

Original Article

Association Between Sacubitril/Valsartan and Health Care Use: A Single-Center Retrospective Study From Turkey

Onur Osman Şeker¹, MD; Nihan Bahadır², MD; Seçkin Dereli^{2*}, MD

ABSTRACT

Aim: This study aimed to evaluate changes in health care utilization associated with sacubitril/valsartan (S/V) treatment by comparing outpatient clinic visits, emergency unit admissions, and hospitalizations before and after S/V treatment.

Methods: This retrospective study included 108 patients with heart failure with reduced ejection fraction (HFrEF) (mean [SD] age, 67 [20] years; 83% male; 70% ischemic etiology) who had been using S/V for at least 1 year and were followed at a tertiary hospital between December 2021 and January 2023. Patient data for outpatient visits, emergency unit admissions, and hospitalizations were retrieved from the e-Nabız application. Paired statistical analyses (paired-samples *t* test, Wilcoxon signed-rank test, and McNemar test) were performed to compare parameters before and after S/V initiation.

Results: Significant reductions were observed in the mean annual numbers of outpatient clinic visits (5.10 [1.95] vs 3.05 [1.25]; $P < .001$) and emergency unit admissions (4.40 [1.10] vs 2.80 [0.85]; $P < .001$) after S/V initiation. Furthermore, there was a significant decrease in the mean annual number of hospitalizations (3.20 [0.90] vs 1.80 [0.60]; $P < .001$), length of each stay (6.9 [3.5] vs 3.6 [1.9] days; $P < .001$), intensive care unit (ICU) admission rate (41% vs 17%; $P < .001$), and ICU length of stay (3.1 [0.9] vs 1.7 [0.8] days; $P < .001$).

Conclusions: S/V initiation was associated with significant reductions in outpatient clinic visits, emergency unit admissions, and hospitalizations, observed together with clinical and functional improvements in real-life patients with advanced HFrEF. These findings may assist cardiologists in countries where S/V is not reimbursed in deciding on its use. (*Iranian Heart Journal* 2026; 27(4): 25-39)

KEYWORDS: emergency unit admission; heart failure with reduced ejection fraction; hospitalization; outpatient clinic visit; sacubitril/valsartan

¹ Samsun Education And Research Hospital, Department of Cardiology, Samsun, Turkey.

² Ordu University Faculty of Medicine, Department of Cardiology, Ordu, Turkey.

*Corresponding Authors: Seçkin Dereli, MD; Ordu University Faculty of Medicine, Department of Cardiology, Ordu, Turkey.

Email: drseckindereli@gmail.com

Tel: +905333760984

Received: July 10, 2025

Accepted: September 4, 2026

Over the past 2 decades, substantial advances have been noted in the pharmacologic and nonpharmacologic treatment of heart failure with reduced ejection fraction (HFrEF).

Neurohormonal antagonists, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, aldosterone receptor antagonists, and β -blockers, have primarily contributed to

reduced mortality in patients with HFrEF. Despite current guideline-recommended HF treatment, cardiovascular death and HF hospitalizations remain unacceptably high, with an absolute risk of approximately 30%. Nonetheless, many patients with HFrEF experience a low quality of life.^{1, 2} Furthermore, new medications are needed to reduce mortality, improve quality of life, reduce the frequency of hospitalization, and improve left ventricular ejection fraction (LVEF) in symptomatic patients with HFrEF.

Sacubitril/valsartan (S/V), which contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan, is the first drug in the angiotensin receptor–neprilysin inhibitor (ARNI) class.^{3–5} In the study comparing the effects of ARNI and ACE inhibitors on mortality and morbidity in patients with HFrEF (PARADIGM-HF), ARNI reduced cardiovascular death and hospitalization compared with ACE inhibition.^{5, 6} Based on these results, S/V received a Class I recommendation in current HFrEF treatment guidelines.⁷ However, an important aspect of this study was that the beneficial effect of S/V was observed against the highest dose of ACE inhibitors used in randomized controlled trials to date. The strict inclusion and exclusion criteria evaluating the maximum dose tolerability of both S/V and ACE inhibitors in the study led to the hypothesis that these findings might not be equivalent to daily clinical practice. In real life, patients are often older and frailer and may not tolerate the doses used in those randomized trials. In addition, these patients are at higher risk for cardiovascular death and hospitalization compared with the PARADIGM-HF study population. Considering the differences between the study population and patients in clinical practice, we evaluated outpatient clinic visits, emergency department admissions, and hospitalizations of patients with HFrEF

before and after S/V treatment at our tertiary hospital in Turkey. We also assessed the effect in clinically significant subgroups.

METHODS

This was a retrospective, single-center, observational study comparing health care utilization and clinical parameters during 2 matched 12-month periods before and after S/V initiation. Patients with HFrEF who underwent S/V treatment were included in the study. Because of the absence of public health insurance reimbursement for S/V in Turkey during the study period, all participants purchased the drug entirely out-of-pocket and maintained self-funded treatment throughout the 12-month follow-up. The inclusion criteria were as follows: (a) at least 18 years of age; LVEF of 40% or less; New York Heart Association (NYHA) class II to IV symptoms; use of the target S/V dose; and use of the drug for at least 1 year; (b) ACE inhibitor or angiotensin II receptor blocker treatment before the transition to ARNI treatment; and (c) regular follow-up in the cardiology outpatient clinic. Patients with malignancies detected during the specified study periods, those with a history of acute coronary syndrome, surgery, or trauma, and patients who underwent cardiac resynchronization therapy (CRT) at least 6 months before the specified period were excluded.

A total of 108 patients were included in the study. Demographic characteristics, physical characteristics, etiology of HF, comorbidities, functional capacity class, laboratory parameters, transthoracic echocardiographic measurements, and basic medical and HF treatment data were recorded retrospectively at S/V treatment initiation and at the end of month 12. Patient health care utilization data, including cardiology and noncardiology outpatient visits, emergency department admissions, and inpatient stays (ICU and medical ward), were retrospectively retrieved from the central e-Nabız database, the national

health information exchange infrastructure operated by the Turkish Ministry of Health and integrated across all public, university, and private health care institutions. Because national regulations require real-time digital registration linked to the patient's national identification number for any medical evaluation or intervention, no health care service can be delivered without a system entry, ensuring nationwide capture of events occurring at facilities outside our index center. Patients with incomplete central registry synchronization or unverified national records were excluded. The study protocol was approved by the local research ethics committee in accordance with the Declaration of Helsinki. Patients were informed verbally, and written informed consent was obtained. Patient data were evaluated in 2 separate groups-before and after S/V treatment-to determine the efficacy of S/V on outpatient clinic visits, emergency department admissions, and hospitalizations. The percentage of patients admitted to the cardiology outpatient clinic was reported by study group, and the mean annual number of outpatient clinic visits per patient was calculated using the total number of outpatient clinic visits. Similarly, the percentage of patients admitted to the emergency department was reported, and the mean annual number of admissions to the emergency department per patient was calculated using the total number of emergency department admissions. Hospitalization was evaluated in 2 subgroups: initial admission to the cardiac intensive care unit (CICU) and initial admission to the medical ward. The percentage of hospitalized patients is reported. The mean annual number of hospitalizations per patient was calculated using the total number of hospitalizations, and the mean length of each stay was calculated using the total number of hospitalization days.

Statistical Analysis

The present study was approved by the university's clinical research ethics committee on August 12, 2021 (decision 2021/43). During the preparation of the revised manuscript, an artificial intelligence-assisted technology (a large language model) was used solely for language editing and improvement of readability. No artificial intelligence tool was used to generate or analyze data, perform statistical calculations, produce figures or images, or draw scientific conclusions. All authors reviewed and verified the final text and accept full responsibility for the integrity of the submitted work.

Statistical evaluation was performed using SPSS version 22.0 (IBM Corp). Continuous variables were tested for normality using the Shapiro-Wilk test in combination with visual inspection of normal Q-Q plots and histograms. Normally distributed continuous variables are presented as mean (SD), whereas non-normally distributed continuous variables are expressed as median (IQR). Categorical variables are expressed as counts and percentages. The sample size ($n = 108$) reflects the total consecutive cohort of eligible patients with HFrEF followed at our center who met all inclusion criteria during the study period. Because the cohort comprised all consecutive eligible patients, no a priori sample size calculation was performed, and no post hoc power analysis derived from the observed effect sizes is reported, as such an analysis is circular and adds no information beyond the observed estimates. Two-sided 95% confidence intervals (CIs) for the paired mean differences are reported for all normally distributed continuous endpoints analyzed with the paired-samples *t* test. CIs are not presented for variables analyzed with the Wilcoxon signed-rank test. For descriptive purposes, the standardized effect sizes for the primary outcomes were large (1.87 for annual hospital stay frequency and 0.75 for LVEF). These values were computed using the

averaged SD of the 2 time points and are reported explicitly as Cohen d_{av} , not as a paired-difference Cohen d .

In line with the normality assessment and to account for the paired (before-and-after) structure of the data, pre- and posttreatment continuous parameters were compared using the paired-samples t test (for normally distributed data) or the Wilcoxon signed-rank test (for non-normally distributed data). Serum creatinine, white blood cell count, potassium, total cholesterol, serum proBNP, and the annual number of CICU admissions were non-normally distributed and were analyzed with the Wilcoxon signed-rank test and presented as median (IQR); all remaining continuous variables were analyzed with the paired-samples t test and presented as mean (SD). Differences in paired categorical variables across time points (such as NYHA functional class and medication rates) were evaluated using the McNemar test or the Marginal Homogeneity test. Absolute differences (Δ) between the 2 time points are reported for all endpoints. Correlations between continuous variables were assessed using Spearman rank correlation coefficients calculated on all 108 patients for every variable pair; these analyses were exploratory and were not adjusted for multiple comparisons. A 2-tailed P value less than .05 was considered statistically significant.

Length-of-stay parameters (hospital, CICU, and medical ward) were calculated only among patients who had at least 1 corresponding admission in both 12-month periods, so that every length-of-stay comparison is a genuinely paired within-patient analysis. These comparisons, therefore, refer to that subgroup rather than to the entire cohort. To control for inflation of the type I error rate arising from multiple endpoints, a Bonferroni correction was applied separately within each of 3 prespecified outcome families: health care utilization endpoints ($k = 14$), clinical and

echocardiographic endpoints ($k = 9$), and laboratory parameters ($k = 8$). Within each family, the adjusted significance threshold was $\alpha = .05/k$; unadjusted P values reported in Table 2 are interpreted against the adjusted threshold of the family to which each endpoint belongs ($\alpha = .0036$, .0056, and .0063, respectively). Endpoints that no longer met the adjusted threshold are named individually below rather than being described collectively as retaining significance. Applying these thresholds, 3 endpoints that were nominally significant did not remain significant after Bonferroni adjustment: the reduction in the cardiology outpatient admission rate ($P = .004$), the increase in ivabradine use ($P = .024$), and the increase in serum potassium ($P = .028$). All other endpoints reported as significant retained significance after adjustment. To assess clinical significance alongside statistical hypothesis testing, standardized effect sizes were also calculated: Cohen d for paired t test comparisons (0.2 = small, 0.5 = medium, and ≥ 0.8 = large effect) and Wilcoxon r ($r = Z/\sqrt{N}$) for nonparametric paired continuous comparisons.

RESULTS

Basic Characteristics

The basic characteristics of the study population are shown in Table 1. Patients had a mean (SD) age of 67 (20) years, 83% were male, and 70% had ischemic heart disease in the etiology of HF. When comorbidities were examined, hypertension was observed in 61%, diabetes in 33%, and chronic obstructive pulmonary disease in 12%; 19% had atrial fibrillation, and 9% had a history of valvular surgery. The rate of patients with an implantable cardioverter defibrillator (ICD) and CRT was 22%. When functional capacity was evaluated, 26% of the patients were NYHA class II and 74% were class III or IV, which were accepted as advanced stage.

Table 1. Baseline Characteristics

Variable	Total Population (No. = 108)
Demographics	
Age, y	67 (20)
Male, %	83
Active smoker, %	11
Duration of heart failure, y	6.4 (3.3)
Ischemic etiology, %	70
Physical Features	
Systolic blood pressure, mm Hg	116.8 (21)
Diastolic blood pressure, mm Hg	63.5 (16)
Weight, kg	76.50 (13.80)
BMI, kg/m ²	26.80 (4.90)
Heart rate, beats/min	78.5 (17)
Comorbidities, %	
Atrial fibrillation	19
COPD	12
Hypertension	61
Dyslipidemia	33
Diabetes	33
Valve surgery	9
Echocardiography	
Left ventricular end-diastolic diameter, mm	60.30 (8.90)
LVEF, %	27.4 (9.25)
Laboratory Analysis	
Sodium, mmol/L	136.5 (4.8)
Potassium, mmol/L	4.20 (0.70)
Hemoglobin, g/dL	13.20 (1.40)
Albumin, g/dL	3.50 (0.85)
Creatinine, mg/dL	1.25 (0.60)
Cholesterol, mg/dL	170.00 (35.00)
proBNP, ng/L	795 (310)
White blood cell count, ×10 ³ /μL	7.90 (3.50)
NYHA Class, %	
Class II	26
Class III	56
Class IV	18
Guideline-Directed Heart Failure Therapy	
ACE-I or ARB, %	100
β-Blocker, %	84
Aldosterone antagonist, %	62
Loop diuretic, %	77
Ivabradine, %	15
Statin, %	25
ICD and CRT, %	22

Values are mean (SD) or No. (%). Variables that did not meet the normality assumption on Shapiro-Wilk testing (potassium, creatinine, total cholesterol, white blood cell count, and proBNP) are expressed as median (IQR).

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; ICD: implantable

cardioverter-defibrillator; IQR: interquartile range; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; proBNP: pro-B-type natriuretic peptide

Table 2 also compares the data before and after S/V treatment. At the end of 12 months, when the S/V dose of the patients was examined, 46% of patients were using 24/26 mg, 39% were using 49/51 mg, and 15% were using 97/103 mg.

Paired statistical analyses demonstrated significant clinical, echocardiographic, and health care utilization improvements following 12 months of S/V treatment. Echocardiographic LVEF significantly increased by an absolute mean difference of +6.7% (from 27.4 [9.25]% to 34.1 [8.60]%; 95% CI, 5.53 to 7.87; paired *t* test *P* < .001). Concurrently, serum proBNP levels decreased significantly from a median of 795 (IQR, 310) ng/L to 440 (IQR, 145) ng/L (median reduction, −355 ng/L; Wilcoxon signed-rank *P* < .001). NYHA functional capacity showed marked improvement: at 12 months, 80% of patients were in NYHA class I or II, and 74% of patients improved by at least 1 NYHA class (*P* < .001 by marginal homogeneity test). Regarding co-medications, loop diuretic use significantly decreased by 19% (77% vs 58%; McNemar *P* = .003), while ivabradine use increased from 15% to 24% (McNemar *P* = .024). Serum creatinine remained stable (median, 1.25 [IQR, 0.60] vs 1.30 [IQR, 0.55] mg/dL; Wilcoxon *P* = .404), whereas serum potassium showed a small but significant increase (median, 4.20 [IQR, 0.70] vs 4.40 [IQR, 0.80] mmol/L; Wilcoxon *P* = .028).

Beyond statistical significance, the primary endpoints showed clinically meaningful effect sizes: the improvement in LVEF corresponded to a medium-to-large effect (Cohen *d* = 0.75), and the reduction in proBNP corresponded to a large nonparametric effect (Wilcoxon *r* = 0.77). Health care utilization changes were of

similar magnitude, with a Cohen *d* of 1.87 for the annual number of hospitalizations and 1.22 for the mean length of each stay.

Complete point estimates, absolute changes, statistical tests, and *P* values are presented in Table 2.

Table 2. Comparison of Clinical, Laboratory, and Echocardiographic Parameters and Health Care Utilization Before and After S/V Treatment (No. = 108)

Variable	Before S/V	After S/V	Absolute Change (Δ)	95% CI of Difference	Statistical Test	<i>P</i>
Laboratory Parameters						
Sodium, mmol/L	136.5 (4.8)	138.8 (5.1)	+2.3	1.49 to 3.11	Paired <i>t</i> test	< .001
Potassium, mmol/L	4.20 (0.70)	4.40 (0.80)	+0.2	—	Wilcoxon signed-rank	.028
Albumin, g/dL	3.50 (0.85)	3.80 (0.75)	+0.3	0.15 to 0.45	Paired <i>t</i> test	< .001
Hemoglobin, g/dL	13.20 (1.40)	13.50 (1.25)	+0.3	0.09 to 0.51	Paired <i>t</i> test	.006
Creatinine, mg/dL	1.25 (0.60)	1.30 (0.55)	+0.05	—	Wilcoxon signed-rank	.404
Cholesterol, mg/dL	170.00 (35.00)	175.00 (42.00)	+5.0	—	Wilcoxon signed-rank	.151
proBNP, ng/L	795 (310)	440 (145)	−355	—	Wilcoxon signed-rank	< .001
White blood cell count, $\times 10^3/\mu\text{L}$	7.90 (3.50)	7.80 (3.20)	−0.1	—	Wilcoxon signed-rank	.533
Weight, kg	76.50 (13.80)	76.80 (13.20)	+0.30	−0.68 to 1.28	Paired <i>t</i> test	.543
BMI, kg/m ²	26.80 (4.90)	27.00 (4.80)	+0.20	−0.70 to 1.10	Paired <i>t</i> test	.661
Guideline-Directed Therapy, %						
β -Blocker	84	86	+2.0	—	McNemar test	.650
Aldosterone antagonist	62	60	−2.0	—	Exact McNemar test	.804
Loop diuretic	77	58	−19.0	—	McNemar test	.003
Ivabradine	15	24	+9.0	—	McNemar test	.024
Echocardiography						
LV end-diastolic diameter, mm	60.30 (8.90)	59.10 (9.40)	−1.20	−2.85 to 0.45	Paired <i>t</i> test	.153
LVEF, %	27.4 (9.25)	34.1 (8.60)	+6.7	5.53 to 7.87	Paired <i>t</i> test	< .001
NYHA Functional Class, %			Marginal homogeneity	< .001 (omnibus)		
NYHA class I	0	23	+23.0	—	—	—
NYHA class II	26	57	+31.0	—	—	—
NYHA class III	56	20	−36.0	—	—	—
NYHA class IV	18	0	−18.0	—	—	—
Dose of S/V at 12 months, %						
24/26 mg	—	46	—	—	Not applicable	—
49/51 mg	—	39	—	—	Not applicable	—
97/103 mg	—	15	—	—	Not applicable	—
Outpatient Visits						
Cardiology outpatient admission rate, %	100	92	−8.0	—	Exact McNemar test	.004
Cardiology outpatient visits per year (No. = 100)	5.10 (1.95)	3.05 (1.25)	−2.05	−2.39 to −1.71	Paired <i>t</i> test	< .001
Other specialty visits per year (No. = 108)	5.3 (3.72)	3.9 (1.7)	−1.40	−2.12 to −0.68	Paired <i>t</i> test	.003
Emergency Unit Admission						
Emergency admission rate, %	89	71	−18.0	—	McNemar test	.002
Emergency unit admissions per year (No. = 71)	4.40 (1.10)	2.80 (0.85)	−1.60	−1.88 to −1.32	Paired <i>t</i> test	< .001

Variable	Before S/V	After S/V	Absolute Change (Δ)	95% CI of Difference	Statistical Test	P
Hospitalization Data						
Overall hospitalization rate, %	63	27	-36.0	—	McNemar test	< .001
Hospitalization stays per year (No. = 29)	3.20 (0.90)	1.80 (0.60)	-1.40	-1.72 to -1.08	Paired <i>t</i> test	< .001
Length of each hospital stay, d (No. = 29)	6.9 (3.5)	3.6 (1.9)	-3.30	-4.69 to -1.91	Paired <i>t</i> test	< .001
Initial Admission to ICU						
ICU admission rate, %	41	17	-24.0	—	McNemar test	< .001
ICU admissions per year (No. = 18)	2.00 (1.00)	1.00 (1.00)	-1.0	—	Wilcoxon signed-rank	< .001
Length of each ICU stay, d (No. = 18)	3.1 (0.9)	1.7 (0.8)	-1.40	-2.15 to -0.65	Paired <i>t</i> test	< .001
Medical ward stay following ICU, d (No. = 18)	3.9 (1.5)	2.0 (0.6)	-1.90	-2.77 to -1.03	Paired <i>t</i> test	< .001
Initial Admission to Medical Ward						
Medical ward admissions per year (No. = 11)	3.50 (1.10)	1.90 (0.70)	-1.60	-2.24 to -0.96	Paired <i>t</i> test	< .001
Length of stay in medical ward, d (No. = 11)	6.4 (2.6)	3.1 (1.5)	-3.30	-5.27 to -1.33	Paired <i>t</i> test	< .001

Values are mean (SD), median (IQR), or No. (%). Serum potassium, creatinine, total cholesterol, white blood cell count, proBNP, and the annual number of ICU admissions were nonnormally distributed on Shapiro-Wilk testing and were analyzed with the Wilcoxon signed-rank test; all other continuous variables were analyzed with the paired-samples *t* test. The 95% CI of the difference is reported for paired-samples *t* test comparisons and is not defined for Wilcoxon signed-rank comparisons. The number of patients contributing to each paired comparison is stated in parentheses beside the corresponding row name; comparisons without a stated subgroup size include the entire cohort (No. = 108). The change in the cardiology outpatient admission rate was tested with the exact McNemar test (9 discordant pairs). The number of tests in each outcome family and the resulting adjusted significance threshold are stated in the Statistical Analysis section. The marginal homogeneity test provides a single omnibus *P* value for the overall shift in the NYHA class distribution; the class-specific rows are descriptive only, and no separate *P* value is reported for each individual class.

BMI: body mass index; ICU: intensive care unit; IQR: interquartile range; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; proBNP: pro-B-type natriuretic peptide; S/V: sacubitril/valsartan

Health care utilization was significantly reduced across all parameters. The mean annual number of cardiology outpatient visits decreased from 5.10 (1.95) to 3.05 (1.25) (mean difference, -2.05; 95% CI, -2.39 to -1.71; paired *t* test *P* < .001). The proportion of patients requiring emergency unit admission dropped from 89% to 71% (*P* = .002), with annual emergency visits decreasing from 4.40 (1.10) to 2.80 (0.85) (mean difference, -1.60; 95% CI, -1.88 to -1.32; paired *t* test *P* < .001). Overall hospitalization rate decreased from 63% to 27% (absolute change, -36.0%; McNemar *P* < .001). Mean annual hospital stay frequency fell from 3.20 (0.90) to 1.80 (0.60) (mean difference, -1.40; 95% CI, -1.72 to -1.08; paired *t* test *P* < .001), and

mean length of hospital stay decreased by 3.3 days (from 6.9 [3.5] to 3.6 [1.9] days; paired *t* test *P* < .001). ICU admission rate (41% vs 17%; *P* < .001), ICU length of stay (3.1 [0.9] vs 1.7 [0.8] days; *P* < .001), and medical ward stay all experienced statistically significant reductions (*P* < .001 for all paired comparisons).

In addition, in Figure 1, the mean annual numbers of hospital stays, cardiology outpatient clinic visits, and emergency department admissions were compared before and after treatment according to each functional NYHA class of patients, and significant decreases were observed in all 3 parameters for all NYHA classes (*P* < .001 for all). When patients were stratified according to their maintained S/V dose tiers (24/26 mg

[46%], 49/51 mg [39%], and 97/103 mg [15%]), statistically significant reductions in annual hospital stays, cardiology outpatient visits, and emergency department admissions compared with the pretreatment baseline were observed within each individual dose tier ($P < .001$ for all tiers; Figure 2). Nevertheless, owing to unequal subgroup sample sizes, direct formal comparative superiority testing between dose tiers was not performed.

Table 3 shows the correlation analysis between cardiology outpatient clinic visit, emergency department admission, and hospitalization parameters and changes in the different variables of the treatment process in patients with HFrEF. After

treatment, there was a statistically significant negative correlation between age and changes in hospitalization, cardiology outpatient clinic visit, and emergency department admission parameters, while significant positive correlations were shown with improvement in NYHA class, LVEF, and decrease in proBNP. There was no significant correlation observed between S/V dose, duration of HF, and hospitalization and outpatient admission parameters. These bivariate associations are exploratory and unadjusted for potential confounding variables, and are therefore presented as parallel clinical trends rather than independent causal relationships.

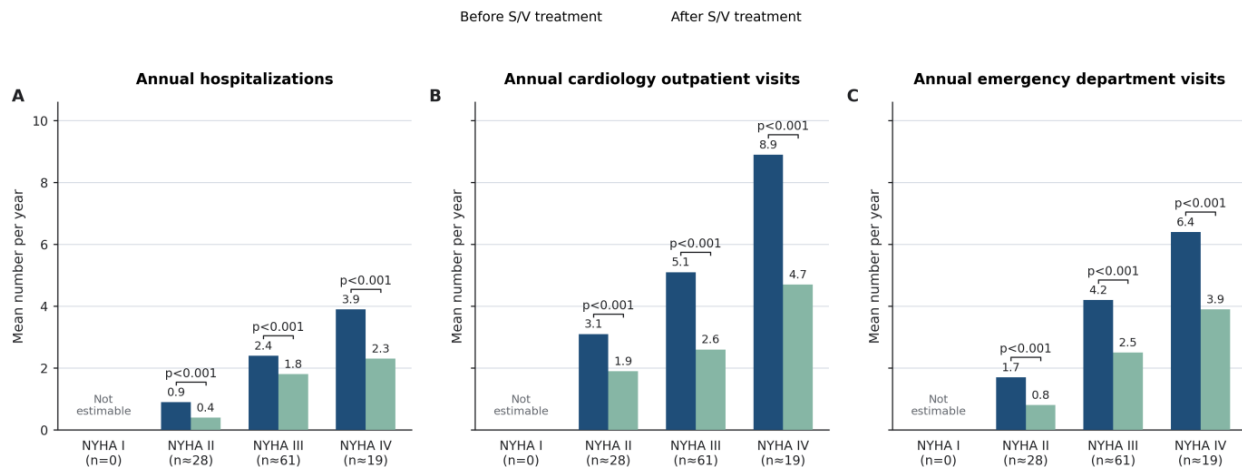


Figure 1. New York Heart Association (NYHA) health care utilization

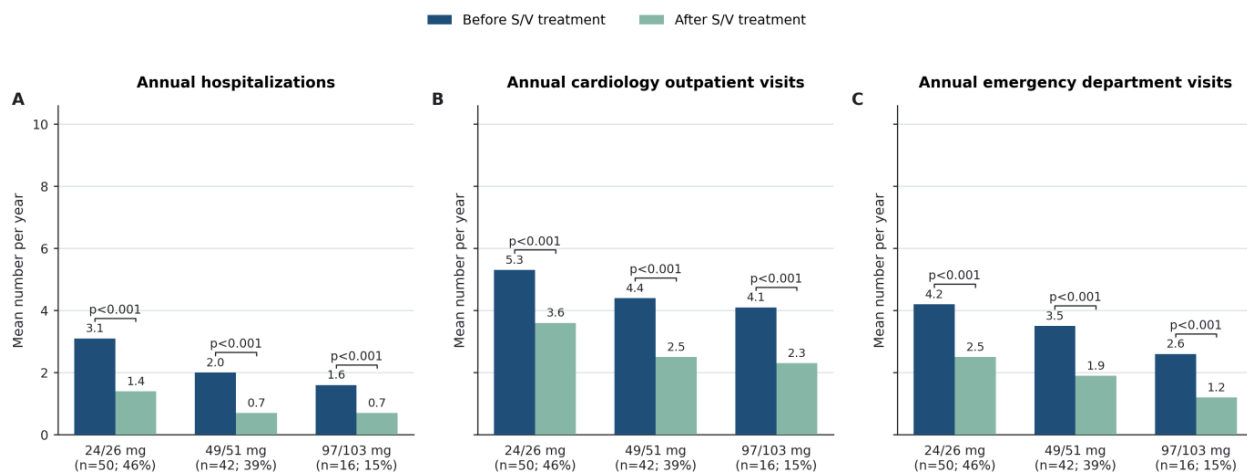


Figure 2. Dose health care utilization

Table 3. Correlation Analysis of HFrEF Variables and Hospitalization, Outpatient Clinic Visits, and Emergency Unit Admission Parameters (Exploratory Analysis)

		Δ Average Annual Number of Cardiology Outpatient Visits	Δ Average Annual Number of Emergency Unit Admissions	Δ Average Annual Number of Hospitalization Stays	Δ Length of Each Stay	Δ Average Number of Admissions to ICU	Δ Length of Each Stay in ICU
Age	<i>r</i>	-0.323	-0.369	-0.298	-0.575	-0.145	-0.397
	<i>p</i>	.001	<.001	.003	.002	.180	.027
Δ NYHA class	<i>r</i>	0.750	0.474	0.695	0.338	0.570	0.397
	<i>p</i>	<.001	<.001	<.001	.014	<.001	.041
Dose of S/V	<i>r</i>	0.220	0.196	0.124	0.056	0.167	0.035
	<i>p</i>	.029	.055	.235	.796	.098	.906
Δ Left ventricular ejection fraction	<i>r</i>	0.605	0.321	0.417	0.421	0.532	0.299
	<i>p</i>	<.001	.001	<.001	.027	<.001	.033
Δ proBNP	<i>r</i>	0.317	0.421	0.567	0.339	0.298	0.493
	<i>p</i>	.001	<.001	<.001	.039	.003	.029
Duration of heart failure	<i>r</i>	-0.158	-0.197	-0.201	-0.129	-0.089	-0.104
	<i>p</i>	.121	.055	.049	.536	.410	.708

Correlation coefficients are Spearman rank correlation coefficients, calculated on all 108 patients for every variable pair. All correlations in this table are exploratory, unadjusted for multiple comparisons, and unadjusted for confounding variables; the *P* values shown are nominal, and with 36 tests performed, several nominally significant results would be expected by chance alone. They are presented for hypothesis-generating purposes only and should not be interpreted as confirmatory evidence of association.

HFrEF: heart failure with reduced ejection fraction; ICU: intensive care unit; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; proBNP: pro-B-type natriuretic peptide; S/V: sacubitril/valsartan

DISCUSSION

This is the first study conducted in a tertiary hospital to investigate the effects of S/V treatment on hospitalization, outpatient clinic visits, and emergency department admissions among patients with HFrEF in real-world clinical practice. During the 1-year follow-up after S/V treatment, compared with the pretreatment period, we observed significant decreases in hospitalizations, cardiology outpatient clinic visits, and emergency department admissions, despite the more advanced disease and greater frailty of the patients.

HF is one of the major health problems of the 21st century, with increasing incidence and prevalence.⁸ The HAPPY study, which investigated the prevalence and risk factors of HF among adults in Turkey, reported that 1.5 million people were affected, with an HF prevalence of 2.9%, and estimated that 3 million people would be at risk in the near future.⁹ Although HF is more common in

our country, it remains one of the most important causes of hospitalization.¹⁰ One important goal of HF treatment is to reduce the burden on the health care system. S/V has had a substantial effect on the treatment of HFrEF, particularly in terms of reducing mortality and hospitalization rates. This novel combination offers an alternative to previously available treatments and addresses the unmet need for improved patient outcomes. Still, the transition from ACE inhibitors, which are available as low-cost generic drugs, to S/V raises questions about cost-effectiveness, particularly in regions such as Asia, where health care budgets are limited and the economic evaluation of new drugs is as important as their clinical efficacy.

Our study shows that S/V may improve symptoms in patients with HFrEF and facilitate treatment management in older patients with advanced HF and frailty. Nonetheless, our findings suggest that

reimbursement could facilitate wider use of the drug throughout the HFrEF population by reducing cost-related concerns among cardiologists. Although short-term studies with small sample sizes¹¹⁻¹³ have generated uncertainty regarding the cost of the drug, subsequent studies have provided stronger evidence regarding the use of ARNI.¹⁴ We anticipate that our findings will contribute to future cost-effectiveness studies in countries where S/V is not covered by reimbursement, given the observed short-term reduction in health care system workload. The economic burden of disease includes not only direct diagnostic and treatment costs but also indirect costs. Depending on the disease, productivity losses among patients and caregivers should also be considered an important component of the health care burden associated with HF.¹⁵ Improvements in functional capacity among patients with HFrEF may reduce indirect health care expenditures by improving quality of life and functional status, in addition to reducing direct costs associated with outpatient clinic visits and hospitalizations after S/V treatment.

When we compared the baseline characteristics of our study population with those of the population in the study by Aras et al¹⁶ from Turkey, we observed that our population consisted of patients with more advanced HF. Our patients were also older than those in the SELFIE-TR study, which provided a snapshot of patients with HF in Turkey.¹⁷ Considering that patients treated in real-world clinical practice may be older and frailer than those enrolled in the PARADIGM-HF study, cardiologists may be reluctant to initiate S/V treatment.¹⁸ Despite this concern, the mean age of our study population receiving S/V treatment was higher. Accordingly, outpatient clinic visits, emergency department admissions, and hospitalizations were more frequent, and hospital stays were longer in our study

population before S/V treatment, regardless of whether patients were admitted to the CICU or a medical ward. Because of the high cost of S/V and the absence of reimbursement, cardiologists initiated treatment primarily in symptomatic patients with advanced HF despite standard therapy. Nevertheless, our correlation analysis suggests that the effectiveness of S/V was not reduced with increasing age, and our results are consistent with those of studies by Martens et al¹⁹ and Simpson et al.²⁰

After 1 year of follow-up, we observed improvements in functional capacity and significant decreases in proBNP levels, consistent with the existing literature, particularly the PROVE-HF study. In addition, we found a strong positive correlation between changes in NYHA class and proBNP levels and reductions in outpatient admissions and hospitalizations.²¹⁻²⁴ A significant correlation was also found between improvements in LVEF and changes in hospitalization and outpatient admission parameters. Nevertheless, no correlation was found between S/V dose and hospitalization or outpatient admission parameters, which were significantly reduced after treatment. As in the TITRATION study, more gradual uptitration may facilitate achievement of a higher dose in patients initiating S/V treatment, potentially revealing a significant correlation between the parameters examined in our study and individual S/V doses. Be that as it may, as shown in Figure 2, significant changes in hospitalization and outpatient admission parameters were detected at each S/V dose. This finding is consistent with the hypothesis highlighted in different studies that the drug may provide clinically meaningful efficacy at every maintained dose, even when the target dose cannot be achieved.²⁵ An important finding of our study was that, despite the inclusion of older patients and patients with advanced

HF, renal function did not deteriorate and diuretic doses decreased during S/V treatment. These findings may be related to the beneficial effects of natriuretic hormones on glomerular hemodynamics, in contrast to the deterioration in renal function that represents an important barrier to S/V treatment initiation for cardiologists.²⁶

In line with the clinical trial literature, including the PROVE-HF study, we observed consistent bivariate associations between improvements in clinical surrogates (Δ LVEF, Δ proBNP, and Δ NYHA class) and reductions in health care utilization parameters. However, these correlation results should be interpreted with caution. Improvements in left ventricular systolic function, reductions in natriuretic peptide levels, and gains in functional capacity represent collinear, mutually dependent clinical manifestations of cardiac reverse remodeling during S/V therapy rather than isolated, independent mechanisms. Consequently, these associations reflect a convergent clinical response to optimized guideline-directed medical therapy (GDMT) rather than direct individual cause-and-effect relationships with admission rates.

In pivotal clinical trials, including subanalyses of the PARADIGM-HF and TITRATION studies, S/V has been shown to provide clinically meaningful benefits across its dosing spectrum. Patients maintained on lower starting doses, such as 24/26 mg twice daily, because of advanced age, frailty, or lower baseline blood pressure may experience symptomatic improvement, reductions in proBNP levels, and lower hospitalization rates compared with baseline therapy. Real-world evidence suggests that, although uptitration toward the target maintenance dose of 97/103 mg twice daily may further enhance therapeutic efficacy and cardiac remodeling, maintenance at any tolerated dose may be associated with more favorable outcomes than omission of the

drug. Our findings reinforce this observation: although reductions in health care utilization were documented across all maintained dose levels (Figure 2), clinicians should be encouraged to initiate S/V at lower doses when necessary and uptitrate as tolerated to achieve optimal long-term outcomes.

Although the effectiveness of this drug has been established, its accessibility and prescribing are often influenced by cost.²⁷ Cost is also an important consideration for many countries when determining whether drugs should be included in reimbursement programs administered by public or private insurance systems.²⁸ The cost-effectiveness of S/V has been demonstrated in Western countries, including the United States, United Kingdom, Denmark, Colombia, and the Netherlands.^{29–32} Nonetheless, no cost-effectiveness study has evaluated the health care costs of S/V in countries where it is not covered by reimbursement, such as Turkey. Although safety and efficacy results from controlled clinical trials support the clinical value of the drug, cost concerns may limit the transfer of its expected benefits to patients after approval.^{33,34} Although cardiologists are convinced of the effects of S/V based on the results of the PARADIGM-HF study, prescriptions remain relatively infrequent because of the absence of reimbursement. Our real-world data on the treatment of HFrEF may provide additional evidence to support consideration of S/V initiation by cardiologists.

An important observation in our study was the significant modification of coprescribed HF medications following S/V initiation. Loop diuretic use decreased significantly from 77% to 58% (absolute reduction, -19.0% ; McNemar $P = .003$), a finding compatible with clinical decongestion and favorable cardiac reverse remodeling, although the contribution of neprilysin inhibition cannot be established in an

uncontrolled before-and-after design. Downtitration of loop diuretics was observed after S/V initiation without apparent loss of clinical stability and may be related to enhanced natriuresis attributed to S/V. Still, this change cannot be attributed solely to S/V because concomitant treatment adjustments and the clinical course may also have contributed. Conversely, ivabradine use increased from 15% to 24% (McNemar $P = .024$) to achieve target heart rate control in eligible patients. Although heart rate optimization with ivabradine provides incremental functional benefits, this adjustment occurred in a minority of patients ($n = 10$) as part of standard guideline-directed care. Nevertheless, these concurrent adjustments in background therapies reflect the reality of comprehensive HF management, in which S/V serves as an anchor for broader GDMT optimization.

In countries where novel GDMT therapies are not covered by public reimbursement, out-of-pocket financial burden poses a major barrier to drug initiation and long-term persistence. In our study, all enrolled patients paid for S/V out of pocket, representing a cohort of patients who maintained continuous treatment. Although this economic requirement may select for patients with sufficient financial resources and treatment adherence, our findings provide real-world health economic insights for cardiologists practicing in health care settings without reimbursement coverage.

Limitations

Our study has several limitations. It was conducted at a single center in a relatively small cohort, which limits the generalizability of the findings. The design was observational and uncontrolled; randomized clinical trials remain the reference standard for evaluating drug therapy. In addition, after S/V treatment initiation, hospitalizations occurred because

of symptomatic hypotension, dizziness, and related trauma, as well as electrolyte imbalance; these hospitalizations were included among hospitalizations due to HF. Although each patient served as their own control, the before-and-after design cannot distinguish changes associated with S/V initiation from regression to the mean, natural fluctuations in disease severity, secular changes in health care delivery, or other concomitant treatment modifications. Consequently, the observed associations should not be interpreted as evidence of causality. Finally, nonnormally distributed variables analyzed using the Wilcoxon signed-rank test are presented as median (IQR). Because this test does not yield a mean difference estimate, no 95% CI is reported for those endpoints; 95% CIs of the paired differences are provided for all paired-samples t test comparisons.

The study population was derived from a single tertiary referral center in Turkey and may therefore differ from patients managed in other institutions or health care systems. Because data collection was retrospective and not prospectively protocolized, some potential confounding variables may not have been consistently recorded, leaving the possibility of residual confounding. Confirmation in prospective, multicenter studies is warranted.

Concurrent modifications in background HF therapy during follow-up may also have contributed to the observed changes. The reduction in loop diuretic burden and the modest increase in ivabradine use may have exerted synergistic effects on functional class, proBNP levels, and admission rates, and the observational design precluded multivariable adjustment for every longitudinal medication change. In addition, although e-Nabız captures all registered admissions nationwide, data collection relies on administrative diagnostic and procedural

coding, which carries a minor potential for coding variability.

Furthermore, requiring at least 1 year of continuous S/V use introduces inherent selection and survivor bias. Patients who discontinued S/V prematurely because of drug intolerance, severe adverse events, early cardiovascular mortality, or financial inability to sustain out-of-pocket drug purchases were excluded. Consequently, our final study population represents a more adherent and stable subset of patients with HFrEF, and the findings should be interpreted as an on-treatment analysis rather than an intention-to-treat real-world initiation cohort.

Finally, some analyses were constrained by statistical power and the nature of the statistical approach. Although the dose subgroups were unevenly distributed (46% receiving 24/26 mg, 39% receiving 49/51 mg, and 15% receiving 97/103 mg; the last group comprised only 16 patients), inter-dose comparisons were not formally powered and should be interpreted descriptively rather than as dose-response gradients. Likewise, the correlations presented in Table 3 were unadjusted for confounding variables and did not account for multicollinearity among closely linked markers (proBNP, NYHA class, and LVEF). These correlations should therefore be interpreted strictly as exploratory associations.

CONCLUSIONS

In the current retrospective, uncontrolled before-and-after study, S/V initiation was associated with reductions in health care utilization and improvements in several clinical parameters. However, these findings do not establish that the observed changes were caused solely by S/V. In this elderly and fragile population, preserved renal function and lower loop diuretic doses were observed after S/V initiation; these changes were associated with, but cannot be attributed

solely to, S/V treatment. We believe that our results may be encouraging for cardiologists deciding on S/V use in countries where S/V is not covered by reimbursement.

Conflict of Interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Lee H, Oh S-H, Cho H, Cho H-J, Kang H-Y. Prevalence and socio-economic burden of heart failure in an aging society of South Korea. *BMC Cardiovasc Disord.* 2016; 16(1):215.
2. Bellotti P, Badano L, Acquarone N, et al. Specialty-related differences in the epidemiology, clinical profile, management and outcome of patients hospitalized for heart failure. The OSCUR study. *Eur Heart J.* 2001; 22(7):596-604.
3. Von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nature Reviews Cardiology.* 2017; 14(6):323.
4. Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J.* 2015; 36(30):1990-1997.
5. Bonow RO, ElGuindy AM. PARADIGM-HF: Have we achieved a new paradigm in the treatment of heart failure? *Global Cardiology Science and Practice.* 2014:34.
6. Minguet J, Sutton G, Ferrero C, Gomez T, Bramlage P. LCZ696: a new paradigm for the treatment of heart failure? *Expert Opin Pharmacother.* 2015; 16(3):435-446.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure

- Society of America. *J Am Coll Cardiol*. 2017; 70(6):776-803.
8. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292(3):344-350.
9. Degertekin M, Erol Ç, Ergene O, et al. Heart failure prevalence and predictors in Turkey: HAPPY study. *Türk Kardiyol Dern Ars*. 2012;40(4):298-308. doi:10.5543/tkda.2012.65031
10. Tokgözoğlu L, Kayıkçıoğlu M, Altay S, et al. EUROASPIRE-IV: European Society of Cardiology study of lifestyle, risk factors, and treatment approaches in patients with coronary artery disease: Data from Turkey. *Archives of the Turkish Society of Cardiology*. 2017; 45(2):134-144.
11. Krittayaphong R, Permsuwan U. Cost-Effectiveness Analysis of Sacubitril-Valsartan Compared with Enalapril in Patients with Heart Failure with Reduced Ejection Fraction in Thailand. *Am J Cardiovasc Drugs*. 2018; 18(5):405-413.
12. Liang L, Bin-Chia Wu D, Aziz MIA, et al. Cost-effectiveness of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction. *J Med Econ*. 2018; 21(2):174-181.
13. Kałużna-Oleksy M, Kolasa J, Migaj J, et al. Initial clinical experience with the first drug (sacubitril/valsartan) in a new class—angiotensin receptor neprilysin inhibitors in patients with heart failure with reduced left ventricular ejection fraction in Poland. *Kardiologia Polska (Polish Heart Journal)*. 2018; 76(2):381-387.
14. Park S-K, Hong S-H, Kim H, Kim S, Lee E-K. Cost-Utility Analysis of Sacubitril/Valsartan Use Compared With Standard Care in Chronic Heart Failure Patients With Reduced Ejection Fraction in South Korea. *Clin Ther*. 2019; 41(6):1066-1079.
15. McMurray J, Stewart S. The burden of heart failure. *European Heart Journal-Supplements*. 2003; (5):3-13.
16. Aras D, Aydoğdu S, Bozkurt E, et al. Cost of heart failure management in Turkey: results of a Delphi Panel. *Anatolian journal of cardiology*. 2016; 16(8):554.
17. Yılmaz MB, Çelik A, Çavuşoğlu Y, et al. Turkey'de kalp yetersizliğinin anlık görüntüsü: SELFIE-TR bazal karakteristik özellikleri. 2019;
18. Packer M, Armstrong WM, Rothstein JM, Emmett M. Sacubitril-valsartan in heart failure: why are more physicians not prescribing it? *Ann Intern Med*. 2016; 165(10):735-736.
19. Martens P, Lambeets S, Lau CW, Dupont M, Mullens W. Impact of sacubitril/valsartan on heart failure admissions: insights from real-world patient prescriptions. *Acta Cardiol*. 2019; 74(2):115-122.
20. Simpson J, Jhund PS, Cardoso JS, et al. Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF. *J Am Coll Cardiol*. 2015; 66(19):2059-2071.
21. Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure*. 2020; 8(5):372-381.
22. Malfatto G, Ravaro S, Caravita S, et al. Improvement of functional capacity in sacubitril-valsartan treated patients assessed by cardiopulmonary exercise test. *Acta Cardiol*. 2019:1-5.
23. Januzzi JL, Prescott MF, Butler J, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA*. 2019; 322(11):1085-1095.
24. Polito MV, Silverio A, Rispoli A, et al. clinical and echocardiographic benefit of Sacubitril/Valsartan in a real-world population with HF with reduced ejection fraction. *Sci Rep*. 2020; 10(1):1-10.

25. Dieterle T, Schaefer S, Meyer I, Ackermann G, Ahmed K, Hullin R. Introduction of sacubitril/valsartan in primary care follow-up of heart failure: a prospective observational study (THESEUS). ESC Heart Failure. 2020;
26. Spannella F, Marini M, Giulietti F, et al. Renal effects of Sacubitril/Valsartan in heart failure with reduced ejection fraction: a real life 1-year follow-up study. Intern Emerg Med. 2019; 14(8):1287-1297.
27. Kanavos P, Üstel İ, Costa-i-Font J. Turkey'de ilaç geri ödeme politikası. SUVAK; 2005.
28. AKYÜREK AGÇE. Sağlıkta bir geri ödeme yöntemi olarak global bütçe ve Turkey. SGD-Sosyal Güvenlik Dergisi. 2012; 2(2)
29. Gandjour A, Ostwald DA. Sacubitril/Valsartan (LCZ696): A Novel Treatment for Heart Failure and its Estimated Cost Effectiveness, Budget Impact, and Disease Burden Reduction in Germany. Pharmacoeconomics. 2018; 36(10):1285-1296.
30. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. JAMA cardiology. 2016; 1(6):666-672.
31. McMurray JJ, Trueman D, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart. 2018; 104(12):1006-1013.
32. Ramos IC, Versteegh MM, de Boer RA, et al. Cost effectiveness of the angiotensin receptor neprilysin inhibitor sacubitril/valsartan for patients with chronic heart failure and reduced ejection fraction in the Netherlands: a country adaptation analysis under the former and current Dutch Pharmacoeconomic Guidelines. Value Health. 2017; 20(10):1260-1269.
33. Kennedy C, Smith A, Doran S, Barry M. Sacubitril/Valsartan (Entresto®) utilisation and prescribing patterns in the context of a Reimbursement Application System. Br J Clin Pharmacol. 2020;
34. Martens P, Beliën H, Dupont M, Mullens W. Insights into implementation of sacubitril/valsartan into clinical practice. ESC heart failure. 2018; 5(3):275-283.