Progress in study on natriuretic peptides

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Abstract

Natriuretic peptides (NP) are hormones mainly involved in the regulation of water and electrolyte balance and the regulation of cardiovascular function. So far, six classic NPs have been described: type A natriuretic peptide, urodilatin, type B natriuretic peptide, type C natriuretic peptide, type D natriuretic peptide and uroguanylin. The family of natriuretic peptides also includes osteocrin and musculin, which have different metabolic activities. NP carry out their biological activities by interacting with three membrane receptors. The bioavailability of these compounds is regulated, among others, by neprilysin. Plasma NP concentrations change during many diseases. The most important of these include heart failure (HF). The guidelines of the European Society of Cardiology indicate that the determination of plasma peptide concentrations is helpful in the diagnosis of HF.

Understanding the physiology of natriuretic peptides has led to the search for new drugs that would mimic their beneficial effects. In addition to the beneficial effects of natriuretic peptides on the cardiovascular system, it has been shown that these compounds are involved in the regulation of many other metabolic processes — among others in the regulation of the center of hunger and satiety in the hypothalamus.

The purpose of this work is to present the definitions, history, mechanisms of natriuretic peptides, as well as their role in human physiology and pathology and to present clinical issues related to these hormones.

Key words: natriuretic peptides, cardiovascular system, heart failure, cardiovascular diseases

Definition of natriuretic peptides

Natriuretic peptides (NP) are oligopeptide hormones mainly involved in the regulation of water and electrolyte balance and the regulation of cardiovascular system. So far, six NPs have been identified in the human body. The family of NP includes atrial natriuretic peptide (ANP), urodilatin (URO; known as renal natriuretic peptide), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), D-type natriuretic peptide (DNP) and uroguanylin [1, 2]. This family also includes osteocrin (OSTN) and musculin, which are not typical NPs but they interact with their receptors [3, 4].

There are three types of receptors for NP: natriuretic peptide receptor type A (NPR-A) or guanylate cyclase A (GC-A), which binds ANP and BNP and urodilatin; natriuretic peptide receptor type B (NPR-B), which is highly specific for CNP, and natriuretic peptide receptor type C (NPR-C), which interacts with ANP, BNP, URO and CNP [5].

Historical background

The history of NP dates back to 1956, when Kish et al. [6] carried out research with the use of electron microscope and described granules present in atrial cardiomyocytes,
which proved to be similar to granules in endocrine glands. In 1964, Jamieson and Palade found that some atrial cardiomyocytes contained secretory granules [7]. Then, in 1981, de Bold et al. [8] demonstrated that intravenous administration of atrial homogenate to rats clearly increased diuresis and natriuresis and significantly decreased blood pressure. Further works were carried out to isolate a chemical substance from that extract, which was called an atrial natriuretic peptide [8]. ANP was therefore the first NP described. Another NP discovered was BNP, which was first isolated from the brain of pigs by Sudoh in 1988. CNP was another NP discovered by Sudoh in 1990 during the research on pig brain extracts [9]. In 1988, Shultz-Knappe et al. discovered and described URO [10]. The discovery of another NP — DNP, took place in 1992 [11]. Urogauylin was discovered in rats in 1992, whereas a year later, it was found in opossums [12]. Musculin was discovered by Nishizawa et al. in 2003 [4]. In the same year, OSTN was discovered by Thomas et al. [3].

**Epidemiology of cardiovascular diseases in Poland and worldwide**

Cardiovascular diseases (CVD) are the main cause of death in Poland. Mortality from CVD is higher in women. According to the Central Statistical Office (GUS, Główny Urząd Statystyczny), in 2015, CVD caused 51% of deaths in women and 41% in men. The data concerning the European population indicate that CVD constituted 42% of all causes of death in men, and 52% in women [13]. Such a high prevalence of these diseases is caused by a number of conditions. First of all, it is worth noting that the prevalence of risk factors of CVD is high. According to the NATPOL 2011 survey, hypercholesterolemia is the most common CVD risk factor in Poland and affects 18 million people (61%) [14]. Secondly, there is little public awareness of CVD and the factors causing these diseases. Study reviews carried out by Surma et al. [15, 16] indicate that this low awareness concerns both young people and adults.

As a result of such a high prevalence of CVD risk factors and CVD themselves, researchers search for laboratory indicators (biomarkers) that would help in the early diagnosis of these conditions and enable more effective treatment. An example of such biomarkers is BNP; the determination of its level is recommended in patients with heart failure (HF) by the European Society of Cardiology (ESC) [17].

**Most common NPs**

All NPs known so far can be found in the human body. ANP reaches the highest plasma concentration — 10 ± 0.9 pM with a half-life of about 2 minutes. The second most frequent NP is CNP, which is characterized by a plasma concentration of 1.4 ± 0.6 pM and a half-life of about 3 minutes. The B-type natriuretic peptide reaches the plasma concentration of 1 ± 0.7 pM, and its half-life is about 20 minutes [18]. The concentrations of these NP undergo various changes in the course of diseases such as congestive heart failure or chronic renal failure [19]. Urodilatin and DNP are present in plasma in trace amounts [18].

**Place of biosynthesis of NP**

The biosynthesis of specific NP takes place in different tissues.

Atrial natriuretic peptide is a cyclic polypeptide comprising 28 amino acids. This peptide is mainly secreted by atrial cardiomyocytes. The ANP gene is NPPA (natriuretic peptide precursor A gene). The NPPA product is a prepro-ANP that undergoes posttranslation modification to pro-ANP, which in turn is stored in the secretory granules of atrial cardiomyocytes. After release from the cell, proANP undergoes proteolysis with the help of corrin (a serine protease), which results in biologically active ANP. The aforementioned corrin splits the so-called N-terminal proatrial natriuretic peptide (NT-proANP) [20]. NT-proANP produces three other biologically active peptides: long acting natriuretic peptide (LANP), kaliuretic peptide and vessel dilator peptide (Figure 1) [21, 22].

The stimulus for the secretion of ANP by atrial cardiomyocytes is the expansion of their walls due to increased pressure and increased frequency of heart contractions, particularly atrial contractions [23]. The release of ANP also increases in cases of hypoxia or hypernatremia, and under the influence of catecholamines, endothelin 1, angiotensin II, vasopressin, tumor necrosis factor alpha (TNF-α), prostaglandin F2α and vitamin D₃. Nitric oxide reduces ANP secretion [18].

Urodilatin is considered to be a renal degradation product in the form of diuretic ANP (it is an ANP homolog that is shorter by 4 amino acids). It is formed in the distal convoluted tubule and the collecting tubule in response to increased blood pressure and volume of extracellular fluid (EFC) [24].

The B-type natriuretic peptide is secreted mainly by ventricular cardiomyocytes and central nervous system (CNS) cells. It is made up of 32 amino acids. The BNP gene found in humans is called NPPB (natriuretic peptide precursor B gene). Under the influence of serine protease, preproBNP produces proBNP, which in turn is transformed into biologically active BNP with the help of the corrin enzyme [25]. N-terminal proB-type natriuretic peptide (NT-proBNP) is a by-product of the BNP formation (Figure 2).

A direct stimulator for the secretion of BNP is an increase in the ventricular pressure, which increases the expression of this peptide gene. Under experimental conditions, endothelin 1 has been shown to increase BNP secretion in rat hearts [18]. The BNP catabolism takes place with
the involvement of enzymes such as dipeptidyl-peptidase-IV (DPP-IV), neprilysin, and insulin-degrading enzyme (IDE). Dipeptidyl-peptidase IV degrades also NT-proBNP [26].

The C-type natriuretic peptide is produced by the CNS, endothelium, heart, kidneys, and suprarenal gland cells and chondrocytes [27]. Originally it is formed as preproCNP, which is converted to proCNP by the serine protease. The intracellular enzyme furin (an endopeptidase) then cleaves the N-terminal pro-C-type natriuretic peptide (NT-proCNP), resulting in the formation of biologically active CNP 1-53. In some tissues, the CNP 1-53 is transformed into CNP 1-22. Both forms of CNP are biologically active, but differ in their location: CNP 1-53 occurs mainly in the brain, endothelial cells and the heart, while CNP 1-22 occurs in plasma and cerebrospinal fluid [19] (Figure 3).

The main factor stimulating the release of CNP by endothelial cells is the so-called shear stress, which is a sudden change in arterial pressure. Under experimental conditions, an increased release of CNP by endothelial cells is observed under the influence of bradykinin, TNF-α, interleukin 1-alpha, interleukin 1-beta, lipopolysaccharides as well as ANP and BNP [18, 19].
The D-type natriuretic peptide occurs in trace amounts in the human body in the myocardium and blood plasma [28].

Uroguanylin in the form of prouroguanylin is mainly synthesized by enterocytes. The main stimulus for its secretion is the consumption of foods containing sodium [29].

Osteocrin and musculin are secreted by bone cells (osteoblasts and young osteocytes) and skeletal muscle cells [3, 4].

**The NP action mechanism**

Natriuretic peptides function through interaction with membrane receptors. Thus far, three types of NP receptors have been identified and described (Table 1) [18, 19, 30].

The NPR-A and NPR-B are membrane receptors consisting of an extracellular domain combining NP, a transmembrane domain and an intracellular domain that activates the guanylate cyclase (GC). The cyclic guanosine monophosphate (cGMP) which is produced as a result of the GC function is a secondary messenger that activates protein kinase G (PKG). The PKG stimulation leads to the activation of biochemical pathways, which result in the regulation of cardiovascular system functioning. The NPR-C receptor, which is not associated with GC, is responsible for NP internalization and degradation NP inside the cell (in the lysosome). NP degradation is also catalysed by neutral endopeptidase (NEP, nepriylisin), which is dissolved in plasma and bound to the cell membrane. NEP is subject to various regulatory mechanisms.
— among others, it is inhibited by an increased concentration of BNP in plasma. Beside the NP catabolism, NEP is also involved in the metabolism of such compounds as endothelin 1, bradykinin, adrenomedullin and substance P [23]. Importantly, NEP also catalyzes the angiotensin I and angiotensin 1-9 transformation reaction into angiotensin 1-7. Angiotensin 1-7, through the Mas receptor, improves the functioning of the cardiovascular system [26].

The NPR-C receptor and NEP are therefore involved in regulating the NP bioavailability. Natriuretic peptides are compounds acting in the paracrine or endocrine mechanisms. Their effect is that they regulate the volume of ECF and blood pressure by increasing natriuresis and diuresis, and inhibit the renin-angiotensin-aldosterone system (RAA), the activity of the sympathetic nervous system, and the secretion of the antidiuretic hormone (ADH) and the adrenocorticotropic hormone, (ACTH) as well as reduce thirst and vasodilation [30]. The NP action mechanism and metabolism is presented in Figure 4.

**The NP importance for human physiology and pathology**

The NP discovery led to the development of knowledge on the functioning of the cardiovascular system. The NP abnormalities were initially linked with two conditions — hypertension and HF [31, 32]. Further research into the NP biochemistry and physiology have led to recognition of subsequent molecular mechanisms of their action and facilitated learning more about the pathogenesis of other CVDs [33, 34].

**Atrial natriuretic peptide and URO**

The action of ANP is multidirectional and mainly concerns the regulation of cardiovascular and renal functions. In the cardiovascular system, ANP regulates the response from baroreceptors and reduces the stimulation of the sympathetic nervous system. Moreover, the effect of ANP is the relaxation of smooth muscles of blood vessels due to increased activity of nitric oxide synthase which is dependent
on calcium ions and calmodulin. By increasing endothelial permeability, ANP regulates the volume of intracellular fluid. It has been proven recently that ANP reduces myocardial hypertrophy. It also reduces its fibrosis [34]. In kidneys, ANP leads to increased diuresis and natriuresis. To achieve these results, ANP affects many factors. By increasing the permeability of glomerular vessels, as it is well known, ANP increases the glomerular filtration rate (GFR). The A-type natriuretic peptide reduces the effects of the RAA system by reducing the Na⁺/K⁺-ATPase membrane activity, reducing the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) activity in the ascending limb of the loop of Henle and reducing the activity of the cyclic nucleotide-gated cation channels (CNGC) and the epithelial sodium channels (ENaC), as well as transient potential receptor cation channel subfamily V member 4 (TRPV4) in the renal collecting tubule [34, 35]. The reduced effects of aldosterone may also result from the fact that ANP reduces the secretion of ACTH by the pituitary gland, which to some, limited extent, stimulates the secretion of this mineralocorticoid by the glomerular layer of the adrenal cortex [36]. Increased diuresis also results from decreased ADH secretion by the posterior pituitary lobe [37].

It has been proven in experimental studies that the lack of ANP (NPPA) or NPR-A gene leads to hypertension and is associated with myocardial hypertrophy, which is independent of blood pressure levels [38]. Moreover, it has been demonstrated that the lack of NPR-A leads to sodium sensitive hypertension, while the duplication of this gene results in protection against the high salt content diet [39, 40]. Natriuretic peptides control the lipid metabolism through the antilipolytic effect [41]. It is worth noting that they promote the biogenesis of mitochondria in adipocytes and “browning” of white adipocytes [42]. The aforementioned antilipolytic effect is associated with a reduction in the activity of proprotein convertase subtilisin/ kexin type 9 (PCSK9) by ANP [43], which is responsible for the degradation of low-density lipoprotein receptor (LDLR) in hepatocytes [44]. By reducing the PCSK9 activity, the atrial natriuretic peptide, leads to an increase in the number of LDL receptors on the hepatocyte membrane surface, which results in a more efficient capture of circulating LDL [45]. A similar strategy of action has been demonstrated by new normolipemic medicines, such as evolocumab and alirocumab [46]. In the future, interest may shift to the observations of patients using AT1 receptor antagonists for angiotensin II receptor and neprilysin inhibitor [angiotensin receptor neprilysin inhibitor (ARNI)] in the context of LDL fraction cholesterol plasma concentration [47].

Proprotein convertase subtilisin/kexin type 6 (PCSK6) is a serine prosthesis. The PCSK6 gene mutation leads to sodium-dependent hypertrophy. This protease serves a corrin activator. Corrin is a transmembrane serine protease involved in the ANP activation. In cardiomyocytes, the precursor form of ANP — pro-ANP — is cleaved by corrin to produce ANP. Experimental studies have shown that the use of benznamidine (PCSK6 inhibitor) leads to the inhibition of corrin activation. A secondary deficiency of the biologically ANP results in increased natriuresis and blood pressure [48].

Urodailatin participates in water and electrolyte management. Unlike ANP, it has a purely paracrine mechanism. When blood pressure and volume increase, URO increases diuresis by increasing blood flow through the kidneys [27].

**B-type natriuretic peptide**

The physiological function of BNP is not as well examined as that of ANP. The results of the research indicate that BNP is involved in reducing the production and accumulation of collagen, thereby reducing fibrosis and ventricular wall remodeling. In addition, BNP has a diastolic effect on ventricular cardiomyocytes. Similarly to ANP, BNP reduces the activity of RAA by limiting vasoconstriction, as well as sodium and water retention in the kidneys [49].

**C-type natriuretic peptide**

The effect of this NP on the cardiovascular system is relatively little known. It causes both paracrine and endocrine effects. The main physiological function of CNP is to stimulate the development of long bones by affecting the chondrocyte functions. It has been proven that genetic defects associated with the CNP gene result in dwarfism. An increased expression of the CNP gene leads to skeletal hypertrophy [18, 19].

The diuretic effect caused by CNP is small despite the fact that the NPR-B receptors are located in the kidneys. CNP has a much more significant impact on the cardiovascular system. By reducing proliferation, fibrosis, collagen synthesis and multiplication of fibroblasts and myocytes, this peptide also has a significant role in the regeneration of vascular endothelial cells. It has also been shown that CNP has antiplatelet properties. Through the NPR-C receptor, it reduces platelet aggregation [50].

**D-type natriuretic peptide**

Due to trace amounts of DNP in the human body, its physiological function is not fully understood [18].

**Uroguanylin**

Uroguanylin is an NP involved in many physiological processes. This peptide uses both the endocrine and paracrine mechanisms. The secreted uroguanylin enters the kidneys through the blood stream, where it intensifies natriuresis in a GC-dependent and GC-independent mechanisms. The results of recent years’ research also suggest that uroguanylin has been involved in regulating appetite by interacting with the GUCY2C receptor in the hypothalamus. The effect of uroguanylin in the hypothalamus is the feeling of satiation [51, 52]. The results of experimental studies
on mice without the uroguanylin gene showed that these animals have significantly higher blood pressure than their wild counterparts, which is associated with reduced renal sodium excretion [53]. The clinical trials provided some evidence suggesting that uroguanylin has an influence on HF and renal failure [51].

Osteocrin and musculin
Osteocrin and musculin are not directly involved in water and electrolyte management. Osteocrin is involved in the vitamin D\textsubscript{3} management, while musculin is involved in glucose metabolism [3, 4]. Experimental studies have shown that OSTN reduces the concentration of osteocalcin and alkaline phosphatase, contributing to the reduction of bone mineralisation. Vitamin D\textsubscript{3} reduces the OSTN gene expression [54]. It has been demonstrated that OSTN, when combined with NPR-C, increases the NP bioavailability, which may limit the HF deterioration following a myocardial infarction [54]. In obese mice, an increase in musculin plasma concentration has been observed. Musculin reduces the insulin action, which may lead to the development of insulin resistance of tissues [4].

Reports from recent years indicate an important role of NP in cardiovascular system remodelling. The cellular effects of natriuretic peptides affect both myocardial and vascular cells and include processes such as proliferation, angiogenesis, apoptosis, fibrosis and inflammation of these cells [1].

Natriuretic peptides in cardiac diagnostics
The atrial natriuretic peptide, due to its shorter half-life and higher lability compared to BNP, is not routinely used as a HF biomarker. The recently described mid-regional pro-atrial natriuretic peptide (MR-proANP) is more stable and may turn out to be a more promising biomarker than ANP [55]. It is created when preproANP is converted into ANP. At present, MR-proANP measurement in plasma is treated on a par with the BNP and NT-proBNP determination on the list of biomarkers whose determination is recommended by ESC [17].

Numerous studies have shown that BNP and NT-proBNP concentrations have diagnostic and prognostic value in HF, therefore the latest ESC guidelines recommend BNP and NT-proBNP determinations in patients with suspected HF. It is worth mentioning that HF is a chronic disease, resulting in serious prognosis as well as social and economic consequences. In Poland, 600–700 thousand people suffer from HF. Its incidence in the general population is about 2.6% [56, 57].

Depending on the clinical symptoms and plasma concentrations of BNP and NT-proBNP, additional tests are recommended. It is important to remember about other clinical settings in which there are changes in NP plasma concentrations (Table 2) [58, 59].

In the absence of HF symptoms with concurrent BNP plasma concentration higher than or equal to 35 pg/mL and NT-proBNP higher than or equal to 125 ng/mL, the ESC guidelines indicate the need for an echocardiography. BNP and NT-proBNP concentrations are also therapeutically relevant. In patients with chronic heart failure and reduced left ventricular ejection fraction who use \(\beta\)-adrenolytics and angiotensin-converting enzyme inhibitor (ACE), an aldosterone antagonist (spironolactone, eplerenone) should be added if the plasma concentration of BNP exceeds 250 pg/mL or NT-proBNP is over 500 pg/mL in men and over 750 pg/mL in women. The ESC guidelines indicate that in the situation of persisting HF symptoms in patients treated with \(\beta\)-adrenolytic, ACE inhibitor and aldosterone antagonist, sakubitril/valsartan should be included instead of ACE inhibitor. The determination of BNP

Table 2. Clinical situations affecting plasma concentrations of natriuretic peptides (NP) (based on [58, 59])

<table>
<thead>
<tr>
<th>Factors increasing NP plasma concentration other than heart failure</th>
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<tr>
<td>Old age</td>
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<td>Left ventricular dysfunction</td>
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<td>Valvular defects (aortic stenosis, mitral regurgitation)</td>
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<td>Atrial fibrillation</td>
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<td>Arterial hypertension</td>
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<td>Kidney failure</td>
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<td>Acute coronary syndromes</td>
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<td>Lung diseases</td>
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<td>Cardiogenic syncope</td>
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<td>Pulmonary embolism</td>
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<td>Diseases with elevated cardiac output, such as hyperthyroidism</td>
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<tr>
<td>Medicines:</td>
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<tr>
<td>• digitalis glycosides</td>
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<td>• acetylsalicylic acid</td>
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<tr>
<th>Factors reducing NP plasma concentration</th>
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<tbody>
<tr>
<td>Overweight and obesity</td>
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<tr>
<td>Cardiac tamponade</td>
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<tr>
<td>Constrictive pericarditis</td>
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<tr>
<td>Sudden pulmonary oedema</td>
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<tr>
<td>Medicines:</td>
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<td>• diuretics</td>
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<td>• ACE inhibitors</td>
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<td>• allopurinol</td>
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<td>• amiodaron</td>
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<td>• sympathetic mimetic amines</td>
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<td>• vasodilators</td>
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<td>• statins (not quite proven)</td>
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<tr>
<td>• (\beta)-adrenolytics (at the beginning of therapy, chronic use increases concentration)</td>
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ACE — angiotensin-converting enzyme
and NT-proBNP concentrations is also recommended in the diagnostic algorithm for acute HF. In patients with dyspnea and suspected acute HF, in whom BNP concentration is lower than 100 pg/mL, NT-proBNP lower than 300 pg/mL and MR-proANP lower than 120 pg/mL, the diagnosis of this condition is unlikely [17, 37].

It is also worth mentioning that low concentrations of NT-proBNP and BNP in patients with HF indicate the improvement of heart function thanks to the interventions undertaken. Heart failure is often associated with atrial fibrillation, which itself occurs with higher BNP plasma concentrations [60, 61]. It happens that the BNP value does not differ between patients with HF and atrial fibrillation and patients with HF without atrial fibrillation [62]. In clinical practice, higher plasma concentrations of BNP should be taken into account to improve the specificity and probability of proper HF diagnosis in a person with atrial fibrillation [63].

BNP and NT-proBNP plasma concentrations may also be used in the assessment of the risk of death due to HF (BCN Bio-HF, Barcelona Bio-Heart Failure Risk Calculator) [17, 61].

Natriuretic peptides as drugs

The beneficial effects of NPs resulted in the testing of these agents as potential drugs in CVD therapy. Nesiritide is a recombinant human BNP. This drug alleviates symptoms associated with pulmonary stasis and dilates arterial and venous vessels, reducing preload. It has been demonstrated that nesiritide combined with conventional diuretic treatment results in significant decrease in dyspnea [64].

The indication for the use of nesiritide is exacerbation of congestive HF with symptoms of dyspnea at rest or during low activity (NYHA class III–IV). In the United States, nesiritide has been approved for the treatment of acute decompensated HF since 2001. Human recombinant ANP (carperetide) is also used in acute HF. A significant problem in the use of carperetide is the necessity of its continuous infusion due to short half-life [65]. The combination of CNP and 15-amino acid C-terminal fragment of DNP (cenderitide) is resistant to enzymatic degradation [66]. An analogue of ANP (MANP), a 40-amino acid peptide with 12-amino acid carboxylic end extension of ANP, is being developed [36]; MANP is more resistant to degradation than endogenous ANP. This compound has been studied under both experimental and clinical conditions, obtaining the evidence of antihypertensive effect. Further studies on the safety of therapy and other beneficial effects of MANP are underway [67]. It is worth mentioning that in phase I and II clinical trials the beneficial effects of synthetic URO (ularitide) were confirmed [68].

Recombinant human NPs are currently not registered in Poland.

The knowledge of the effects of NP led to the development of ARNI, a drug which is a combination of NEP inhibitor (sacubitril) and angiotensin II type 1 receptor inhibitor (valsartan). Decreasing NEP activity results, on the one hand, in increased bioavailability of NP and, on the other hand, reduces the amount of angiotensin 1-7. Valsartan, in turn, reduces the AT$_1$ receptor activity, increases the amount of angiotensin 1-7 produced and increases the AT$_2$ receptor stimulation (Figure 5) [17, 41]. The indication for the use of ARNI is symptomatic, chronic HF with reduced ejection fraction.

Currently, a preparation containing sacubitril and valsartan in one tablet is available in Poland.

Valentino et al. suggest [51] that in the future uroguananlylin may be used in obesity treatment.

Summary

Understanding the mechanisms of NP in recent years has led to the recognition of these peptide hormones as an important system regulating the functioning of the cardiovascular system and water and electrolyte management. These compounds intensify diuresis and natriuresis and dilate blood vessels. Moreover, the study revealed other beneficial effects of NP, such as reduction of fibrosis and cell proliferation. New drugs used in the CVD, such as ARNI, increase the bioavailability of NP. Recombinant NPs were synthetized for use in CVD therapy.
In HF laboratory diagnostics BNP and ANP are used as the most important NPs.

**Conflict of interest**

The authors declare no conflict of interest.

**References**


