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## **Natriuretic peptide pathways in heart failure in the context of the analysis of the mechanism of action and potential usages of sacubitril/valsartan**

1. Kamila Babkiewicz-Jahn [KBJ]  
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049  
Lublin, Poland  
<https://orcid.org/0009-0001-1597-273X>  
[kamila.babkiewicz@gmail.com](mailto:kamila.babkiewicz@gmail.com)
2. Justyna Matuszewska [JM]  
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049  
Lublin, Poland  
<https://orcid.org/0009-0005-6038-037X>  
[matuszewskajustyna97@gmail.com](mailto:matuszewskajustyna97@gmail.com)
3. Adrianna Szymańska [AS]  
Independent Public Health Care Center in Puławy, Józefa Bema 1 street, 24-100 Puławy,  
Poland  
<https://orcid.org/0000-0002-1093-7935>  
[adrianna.szymanska95@gmail.com](mailto:adrianna.szymanska95@gmail.com)
4. Wiktoria Wilanowska [WW]  
Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718  
Lublin, Poland  
<https://orcid.org/0009-0000-8388-8479>  
[wiktoria.wilanowska@gmail.com](mailto:wiktoria.wilanowska@gmail.com)

5. Izabela Oleksak [IO]  
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue,  
20-049 Lublin, Poland  
<https://orcid.org/0000-0001-7155-9010>  
[i.oleksak203@gmail.com](mailto:i.oleksak203@gmail.com)
  
6. Karolina Maliszewska [KM]  
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue,  
20-049 Lublin, Poland  
<https://orcid.org/0000-0003-2068-3112>  
[karolina.maliszewska2149@gmail.com](mailto:karolina.maliszewska2149@gmail.com)
  
7. Natalia Załęska [NZ]  
Medical University of Lublin, Raclawickie 1 avenue, 20-059 Lublin, Poland  
<https://orcid.org/0009-0003-4406-927X>  
[zaleska.natalia@gmail.com](mailto:zaleska.natalia@gmail.com)

## **ABSTRACT**

### Keywords:

pathophysiology of heart failure; natriuretic peptide pathways; treatment of heart failure; sacubitril/valsartan.

### Introduction and purpose

Heart failure has become a civilization disease, affecting 1-2% of the world's population. It is a condition with various etiologies and phenotypes. The annual mortality rate due to heart failure is approximately 10%, with organ dysfunction caused by hypoperfusion and sudden cardiac death being the leading causes of death. The aim of this study is to present current knowledge of heart failure, focusing on its pathophysiology, and the mechanism of action and applications of sacubitril/valsartan.

### Material and methods

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included pathophysiology of heart failure; natriuretic peptide pathways; treatment of heart failure; sacubitril/valsartan.

### Conclusions

Heart failure is a syndrome marked by the activation of various neurohormonal systems such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS)

and natriuretic peptides (NP). Historically, the therapeutic approach has focused on reducing RAAS activity and SNS activity. In recent years, increasing attention has been given to potential benefits associated with the NP system.

Following disappointing outcomes from studies involving neprilysin (NEP) inhibitors, administered alone or in conjunction with an ACE inhibitor and vasopeptidase inhibitors, there have been findings with the pharmacological class termed ARNI (angiotensin receptor and NEP inhibitors). Sacubitril/valsartan has proven to be an effective and safe treatment that reduces the need for hospitalization, enhances the quality of life and longevity of patients with chronic HFrEF.

## Natriuretic peptide pathways in heart failure in the context of the analysis of the mechanism of action and potential usages of sacubitril/valsartan.

### 1. Introduction

Heart failure (HF) is a state of cardiac dysfunction in which there is a decrease in cardiac output relative to the metabolic demands of body tissues or an increase in filling pressure with appropriate cardiac output, resulting in clinical symptoms. Cardiac damage, such as from increased afterload or preload or myocardial infarction, leads to cellular, structural, and neurohumoral changes. The primary pathophysiological mechanisms underlying heart failure include reduced sensitivity to natriuretic peptides and activation of the RAAS (renin-angiotensin-aldosterone system) and sympathetic-adrenergic system, ultimately leading to adaptive mechanisms manifested by tachycardia, volume overload, and worsening cell function. Cellular dysfunction is evidenced by increased levels of natriuretic peptides such as NT-proBNP and levels of neurohormones such as noradrenaline. Increasing the level of natriuretic peptides by blocking their degradation with neprilysin leads to a series of biological actions that improve cardiac function. A relatively new drug combining valsartan and sacubitril, acting as a neprilysin inhibitor, offers new possibilities in heart failure pharmacotherapy by intensifying RAAS blockade and enhancing the effectiveness of natriuretic peptides while limiting side effects [1,2].

The main risk factors for heart failure include hypertension, diabetes, obesity, coronary artery disease, positive family history of heart disease, metabolic disorders, alcohol abuse, and pharmacotherapy with cardiotoxic drugs.

### 2. Methodology

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included pathophysiology of heart failure; natriuretic peptide pathways; treatment of heart failure; sacubitril/valsartan.

### 3. State of knowledge

Natriuretic peptides (NPs) are primarily responsible for natriuresis and vasodilation. We can distinguish atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). All these peptides are synthesized as pre-prohormones [3,4].

Increasing concentrations of circulating natriuretic peptides are considered a significant compensatory mechanism in heart failure, leading to a reduction in effective blood volume and peripheral vascular resistance. Natriuretic peptides counteract the adverse effects of sodium-retaining systems in heart failure, making them the subject of research into their use in treating this condition [3].

Recently, a combination of neprilysin inhibitor and angiotensin receptor antagonist (ARNI) has been developed, namely sacubitril/valsartan. The first reports on this substance appeared in 2010 [5,6]. This is a two-component drug consisting of sacubitril (NEP) and valsartan (ARB) in a 1:1 ratio. This enabled intensification of the RAAS blockade and the effectiveness of natriuretic peptides while limiting side effects.

## 4. Heart failure

According to the definition proposed by the European Society of Cardiology (ESC) in 2016, heart failure is characterized by a spectrum of clinical symptoms such as dyspnea, fatigue, reduced exercise tolerance, and peripheral edema, most commonly manifested as lower extremity edema, accompanied by deviations in physical examination, such as lung crackles and elevated jugular venous pressure. These symptoms are caused by disorders in the function and/or structure of the heart, leading to decreased cardiac output and/or increased intracardiac pressure at rest or during exertion [7].

The most common pathology underlying heart dysfunction is impaired systolic and/or diastolic function. Other causes may include conduction disorders, rhythm disturbances, and abnormalities within the atria, pericardium, or valves. Identifying the underlying cause of heart failure is essential in diagnosis and further therapy, including reducing heart rate in patients with tachycardia-induced cardiomyopathy, repairing valvular defects, or appropriately selecting pharmacotherapy in HFrEF.

The diagnosis of heart failure involves non-invasive methods such as echocardiography, measurement of NT-proBNP levels, or MRI, as well as invasive procedures such as biopsy or cardiac catheterization. On the other hand, therapeutic options can be divided into interventional and surgical methods, as well as pharmacotherapy, which includes the use of beta-blockers, ACE inhibitors, and ARNI.

The New York Heart Association (NYHA) has developed a scale for classifying the clinical severity of heart failure based on various levels of patient physical activity. The American Heart Association (AHA) and the American College of Cardiology (ACC), on the other hand, have proposed a classification that combines the clinical symptoms of heart failure, accompanying diseases, and risk factors [1,2,7].

### 4.1. Heart failure classification

Heart failure can be divided into left ventricular and right ventricular, but also based on the ejection fraction of the left ventricle, we can divide it into: with reduced ejection fraction (HFrEF, systolic heart failure;  $EF < 40\%$ ), with preserved ejection fraction of the left ventricle (HFpEF, diastolic heart failure;  $EF > 50\%$ ), with mildly reduced ejection fraction (HFmrEF,  $EF 40-49\%$ ). Patients with HFpEF are most commonly obese, elderly, female individuals, who have a history of atrial fibrillation and/or hypertension. Patients with HFrEF are most commonly affected by mitral valve regurgitation, aortic valve stenosis, uncontrolled hypertension, coronary artery disease, or myocardial infarction.

### 4.2. Pathophysiology of heart failure

Adaptive cardiac remodeling depends on comorbidities, risk factors, and damaging factors such as NSAIDs, cardiac muscle stress, and high heart rate. We can divide it into concentric remodeling occurring due to pressure overload, aortic valve stenosis, eccentric remodeling resulting from volume overload, myocardial infarction, and a combination of both. Eccentric remodeling of the heart is involved in the pathomechanism of HFrEF, leading to chamber dilation and volume overload. Volume overload most commonly occurs due to sustained activation of the neurohumoral RAAS system. Concentric remodeling of the heart and/or chamber hypertrophy are involved in the pathomechanism of HFpEF, resulting in pressure

overload and backward failure. In this type of failure, we observe increased chamber stiffness, elevated filling pressure, and impaired relaxation and/or chamber filling.

Understanding the differences in the pathophysiology of HFrEF and HFpEF ensures appropriate therapy selection. Evidence-based therapy exists only for HFrEF. HFpEF is characterized by cellular and structural changes resulting in the inability of the left ventricle to relax properly due to factors such as cardiomyocyte hypertrophy, inflammation, altered cardiomyocyte relaxation, or interstitial fibrosis. HFpEF often coexists with hypertension, obesity, type 2 diabetes, sleep apnea, gout, liver diseases, or lung diseases.

Clinical symptoms mainly differ based on the area of heart dysfunction. Dysfunction of the left ventricle leads to increased pressure in the pulmonary vessels (backward failure). As a result, pulmonary congestion occurs, manifesting as dyspnea and tachypnea. Decreased peripheral circulation leads to peripheral anemia and kidney dysfunction. Constant activation of neurohumoral systems results in ascites, hepatomegaly, lower limb edema, acrocyanosis, exertional and resting tachycardia, and worsening cardiovascular function. Anemia of a moderate degree (below 12g/dl in women and below 13g/dl in men) is often present in patients with heart failure regardless of the type (HFrEF, HFpEF). It is more common in patients with renal failure, diabetes, older individuals, and women. Anemia is favored by reduced iron and vitamin B12 absorption, therapy with acetylsalicylic acid, or oral anticoagulants. The impact of iron deficiency and anemia has not been fully understood yet, hence it is unknown whether it affects the prognosis of heart failure or serves as an indicator of severity. In patients with heart failure, intravenous ferric carboxymaltose improved quality of life and NYHA class, regardless of the presence of anemia. However, it did not affect the patient prognosis.

Chronic kidney disease negatively affects the prognosis of patients with heart failure. Patients with chronic kidney disease are often excluded from clinical trials, which limits access to evidence-based therapy.

Disorders in carbohydrate metabolism worsen the prognosis of patients with heart failure. It has been proven that metformin therapy in patients with heart failure is safe and effective. It has been hypothesized that SGLT2 inhibitors slow down the progression of heart failure by alleviating cardiotoxicity [1,2,7,8].

#### 4.3. Neurohormonal pathways

In the early stages of heart failure development, cellular and molecular adaptive mechanisms are activated, as well as compensatory mechanisms such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, maintaining circulatory homeostasis by intensifying peripheral vasoconstriction and supporting cardiac function. Prolonged activity of both systems leads to the progression of heart failure [3].

Through the activation of beta-adrenergic receptors, the level of catecholamines increases. This leads to an increase in intracellular calcium concentration, which in turn leads to increased contractility. In the longer term, catecholamines cause increased oxygen demand by the cardiac muscle, activation of hypertrophy signaling pathways and cell death, and predispose to life-threatening arrhythmias. Continuous neurohormonal activation affects cell functions through the Frank-Starling mechanism (force generation induced by stretching), the Bowditch effect (force generation induced by frequency), as well as intercellular and structural interactions (fibrosis, hypertrophy) [2].

## 5. Pharmacotherapy in heart failure

At present, there exist seven categories of medications that have demonstrated improved clinical outcomes in heart failure with reduced ejection fraction (HFrEF), namely: inhibitors of the renin-angiotensin system (RAS), angiotensin receptor neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), beta-blockers, If-channel inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors and soluble guanylate cyclase stimulators [9].

Until recently, the goal of pharmacotherapy has been to reduce sympathetic nervous system activity by using beta-blockers and to reduce the activity of the renin-angiotensin-aldosterone system (RAAS) by using angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and mineralocorticoid receptor antagonists (MRAs). Despite such pharmacotherapy, the quality of life and prognostic outlook for heart failure patients experiencing disease exacerbation has been low [3]. In the Framingham cohort study, it was shown that 62% of men and 42% of women died within 5 years of being diagnosed with heart failure [10].

A potentially beneficial solution to improving the quality of life for heart failure patients may be the inhibition of bradykinin degradation, which can inhibit cell growth and division, and support vasodilatory and fibrinolytic effects, thereby enhancing the action of ACE. Unfortunately, increased bradykinin levels are associated with adverse effects such as angioedema, hypotension, rash, or cough [11].

## 6. Natriuretic peptides (NPs)

Another promising substance that may help in the treatment of heart failure is natriuretic peptides (NP).

### 6.1. A-type natriuretic peptide (atrial natriuretic peptide, ANP)

In humans, pre-proANP consists of 151 amino acids. Following cleavage of the N-terminal signal sequence, the resulting proANP is 126 amino acids long, predominantly stored in atrial granules. Upon secretion, proANP undergoes rapid cleavage by a transmembrane cardiac serine protease, yielding a biologically-active C-terminal 28-amino acid peptide and an inactive fragment (98 amino acids) of the ANP prohormone, known as N-terminal proANP (NT-proANP). An alternative processing pathway involving an unidentified protease in the kidney produces a 32-residue peptide called urodilatin, which may play a role in regulating renal sodium and water excretion [12].

ANP is mainly stored in the atria, while in lower concentrations, it is present in the ventricles of the heart and the kidneys. The primary stimulus for ANP release is increased intravascular pressure or transmural pressure resulting in atrial wall stretching. This can lead to the biosynthesis and expression of ANP in the heart ventricles in heart failure. Stimulation of the vagus nerve associated with cardiac mechanoreceptors or reflexes from baroreceptors regulates the production and release of ANP from the heart. Upon release, ANP enters the coronary sinus, facilitating distribution to various target organs.

In healthy individuals, the serum concentration of ANP is 10 fmol/ml (20 pg/ml). In patients with heart failure, this level is positively correlated with the severity of the disease and can be 10-100 times higher. Serum ANP levels correlate with the severity of heart failure symptoms. ANP and NT-proANP are used to diagnose asymptomatic left ventricular dysfunction [4,12].

## 6.2. B-type natriuretic peptide (BNP)

BNP is produced as a pre-prohormone consisting of 134 residues. It includes a signal sequence that is cleaved, yielding a 108-amino acid prohormone (proBNP). proBNP is produced in cardiomyocytes. It undergoes cleavage between residues 76 and 77 by enzymes (corin or furin), resulting in the formation of the biologically active 32-amino acid BNP and a 76-amino acid N-terminal peptide (NT-proBNP) [13,14]. proBNP, BNP and NT-proBNP are discharged by the heart and circulate within the human body. Human BNP comprising 32 amino acids.

In patients with heart failure, BNP(1-32) is present in small quantities in peripheral plasma. After an incubation period under the influence of the enzyme dipeptidyl peptidase IV (DPP IV), it is rapidly converted to BNP(3-32) or BNP(8-32) by removing the N-terminal dipeptide serine-proline from BNP. These reduced forms are responsible for the decreased vasodilatory, diuretic, and natriuretic response, as well as for the increased excretion of cGMP in urine [13]. Like ANP, BNP is stored in granules in the atria, but unlike ANP, it is not stored in ventricular granules. Stretching of the heart wall due to transmural gradient or volume overload leads to the production of BNP in the ventricles. In healthy individuals, the serum level of BNP is about 1 fmol/mL (3.5 pg/mL), while NT-proBNP is around 51 pg/mL. Heart failure causes a 100-fold increase in the concentration of BNP and NT-proBNP. Both peptides serve as prognostic markers for chronic heart failure and play a role in "rule-out" tests in the diagnosis of heart failure. The cut-off values for chronic heart failure are 125 pg/mL for NT-proBNP and 35 pg/mL for BNP, and for acute heart failure, they are 300 pg/mL for NT-proBNP and 100 pg/mL for BNP [15].

## 6.3. C-type natriuretic peptide (CNP)

The C-type natriuretic peptide is synthesized in the endothelium and in the kidney and is a ligand for the receptor guanylate cyclase-B (GC-B, NP2), stimulation of which leads to the production of cGMP [16]. The pathway involving CNP, GC-B, and cGMP is responsible for stimulating angiogenesis, inhibiting fibrosis and smooth muscle proliferation, dilating venous vessels and microcirculation, as well as exerting anti-inflammatory actions [17,18].

## 6.4. Natriuretic peptide receptors

There are known to be 3 proteins that bind natriuretic peptides. These include receptors type A (NPR-A), B (NPR-B), and C (NPR-C). Only type A and B receptors mediate the biological effects of natriuretic peptides. mRNA of NPR-A shows strong expression in the aorta, lungs, adipose tissue, adrenal glands, kidneys, and the distal segment of the small intestine. Type B receptor exhibits strong expression in fibroblasts.

Natriuretic peptides, by binding to the NPR-A receptor, activate the secondary messenger cGMP. Further cGMP signaling occurs through protein kinase G (PKG) and serine-threonine kinases activated by cGMP binding. As a result, natriuretic peptides induce a variety of actions. The coupling between ANP and NPR-A seems to be suppressed in heart failure [3,4,16].



## 7. The mechanism of action of natriuretic peptides and their biological effects

Natriuretic peptide type A (ANP) and type B (BNP) exhibit pleiotropic cardiovascular, renal, metabolic, and hormonal effects through guanylate cyclase A receptors (GC-A) and cGMP. ANP and BNP stimulate guanylate cyclase molecular A (GC-A, NP1) receptor. As a result, the secondary messenger cyclic guanosine monophosphate (cGMP) is produced, which mediates the biological actions of ANP and BNP. The main action is the inhibition of the sympathetic nervous system, the renin-angiotensin-aldosterone (RAA) axis, AVP, and endothelin, vasodilation, inhibition of apoptosis and hypertrophy of heart myocytes, and stimulation of vascular regeneration. Activation of GC-A/cGMP also leads to lipolysis, increased formation of high-density lipoproteins (HDL), and facilitation of glucose absorption by regulating the secretion and sensitivity of cells to insulin and the release of adiponectin [16,17,18]. Moreover, in cultured adipocytes, atrial natriuretic peptides (ANP) and BNP stimulate lipolysis and increase the synthesis and secretion of adiponectin [19,20].

Natriuretic peptides decrease renin secretion, thereby influencing blood pressure regulation, increase glomerular filtration rate (GFR) by raising the pressure in the glomerular capillaries (dilation of afferent arterioles and constriction of efferent arterioles), leading to increased glomerular filtration, enhance renal blood flow, inhibit the Na<sup>+</sup>/H<sup>+</sup> exchanger in the collecting duct, inducing natriuresis, inhibit AVP-induced aquaporin-2 incorporation into collecting ducts' apical membrane, causing diuresis, and restrict water and sodium reabsorption throughout the nephron - in the proximal tubules, it inhibits water and sodium transport via angiotensin II, and inhibits the amiloride-sensitive sodium channel, reducing sodium reabsorption in the collecting ducts [3,4].

They also directly inhibit aldosterone production in the adrenal glomeruli. Research data suggest that ANP inhibits cardiomyocyte hypertrophy induced by endothelin-1 and angiotensin II [21].

In the heart, they are responsible for reducing both preload and afterload, inhibiting fibroblast hypertrophy, and decreasing cardiac output due to the reduction of preload [3]. Natriuretic peptides also exhibit antifibrotic, anti-inflammatory, and antihypertrophic effects in vitro in cardiomyocytes or cardiac fibroblasts [19].

All natriuretic peptide receptors exhibit significant expression levels in the lungs. ANP stimulates the dilation of pulmonary blood vessels and airways. ANP and BNP reach elevated levels in patients suffering from pulmonary hypertension, thus serving as indicators of increased right ventricular strain [4].

## 8. The application of natriuretic peptides in pharmacotherapy

Despite high serum levels of ANP and BNP, heart failure is essentially characterized by a deficiency of natriuretic peptides (NPs). An additional factor conditioning the development of heart failure is the desensitization of the GC-A receptor [16].

Chen et al. conducted an 8-week randomized, double-blind study involving subcutaneous injections of BNP twice daily compared to placebo in patients with HFrEF. This approach resulted in a reduction in left ventricular systolic and diastolic volumes, left ventricular mass, inhibition of serum renin activity, preservation of glomerular filtration rate (GFR), and an increase in serum cGMP levels. This study contributed to deepening our understanding of the impact of natriuretic peptides and their application in the pharmacotherapy of heart failure [16,22].

Sensitivity to natriuretic peptides such as ANP and BNP decreases during the development of heart failure, which may be due to a reduced number of receptors for natriuretic peptides or increased NEP activity leading to increased clearance of BNP. Another factor playing a role in heart failure may be increased phosphodiesterase 5 (PDE5) activity, which breaks down cGMP [19,23,24].

## 9. Neprilysin (NEP)

Natriuretic peptides are degraded through enzymatic cleavage by neutral endopeptidase or neprilysin, as well as through internalization by the NPR-C receptor, leading to lysosomal degradation. Neprilysin is an enzyme belonging to the group of zinc-dependent extracellular proteases. It is expressed on the cell membrane and exhibits a wide tissue distribution and broad substrate specificity. It cleaves substrates on the amino-terminal side of hydrophobic residues [3,4]. The substrates for neprilysin include active biological natriuretic peptides, angiotensin II, endothelin, adrenomedullin, substance P, glucagon, bradykinin, vasoactive intestinal peptide (VIP), and amyloid  $\beta$  peptide [19,25]. In the case of ANP, initially, it breaks the ring and deactivates the peptide between residues Cys7 and Phe8. BNP is degraded between M5-V6 and R17-I18 [25,26].

Inhibition of neprilysin leads to a reduction in the degradation of natriuretic peptides, thereby increasing their concentration. It also increases the level of vasoconstrictive angiotensin II by impairing its metabolic clearance and raises serum levels of angiotensin I, aldosterone, and catecholamines [3,4]. The NEP inhibitor, without altering vascular resistance, enhances the natriuretic effect of ANP [19].

## 10. Sacubitril/valsartan (LCZ696)

Recently, a combination of neprilysin inhibitor and angiotensin receptor antagonist (ARNI) such as sacubitril/valsartan has been developed. Administration of sacubitril/valsartan increases the natriuretic peptide BNP and reduces the N-terminal pro-brain natriuretic peptide NT-proBNP. Natriuretic peptides bind to the receptor C of natriuretic peptide (NPR-C) and then are degraded by neprilysin and eliminated from circulation [19]. Neprilysin exhibits greater affinity for atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) than for B-type natriuretic peptide (BNP) [26].

The use of sacubitril/valsartan reduces the degradation of natriuretic peptides, contributing to the limitation of natriuresis resistance caused by any of the above-mentioned mechanisms. Taking sacubitril/valsartan led to an increase in the concentration of B-type natriuretic peptide and cyclic guanosine monophosphate (cGMP) [19].

Valsartan is an angiotensin receptor inhibitor responsible for reducing aldosterone production, decreasing vascular constriction, and blocking vascular and adrenal AT1 receptors, leading to increased natriuresis. Additionally, by reducing inflammation, fibrosis, and hypertrophy involving AT-1 receptors, mineralocorticoid receptors, or aldosterone, it causes a reduction in heart, kidney, and vascular damage [27]. Sacubitril is a neprilysin inhibitor in the form of a prodrug [(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester] [28].

### 10.1. Dosage of sacubitril/valsartan

To minimize the risk of angioedema, it is recommended to observe a washout period of at least 36 hours after the last dose of ACE inhibitors before initiating sacubitril/valsartan (this precaution is unnecessary if the patient has been receiving an ARB). Sacubitril/valsartan is an oral medication administered twice daily, available in three doses in most countries: 24/26mg, 49/51mg, and 97/103mg (the target dose). Previous use and tolerance of ACE inhibitors or ARBs assist in determining the appropriate starting dose of ARNI. According to the American College of Cardiology Expert Consensus Decision Pathway, patients should begin with the 49/51mg dose if they tolerate the equivalent of enalapril 10mg twice daily or valsartan 160mg twice daily. Patients who are new to RAS blockers, tolerate less than this dose or have severe renal dysfunction or moderate hepatic dysfunction should initiate treatment with the 24/26mg dose.

In clinical practice, dose escalation towards the target dose of 97/103 mg may occur every 2–4 weeks, contingent upon tolerability as evaluated by symptoms of blood pressure, hypotension, potassium levels, and renal function. Sacubitril/valsartan appears to have a "diuretic-sparing" effect, and the dosage of loop diuretics may need to be decreased during or after titration. In the case of patients with euvoemia, it may be advisable to reduce the dosage of diuretics before initiating or transitioning to sacubitril/valsartan. Discontinuing other antihypertensive medications that have not been shown to improve clinical outcomes in HFrEF (such as nitrates, calcium channel blockers, and alpha-adrenoceptor antagonists) could facilitate the initiation of sacubitril/valsartan [29].

### 10.2. The application of sacubitril/valsartan in heart failure with reduced ejection fraction (HFrEF)

The Prospective comparison of ARNI with ACEI to Determine the Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) study compared the effectiveness of treating patients with heart failure. The study involved 8,442 patients with a mean age of 64 years (13% were women, 87% were men) with heart failure with reduced left ventricular ejection fraction ( $\leq 40\%$ ) and classified according to the severity of heart failure symptoms proposed by the New York Heart Association (NYHA) as class II-IV. Patients enrolled in the study had to have been stably treated with a beta-blocker and an ARB (1,892 individuals) or ACE inhibitors (6,532 individuals) for a minimum of four weeks prior to the study. Additionally, the concentrations of cardiac natriuretic peptides in the patients blood had to be no less than 150 pg/ml for BNP or no less than 600 pg/ml for NT-proBNP.

The patients were randomly divided into two groups, with one group receiving 200mg valsartan/sacubitril twice daily, while the other group received 10mg enalapril twice daily. At the time of randomization, 94% of the participants were taking beta-blockers, 82% were taking diuretics, and 58% were taking a mineralocorticoid receptor antagonist.

The median follow-up period was 27 months. Comparing the overall rates of death from cardiovascular causes or hospitalization due to worsening heart failure, the percentage of patients receiving valsartan/sacubitril was 21.8%, while for enalapril, it was 26.5%. This meant that the risk decreased by 20% compared to the control group ( $p < 0.001$ ). Mortality from other causes was significantly lower in the valsartan/sacubitril group (17%) compared to the enalapril group (19.8%) ( $p = 0.0009$ ). No significant differences were observed between the two study groups in terms of new episodes of atrial fibrillation or worsening renal function. A significant correlation was noted between treatment response and NYHA class at

randomization ( $p=0.03$ ). The use of valsartan/sacubitril compared to enalapril significantly improved the results of the Kansas City Cardiomyopathy Questionnaire (KCCQ) ( $p=0.001$ ), which measures physical limitations associated with heart failure and significantly reduced the risk of hospitalization due to heart failure by 21% ( $p<0.001$ ). The combination of neprilysin inhibitor and valsartan reduced the need for intensifying heart failure treatment and also reduced emergency department visits due to exacerbation of heart failure. Within 4 weeks of starting sacubitril/valsartan treatment, a decrease in serum NT-proBNP concentration was observed.

The PARADIGM-HF study showed that the incidence of hyperkalemia, defined as a blood potassium concentration  $>6$  mmol/L, and renal dysfunction, defined as a serum creatinine concentration  $\geq 2.5$  mg/dL, occurred more frequently with the use of enalapril. The incidence of cough was lower in the groups receiving valsartan/sacubitril (11.3%) compared to the enalapril group (14.3%) ( $p<0.001$ ). As a result of neprilysin inhibition, despite a slight increase in the urinary albumin-to-creatinine ratio (UACR), the decline in estimated glomerular filtration rate (eGFR) was slower than with enalapril [19,30].

#### 10.3. The application of sacubitril/valsartan in heart failure with preserved ejection fraction (HFpEF)

In the PARAMOUNT study (Prospective comparison of ARni with ARB on Management Of heart failUre with preserved ejectionN fracTion) conducted by Solomon et al., the impact of valsartan/sacubitril was analyzed in a group of patients with heart failure classified as II-IV according to NYHA and with NT-proBNP concentration above 400 pg/ml and preserved ejection fraction (minimum 45%). Patients received a placebo initially for 2 weeks before randomization. Subsequently, randomized groups were created, with one group receiving 160 mg of valsartan twice daily, while the other group received 200 mg of valsartan/sacubitril twice daily. The endpoint was defined as the reduction of NT-proBNP concentration, which is not a substrate of neprilysin. The mean age of the subjects was 71 years, with 43% being male and 57% female. Before randomization, 39% of the subjects were taking ARBs, and 54% were taking ACE inhibitors.

After 12 weeks, the NT-proBNP concentration in the group receiving valsartan/sacubitril was significantly lower than in the group receiving valsartan alone ( $p=0.005$ ). However, this difference did not persist after 36 weeks. Another benefit in the group receiving valsartan/sacubitril compared to the group receiving valsartan alone was a reduction in left atrial size by an average of 4.6 ml (in the valsartan group, left atrial size increased by an average of 0.37 ml) ( $p=0.003$ ). This suggests that valsartan/sacubitril may improve left ventricular filling pressures [31].

#### 10.4. The application of sacubitril/valsartan in patients with diabetes

Docherty et al. in their studies deepened the existing knowledge regarding the use of sacubitril/valsartan, indicating potential indications for use, including in patients with concomitant diabetes [29].

Diabetes coexists with heart failure with reduced ejection fraction in approximately 30-45% of patients. Diabetes worsens the prognosis of patients and is associated with higher morbidity and mortality. One of the targets of neprilysin is glucagon-like peptide-1 (GLP-1), and preventing the degradation of this peptide could lead to a decrease in blood glucose levels. In

the PARADIGM-HF trial, administration of sacubitril/valsartan led to a more substantial decrease in glycated hemoglobin (HbA1c) compared to enalapril in patients with established diabetes mellitus or those with an HbA1c level of  $\geq 6.5\%$  at baseline (with a between-group reduction of  $0.14\%$ , 95% CI  $0.06-0.23$ ,  $p=0.0055$ ). Moreover, the attenuation of the decline in estimated glomerular filtration rate (eGFR) over time, which was more pronounced in patients with diabetes compared to those without, was mitigated by sacubitril/valsartan (to a comparable extent as in individuals without recognized diabetes) ( $p$  for interaction= $0.038$ ) [29,32].

### 10.5. Potential Future Applications

Ongoing studies are investigating the clinical efficacy of sacubitril/valsartan in patients with HFpEF (PARALLAX) [33,34] and acute myocardial infarction (PARADISE-MI) [29,35]. Sacubitril/valsartan may also find a place in the pharmacotherapy of systolic dysfunction in cardiotoxicity caused by doxorubicin due to its cardioprotective properties [36]. However, these applications require further exploration of knowledge and research.

### Conclusions

Sacubitril/valsartan has become a pivotal component of comprehensive disease-modifying medical therapy for managing chronic HFrEF. Results from the PARAGON-HF trial demonstrated that sacubitril/valsartan decreased the incidence of total heart failure hospitalizations and cardiovascular mortality compared to valsartan. Clinical advantages were also evident in secondary endpoints such as quality of life and kidney function. Particular benefits were especially observed in female patients and those with reduced LVEF. Additionally, sacubitril/valsartan also reduced the need for intensification of heart failure treatment. The safety profile of sacubitril/valsartan remained largely consistent with previous trial findings.

Regulatory evaluation for the use of sacubitril/valsartan in the treatment of HFpEF is currently in progress. The PARAMOUNT trial conducted so far provides us with information that sacubitril/valsartan affects the reduction of left atrial size. In the case of patients burdened with diabetes, sacubitril/valsartan lowers glycated hemoglobin levels, contributing to its selection in the pharmacotherapy of heart failure in diabetic patients.

The following years are expected to witness broader adoption of this therapy in clinical practice and potential expansion of its therapeutic indications, for example, usage of this medication in the treatment of acute myocardial infarction.

### Author's contribution

Conceptualization Kamila Babkiewicz-Jahn, Justyna Matuszewska; methodology Wiktoria Wilanowska; software, Karolina Maliszewska; check, Izabela Oleksak and Karolina Maliszewska; formal analysis, Adrianna Szymańska; investigation, Kamila Babkiewicz-Jahn and Wiktoria Wilanowska; resources, Justyna Matuszewska; data curation, Adrianna Szymańska; writing – rough preparation, Kamila Babkiewicz-Jahn; writing – review and editing, Adrianna Szymańska and Justyna Matuszewska; visualization, Natalia Załęska;

supervision, Wiktoria Wilanowska and Natalia Załęska; project administration, Izabela Oleksak; receiving funding, Kamila Babkiewicz-Jahn.

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