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ORIGINAL ARTICLE

Long-term Effect of Sacubitril/valsartan Use on Uric Acid Levels in Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF), characterized by neurohormonal activation and metabolic dysregulation, may lead to elevated serum uric acid (SUA) levels. Although the sacubitril/valsartan (S/V) molecule confers notable cardiovascular benefits and has been observed to influence multiple metabolic parameters, its impact on SUA levels remains incompletely elucidated.

Aim: To investigate the long-term impact of the S/V combination on SUA levels in patients with HFrEF.

Study Design: Longitudinal retrospective cohort study.

Methods: For this single-center, retrospective, cross-sectional analysis, data from patients using S/V for HFrEF were collected from their medical records. In addition to the routine controls, the uric acid levels of patients were measured at the baseline and in the first and second years of their treatment. The parameters obtained at two years included the serum uric acid (SUA) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The SUA and NT-proBNP levels measured in the first and second years were compared with the baseline value.

Results: A total of 148 patients with a functional capacity in New York Heart Association II-IV and those who were using S/V due to HFrEF were included in this study. The mean age of the study patients was 66.6±10.3 years, and 61.5% of them were male. The baseline SUA levels were 6.6±1.6, which reduced to 6.2±1.8 at the end of the first year and to 6±1.6 at the end of the second year ($p<0.001$).

Conclusion: The administration of S/V can reduce the SUA concentration in patients with HFrEF.

Keywords: Sacubitril/valsartan, heart failure, uric acid, NT-proBNP

INTRODUCTION

Patients with heart failure (HF) exhibit hyperuricemia with a prevalence rate of 50%,[1,2] probably due to the use of diuretic drugs in the treatment of HF patients. An association has also been observed between poor long-term prognosis and the use of diuretic drugs in these patients.[2,3] In the case of HF patients, the risk of all-cause mortality is increased by 4% with every 1 mg/dL increment in the serum uric acid (SUA) level. Similarly, this increment is associated with a 28% greater risk of hospitalization.[4] Although agents such as allopurinol and febuxostat are available for reducing SUA, researchers are continuing to investigate novel therapeutic approaches for the treatment of this condition in HF patients.

Sacubitril/valsartan (S/V) has been reported to cause a significant reduction in all-cause mortality, hospitalization, and cardiovascular mortality in HF patients demonstrating HF and reduced ejection fraction (HFrEF).

S/V serves as an angiotensin receptor-neprilysin inhibitor (ARNI)[5] and results in several metabolic changes.[6] The majority of these metabolic changes brought about by this molecule are actually due to the neprilysin inhibitor sacubitril. PARAGON and PARADIGM studies

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involve investigations focusing on the impact of S/V molecules on the concentration of SUA. Nevertheless, the long-term impact of S/V on the SUA levels warrants further investigation. Accordingly, the present research investigated the different long-term effects of S/V on the concentration of SUA in HFrEF patients.

METHODS

This longitudinal retrospective cohort study examined 148 patients classified as New York Heart Association (NYHA) functional class II-IV who initiated ARNI therapy for HFrEF [left ventricular ejection fraction (LVEF) <40%] during April 2019 to March 2020. ARNI dosing was systematically titrated to the maximum tolerated dose for all participants. The exclusion criteria encompassed severe non-cardiac comorbidities (e.g., end-stage organ dysfunction, dialysis-dependent renal failure, metastatic malignancy, sepsis/septic shock), age <18 years, pregnancy, concomitant serum urate (SUA)-lowering therapy, and irregular clinical follow-up. The study protocol adhered to the Declaration of Helsinki guidelines and received approval from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee (permission date: 18.07.2022, file number: 431869). All therapeutic interventions were individualized in accordance with contemporary clinical guidelines.

Definitions

HFrEF was defined as an LVEF <40% accompanied by clinical signs and symptoms of HF, which is consistent with the established diagnostic criteria.[7] Ischemic heart disease (IHD) encompasses a documented history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery, or objective evidence of myocardial ischemia via invasive coronary angiography or non-invasive testing (e.g., stress echocardiography and myocardial perfusion imaging).[8] Hypertension (HT) was characterized by either (1) two consecutive seated blood pressure measurements of ≥140/90 mm Hg recorded during separate clinical encounters or (2) the active use of antihypertensive pharmacotherapy. Diabetes mellitus (DM) was diagnosed on the basis of (1) two independent fasting plasma glucose measurements of ≥126 mg/dL or (2) the current use of glucose-lowering agents (either oral or injectable). The NYHA functional classification was employed to stratify symptom severity and exercise capacity. Two cardiologists independently evaluated and categorized patients into NYHA classes I-IV through a retrospective chart review, with discrepancies resolved via consensus adjudication. This dual-assessment approach aimed to enhance the classification accuracy and minimize the interobserver variability.

Transthoracic Echocardiography

Transthoracic echocardiography was conducted using a standardized protocol with the Philips Epiq 7 Ultrasound system (Philips Healthcare, Inc., Andover, MA, USA) equipped with an X5-1 phased-array transthoracic transducer. All examinations adhered to the American Society of Echocardiography guidelines,[9] incorporating M-mode, two-dimensional (2D), and pulsed/continuous-wave Doppler modalities. LVEF was determined using the biplane Simpson's method of discs. Endocardial borders were manually traced in apical four- and two-chamber views during end-diastole and end-systole, taking due care to ensure orthogonal plane alignment and the inclusion of the entire ventricular cavity from the apex to the mitral annulus. Volumetric calculations were derived from the average of three consecutive cardiac cycles to minimize the beat-to-beat variability.[10] To ensure methodological rigor, two independent cardiac sonographers, blinded to the clinical data, analyzed all the echocardiographic images. Interobserver discrepancies of >5% in LVEF measurements underwent adjudication by a senior cardiologist, with the final values representing the consensus assessment. This protocol minimized the intra- and interoperator variability while maintaining alignment.

Laboratory Measurements

Venous blood samples were collected in serum separator gel tubes (without anticoagulant). Following centrifugation at 1,800×g for 15 min, the serum was aliquoted. Biochemical parameters, including the fasting plasma glucose, glycated hemoglobin (HbA1c), NT-proBNP, total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), creatinine, albumin, and SUA, were quantified by standardized enzymatic colorimetric assays. The HbA1c levels were measured via high-performance liquid chromatography, while the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined by electrochemiluminescence immunoassay, in accordance with the corresponding kit manufacturer's protocols.

Statistical Analysis

All analyses were performed using IBM Statistical Package for the Social Sciences statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of the continuous variables was assessed using the Kolmogorov-Smirnov test. The normally distributed data were presented as the mean±standard deviation, while the nonnormally distributed variables were reported as median with interquartile range (IQR; 25^{th}-75^{th} percentiles). Categorical variables were expressed as frequencies and percentages. Intergroup comparisons were conducted using Pearson's chi-square test. For the continuous variables, the independent Student's t-test (normal distribution) or Mann-Whitney U test (non-normal distribution) was applied. Longitudinal changes in the SUA levels were evaluated using repeated-measures analysis of variance, while the non-parametric repeated-measures Friedman test was employed for NT-proBNP because of its skewed distribution. A two-tailed $p<0.05$ was considered to indicate statistical significance.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of 148 patients experiencing HFrEF and utilizing ARNI. Of the total study patients, 91 (61.5%) were male. Moreover, the average age of the patients was 66.6±10.3 years. The frequencies of atrial fibrillation, IHD, DM, dyslipidemia, and HT were 37.8%, 67.6%, 58.8%, 81.1%, and 62.2%, respectively. Of the total, 40 (27.0%) patients were using low-dose S/V (24/26 mgx2), while 108 (72.9%) were using high-dose S/V (49/51 mgx2). In addition, 148 (100%) patients were receiving beta-blocker therapy, 106 (71.6%) were on mineralocorticoid receptor antagonists, and 139 (93.9%) were using diuretics. The mean LVEF was found to be 40.7±14.3. As per the laboratory findings, the creatinine, HbA1c,

glucose, HDL-C, and TC levels were 1.0±0.3, 7.0±1.7, 132.1±54.3, 46.1±15, and 183.4±46.8 mg/dL, respectively. The mean SUA and NT-proBNP levels were recorded to be 6.6±1.9 mg/dL and 67-32772 pg/mL, respectively.

The baseline levels of SUA and NT-proBNP parameters of all patients were compared with the levels recorded in the following years (Figures 1, 2, Table 2). The baseline level of SUA was 6.6±1.9 mg/dL and that of NT-proBNP was 1645 (67-32772) pg/mL. However, these levels demonstrated a significant (p<0.001) decrement in the following years. Another comparison was drawn between the levels of SUA and NT-proBNP during 1st year and the corresponding levels of these parameters in the second year (Figures 1, 2, Table 2). Once again, a

Table 1. Demographic and clinical data of the study population

Variables (n=148)	Total (n=148)
Age (years)	66.6±10.3
Male, n (%)	91 (61.5)
Smoke, n (%)	15 (10.1)
Hypertension, n (%)	92 (62.2)
Diabetes mellitus, n (%)	87 (58.8)
Dyslipidemia, n (%)	120 (81.1)
Ischemic heart disease, n (%)	100 (67.6)
Using low dose S/V (24/26 mgx2)	40 (27.0)
Using high dose S/V (49/51 mgx2)	108 (72.9)
Beta-blocker	148 (100)
MRA	106 (71.6)
Diuretic	139 (93.9)
Atrial fibrillation, n (%)	56 (37.8)
Left ventricular ejection fraction (%)	40.7±14.3
Left atrial diameter (mm)	43.9±6.3
Total cholesterol (mg/dL)	183.4±46.8
HDL-C (mg/dL)	46.1±15
Triglyceride (mg/dL)	123 (38-413)
Glucose (mg/dL)	132.1±54.3
HbA1c (%)	7.0±1.7
Creatinine (mg/dL)	1.0±0.3
Serum uric acid (mg/dL)	6.6±1.9
NT-ProBNP (pg/mL)	1645 (67-32772)

HDL-C: High-density lipoprotein cholesterol, HbA1c: Hemoglobin A1c, NT-proBNP: N-terminal pro-B-type natriuretic peptide, MRA: mineralocorticoid receptor antagonists, S/V: Sacubitril/valsartan

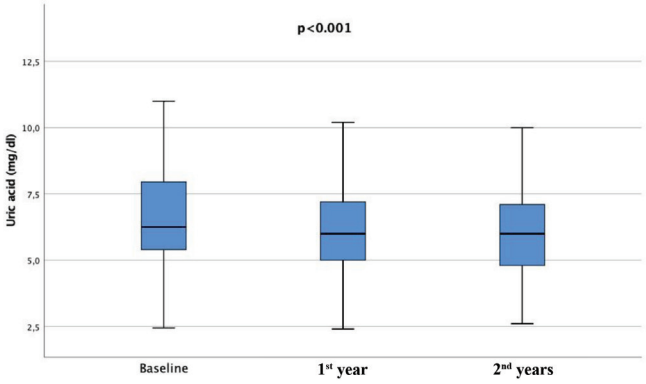

Figure 1. Changes in the SUA levels at the baseline and the end of the 1st and 2nd years
SUA: Serum uric acid

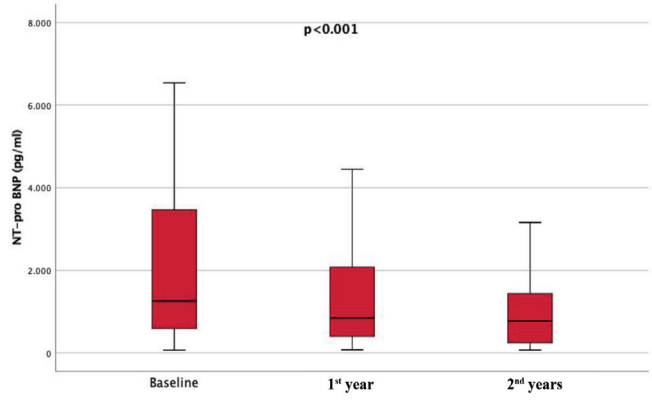

Figure 2. Changes in the NT-proBNP levels at the baseline and the end of 1st and 2nd years
NT-proBNP: N-terminal pro-B-type natriuretic peptide

Table 2. Changes in the 1st and 2nd-year uric acid level and NT-proBNP level when compared with the baseline values

Variables	Time				
		Mean	Standard error	Mean difference	p value
Uric acid (mg/dL)	Baseline	6.6	1.6		*a
	1. year	6.2	1.8	0.4	*β
	2. year	6.0	1.6	0.6	aβ
		Median	Min	Max	
NT-proBNP (pg/mL)	Baseline	1645	67	32772	*a
	1. year	987	78	25321	*β
	2. year	854	70	11300	aβ

*p<0.01 between baseline and 1st year; ap<0.01 between baseline and 2nd year; βp<0.01 between 1st and 2nd year.
NT-proBNP: N-terminal pro-B-type natriuretic peptide, min: Minimum, max: Maximum

significant decrement ($p<0.001$) was recorded in the levels of the studied parameters during the first and second years.

DISCUSSION

This research aimed to investigate the long-term effects of S/V on the levels of SUA in HFrEF patients. It was found that patients treated with S/V demonstrated a significant reduction in SUA levels during the first and second years in comparison to the respective baseline levels. Moreover, the NT-proBNP levels showed a significant reduction similar to the SUA levels. These findings highlight the potential metabolic effects of S/V in cardiovascular patients. The mechanisms underlying this effect may involve multiple pathways. Neprilysin inhibition increases natriuretic peptides (such as ANP and BNP), enhancing renal salt and water excretion, which may reduce SUA levels. In addition, angiotensin II inhibition may further promote uric acid excretion by increasing the glomerular filtration rate. These mechanisms, when combined with improvements in cardiac metabolism and hemodynamics, likely contribute to changes in uric acid metabolism, thereby emphasizing the need for further exploration of the broader cardiovascular and metabolic effects.

SUA has proven to be a vital parameter while dealing with patients with acute and chronic HF. SUA has turned into an important predictor of cardiovascular and all-cause mortality in HF patients. For individuals experiencing acute HF, SUA can be used as an adjunctive prognostic biomarker pointing toward adverse outcomes. For patients experiencing moderate-to-severe HF, raised levels of SUA can be considered to act as an independent prognostic marker of impaired prognosis.

In humans, SUA is formed as an end-product of the purine metabolism pathway. Xanthine oxidase (XO) catalyzes the final two steps of this pathway. XO is one of the most important and strong sources of ROS. In addition to XO, UA has been found to trigger the production of ROS in different cells such as renal tubular cells, hepatocytes, vascular smooth muscle cells, and endothelial cells. Increased levels of UA and XO therefore cause ROS-mediated negative outcomes such as mitochondrial damage, inflammatory activation, endothelial dysfunction, and disturbed cardiac contractility, which are usually recorded in the case of HF patients. In the extracellular hydrophilic environment, UA behaves like an antioxidant agent. Conversely, in an intracellular environment, the antioxidant effect is mediated by UA. In the context of the direct impact of UA on cardiomyocytes, the inhibition of myocardial cell activity by hyperuricemia via oxidative stress leading to apoptosis has been reported. Frequently recorded events in HF patients like hypoxia, insulin resistance, augmented catabolism, and cell death, are caused by the upregulation of XO. Researchers have found that XO contributes to the occurrence of HF via cardiac mechano-energetic coupling, myocyte apoptosis, and endothelial dysfunction.[11-13]

Previous studies have reported confusing data relating to the significance of reducing SUA levels in HF patients. An association between allopurinol utilization and a reduced rate of cardiovascular and all-cause mortality was reported by a prospective, double-blinded, multicenter, non-inferiority research that involved 6,190 patients having CV and gout disease. Of the total, 20% of the patients had HF and their median follow-up duration was 32 months.[14] Although allopurinol has proven to be a drug of choice with no contraindications for reducing the SUA levels in HF patients, no report has indicated whether the SUA-reducing approach is advantageous for left ventricular function, relevant symptoms, or outcomes in HF patients.[15,16] As per the PARADIGM-HF trial, S/V caused an SUA reduction of 0.24 mg/dL during one year ($p<0.0001$) in comparison to enalapril. Moreover, an association was recorded between the utilization of S/V and improved outcomes, irrespective of the levels of SUA in patients.[17]

In the PARAGON-HF trial, S/V reduced SUA by 0.38 mg/dL (95% confidence interval: 0.31-0.45) when compared with valsartan at 4 months, with greater effect noted in those with elevated SUA vs. normal SUA (-0.51 mg/dL vs. -0.32 mg/dL) (p value for interaction=0.031). S/V reduced the odds of initiating SUA-related treatments by 32% during follow-up ($p<0.001$).[18] The meta-analysis by Tamariz et al.[16] revealed a linear association between SUA and all-cause mortality above SUA levels of 7 mg/dL and with several other large prospective studies with longer follow-ups. In the study of Park et al.,[17] the combination of SUA and NT-proBNP levels was more beneficial than either marker alone for short-term outcomes in patients with acute HF. In our study, patients with chronic HF using S/V were evaluated, and, in the long-term follow-up of these patients, the decrease in the NT-proBNP levels was determined in addition to the decrease in the SUA levels.

Although the action mechanism of S/V on the SUA level is not known exactly, various mechanisms have been implicated. S/V increases the excretion of UA by slowing down the decline in renal function. In addition, the co-inhibition of angiotensin-converting enzyme and neprilysin has been demonstrated to have uricosuric effects. Finally, the lower diuretic requirements of patients using S/V (as observed with PARADIGM-HF) may lower the SUA levels.[17,18]

Study Limitations

Our study has some limitations. First, this study was conducted at a single center. Second, the number of patients was relatively small. Third, the relationship between the change in the SUA levels and the prognosis was not evaluated. Fourth, the effect on patients using SUA-lowering drugs was not evaluated. Another limitation of our study is the absence of a comparative group constituting patients receiving ARB/ACE inhibitors. This comparison would have provided a clearer understanding of the specific effects of S/V on the uric acid levels in contrast to that with the conventional treatments. Future studies should incorporate such a comparison group to further elucidate the benefits and mechanisms of S/V in HF patients.

CONCLUSION

In conclusion, S/V, which has several metabolic effects, appears to be a cardiovascular drug with pluripotential effects. The use of S/V in patients with HFrEF reduced the SUA levels. Large randomized clinical trials are thus warranted to demonstrate the beneficial clinical and metabolic effects of S/V.

Ethics Committee Approval: Permission was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee for the study (permission date: 18.07.2022, file number: 431869).

Informed Consent: Because it is a retrospective study, informed consent is not required.

Authorship Contributions: Concept: Ö.D., A.Ö.E., Ş.İ.E., S.Ö., Z.Y., Design: Ö.D., A.Ö.E., Ş.İ.E., S.Ö., Z.Y., Data Collection or Processing: Ö.D., A.Ö.E., S.T., Ş.İ.E., K.M., Analysis or Interpretation: A.Ö.E., Ş.İ.E., A.A., Literature Search: Ö.D., S.T., A.A., S.Ö., Writing: Ö.D., K.M., Z.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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