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Pathological and clinical aspects of angiotensin receptor-neprilysin inhibitor in patients with congestive heart failure with reduced ejection fraction

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The current review article discusses the results of randomized clinical trials of angiotensin receptor-neprilysin inhibitor (ARNI) in patients with congestive heart failure. We explore the pathophysiologic basis of ARNI use and its effects on prognosis in patients with various heart failure phenotypes. We present evidence that support earlier initiation of ARNI in patients with decompensated heart failure after hemodynamic stabilization. ARNI tolerance and approaches to dose titration is also discussed.

Keywords: *congestive heart failure, pharmacologic therapy, angiotensin receptor-neprilysin inhibitor*

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Pharmacologic management of congestive heart failure (CHF) is still a relevant issue worldwide. CHF prevalence in the Russian Federation is higher than in western countries and reaches 7% in the general population with lethality in symptomatic patients around 12%. Identification of CHF phenotypes allowed to choose more personalized therapeutic strategies in patients with HF with reduced ejection fraction (HfrEF) and HF with preserved ejection fraction (HFprEF). In 1980-90s the understanding of CHF pathophysiology changed when the role of neurohumoral theory of development and progression of heart failure was shown. Today, the main groups of pharmacologic agents that all patients with CHF should get provide their positive effects by blocking various components of renin–angiotensin–aldosterone system (RAAS). RAAS inhibitor protective effects have been mostly shown in patients with HFrEF [1]. Lately, a new agent, angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan, was developed. Human neutral endopeptidase (neprilysin) inhibition increases concentration of natriuretic peptides, bradykinin and adrenomedullin. There are several types of natriuretic peptides: Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and urodilatin. Natriuretic peptides are polypeptides that have different amino- and carboxyl-terminal ends. Of all the peptides, BNP has the highest clinical value. That is due to the way it is secreted and metabolized. Urodilatin has local or autocrine signaling effects and isn't secreted into the bloodstream. Urodilatin is synthesized in the renal distal tubules and doesn't affect sodium reabsorption. Another NP plasma concentration, CNP, is low and it's metabolized at a high rate. CNP production by the endothelium is increased by various cytokines, growth factors and tumor necrosis factors [2]. Unlike BNP, ANP is less stable in plasma and has slower gene transcription in the setting of chronic atrial distention. ANP accumulates in high concentrations inside the cell and can be rapidly secreted to regulate electrolyte balance in the setting of increased preload. In patients with chronic myocardial distention BNP production is increased. BNP precursor, pro-BNP, is synthesized in cardiomyocytes and in mature myocardial fibroblasts. Intracellular enzyme furin cleaves pro-BNP into active BNP and biologically inactive N-terminal pro b-type natriuretic peptide (NTproBNP). BNP molecule consists of 32 aminoacids, NTproBNP – 76. Half-life of these compounds is 20 minutes for BNP and 120 minutes for NTproBNP [3]. Therefore, for CHF exclusion and assessment of treatment effectiveness in diagnosed CHF it is recommended to measure the levels of BNP precursor NT-pro-BNP. The main effects of ANP/BNP are presented int the following table 1 [4, 5, 6, 7].

NP are degraded by a zinc-dependent protease metalloproteinase – neutral endopeptidase – nepri-

Table 1. **Main effects of type A and B natriuretic peptides**

Organ	Effect
Kidney	Stimulate sodium ions and water excretion, water-electrolyte balance support via: Inhibition of antinatriuretic factors (angiotensin, noradrenalin) and suppression of pathologic water and sodium ions reabsorption in proximal tubule. Vasopressin suppression and reduction of sodium and chloride reabsorption in the loop of Henle; Sodium channels inhibition, sodium pump activity reduction, blockade of vasopressin cAMP-dependent effects, stimulation of sodium secretion in the terminal nephron. Increase of glomerular filtration rate (GFR) by afferent arteriole dilation and efferent arteriole constriction and mesangial cells relaxation and the creation of a larger effective filtration surface area.
Microcirculation	Increased endothelial cell permeability. Water and albumin migration into interstitial place and the reduction of circulating blood volume. Increased postcapillary resistance and microvascular pressure.
Heart	Improvement of LV diastolic function both in healthy individuals and patients with CHF because of cGMP suppression and changes in calcium intracellular metabolism, end-systolic pressure and volume reduction and end-systolic myocardial elasticity improvement. Increase of heart rate and sinoatrial and interatrial impulse conduction via the effects on NRP-A and NRP-C receptors. Sympathetic activity suppression and vagal effects stimulation with positive chronotropic and bathmotropic effects. Fibroblast proliferative and functional activity suppression. Pathologic myocardial remodeling reduction.
Arteries	Sympathetic activity suppression and vasodilation, NO secretion stimulation, angiotensin II effects inhibition (more in aorta, kidney arteries, pulmonary arteries, epicardial coronary arteries). Suppression of smooth muscle cells growth and proliferation.
Veins	Venous relaxation more prominent than arterial. Effects achieved at higher concentrations seen in CHF.
RAAS	Renin, angiotensin II and aldosterone antagonism
The autonomic nervous system (ANS)	Sympathetic nervous system antagonism (studied mostly for ANP)
Lipids and carbohydrate metabolism	Activate lipolysis. Reduce insulin resistance. Stimulate white adipose tissue conversion to brown adipose tissue. Affect insulin secretion via ATP-dependent potassium channels.

lysin, NEP). NEP is also involved in degradation of other vasoactive peptides such as ATI, ATII, endothelin 1, glucagon, enkephalins, oxytocin and bradykinin. Moreover, NEP degrades beta-amyloid and is the marker of various malignancies. Therefore, inhibition of NP degradation combined with ACEi positive effects resulted into the development of pharmacologic agents with double effect – vasopeptidase inhibitors. However, they haven't met all the expectations. Positive effects of omapatrilat in CHF patients were decreased by frequent angioedema cases [8-11]. Then, a new two-component molecule was developed, that consisted of NEP inhibitor neprilysin and ARB valsartan. This component choice was determined by the potential induction of clinical effects and angioedema risk reduction. PARADIGM-HF trial published in September 2014 has shown that 200 mg of sacubitril/valsartan twice per day was more effective in patients with NYHA class II-IV HFrEF compared with enalapril 10 mg twice per day (inclusion criteria: HFrEF, LVEF≤ 35 %). At randomization over 90% of patients were taking beta-blockers and only around 55% - mineralocorticoid receptor antagonists (MRA) (54.2% in treatment group and 57% in control group), 80% were taking diuretics. Patients were included in the trial if screening revealed NT-proBNP≥ 600 pg/mL or ≥ 400 pg/mL in patients who were previously hospitalized for CHF over the past 12 months. The trial included totally 10 513, 9419 were randomized, of those, 34% had concomitant diabetes. Most participants (around 70%) were classified as class II HF. Median follow-up time was 27 months. The trial was ended early because of obvious beneficial effects of sacubitril/valsartan. The main results of this trial are summarized in table 2 [12].

According to table 2, the use of sacubitril/valsartan was associated with statistically significant cardiovascular mortality reduction, hospitalization for CHF exacerbation and all-cause mortality compared with enalapril. Patients in sacubitril/valsartan group also had better quality of life 8 months after discharge. The review of Kansas City Cardiomyopathy Questionnaire (KCCQ) has shown that the standard deviation has decreased by 2.99±0.36 in sacubitril/valsartan group compared with 4.63±0.36 in the control group (p<0.001).

Drug tolerance was similar to enalapril. Although patients in sacubitril/valsartan group developed arterial hypotension more frequently (14%) compared with enalapril (9.2%), it didn't result in them stopping treatment or in any alterations of kidney perfusion. On the contrary, enalapril use was more often associated with kidney dysfunction and higher creatinine levels and was therefore stopped. PARADIGM-HF authors have concluded that neprilysin inhibitors combined with ARBs were more effective in patients with HFrEF compared with ACEi enalapril [12]. Later, in august 2018, the results of TRANSITION study that included 1124 patients (1002 were randomized) with HFrEF (LVEF 29%) were presented at the European Society of Cardiology congress; mean age was 67 years. More than a half of all patients had NYHA class II HF. The study has shown that earlier start of sacubitril/valsartan after CHF exacerbation in a still hospitalized patient was as effective and safe as sacubitril/valsartan initiation in the two weeks after discharge. More than 86% of patients from in-hospital treatment group continued the use of sacubitril/valsartan for up to 10 weeks and 45% of them reached target dose of 200 mg twice a day. Similar results were showed in the group where sacubitril/valsartan was started later during outpatient treatment – 88.8% (p=0.262) continued to use the drug until the end of the study and in 50.4% (p=0.092) target doses were reached. Sacubitril/valsartan was well tolerated. Hyperglycemia and hypotension happened in 0.6% and 0.8% of patients, respectively, in the group of early drug use and in 0.4% (p=0.1) and 0.4% (p=0.6866) of patients who started

Table 2. **PARADIGM-HF results**

Parameter	sacubitril/valsartan n=4187		enalapril n=4212		Relative risk (RR) (95 % confidence interval)	p
	Absolute values	%	Absolute values	%		
Primary composite outcome						
Cardiovascular death or first hospitalization for CHF exacerbation	914	21.8	1117	26.5	0.80 (0.73-0.87)	< 0.001
Cardiovascular death	558	13.3	693	16.5	0.80 (0.71-0.89)	< 0.001
First hospitalization for CHF exacerbation	537	12.8	658	15.6	0.79 (0.71-0.89)	< 0.001
Secondary outcome						
Death from any cause	711	17	835	19.8	0.84 (0.76-0.93)	< 0.001

to take sacubitril/valsartan during outpatient management [13]. Similar results were reported in the PIONEER-HF study that was presented at the 2018 American heart association congress [14]. Patients with LVEF≤40 %, signs and symptoms of CHF decompensation, SBP≥100 mmHg over the past 6 hours in the absence of symptomatic hypotension and the use of intravenous vasodilators in the past 6 hours and intravenous inotropic agents in the 24 hours before randomization. One of the inclusion criteria was an increased level of NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL. Most patients had a history of arterial hypertension: 87.3% in sacubitril/valsartan group and 83.7% in enalapril group; 6.1% of patients in sacubitril/valsartan group and 7.9% of patients in the control group had a history of myocardial infarction. Diabetes was present in 18% of patients in the treatment group and in 20.2% in enalapril group; chronic kidney disease – in 29.5% of patients in the treatment group and in 27.2% of patients in control group). Follow-up period was 8 weeks. Mean NT-proBNP values at different follow-up periods are presented in Table 3 [15].

According to the Table 3, use of sacubitril/valsartan during the 1st week resulted in a significant reduction of NT-proBNP, which means that early administration of this agent is associated with more positive effects in hospitalized patients. By the end on the trial the levels of NT-proBNP have reduced by 46.7%. The ratio of mean NT-proBNP levels taken on the 4th and 8th weeks and baseline values were 0.53 in sacubitril/valsartan group and 0.75 in enalapril group (difference ratio was 0.71; 0.95% CI 0.63-0.81; p<0.001). The use of sacubitril/valsartan was associated with 46% (RR 0.54, 95% CI 0.37-0.79; p=0.001) reduction of composite outcome risk (composite outcome included cardiovascular death or the hospitalization for CHF exacerbation, ventricular assist device implantation, getting on heart transplant waiting list, intravenous diuretics requirement, increase of diuretics dose by more than 50%, the need of additional medications for CHF). Lower risk of composite outcome in sacubitril-valsartan group was primarily due to significantly lower frequency of repeated hospitalizations for CHF – 35 (8%) versus 61 (13.8%). In sacubitril/valsartan group, 51 patient (11.5) left the trial early due to adverse effects of the medication, in enalapril group – 45 (10.1%), mainly because of symptomatic hypotension (11 patients in each group), acute kidney injury (6 patients in control group and 3 patients in the treatment group), hyperkalemia (4 patients in enalapril group and 2 patients in the treatment group), angioedema (6 patients in enalapril group). During 8-week treatment the frequency of adverse events was similar in both groups. More patients in sacubitril/valsartan group developed hyperkalemia (51 – 11.6% versus 41 – 9.3% in enalapril group, RR 1.25; 95% CI 0.84-1.84) and symptomatic hypotension (66 – 15.0% patients versus 56 (12.7%) patients in enalapril group); RR-1.18; 95% CI 0.85-1.64). However, more patients in enalapril group had worsening renal function (65 – 14.7% versus 60-13.6%, RR 0.93, 95% CI 0.67-1.28) and angioedema (6 (1.4%) versus 1 (0.2%), RR 0.17; 95% CI 0.02-1.38) [13, 14]. Results of the PIONEER-HF trial show that earlier initiation of ARNI in patients with decompensated heart failure after hemodynamic stabilization is beneficial. Evidence suggest that sacubitril/valsartan should be used in patients with HFrEF instead of ACEi/ARBs who are symptomatic despite receiving ACEi/ARBs, beta-blockers and MRA to reduce mortality and repeated hospitalizations for CHF. Initial recommended dose of sacubitril/valsartan is 24/26 mg twice a day after hemodynamic stabilization. Therapy should be initiated after at least 36 hours after the last dose of ACEi in starting dose 49/51 mg twice per day if SBP 120 and higher and 24/26 mg twice per day if SBP 100 mmHg and higher but less than 120 mmHg with weekly titration to target dose of 97/103 mg twice per day depending on SBP [14, 15]. Less promising results of sacubitril/valsartan use were received in patients with HFprEF. The PARAGON-HF trial included 4822 patients with class II-IV HFprEF (EF>45%). Mean follow-up period was 57 months. Patients in the control group received valsartan (target dose 160 mg twice per day). Although

Table 3. **Mean NT-proBNP values in the PIONEER-HF trial**

Follow-up periods	Study groups					
	Sacubitril/valsartan			Enalapril		
	n, number of patients	Mean values, pg/mL	CI	n, number of patients	Mean values, pg/mL	CI
Baseline	397	2972	(2700, 3273)	394	2536	(2306, 2788)
1 week	366	1704	(1525, 1903)	368	1944	(1747, 2164)
2 week	373	1733	(1540, 1951)	361	2028	(1819, 2261)
4 week	372	1546	(1368, 1746)	358	1982	(1769, 2221)
8 week	358	1232	(1076, 1411)	356	1595	(1406, 1810)

by the end of the trial sacubitril/valsartan (target dose 97/103 mg twice per day) reduced the risk of primary composite outcome (cardiovascular death, hospitalization for CHF) by 13% (RR 0.87; 95% CI 0.75-1.01; p=0.06), these results were not statistically significant. NYHA class improved in15.0% of patients in sacubitril/valsartan group and in 12.6% of patients in valsartan group (RR 1.45; 95% CI 1.13-1.86). More patients from sacubitril/valsartan group developed hypotension and angioedema. However, frequency of treatment discontinuation due to adverse effects was similar in both groups and rare cases of angioedema didn't result into respiratory obstruction or death. Renal function worsened in 1.4% of patients in sacubitril/valsartan group and in 2.7% of patients in control group (RR 0.5: 95% CI 0.33-0.77). More patients taking valsartan developed hyperkalemia. Result analysis in 12 subgroups of patients has shown that sacubitril/valsartan was more effective in women and in patients with lower LVEF. Risk reduction of primary composite outcome in the subgroup with LVEF≤57% was 22% (RR 0.78; 95% CI 0.64-0.95) and in women 27% (RR 0.73; 95% CI 0.59-0.90). Sacubitril/valsartan beneficial effects were due to decreased frewuency of repeated CHF hospitalizations. Positive changes in NYHA class and kidney function were similar in both men and women taking sacubitril/valsartan. At the same time, life quality improved more in men than in women according to the KCCQ scal. Frequency of adverse effects were similar in both groups [16, 17].

To conclude, sacubitril/valsartan introduction has widened the abilities of pharmacologic HFrEF treatment. Sacubitril/valsartan should be initiated as early as possible after the patient was hemodynamically stabilized. Blood pressure, creatinine, electrolytes should be regularly controlled. In hypotensive parties sacubitril/valsartan should be titrated from 24/26 mg twice per day.

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