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Case Report

Experience of Using Sacubitril/Valsartan in an Asian Patient with Comorbidities: Chronic Heart Failure, Atrial Fibrillation, and Chronic Kidney Disease

Zhuldyz Ospanova [1], Manchuk Karzhaubayeva[2]

[1]*Department of Internal Medicine/Cardiology, Almaty SEMA Hospital, Almaty, Kazakhstan*
[2]*Department of General Medical Practice, Faculty of Medicine and Healthcare, Al-Farabi Kazakh National University, Almaty, Kazakhstan*

Abstract:

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Corresponding author's email:
manshuk.md9028@gmail.com

A 68-year-old asian man was admitted with decompensated chronic heart failure with a left ventricular ejection fraction of 20%, permanent arterial fibrillation, and chronic kidney disease. Sacubitril/Valsartan (Uperio) was prescribed.

This review details the initiation of sacubitril/valsartan in an Asian patient with heart failure with low ejection fraction (20%) and comorbidities. The paper highlights the pharmacodynamic and pharmacokinetic profiles of Sacubitril/Valsartan. The focus is on a thorough review of clinical trials to assess the therapeutic efficacy and potential adverse events associated with Sacubitril/Valsartan administration in this specific patient group.

Since 2014, sacubitril/valsartan has been widely prescribed for heart failure. Nevertheless, the coexistence of additional diseases such as arthritis, renal insufficiency, diabetes mellitus, or chronic lung disease with the heart failure syndrome should logically require a modification of treatment, outcome assessment, or follow-up care.

Keywords: Sacubitril/Valsartan; Neprilysin; Chronic Heart Failure; Arterial Fibrillation; Chronic Kidney Disease

Introduction

Sacubitril/valsartan is a neprilysin inhibitor and angiotensin II receptor antagonist widely used in the treatment of chronic heart failure (CHF) with reduced ejection fraction (HFrEF) (1). It was approved in 2015 by the US Food and Drug Administration (FDA) to reduce the risk for cardiovascular (CV) death and hospitalization in patients with CHF (2,3). The therapeutic action of the combined agent is initiated by sacubitril, an inactive prodrug that requires in vivo esterase cleavage to yield the active metabolite, sacubitrilat. Sacubitrilat's mechanism is predicated on neprilysin inhibition, preventing the breakdown of natriuretic and other vasoactive peptides. The resulting increase in natriuretic peptide concentration induces beneficial hemodynamic and renal effects, notably systemic vasodilation and increased sodium excretion, leading to ECF volume reduction. The dual component, valsartan, acts independently as an angiotensin II type 1 receptor blocker (ARB) to oppose the biological consequences of angiotensin II signaling (4). Since the landmark PARADIGM-HF trial in 2014, sacubitril/valsartan (LCZ696, Entresto®) has been widely adopted and is now a recommended standard of care for the treatment of heart failure (HF), including in the elderly population (5,6). However, in patients with comorbid conditions such as atrial fibrillation (AF) and chronic kidney disease (CKD), therapy requires a special approach, considering potential risks and individual patient characteristics.

CHF represents a heterogeneous and complex clinical syndrome defined by underlying structural or functional abnormalities that compromise the heart's ability to fill or eject blood adequately. The primary clinical features of HF are dyspnea and fatigue, typically resulting in limited physical capacity (exercise intolerance), alongside fluid retention that commonly presents as peripheral edema or pulmonary and/or

splanchnic venous congestion. Clinical presentation is highly variable, a subset of patients may predominantly experience exercise limitation with scant evidence of fluid accumulation, while others report a greater focus on symptoms such as edema, dyspnea, or chronic fatigue (7). The defining criteria for heart failure with reduced ejection fraction (HFrEF) have evolved, with different established guidelines proposing left ventricular ejection fraction (LVEF) thresholds of ≤35%, <40%, and ≤40% (8-10).

The prevalence of HF is increasing as the population ages (11). Each hospitalization event is associated with worsening long-term prognosis. Approximately one in four patients is readmitted for HF, and 10 percent may die within 30 days of discharge (12,13). Although survival has improved, the absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis (14,15). In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively (16).

In the Republic of Kazakhstan, mortality from cardiovascular disease decreased from 160.4 cases per 100 thousand population in 2019 to 128.9 cases per 100 thousand population in 2022. The incidence of HF also decreased, from 601.2 cases per 100 thousand population in 2019 to 585.1 cases per 100 thousand population in 2022 (17).

The ACCF/AHA staging criteria for heart failure (HF) incorporate both cardiac structural changes and underlying risk factors as determinants of the condition. Relative to the general population, patients diagnosed with HF demonstrate an increased susceptibility to developing atrial fibrillation (AF) (18). Furthermore, a pronounced relationship exists between the severity of HF, as defined by the NYHA functional class, and the prevalence of AF; this prevalence escalates markedly from 4% in NYHA class I patients to 40% in those categorized as NYHA class IV (19). AF is also a strong independent risk factor for the subsequent development of HF (20). Atrial fibrillation (AF) is recognized as the most clinically significant arrhythmia encountered in routine practice. Its prevalence is estimated at 1–3% in the general population, yet it increases sharply with advancing age, reaching up to 9% in individuals ≥65 years old and up to 17% in those ≥80 years old (20, 21). Furthermore, heart failure (HF) represents the primary cause of mortality and is a major contributor to hospitalizations among patients with AF (22).

Another risk factor for developing HF is chronic kidney disease. The global prevalence of Chronic Kidney Disease (CKD) has seen a marked increase, impacting an estimated 843.6 million individuals globally in 2017 (23). Despite advancements leading to a reduction in mortality among patients with End-Stage Kidney Disease (ESKD) (24), comprehensive analyses from the Global Burden of Disease (GBD) studies indicate that CKD has concurrently risen to prominence as a major worldwide cause of death (25).

The FortiHFy clinical development program represents the largest worldwide effort in the heart failure field, comprising over 40 studies. It includes pivotal trials across the entire spectrum of heart failure, such as PARADIGM-HF, PIONEER-HF, TRANSITION, PROVE-HF, PARAGON-HF, and PARAMOUNT. To date, more than 30,000 patients globally have participated in the clinical trials of Entresto, which is currently prescribed to an estimated 2.8 million patients worldwide (26). Data from these trials demonstrate that sacubitril/valsartan therapy significantly reduces the risk of cardiovascular (CV) death or HF hospitalization by 20% (relative reduction), and all-cause mortality by 16% (relative reduction) (27).

Safety data on important safety topics of interest, such as hypotension, hyperkalemia, renal impairment, angioedema, and hepatotoxicity, were consistent with extensive prior experience in adults. Adverse effects observed very commonly (≥10%) with sacubitril/valsartan administration are hypotension (systolic blood pressure ≤95 mmHg or symptomatic), hyperkalemia, and renal impairment.

Case Presentation

A 68-year-old asian man was admitted with decompensated CHF (left ventricular ejection fraction of 20%), permanent AF, and CKD (eGFR – 38 mL/min/1.73 m²). Before admission, the patient was maintained on standard medical therapy, which encompassed a β-blocker, a mineralocorticoid receptor antagonist, an angiotensin-converting enzyme inhibitor (ACEI), diuretics, and an anticoagulant (dabigatran). Hospitalization frequency was two times in one month, and symptoms such as dyspnea, fatigue, and recurrent hospitalizations for CHF persisted.

Medical history: The patient has been under the observation of a general practitioner since 2014, with the following diagnoses: Coronary artery disease. Effort angina, functional class III. Myocardial infarction in 2014. Arterial hypertension grade 3, stage 3. Since 2018, the patient has been monitored by a nephrologist, phar-

macological treatment was not consistently administered, management relied on diet adherence. The first episodes of shortness of breath during physical exertion, discomfort in the heart, and severe fatigue appeared 4-5 years ago. Over the past year, a gradual deterioration in the tolerance of physical activity has been noted. Anthropometrics: Height: 165 cm, weight: 70 kg. Laboratory tests on admission day: WBC 8.4×10^9/L, RBC 4.5×10^{12}/L, Hemoglobin 146g/L, Platelets 336×10^9/L, ESR 29mm/h. Biochemistry: Total protein 69g/L, Urea 8.7mmol/L, Creatinine 125μmol/L, Glucose 5.6mmol/L, Magnesium 1.1mmol/L, ALT 35U/L, AST 25U/L, Total bilirubin ~7.4μmol/L, High-sensitivity CRP 7.1mg/L, Creatinine clearance 38mL/min/1.73m². Urinalysis: urine volume 40mL, Density 1.012, Protein 0.30g/L, Glucose negative, Bilirubin negative, pH 5.00, Ketones 2.00mmol/L, Leukocytes 10–15. Electrolytes: Ionized calcium 1.18mmol/L, Potassium 4.8mmol/L, Sodium 133mmol/L. Lipid profile: Total cholesterol 8.6mmol/L, HDL 1.05mmol/L, LDL 6.89mmol/L, Triglycerides 2.1mmol/L, Atherogenic coefficient 7.1, Cardiovascular risk index 6.5. Cardiac Markers: Troponin I 0.028ng/mL, ProBNP – 4500ng/mL.

Instrumental examinations. ECG from May 2025: Atrial fibrillation with a heart rate of 92 beats per minute. Incomplete right bundle branch block.

Cardiac ultrasound from May 2025 (before treatment): Aortic valve - tricuspid, cusps thickened, opening not restricted. Mitral valve: cusps thickened, movements asynchronous. Tricuspid valve and pulmonary valve cusps are unchanged. Interatrial and interventricular septa intact. Heart chambers dilated. Global and regional myocardial contractility was significantly reduced. Pericardium without abnormalities. The inferior vena cava (I) – dilated, collapses on inspiration less than 50%. Heart chambers: dilated. Diffuse hypokinesis of the left ventricle (LV) walls. Global systolic function of the left ventricle – EF 20%. Tricuspid regurgitation grade 2, mitral regurgitation grade 1. Moderate pulmonary hypertension. Right ventricular systolic pressure (RVSP) – 60 mmHg. Diastolic dysfunction of the left ventricle, type I.

Laboratory tests (10th day of hospitalization): Total cholesterol 3.9mmol/L, Troponin I up to 0.04 ng/mL, ProBNP before treatment – decreased to 2700ng/mL. Urea 7.7mmol/L, Creatinine 121μmol/L. Urinalysis: Density 1.015, Protein 0.20g/L, Ketones 1.08mmol/L, Leukocytes 7-10.

Cardiac ultrasound on the 10th day of hospitalization: The study was conducted against the background of atrial fibrillation. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 36%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1 (Figure 1).

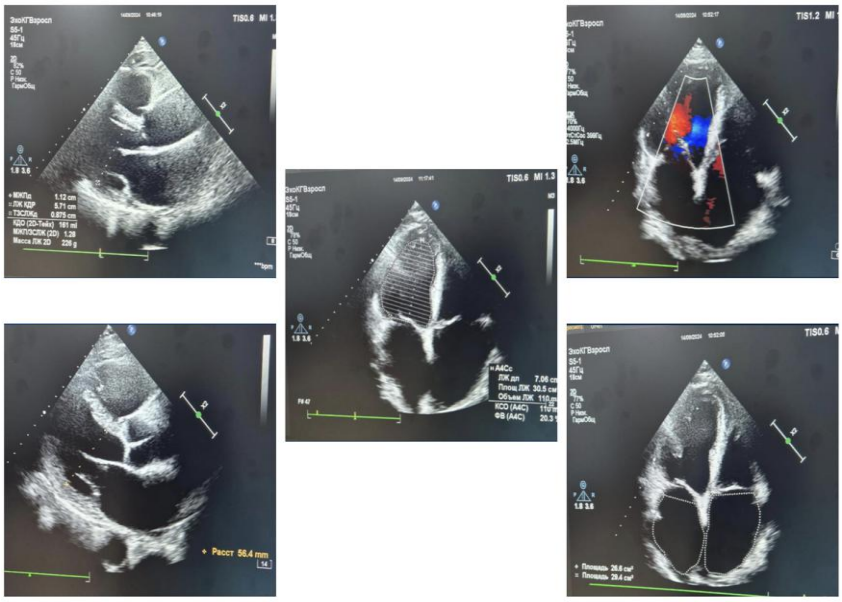

Figure 1. Cardiac ultrasound on the 10th day of hospitalization. The study was conducted against the backgrounds of atrial fibrillation. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 36%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1.

Coronary Angiography from May 2025: Left type of blood supply. LEFT MAIN: Patent, no abnormalities. PDA: Tandem stenosis of the distal third up to 70%, blood flow velocity (TIMI III). OM: Patent, no abnormalities, blood flow velocity (TIMI III). RCA: Patent, no abnormalities, blood flow velocity (TIMI III) (Figure 2).

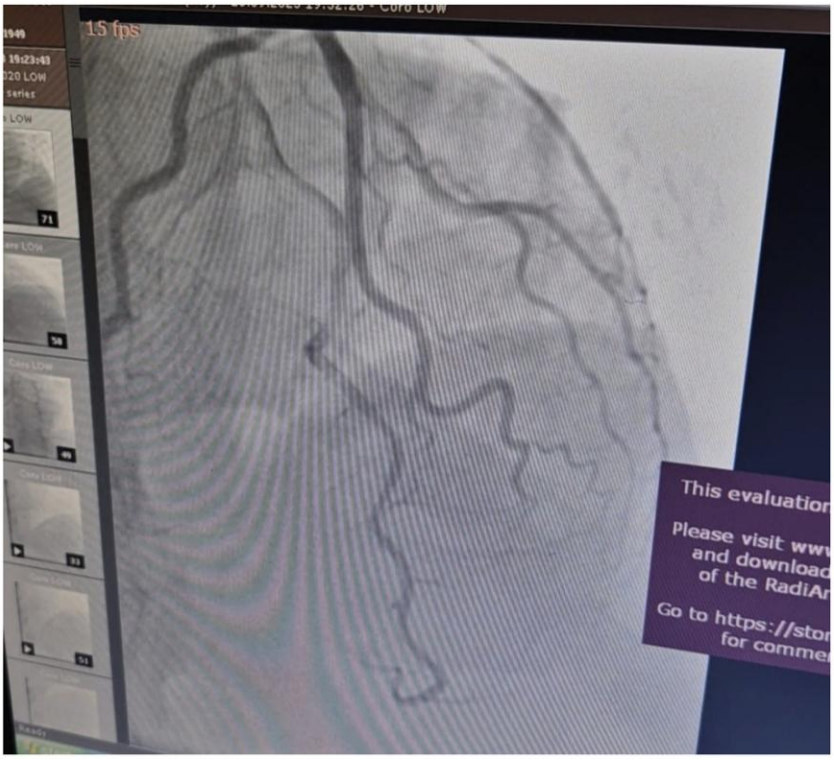

Figure 2. Coronary Angiography from May, 2025: Left type of blood supply. LEFT MAIN: Patent, no abnormalities. PDA: Tandem stenosis of the distal third up to 70%, blood flow velocity (TIMI III). OM: Patent, no abnormalities, blood flow velocity (TIMI III). RCA: Patent, no abnormalities, blood flow velocity (TIMI III).

A clinical diagnosis was made: Coronary artery disease. Effort angina pectoris, functional class III. Myocardial revascularization by stenting of the left anterior descending artery (LAD). History of myocardial infarction (2014). Chronic heart failure, NYHA functional class II, stage lIA. Arterial hypertension, grade 3, stage 3, very high cardiovascular risk (SCORE 20%). Chronic kidney disease, stage 3B (eGFR 38ml/min/1.73m2). Permanent atrial fibrillation. CHA2DS2-VASC score: 6. HAS-BLED score: 3.

Treatment plan: Atorvastatin 20mg – once daily after meals in the evening, Dabigatran 110mg – 1 tablet 2 times daily (morning and evening), Carvedilol 6.25mg – ½ tablet twice daily (morning and evening), Verospiron 100mg – 1 capsule once daily in the morning, Trigrim 5mg – 1 capsule once daily in the morning, then increase to 10mg once daily, Dapagliflozin 10mg – 1 tablet once daily after meals.

Introduction of Sacubitril/valsartan into the therapeutic strategy. The ACE inhibitor (Perindopril 5mg) was discontinued, and after a 36-hour washout period, the patient started Uperio at a dose of 50mg (24/26mg) twice daily. On the 3rd day of hospitalization, the dose was increased to 100mg twice daily. Blood pressure and potassium levels were monitored at the first and second weeks (within normal limits).

Discussion

Patient's general condition improved, symptoms such as dyspnea, fatigue declined on the 10th day of hospitalization. The patient continues to take Uperio at a dose of 100mg twice daily. After three months of therapy, there was a reduction in hospitalization frequency (one in three months), improvement in dyspnea (NYHA II), and increased exercise tolerance.

Cardiac ultrasound from August 2025 (after three months of discharge). Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 38%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1 (Figure 3).

The ejection fraction improved from 20% to 36% (on the 10th day of hospitalization), to 38% (after three months). NT-proBNP levels decreased by 60% on the 10th day of hospitalization (from 4500 ng/mL to 2700 ng/mL), and after three months, decreased from 2700 ng/mL to 560 ng/mL. Blood pressure stabilised at 110/70 mmHg. Renal function remained stable (eGFR at 36 mL/min/1.73 m2, potassium – 4.8 mmol/L, Urea 7.2 mmol/L, Creatinine 119 μmol/L).

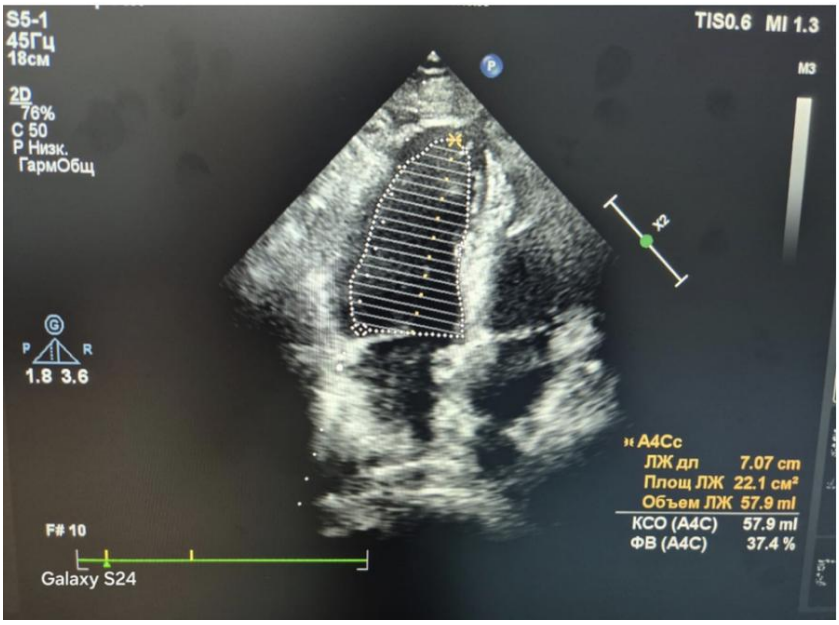

Figure 3. Cardiac ultrasound after three month of discharge. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 38%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1.

Clinical efficacy and good tolerability of sacubitril/valsartan were demonstrated in an Asian patient with concomitant CHF, AF, and CKD. Successful management necessitated meticulous dose titration and rigorous monitoring of blood pressure, potassium homeostasis, and kidney function.

In Study B2314, the incidence of renal impairment adverse events/serious adverse events (AEs/SAEs) was consistently lower with sacubitril/valsartan vs enalapril in adults with HFrEF. Also, the percentages of adults with categorical eGFR decreases, and notably abnormal serum creatinine elevations were lower in the sacubitril/valsartan group compared with the enalapril group. The proportion of reported deaths is relatively low, with fewer deaths in the sacubitril/valsartan group (4.3% (n=8)) compared with the enalapril group (6.4% (n=12)), which is reassuring (26). During the administration of the drug, our patient had an improvement in the ejection fraction, and no deterioration was observed in the kidneys. The indicators of laboratory tests of kidney function were within normal limits on the 10th day of hospitalization and three months after discharge. Comparatively, previously, the patient had frequent hospitalizations (up to 2 times a month) while taking an angiotensin-converting enzyme inhibitor, persistent complaints of shortness of breath, and edema on the lower extremities.

Conclusion

Data regarding the effectiveness of medical therapy for patients with advanced HFrEF is limited, and survival without heart transplantation or Left Ventricular Assist Device (LVAD) therapy remains exceedingly poor (28). Despite established clinical advantages of sacubitril/valsartan in HFrEF patients with mild-to-moderate symptomatology, robust evidence regarding its safety profile, efficacy, and tolerability in individuals with advanced heart failure is currently restricted. Following the initiation of the therapy, a reduction in the patient's hospitalization frequency was observed; notably, no hospital admissions occurred during the entire observation period.

Ongoing research and clinical trials will further elucidate the benefits and safety profiles of this innovative treatment in diverse populations. In conclusion,

Sacubitril/Valsartan represents a vital advancement in heart failure management. Its application in patients with complex medical histories requires careful monitoring and management strategies to maximize its benefits while minimizing risks.

Patient consent

Patient was examined and treated at the «Almaty Sema clinic» in May 2025. The diagnostic search included clinical examination, laboratory tests, and instrumental methods, such as cardiac ultrasound and selective coronary angiography. The treatment program included: drug correction of CHF. Status dynamics were monitored during the hospitalization period and three months after discharge. The patient provided informed consent for the publication of their clinical data.

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Ethics declaration: Voluntary informed consent for publication was obtained from patient.

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