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OPTIMIZATION OF TREATMENT STRATEGIES FOR CARDIORENAL SYNDROME IN PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT:

Chronic heart failure (CHF) and cardiorenal syndrome (CRS) are major global health concerns due to their increasing prevalence and high morbidity rates. This study evaluates the effectiveness of sacubitril/valsartan therapy in comparison to valsartan monotherapy in CHF patients with CRS. A total of 70 patients aged 55–70 years with NYHA class II–III heart failure and stage III chronic kidney disease were analyzed. Patients were divided into two groups: Group 1 received sacubitril/valsartan (200 mg/day), and Group 2 received valsartan (160 mg/day). Clinical, laboratory, and instrumental assessments were conducted over a 90-day period. The results demonstrated that sacubitril/valsartan significantly improved cardiac function, renal hemodynamics, and overall patient quality of life compared to valsartan alone. The findings suggest that sacubitril/valsartan may serve as a superior therapeutic option for CHF patients with CRS, providing both cardioprotective and nephroprotective benefits.

INTRODUCTION. Chronic heart failure (CHF) affects millions of individuals worldwide and remains a leading cause of hospitalization. One of the most challenging complications of CHF is cardiorenal syndrome (CRS), a condition characterized by the bidirectional deterioration of cardiac and renal function. Effective therapeutic strategies for CRS remain under investigation. Recent evidence suggests that neprilysin inhibition

combined with angiotensin receptor blockade may provide superior clinical outcomes by improving both cardiovascular and renal functions. This study aims to compare the efficacy of sacubitril/valsartan versus valsartan alone in CHF patients complicated by CRS.

Cardiorenal syndrome (CRS) is a multifactorial disorder characterized by the bidirectional interaction between the heart and kidneys, leading to progressive dysfunction of both organs. It is classified into five types, with type 1 (acute cardiorenal syndrome) and type 2 (chronic cardiorenal syndrome) being the most commonly observed in patients with heart failure (HF). The pathophysiology of CRS is complex and involves hemodynamic alterations, neurohormonal activation, endothelial dysfunction, and inflammatory pathways.

Chronic heart failure (CHF) is associated with impaired renal perfusion due to reduced cardiac output and increased central venous pressure. The activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and inflammatory mediators further exacerbates renal dysfunction, contributing to sodium and fluid retention, worsening cardiac workload, and accelerating disease progression. The presence of renal dysfunction in CHF is a strong predictor of poor prognosis and increased mortality, making its management a critical aspect of HF therapy.

Recent advancements in HF treatment have focused on therapies that provide both cardioprotective and renoprotective effects. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated superior efficacy in improving outcomes for HF patients with CRS.

CRS involves a complex interplay between hemodynamic disturbances, neurohormonal activation, and inflammatory processes. The key mechanisms include:

- **Hemodynamic Changes:** Reduced cardiac output, increased venous congestion, and decreased renal perfusion pressure contribute to progressive renal dysfunction.
- **Neurohormonal Activation:** The RAAS and SNS become overactive in response to decreased renal blood flow, leading to vasoconstriction, sodium retention, and fluid overload.
- **Inflammation and Oxidative Stress:** Elevated levels of pro-inflammatory cytokines, oxidative stress markers, and endothelial dysfunction accelerate renal fibrosis and myocardial remodeling.

Cardiorenal syndrome (CRS) is a complex pathological condition in which dysfunction of the heart and kidneys is closely interrelated, leading to the progression of heart failure (HF) and chronic kidney disease (CKD). According to the European Society of Cardiology (ESC) and the American College of Cardiology (AHA/ACC), up to 50% of patients with HF exhibit signs of renal dysfunction, significantly worsening disease prognosis.

The pathogenesis of CRS is driven by neurohormonal mechanisms, including activation of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and natriuretic peptides. These processes contribute to fluid retention, increased

venous pressure, and progressive renal damage. Importantly, CRS therapy should aim not only at symptom control but also at modifying these underlying pathological mechanisms.

Modern treatment strategies for CRS involve the use of angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists, and optimized diuretic therapy. In recent years, particular attention has been given to medications capable of simultaneously improving both cardiac and renal function, such as sacubitril/valsartan. Their efficacy has been confirmed in large-scale clinical trials, including **PARADIGM-HF**, **DAPA-HF**, and **EMPEROR-Reduced**.

This article explores the mechanisms of CRS development, diagnostic criteria, laboratory markers, and contemporary treatment approaches based on the latest international guidelines..

Diagnosis and Laboratory Markers

Current guidelines (ESC, AHA/ACC) emphasize the importance of early CRS diagnosis. The following laboratory markers are commonly used:

- **NT-proBNP** – a marker of HF, elevated in volume overload.
- **Serum creatinine and estimated glomerular filtration rate (eGFR)** – assess renal function.
- **Albuminuria** – an early indicator of renal damage.

Treatment of Cardiorenal Syndrome

CRS treatment focuses on correcting hemodynamic and neurohormonal imbalances.

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

Sacubitril/valsartan has demonstrated efficacy in treating HF and CRS. According to the **PARADIGM-HF** trial, ARNI therapy reduces mortality by 20% compared to enalapril. Key mechanisms include:

- Enhanced natriuresis through increased natriuretic peptide levels.
- Reduction of afterload and improved myocardial function.
- Renoprotective effects by lowering intraglomerular pressure.

Other Pharmacological Strategies

- **Mineralocorticoid receptor antagonists (spironolactone, eplerenone)** – reduce myocardial and renal fibrosis but require potassium monitoring.
- **SGLT2 inhibitors (dapagliflozin, empagliflozin)** – provide both cardioprotective and renoprotective effects.
- **Loop diuretics (furosemide, torsemide)** – used for volume overload control but may exacerbate renal dysfunction.

Methods

Study Design and Population

A prospective, controlled clinical trial was conducted at the Republican Specialized Scientific and Practical Medical Center for Therapy and the Tashkent Regional Somatic

Hospital. A total of 70 patients diagnosed with CHF and CRS were enrolled between 2022 and 2024.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Age 55–70 years
- CHF with NYHA class II–III symptoms
- Diagnosed CRS with stage III chronic kidney disease

Exclusion criteria:

- Acute myocardial infarction
- Oncological or hematological diseases
- Severe renal dysfunction (eGFR <30 ml/min/1.73m²)
- Type 2 diabetes mellitus

Study Groups

Patients were divided into two groups:

- Group 1 (n=35): Standard therapy + sacubitril/valsartan (200 mg/day) - Group 2 (n=35): Standard therapy + valsartan (160 mg/day)

Evaluations

Patients underwent clinical evaluations, laboratory tests (serum creatinine, urea, NT-proBNP, eGFR), and instrumental assessments (echocardiography, renal Doppler ultrasonography) at baseline and after 90 days of treatment.

Results

Our study evaluated the effectiveness of sacubitril/valsartan compared to valsartan in CRS patients:

- **NT-proBNP levels decreased by 23.09%** after 90 days of ARNI therapy.
- **eGFR remained stable** in 85% of patients receiving sacubitril/valsartan.
- **Albuminuria reduced by 13.47%** in the primary group, supporting the nephroprotective effects of ARNI therapy.

Improvement in Cardiac Function

Patients in the sacubitril/valsartan group exhibited a significant increase in left ventricular ejection fraction (LVEF) compared to those in the valsartan group ($p<0.05$). Additionally, the 6-minute walk test performance significantly improved in the sacubitril/valsartan group.

Preservation of Renal Function

Renal function was better preserved in the sacubitril/valsartan group, with a slower decline in eGFR and reduced urinary albumin excretion compared to the valsartan group ($p<0.05$).

Hemodynamic Stability

Patients receiving sacubitril/valsartan demonstrated better blood pressure stability and lower central venous pressure, indicating improved systemic and renal hemodynamics.

Discussion. Our findings align with previous studies supporting neprilysin inhibition as a promising therapeutic approach for CRS management. The observed improvements in both cardiac and renal function suggest that sacubitril/valsartan enhances the interplay between the heart and kidneys, reducing hemodynamic stress and preserving renal function. Despite its superior efficacy, potential concerns regarding sacubitril/valsartan include the risk of hypotension and electrolyte disturbances, particularly in patients with advanced renal impairment. Future studies should focus on the long-term effects and optimal dosing strategies in different CRS subpopulations.

Conclusion. Managing cardiorenal syndrome requires a comprehensive approach. Sacubitril/valsartan therapy demonstrates superior efficacy in improving cardiac and renal function in CHF patients with CRS. Its nephroprotective and hemodynamic benefits highlight its potential as a preferred therapeutic option in this patient population. Further research will help refine optimal treatment protocols and identify patient subgroups that derive the greatest benefit from ARNI therapy.

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