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The Benefits of Sacubitril/Valsartan in Low Ejection Fraction Heart Failure

Düşük Ejeksiyon Fraksiyonu ile Kalp Yetmezliğinde Sakubitril-Valsartanın Faydaları

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Abstract

Heart failure (HF) is the cause of impaired exercise capacity due to insufficient peripheral blood flow. The development of natriuretic peptide (NP) through inhibition of the neprilysin enzyme is the therapeutic target in HF. Sacubitril/valsartan reduces mortality and hospitalization and rehospitalization rates for HF compared with enalapril. In HF patients, sacubitril or valsartan may provide significant benefit.

Anahtar Kelimeler: Heart Failure, Natriuretic Peptide, Sacubitril/Valsartan

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Öz

Kalp yetmezliği (KY), perifere yetersiz kan akışı nedeniyle egzersiz kapasitesinin bozulmasının nedenidir. Neprilisin enziminin inhibisyonu yoluyla natriüretik peptit (NP) geliştirmesi, KY' deki terapötik hedeftir. Sakubitril/valsartan, enalapril ile karşılaştırıldığında KY için mortalite ve hastaneye yatış ve yeniden hastaneye yatış oranlarını azaltır. Sakubitril/valsartan KY hastalarında önemli fayda sağlayabilir.

Keywords: Kalp Yetmezliği, Natriüretik Peptit, Sakubitril/Valsartan

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Introduction

The diagnosis of heart failure (HF) is based on symptoms such as dyspnea and/or restricted exercise ability (1). Globally, HF causes significant health and economic costs (2). In the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide (NP) systems, various neurohormonal mechanisms contribute to the initiation of HF. RAAS activation triggers mechanisms that result in cardiac remodeling. A compensating mechanism inside the brain known as the NP system helps counterbalance the RAAS effects, but not completely (3). Because the enzyme neprilysin destroys NPs, it has been postulated that blocking this enzyme might be a key therapeutic target in HF.

The first dual neprilysin/angiotensin receptor inhibitor (ARNI) is sacubitril/valsartan (4). Both the TRANSITION [reduced ejection fraction (rEF)] and PIONEER-HF [comparison of sacubitril/valsartan medication effect in patients before and after discharge] studies showed treatment effectiveness for ARNI (5). Last but not least, the American College of Cardiology (ACC) and the Canadian Society of Cardiology (CSC) have recently updated their guidelines to recommend sacubitril/valsartan for patients with HF (6,7). Despite PARADIGM-results, the actual processes underlying neprilysin inhibition's therapeutic efficacy remain unknown. Figure 1 depicts the neprilysin substrates.

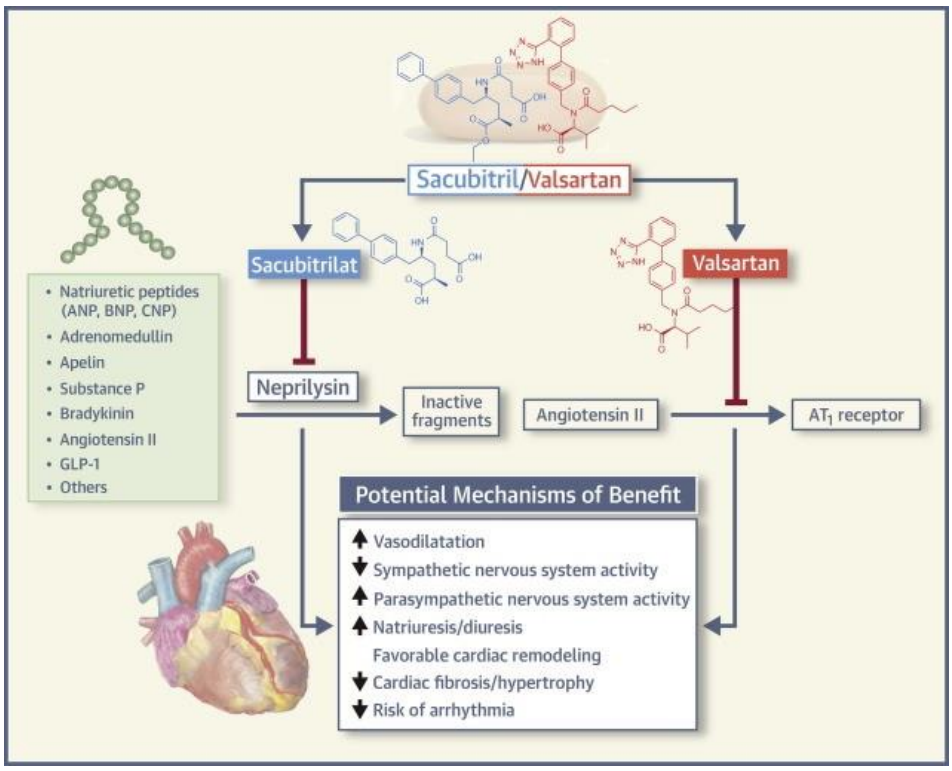

Figure 1. Sacubitril/Valsartan Action Mechanism. Other publication containing the figure in the manuscript include. "Heart Failure 2020, 8(10):800-10."

Sacubitril/valsartan improves quality of life by reducing mortality and disease progression in HF patients. We summarized data on the safety of sacubitril/valsartan in various subpopulations in this review.

Mortality, Sudden Death and Ventricular Arrhythmias

The PARADIGM-HF study showed that sacubitril/valsartan reduced CV mortality by 20 percent compared to enalapril. Aside from improving quality of life, ARNI reduced the risk of mortality by 16% [RR 0.84, 95% (CI) 0.76-0.93, p=0.009] (8).

Arnis And Reduction in Mortality

Sudden death has two basic causes. The first is sustained ventricular arrhythmia, which occurs in HF patients. Bradyarrhythmia or electromechanical dissociation on the ECG are signs of severe left ventricular mechanical failure (9). The positive effects of ARNIs on cardiac remodeling may be more effective than other drugs that decrease the mortality of congestive HF (10). Sacubitril/valsartan improved the clinical situation compared to enalapril in patients with reduced EF (11).

Recurrent Hospitalization

HF is an incurable chronic illness with a poor prognosis. Survival time decreases during hospitalizations. Many registries from other demographics show the same course (12).

Reducing Hospitalizations

In PARADIGM-HF, sacubitril/valsartan reduced hospitalizations for HF by 23%. It reduced recurrent hospitalizations by 33% compared to enalapril (13).

In Acute HF

The PIONEER-HF research was the first to establish that using sacubitril/valsartan therapy in the hospital was safe. After discharge, HF readmissions were lower (8.0%) with sacubitril/valsartan therapy than with enalapril (13.8 percent). Early on after being released from the hospital, the PIONEER-HF trial treatment plan should be favored to prevent readmissions (8)

Cardiac Remodeling

A 10% decrease in the left ventricular end-systolic volume index (LVESVİ) raised the probability of chronic HF mortality by 73%. Reverse cardiac remodeling reduces mortality (8). Increased circulating and myocardial nitric oxide bioavailability leads to increased cyclic guanosine monophosphate (cGMP) and protein kinase G activation. This reduces infarct size and progression. Inhibits pro-inflammatory cytokines and extracellular matrix breakdown, slowing heart remodeling. This avoids LV dysfunction and lowers symptoms of HF (14).

Cardiac Functions

Sacubitril/valsartan improved left ventricular function more significantly than enalapril in the 12-week EVALUATE-HF trial. An early and consistent reduction in NT-proBNP was observed (mainly within 14 days). An increase of 9.4% in LVEF from 28.2% to 37.8% was the most significant result. Overall, all echocardiographic measures showed considerable improvement (15,16). Sacubitril/valsartan, as opposed to angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), resulted in significant functional improvements in HF patients. Following an acute myocardial infarction (AMI), the PARADISE-MI study showed a 42% reduction in global longitudinal strain compared to ramipril (17,18).

Hemodynamic Effects

The ARNI's hemodynamic effects were initially investigated using candoxatrilat, an ANP-inducing inhibitor. This peptide improves the hemodynamic profile of HF patients with reduced EF by decreasing plasma vasopressin, aldosterone, and renin activity. Systemic vascular resistance remained unchanged. One explanation is that non-selective vasoconstrictor molecules like angiotensin II, endothelin 1, and noradrenaline are degraded and their levels rise, counteracting the vasodilatory effects of NPs (8).

Omapatrilat was the first dual neprilysin and AChE inhibitor (ACE). A randomized, double-blind, placebo-controlled study included 369 HFrEF patients. The first dosage lowered pulmonary capillary pressure and systemic vascular resistance. A drop in blood pressure caused an increase in potentially hazardous hormones such as endothelin-1 and noradrenaline, which recovered to normal with continued usage (19).

The combined inhibition with sacubitril/valsartan has substantial systemic vasodilator effects, resulting in a significant drop in blood pressure. Reduced systolic blood pressure (SBP) is related to HF with reduced

EF. Because they are at great risk for adverse effects, these patients seldom receive disease-modifying medications. Sacubitril/valsartan treatment improves hemodynamics by increasing renal sodium and water excretion, vasodilation, and blood volume reduction. It improves ventricular preload and afterload, which helps cardiac remodeling. It lowers blood pressure, ideally SBP, and has been proven to enhance prognosis in all SBP groups, even those with consistently low SBP (20).

Renal Effect of Neprilysin Inhibition

Mechanical Effect

Inhibition of neprilysin increases NP renal bioavailability. This involves reducing kidney damage and decreasing renal remodeling (21).

Clinical Implications of Neprilysin Inhibition's Renal Action

HF

Despite elevated circulating NP levels, chronic HF is characterized by decreased renal (and extrarenal) NP activity. A meta-analysis of three HFrEF trials found that ARNI improved renal dysfunction and serum creatinine increase (22).

Chronic Kidney Disease (CKD)

In the UK HARP-III study, sacubitril/valsartan was compared to irbesartan on renal function and other outcomes. The results on blood pressure and cardiac indicators were more positive than the renal effects. CV events (particularly those associated with HF) may be reduced in people with chronic renal insufficiency (23).

Metabolic Effects: Type 2 Diabetes (Type 2DM) And Uric Acid

HF and Type 2 DM

HF and Type 2DM have the same risk factors and pathophysiological processes. In clinical trials, all HF medications and devices worked equally well with or without Type 2 DM. Dual RAAS and neprilysin inhibition may improve glycemic control. The PARADIGM-HF study's post-hoc analysis suggests this (24). The Paradigm-HF data also allowed the study of the effects of neprilysin inhibition on the progression of kidney damage in type 2 DM patients. NPs improve adiponectin secretion, adiponectin mobilization, and muscle oxidative capability (17). In diabetics, NP improves the kidneys by boosting urine cGMP content (25).

Two trials found that dapagliflozin lowers the risk of mortality in people with reduced EF and Type 2 DM. These findings imply that the two medicines have distinct but complementary biological effects. Empagliosin substantially lowered the hospitalization rate and CV mortality in the EMPEROR-Reduced study (26,27).

Uric Acid

Uric acid is a pro-oxidant that activates the RAAS. Sacubitril/valsartan lowered uric acid by 0.24 mg/dL and improved clinical outcomes in PARADIGM-HF (28).

Life Satisfaction and Functional Ability

HF sufferers have a poor health-related quality of life. The PARADIGM-HF study discovered that it improved sacubitril/valsartan quality. The Kansas City Cardiomyopathy Questionnaire (KCQ) showed that enalapril increased quality of life 4 months after randomization. This discrepancy lasted over 36 months. The largest gains were shown in domestic and sexual activities. Improving health-related quality of life is becoming a focus of emerging HF therapies (29).

Functional Capacity

Physical intolerance has a negative impact on quality of life. Hospitalizations rose by 8% to 14% for every 50 m lost in nine months. The 6MWT results in clinically meaningful functional capacity increases of 30-50 m. There is enough data to suggest that sacubitril/valsartan improves quality of life and function. It should be a focus in clinical practice to include the patient's viewpoint via objective evaluations of these characteristics (30).

Safety

Renal Failure

Sacuitril/valsartan outperformed enalapril in terms of renal safety. Increased serum creatinine and renal impairment were less common in Paradigm-HF. Patients with an eGFR of 30 mL/min/1.73 m2 have experienced success with the medication (31).

Hyperkalemia

The PARADIGM-HF revealed that those on sacubitril/valsartan had less severe hyperkalemia (6 mEq/L serum potassium) than people taking enalapril. Clinical practice recommends MRAs concurrently to decrease morbidity and death (32).

Arterial Hypertension

There was an increased incidence of symptomatic hypotension in those using sacubitril/valsartan (14 percent vs. 9.2 percent for enalapril), but no increase in medication withdrawal (0.9 percent vs. 0.7 percent, $p = 0.38$). Hypotension necessitates a slower rate of titration (33).

Angioedema

Angioedema was infrequent and did not vary across groups in any investigations (8).

Tolerance

Withdrawal due to adverse effects was uncommon in the PARADIGM-HF study. Acute HF patients on sacubitril/valsartan or enalapril discontinue at equal rates (34).

Recent Studies on Sacubitril/Valsartan

According to Rezq et al. (35), starting sacubitril/valsartan early after ST elevation MI may reduce MACE and HF hospitalizations. However, this additional indication needs to be confirmed on a larger scale with a longer follow-up cohort of patients to assure safety and effectiveness. Murphy et al. (36) found that commencing sacubitril/valsartan quadrupled ANP concentrations in HF patients with poor EF. The extent of future reverse cardiac remodeling was related to early ANP rises.

Using sacubitril/valsartan reduces anemia in patients with cardiorenal syndrome (CRS). These individuals had an increase in cystatin levels. There have been few negative effects. More clinical research is required to verify these findings (37). Sacubitril/valsartan and ivabradine used concurrently reduce adverse effects and improve LV reverse remodeling in patients with hypovolemia. However, sacubitril/valsartan therapy improved EF more than ivabradine treatment did (38).

Zandstra et al. (39) described the first cohort of patients treated with sacubitril/valsartan for systemic right ventricular failure. Treatment improves NT-pro-BNP and echocardiographic function. Sacubitril/valsartan may be an alternative for this patient population. Sacubitril/valsartan is a safe and efficient therapy for HF (40).

It also improves health status and reverses cardiac remodeling in individuals with HFrEF and type 2 diabetes (41). The optimal technique to manage HF patients with electrical devices in their hearts is yet unknown. The clinical utility of sacubitril/valsartan is questioned. It is superior to RAS inhibitors for HF patients (42).

With sacubitril/valsartan treatment, KCQ-23 scores improved rapidly, and this was related to a shift in NT-proBNP (43). Galo et al. (44) discovered that neprilysin is involved in the breakdown of brain beta-amyloid. Theoretically, this might cause plaque build up and eventually Alzheimer's.

Patients in the critical care unit may be safely transitioned to sacubitril/valsartan after a permanent improvement in cardiac index with vasoactive medications. Sacubitril/valsartan improved pulsatility index and preserved left and right ventricular function (45). Adding sacubitril/valsartan medication to symptomatic HF patients on the guideline-recommended medications increased EF, decreased NT-proBNP, and improved quality of life (46).

In conclusion, in patients with HFrEF, sacubitril/valsartan outperforms enalapril in lowering all-cause and cardiovascular death. Its vast range of advantages, including cardiac and extracardiac protection, may be explained by many mechanisms. ARNI may help individuals with HF in both the chronic and acute phases.

Current Studies

Intolerance to modest doses of sacubitril/valsartan is frequent in individuals with advanced chronic HFrEF (47). Sacubitril/valsartan decreased HbA1c and the need for new insulin treatment in HF and diabetic patients with different LVEF, but it may increase the risk of hypoglycemia (48). People with HFrEF saw similar improvements in prognostic biomarkers, health status, and cardiac remodeling at different doses of sacubitril/valsartan (49). Sacubitril/valsartan improves hemodynamic conditions in HFrEF patients (50). Sacubitril/Valsartan may halt renal function decline and reverse myocardial remodeling more efficiently than ACEI/ARB, even at low dosages, while its impact on urine protein is not as favorable (51).

HFrEF patients with varied risk profiles are identified using echocardiographic hemodynamic classification. Sacubitril/valsartan improves outcome across hemodynamic profiles in real-world HFrEF outpatients (52). Treatment with low doses of ARNI might successfully improve cardiac function in hemodialysis (HD) patients with heart failure and hypotension. It was also well tolerated and safe (53). 95% of patients began with low and intermediate sacubitril/valsartan dosages. 30% of patients achieved their target dosage during follow-up. Reverse remodelling was evidenced by a high NT-proBNP level, reduced LV size, and increased LVEF. Park et al. demonstrated the discrepancy between clinical trial and real-world treatment trends (54).

Risks of hypotension, renal failure, hyperkalemia, and angioedema seem minimal and tolerable with expanded sacubitril/valsartan use in randomized clinical trials (RCTs) and worldwide clinical practice (55). The stroke volume index (SVi) is related to full sacubitril/valsartan titration. Low-SVi patients are more likely to have hypotension during titration (56). Sacubitril/valsartan inhibits ventricular remodeling following MI, improves cardiac function, and reduces adverse cardiovascular events, rehospitalization, and death (57).

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Table 1.

Cornerstone Studies On Sacubitril/Valsartan

Reference no.	Authors	Subjects	Number of patients	Main theme
Ref [1]	Bozkurt et al.	HFrEF patients	9 recent clinical trials	HF is a clinical condition characterized by structural and/or functional heart abnormalities, increased natriuretic peptide levels, and pulmonary or systemic congestion.
Ref [2]	Virani et al.	Heart disease and stroke	5000 patients	The Statistical Update is a vital resource for policymakers, media professionals, doctors, healthcare administrators, academics, health activists, and anyone seeking the best available statistics on these causes and disorders.
Ref [5]	Velazquez et al.	HFrEF patients	881 patients	Sacubitril-valsartan suppressed NT-proBNP higher than enalapril in hospitalized HFrEF patients
Ref [8]	Pascual-Figal et al.	HFrEF patients	A review	Sacubitril/valsartan as a key therapy for HFrEF.
Ref [12]	Chun et al.	HFrEF patients	8543 patients	Newly discharged HF patients with ischemic etiology had more cardiovascular events early postdischarge and prefatally.
Ref [17]	Jering et al.	HFrEF patients	5669 patient	PARADISE-MI will investigate whether sacubitril/valsartan is more efficacious than an established ACE inhibitor in reducing HF and cardiovascular mortality after AMI.
Ref [27]	Packer et al.	HFrEF patients	3730 patients	Empagliflozin-treated heart failure patients had a reduced risk of mortality or hospitalization than placebo-treated patients, independent of diabetes.
Ref [34]	Nielsen et al.	HFrEF patients	19086 participants	Sacubitril/valsartan may help more heart failure patients than the guideline recommends.
Ref [35]	Rezq et al.	STEMI patients	200 patients	Sacubitril/valsartan may improve myocardial remodelling in post-STEMI patients.
Ref [39]	Zandstra et al.	HF patients	20 patients	They report the first sacubitril/valsartan-treated systemic RV failure cohort. NT-pro-BNP and echocardiographic function improve with treatment.
Ref [42]	Cheng et al.	HF patients with cardiac implantable electronic devices	A review	Sacubitril/valsartan may improve mortality, SCD, clinical, and echocardiographic results in patients with cardiac implantable electronic devices
Ref [47]	Vader et al.	HFrEF patients	445 subjects	Intolerance to modest doses of sacubitril/valsartan is frequent in individuals with advanced chronic HF with decreased ejection fraction.
Ref [50]	Carluccio et al.	HFrEF patients	727 HFrEF outpatients	Sacubitril/valsartan improves hemodynamic conditions in HFrEF patients.
Ref [55]	Kim et al.	HF patients	15,538 patients	In RCTs and worldwide clinical practice, enhanced sacubitril/valsartan absorption reduces the risk of hypotension, renal dysfunction, hyperkalemia, and angioedema.
Ref [57]	Zhang et al.	AMI patients	A total of 5 articles	Sacubitril/valsartan inhibits ventricular remodeling following AMI, improves cardiac function, and reduces adverse cardiovascular events, rehospitalization, and death.