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Results of 6-Month Use of Neprilysin Inhibitors in Chronic Heart Failure

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Abstract Chronic heart failure (CHF) with reduced ejection fraction remains a major cause of morbidity and mortality. This study evaluated the effects of 6-month therapy with the neprilysin inhibitor sacubitril/valsartan in 58 patients with NYHA class II–IV CHF and LVEF <40%. Treatment led to a significant improvement in systolic function (LVEF increased from 40% to 49%) and reduction of ventricular volumes, indicating reverse remodeling. Diastolic function markers improved, and NT-proBNP levels decreased by more than 2.5-fold, reflecting reduced neurohormonal activation. Clinically, 69% of patients improved by at least one NYHA class, and CHF-related hospitalizations decreased by 52%. These findings confirm the medium-term effectiveness of sacubitril/valsartan in improving cardiac function and clinical outcomes in patients with HFrEF.

Keywords Chronic heart failure (CHF), Neprilysin inhibitors, Sacubitril/valsartan, NT-proBNP, Echocardiography, Reverse remodeling

1. Introduction

CHF remains one of the leading causes of disability and mortality among the adult population. Impaired neurohormonal regulation, particularly the activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathoadrenal system, plays a key role in the pathogenesis of CHF [6]. The emergence of neprilysin inhibitors, represented by the combined drug sacubitril/valsartan, has opened new opportunities in the treatment of CHF with reduced ejection fraction [1].

The mechanism of action of sacubitril/valsartan involves simultaneous inhibition of neprilysin and blockade of angiotensin II receptors, which leads to improved hemodynamics, reduction of natriuretic peptide levels, and a favorable impact on myocardial remodeling [3].

Objective: To assess the impact of neprilysin inhibitors (sacubitril/valsartan) on the clinical and functional status of patients with chronic heart failure (CHF) with reduced ejection fraction.

2. Materials and Methods

The study included 58 patients (mean age: 63 ±8 years; 67% men) with CHF class II–IV according to NYHA and LVEF <40%. All participants provided informed consent to take part in the study.

Exclusion criteria: acute coronary syndrome or revascularization within the past 3 months; severe chronic kidney disease (eGFR <30 mL/min/1.73 m²); significant hepatic dysfunction; uncontrolled arterial hypertension (BP >180/110 mmHg); acute inflammatory diseases and active malignant neoplasms; allergy or intolerance to drug components; and poor treatment adherence.

All participants received UPERIO (sacubitril/valsartan, Novartis Pharma Services AG, Russia) in titrated doses (initial dose 50–100 mg twice daily, further increased to 200 mg twice daily) as part of standard CHF therapy. Treatment effectiveness was evaluated based on changes in echocardiographic parameters (LVEF, EDV, ESV), hospitalization rates, and NYHA functional class, as well as quality of life assessment (MLHFQ) and measurement of NT-proBNP levels using FINECARE test systems on the Wondfo FINECARE analyzer. Assessments were performed at baseline and after 3 and 6 months of pharmacotherapy.

Statistical analysis:

Statistical analysis was performed using Jamovi software (version 2.2.5.0). To assess the dynamics of quantitative variables, the paired t-test was used for normally distributed data, or the Wilcoxon signed-rank test for non-normally distributed data. For multiple comparisons, repeated-measures analysis of variance (ANOVA) was applied. Categorical variables were analyzed using the χ^2 test. Statistical significance was defined as $p<0.05$.

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3. Results

Chronic heart failure (CHF) is one of the most common and socially significant cardiovascular diseases, characterized by a progressive decline in myocardial contractile function and impairment of systemic hemodynamics. Clinical and functional parameters play a leading role in the assessment of patients with CHF, as they reflect the degree of cardiac pump dysfunction, exercise tolerance, and disease prognosis [5]. A comprehensive evaluation of these parameters makes it possible to timely detect the progression of the pathological process, optimize therapy, and assess the effectiveness of the treatment provided [2].

For an objective assessment of the obtained echocardiographic parameters and NT-proBNP levels, the study results were compared with reference values presented in current international guidelines [7,4].

Results (continued)

The normal left ventricular ejection fraction (LVEF) ranges from 55% to 70% and serves as the main criterion for preserved myocardial contractile function. End-diastolic volume (EDV) and end-systolic volume (ESV) reflect the geometric characteristics of the left ventricular cavity and allow assessment of the presence or absence of dilation. Interventricular septal thickness and posterior wall thickness of the left ventricle within 6–10 mm correspond to a normal myocardial profile without signs of hypertrophy.

Indicators of diastolic function include the E/A ratio (normal range 1.0–2.0) and the E/e′ index, with values <8 indicating normal filling pressure, and values >14 suggesting pathological elevation of filling pressure. NT-proBNP concentrations below 125 pg/mL in individuals under 75 years of age and below 450 pg/mL in older patients are considered normal and reflect the absence of significant neurohormonal activation.

In accordance with the aim of our study, we evaluated the clinical and functional cardiac parameters in patients with CHF prior to pharmacotherapy with neprilysin inhibitors (Table 1), which demonstrated that …

Assessment of echocardiographic parameters in patients before initiation of therapy revealed significant deviations from reference values, reflecting marked structural and functional myocardial impairment. The mean left ventricular ejection fraction (LVEF) was 40%, which is substantially below the normal range (55–70%) and indicates pronounced systolic dysfunction. The end-diastolic volume (EDV) reached 163 mL (normal 60–150 mL), pointing to left ventricular dilation. The end-systolic volume (ESV) exceeded the upper limit of normal by more than 35 mL (98 mL vs. normal 20–60 mL), reflecting critically impaired blood ejection efficiency.

The interventricular septal thickness before treatment was at the upper limit of normal (10 mm), while the posterior wall thickness (9 mm) remained within the reference range (6–10 mm), suggesting early myocardial remodeling without pronounced hypertrophy. Diastolic function parameters also demonstrated abnormalities: the E/A ratio was 0.82 (normal 1.0–2.0), indicating impaired myocardial relaxation. At the same time, the E/e′ index reached 17.0 (normal <8), which reflects a pathological increase in left ventricular filling pressure.

Table 1. Echocardiographic parameters and NT-proBNP levels in patients before pharmacotherapy

Parameter	Normal values	Baseline values (Mean ± SD)
Left ventricular ejection fraction (LVEF), %	55–70	40,0 ± 2,5
End-diastolic volume (EDV), mL	60–150	163,0 ± 8,0
End-systolic volume (ESV), mL	20–60	98,0 ± 6,5
Interventricular septal thickness, mm	6–10	10,0 ± 0,5
Posterior wall thickness, mm	6–10	9,0 ± 0,4
E/A ratio	1.0–2.0	0,82 ± 0,1
E/e′ index	<8 (normal); >14 (pathological)	17,0 ± 1,2
NT-proBNP, pg/mL	<125 (<75 y); <450 (≥75 y)	1900 ± 150

Table 2. Echocardiographic parameters in patients after pharmacotherapy

Parameter	Baseline (Before therapy)	After 3 months (Mean ± SD)	After 6 months (Mean ± SD)
LVEF, %	40.0 ± 2.5	45,0 ± 2,8	49,0 ± 3,0
EDV, mL	163.0 ± 8.0	152,0 ± 7,5	142,0 ± 6,8
ESV, mL	98.0 ± 6.5	86,0 ± 5,9	77,0 ± 5,2
IVS thickness, mm	10.0 ± 0.5	10,5 ± 0,6	11,0 ± 0,5
Posterior wall thickness, mm	9.0 ± 0.4	10,0 ± 0,5	10,5 ± 0,6
E/A ratio	0.82 ± 0.05	1,0 ± 0,1	1,2 ± 0,1
E/e′ index	17.0 ± 1.2	14,5 ± 1,1	12,5 ± 1,0

The NT-proBNP level before treatment was 1900 pg/mL, which is 15 times higher than the reference value (<125 pg/mL for patients under 75 years), indicating pronounced neurohormonal activation and significant hemodynamic overload.

Subsequently, we evaluated echocardiographic outcomes after 3 and 6 months of neprilysin inhibitor therapy (Table 2).

According to the results of therapy (Table 2), a significant increase in left ventricular ejection fraction (LVEF) was observed: after 3 months — by 5 percentage points, and after 6 months — by 9 percentage points compared to baseline. This dynamic indicates a meaningful improvement in pump function and recovery of myocardial contractile capacity.

Following neprilysin inhibitor therapy, a consistent reduction in end-diastolic volume (EDV) was recorded: after 3 months — by 11 mL, and after 6 months — by 21 mL relative to baseline values. These changes reflect a reduction in left ventricular dilation and the emergence of reverse remodeling signs.

A decrease in end-systolic volume (ESV) by 12 mL at 3 months and by 21 mL at 6 months was established, serving as an objective marker of optimized left ventricular pump function and favorable reverse remodeling dynamics.

A gradual increase in interventricular septal thickness from 10.0 mm to 11.0 mm by the 6th month of follow-up was observed, which may indicate the development of compensatory myocardial remodeling processes. The posterior wall thickness of the left ventricle increased from 9.0 mm to 10.5 mm by the 6th month of therapy, interpreted as a manifestation of concentric myocardial remodeling during treatment.

A consistent increase in the E/A ratio was noted, from 0.82 ± 0.1 to 1.2 ± 0.1 by the 6th month. These changes indicate normalization of diastolic function parameters and improvement of myocardial relaxation processes. A decrease in the E/e′ index from 17.0 ± 1.2 to 12.5 ± 1.0 after 6 months of therapy was also observed, reflecting a reduction in left ventricular filling pressure and improvement of diastolic properties.

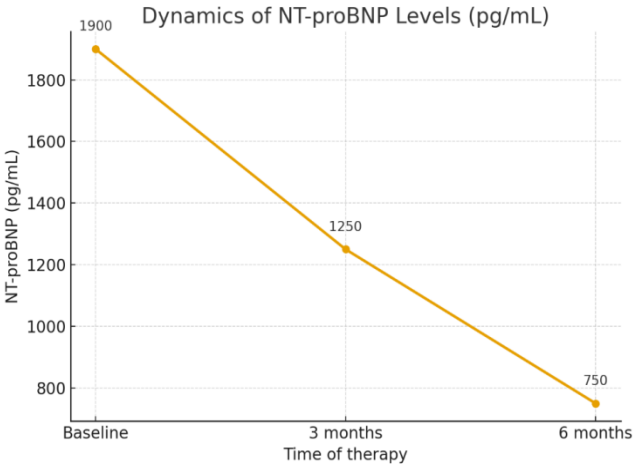

Figure 1. NT-proBNP levels in patients after pharmacotherapy

According to Fig. 1, we observed a pronounced reduction in NT-proBNP concentration: after 3 months by 650 pg/mL and after 6 months by 1150 pg/mL compared to baseline. A more than 2.5-fold decrease indicates a reduction in neurohormonal activation and myocardial workload.

Thus, six months of pharmacotherapy was accompanied by a significant improvement in both systolic and diastolic left ventricular function, reduction of chamber dilation, and decreased markers of neurohormonal overload, which collectively reflect favorable processes of reverse myocardial remodeling.

4. Conclusions

The use of neprilysin inhibitors as part of combination therapy for CHF contributes to a significant improvement in clinical status, left ventricular remodeling, and reduced frequency of decompensations, confirming the high effectiveness of this approach in the medium term.

After 6 months of therapy, positive dynamics were recorded in 87% of patients:

- Mean reduction of NT-proBNP by 38%
- Improvement of CHF functional class by ≥1 stage in 69%
- Reduction of hospitalizations due to CHF decompensation by 52%
- Improvement of subjective quality of life (average reduction of MLHFQ score by 15 points)

In 13% of patients, the therapeutic effect was minimal; this group was predominantly represented by individuals with type 2 diabetes mellitus, anemia, and poor treatment adherence.

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