weight not greater than 3000 daltons [43].

Neprilysin is ubiquitous, mainly expressed in kidneys, lungs, endothelial cells, vascular smooth muscle cells, cardiac myocytes, fibroblasts, neutrophils, adipocytes, testicles, and brain. Though, the highest concentrations of this mole-

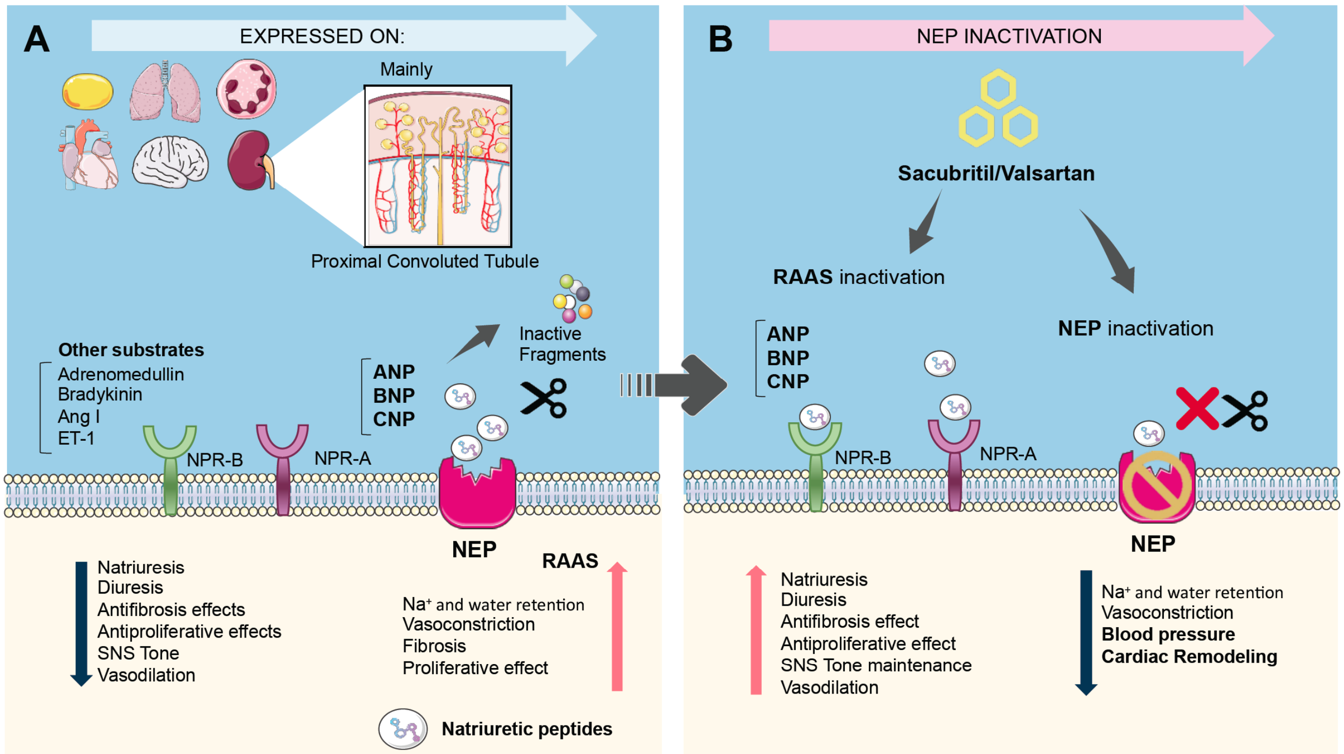

Fig. (2). Functional aspects of Neprilysin and Sacubitril/Valsartan action mechanism. **A-** NEP is extensively expressed in the lungs, endothelial cells, vascular smooth muscle cells, cardiac myocytes, neutrophils, adipocytes, brain and mainly in the proximal convoluted tubule, place where lies the highest concentration of neprilysin. Among its principal substrates natriuretic peptides (**ANP, BNP, and CNP)** stand out, which are hydrolyzed in their hydrophobic residues on the amino-terminal site and then inactivated, which in consequence inactivates RAAS, increasing sodium and water retention but vasoconstriction and antiproliferative effects increase individual cardiometabolic risk. **B-** Enhancement of **NP** hemodynamic actions with the posterior promotion of natriuresis, diuresis, vasodilation which decreases arterial blood pressure and also enhancing antiproliferative effect over cardiac remodeling.
Abbreviations NEP: Neprilysin; **ANP:** Atrial natriuretic peptide; **BNP:** Type-B natriuretic peptide; **CNP:** Type-C natriuretic peptide; **NPR-A:** Natriuretic peptide receptor A; **NPR-B**: Natriuretic peptide receptor B, **RAAS:** Renin-angiotensin-aldosterone system; **Ang I:** Angiotensin I; **ET-1:** Endothelin 1; **SNS:** Sympathetic nervous system. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

cule are found in the proximal renal tubule [44-46]. Besides its extensive distribution, neprilysin is critical in the processing and catabolism of vasoactive peptides implied in diuresis and natriuresis, the most noteworthy being: natriuretic peptides (NP), angiotensin I (Ang I), adrenomedullin (ADM), bradykinin (BK), neurokinin A, neuropeptide Y, substance P and endothelin (ET-1) [47-52]. This enzyme's activity is nowhere near limited to the cardiovascular sphere but also leading to over diverse molecules often playing the role of an antagonist in neurological processes, pain, inflammation, mitogenesis, angiogenesis, digestive and many more [53, 54]. However, our focus is mainly on the cardiovascular field as NPs are one of the most important substrates of neprilysin.

1.5. Therapeutical aspects: the birth of LCZ696 (Sacubitril/Valsartan)

HF treatment includes a variety of pharmaceutical groups, including angiotensin converter enzyme inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARBs) which are a part of the first-line treatment against this disease [55]. In the presence of endogenous natriuretic peptides, showing beneficial effects over the cardiovascular system, they have arisen as an essential non-explored resource against HF [56]. Under this premise, therapies were implemented to raise NP serum levels with exogenous analogs in subjects with acute decompensated HF, among which, nesiritide is worth mentioning (recombinant human BNP) administered by parenteral routes, although in the beginning, it showed favorable hemodynamic and neurohumoral effects. Years later, studies with a greater sample size showed no statistically significant improvement in HF clinical markers nor in the mortality rates of this pathology [57-59].

Another therapeutic perspective was oriented towards elevating NP serum levels through inhibition of their major degrading enzyme (Neprilysin). Candoxatril is one of the very first neprilysin selective inhibitors (NEPi) used in humans, providing a significant increase of NP as well as blood pressure reduction [60, 61]. Nevertheless, antihypertensive effects were nonrelevant due to the wide variety of neprilysin substrates, Ang II among them, leads to an increased RAAS activity, neutralizing the expected effects of this drug in both HT and HF [62].

Considering these findings, the next strategy consisted of combining a NEPi with an ACEi. Omapatrilat, the first known drug with the said composition, after multiple trials compared with enalapril as a single therapy, showed a subtle reduction in mortality rate by chronic HF. Omapatrilat's effect over arterial pressure was not significantly greater within the framework of the clinical trials OVERTURE and OCTAVE [63]. Nonetheless, the most exceptional finding was the appearance of severe angioedema as a side effect leading to drug withdrawal [64]. As a consequence of the negative results found in the use of omapatrilat and with the potential role of dual therapy, using ARB was considered in combination with NEPi. The intention was to decrease the risk of angioedema as a result of blocking the angiotensin converter enzyme (ACE). The novel pharmaceutical group was LCZ696, the first angiotensin receptor-neprilysin inhibitor (ARNi), which is a compound formed by sacubitril, a prodrug that inhibits neprilysin and valsartan an ARB in a 1:1 molar retio [65]. This combination showed a high efficacy and tolerability index on its first analysis, emerging as a potential candidate to evaluate in patients with HT and HF [66].

In a follow up pharmacokinetic analysis, the drug oral administration of sacubitril molecule showed a bioavailability of 60% whereas Valsartan showed a bioavailability higher than 60% if administered dually so that 103 mg of Valsartan in a tablet of 200 mg LCZ696 is equivalent to 160 mg of this drug which is the maximum dose used in the treatment of HF [66, 67]. Additionally, an important rate of plasmatic protein binding was observed independently of the sex whereas, in relation to age, its concentration was observed to be increased in subjects over 65 years, because of the progressive reduction in hepatic and renal function [68]. Using Sacubitril/Valsartan, the typical counterregulatory effects of NP are observed rapidly by promoting diuresis, natriuresis, and cardiac hypertrophy reduction, along with with the suppression of RAAS generated by the blockage of AT1 receptors [69]. There is no evidence of possible drug interactions; however, there are studies of drugs used in HF such as hydrochlorothiazide, amlodipine, and carvedilol, the results of which show no evidence of significant clinical interaction after the combined administration of the aforementioned drugs [70].

1.6. Sacubitril/Valsartan and Cardiovascular Disease

Having as a goal to be considered a therapeutic option, the combination sacubitril/valsartan has been studied in a variety of clinical trials [71, 72]. Moreover, beneficial effects over renal function have been observed, specifically in diabetic patients with HF and a maximum blockage of RAAS, as demonstrated by Parcker *et al*. [73], in a secondary analysis of PARADIGM-HF trial. Jordan *et al*. [74], showed an improvement in insulin sensitivity in patients both obese and hypertensive patients who received this therapy, showing the numerous potential effects that are yet to be discovered by the application of this pharmacological combination.

1.6.1. Sacubitril/Valsartan: Role in Heart Failure

In order to assess the effectivity of this drug combination in HF, the phenotypes of heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) have been considered (Table **1**) [71]. PARAMOUNT-HF study was the first to provide clinical data about Sacubitril/Valsartan in patients with preserved (45% or more) left ventricular ejection fraction (LVEF) and also with high serum levels of NT-proBNP, with their primary objective to compare the efficacy and security of an angiotensin receptor-neprilysin inhibitor against an ARB (Valsartan) [75], noticing a reduction in serum concentrations of this marker in the group of dual therapy, and also showing a similar profile of side effects, independent of their antihypertensive actions [76].

The results obtained by the PARAMOUNT-HF essay were almost simultaneous as those found in the PARADIGM-HF essay which, unlike the former, admitted subjects with chronic HF, reduced LVEF (<40%, posteriorly modified to <35%) and high serum levels of NT-proBNP, comparing the effects of dual therapy against enalapril on top of the standard treatment for HF [10, 77]. The study ended promptly, due to great clinical benefits obtained, with a 20% reduction in cardiovascular mortality and hospitalization rates in those who were treated with sacubitril/valsartan [10]. The most frequent side effect found along the implementation of dual therapy was hypotension with 14%, not that much different than enalapril's group with 9%, in addition to the presence of non-severe angioedema, found in similar proportions between both the groups [78]. Furthermore, an improvement in NT-proBNP and troponin levels as well as an additional benefit in the stoppage of HF progression in contrast with enalapril were observed [78, 79].

In the same way, Velazquez *et al*. [80], showed a reduction in NT-proBNP levels in patients with HFrEF hospitalized by an acute decompensation, who, after hemodynamic stabilization, received sacubitril/valsartan to compare them with those who received enalapril, however, the rates of acute worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema were not different between the groups, within the framework of PIONEER-HF trial. The PARAGON-HF trial, the final results of which are not yet available, aims to compare the effects of sacubitril/valsartan against Valsartan in the reduction of morbimortality of 4822 patients with HFpEF but with a high prevalence of comorbidities, sampled in diverse regions of the world [81].

Another group that has been considered within the clinical trial using sacubitril/valsartan includes those patients with post-myocardial infarction, based on the fact that in animal models, this therapy has attenuated cardiac remodeling and the overall dysfunction after coronary events, which is why it is being carried out in the present PARADISE-MI clinical trial which establishes that the therapy with sacubitril/valsartan reduced the cardiovascular morbimortality rate in approximately 4650 post-infarcted patients who had an LVEF ≤40% and/or pulmonary congestion that required endovenous therapy, a true challenge in front of the leading drugs applied in this clinical context [82].

1.6.2. Sacubitril/Valsartan: Role in Arterial Hypertension

Even though the initial trials using sacubitril/valsartan focused on patients with HF, the results led to FDA approval and specified indication for patients with chronic HFrEF in combination with beta-blockers and aldosterone antagonists [83]. These studies gave evidence of a significantly greater

Table 1. Sacubitril/Valsartan clinical trials on heart failure.

Refs.	Trial's Name	Methodology	Population	Intervention	Results	Time lapse
Solomon *et al.* [75]; Jhund *et al.* [76]	PARAMOUNT-HF	Multicentric, Phase II, Randomized, Parallel and Double-blind	Adults with HFpEF (LVEF ≥45%) in NYHA functional class II-IV and NT-proBNP >400pg/ml n= 301 patients	Sacubitril/Valsartan 200mg BID against Valsartan 160mg BID	After 12 weeks it was observed a reduction in serum levels of NT-proBNP with Sacubitril/Valsartan with a difference of 23% in comparison with Valsartan. Tolerable and similar side effects in both groups	36 Weeks
McMurray *et al.* [10], Packer *et al.* [78]	PARADIGM-HF	Multicentric, Phase III, Randomized, Parallel and Double-blind	Adults with HFrEF (LVEF<35%) in NYHA functional class II-IV and NT-proBNP ≥600 pg/ml . Treated with ACEI o ARB of at least 10mg during 4 weeks n= 8442 patients	Sacubitril/Valsartan 200mg BID against Enalapril 10 mg BID	20% significative reduction of CV mortality and hospitalization rates with Sacubitril/Valsartan against Enalapril. Hypotension was the most frequent side effects in a proportion of 14% with Sacubitril/Valsartan against Enalapril's 9%. Significative better serum levels of NT-proBNP	27 Months
Velazquez *et al.* [80]	PIONEER-HF	Multicentric, Randomized, Parallel and Double-blind	HFrEF (LVEF <40%) and NT-proBNP >1600pg/ml That had been hospitalized by an acute decompensation but after hemodynamic stabilization n= 881 patients	Sacubitril/Valsartan 200mg BID against Enalapril 10 mg BID	Significative reduction of NT-proBNP levels with Sacubitril/Valsartan (Percentage changed: -46,7%) against Enalapril (Percentage changed: -25,3%). Renal function worsening, symptomatic hypotension, hyperkalemia, and angioedema was no different between the groups	27 Months
Solomon *et al.* [81]	PARAGON-HF	Multicentric (Many countries), randomized, Parallel and Double-blind	Adults with HFrEF (LVEF ≥45%) in NYHA functional class II-IV, elevated NT-proBNP n= 4822 patients	During single-blind 100mg Sacubitril/Valsartan in 2 to 4 weeks against 80mg Valsartan in 1 to 2 weeks. Before double-blind randomization with goal dose of 160mg Sacubitril/Valsartan BID	So far the clinical characteristic of the patients are the only features published	57 Months

Abbreviations : HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; HT: Arterial Hypertension; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; BID: Twice a Day; OD: Once a Day; NT-proBNP: N-terminal pro B-type Natriuretic Peptide; ACEI: Angiotensin Converter Enzyme Inhibitor; ARB: Angiotensin Receptor Blockers; NEP: Neprilysin; PARAMOUNT-HF: Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction; PARADIGM-HF: Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PIONEER-HF: Comparison of Sacubitril/Valsartan *versus* Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; PARAGON-HF: Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with ARB Global Outcomes in HF.

reduction in arterial blood pressure compared to the conventionally used treatment [84].

A variety of studies have been designed to evaluate the hypertensive population exclusively (Table **2**). The very first study to prove a superior lowering in arterial blood pressure with Sacubitril/Valsartan against Valsartan as monotherapy and placebo was carried out by Ruilope *et al*. [85]. This group showed in 1215 patients with moderate hypertension, that after eight weeks, there was a progressive reduction in blood pressure readings, especially in diastolic arterial pres-

Table 2. Sacubitril/Valsartan clinical trials on arterial hypertension.

Refs.	Trial's Name	Methodology	Population	Intervention	Results	Timelapse
Ruilope *et al.* [85]	----	Multicentric, randomized, double-blind	Adults 18-75 (Mean= 53 years) with mild to moderate essential HT n= 1215 patients	8 comparative groups were stablished: Sacubitril/Valsartan at doses of 100-200-400mg. Valsartan at doses of 80-160-320mg. Sacubitril at 200mg and placebo group.	Sacubitril/Valsartan generated a greater reduction of average diastolic blood pressure on every dose when compared to Valsartan at equivalent doses (Average reduction: -2,17mmHg 95% CI: –3·28 to –1·06; p=0,010) with more significant reductions at 200mg and 400mg. Good tolerability, without cases of angioedema	8 Weeks
Kario *et al.* [86]	----	Multicentric, open-label	Japonese adults >20 (mean= 51,3 years) with severe essential HT with or without pharmacological treatment 4 weeks prior to the screening n= 35 patients	200mg of Sacubitril/Valsartan that raised to 400mg (2 weeks) or combined with other antihypertensive agents (4 weeks) in case of not reaching the goals	Sacubitril/Valsartan reduced both systolic and diastolic arterial blood pressure and also pulse pressure on an average of 35,3 – 22,1 – 13,2 mmHg, respectively at 8 weeks. The side effects incidence average was 48,6% with no reports of hypotension, angioedema or dizziness	8 Weeks
Williams *et al.* [90]	PARAMETER	Multicentric, phase III, randomized, parallel and double-blind	Adults ≥ 60 años (Mean= 67,7 years) with essential HT with or without treatment and PP > 60mmHG n= 454 patients	Initial doses of Sacubitril/Valsartan 200mg OD against Olmesartan 20mg OD, 40mg > 4 weeks Weeks from 12 to 24 Amlodipine was included at 2,5mg, HCTZ 6,5mg in non-controled BP	Sacubitril/Valsartan on week 12 significantly reduced CASP 3,7mmHg vs Olmesartan (p=0,010) and MASBP 4,1mmHg (p<0,0001). On week 52 similar levels of BP between the treatments (p<0,002) Good tolerability for both treatments.	52 Weeks
Cheung *et al.* [91]	----	Multicenter, randomized, double- blind, double-dummy, parallel-group, active-controlled, phase III	Adults >18 (Mean= 57,6 years) with mild to moderate essential HT n= 354 patients	Sacubitril/Valsartan 200mg OD against Olmesartan 20 mg OD	Sacubitril/Valsartan generated a greater reduction in the average systolic blood pressure in 24 hours compared to Olmesartan (-4,3 mmHg vs -1,1 mmHg, p<0,001). There was also a greater reduction of dyastolic blood pressure in 24 hours, pulse pressure and blood pressure in the consults. The side effects average was similar between the groups.	8 Weeks

Abbreviations: HF: HEART FAILURE; HT: Arterial Hypertension; BP: Blood Pressure; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; BID: Twice a Day; OD: Once a Day; NT-proPNB: N-terminal pro B-type Natriuretic Peptide; NEP: Neprilysin; HTCZ: Hydrochlorothiazide; CASP: Central Aortic Systolic Pressure; PP: Pulse Pressure; MASBP: Mean Ambulatory Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; PARAMETER: Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly.

sure. Afterward, the articles that reproduced these findings were based on Asian subjects with non-complicated hypertension [86], severe hypertension [87], hypertension along chronic renal disease (Glomerular filtration rate between 30-60 mL/min per 1.73m2) [88], uncontrolled hypertension with common drugs such as amlodipine, where arterial blood pressure reduction was noticed even by ambulatory blood pressure monitoring [89]. Moreover, in general, side effects were mild, nasopharyngitis, being the most frequent.

The PARAMETER trial compared the efficacy of high dose sacubitril/valsartan (400 mg) against olmesartan (40 mg) for a period of 12 weeks in aged patients with systolic hypertension. During the extension phase that lasted 52 weeks, there were no significant differences in systolic arterial blood pressure changes, probably influenced by the addition of other drugs, such as diuretics or calcium antagonists, in patients who did not achieve the arterial blood pressure goals. This lack of goal achievement was less frequent in the dual therapy group (sacubitril/valsartan: 32% against olmesartan: 47%) [90]. A recent analysis by Cheung *et al.* [91] used the same drugs but at lower doses (sacubitril/valsartan [200 mg] against olmesartan [20 mg]) in a younger population (57,6 years as average age). They reported a greater reduction in systolic arterial blood pressure taken in the consult (-14,2 against -10,0mmHG) and in the 24- hour monitoring (-4,3 against -1,1 mmHg; $p<0,001$) than in those who received dual therapy.

It is essential to highlight that besides its efficacy, sacubitril/valsartan's security has been appropriate with a profile of side effects in hypertensive patients, similar to conventional therapy and specially in relation to hypotension, frequently reported in patients with HF, in studies analyzing only HT incidence which was lower probably due to the high blood pressure in these patients . An issue that has raised concern is the potential effect that this therapy would have over cognitive dysfunction, as a result of neprilysin degrading peptides and oligomers Aβ, associated with the inverse relationship between this molecule expression and beta-amyloid plaques in animal models [92-95]. Since there are no clear answers related to the use of this drug combination and dementia, the PARAGON-HF results will fulfill this knowledge gap, as it will include Mini-Mental State evaluation. Another source of information will be the PERSPECTIVE trial (NCT02884206), which will include imaging techniques and nuclear medicine to assess brain beta-amyloid plaque's evolution.

Finally, in the new context of paradigms and therapeutic strategies [96, 97], the idea of pharmacological treatment with dual therapy is now highly recommended. Despite lack of approval by international societies of sacubitril/valsartan, the number of trials with findings of its efficacy and safety almost match those of current HF treatment. This brings the question, why not to approve a drug for HT that can generate peripheral vasodilation, diuresis, natriuresis as well as showing satisfactory results even on its leading complications. Without a doubt, the combination of a neprilysin inhibitor and a RAAS blocker is the next step in the therapeutic scale of HT. However, there are still questions to be answered: time of prescription, role in other cardiovascular risk factors, its non-debatable efficacy in refractory HT, and the cost.

CONCLUSION

Currently, there are enormous efforts in the pharmacological ambit as to research new therapeutic targets that allow expanding how to approach multiple physiological systems altered by HT, to improve adherence and control of arterial pressure numbers in hypertensive patients. Neprilysin inhibition constitutes an important therapeutical target. Sacubitril in combination with the angiotensin receptor blocker Valsartan, approved by the FDA and recommended by the international guidelines for chronic HF, has shown significant results regarding greater arterial blood pressure reduction in comparison with usually used drugs that treat HT. Its use can be adapted to the new trends of this disease management but how to start its indication, its role in other cardiovascular risk factors, its non-debatable efficacy in refractory hypertension and its cost are aspects to be considered in the future clinical trials that might influence its application in the clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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