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Sacubitril/Valsartan Treatment in Heart Failure Increases The Left Ventricular Ejection Fraction: A Bayesian Analysis

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ABSTRACT

Introduction: Heart failure is an important leading cause of mortality and morbidity despite optimal medical treatment and device therapy. Sacubitril/valsartan, a first-generation drug, was approved to use heart failure treatment recently. There are limited studies on the relationship between sacubitril/valsartan and left ventricular contraction. In our study, we aimed to evaluate the changes in left ventricular ejection fraction (LVEF) after sacubitril/valsartan treatment.

Patients and Methods: Fifty-two patients with heart failure and reduced ejection fraction (HFrEF) were enrolled in this study. The baseline demographic, clinical, and echocardiographic characteristics of 52 patients were compared using the Bayesian method.

Results: Fifty-two patients with heart failure and reduced ejection fraction (HFrEF) were included in the final analysis (66.2 ± 9.3 years, 69.2% male). Sacubitril/valsartan initial dose was low in 44.2% of patients, and intermediate in 55.8%. In the low initial dose population, the increase in absolute LVEF was 3.87 (95% HDI 1.53-6.20) and in the intermediate initial dose population, the increase in absolute LVEF was 5.89 (95% HDI 4.18-7.61). In the female population, the increase in absolute LVEF was 5.56 (95% HDI 3.49-7.63) and in the male population 4.75 (95% HDI 2.91-6.58) respectively.

Conclusion: In this study, we demonstrated that sacubitril/valsartan is associated with increased LVEF regardless of baseline clinical characteristics.

Key Words: ARNI; bayesian; ejection fraction

Kalp Yetersizliğinde Sakubitril/Valsartan Tedavisinin Sol Ventrikül Enjeksiyon Fraksiyonu Üzerine Etkisi: Bayesian Analiz Çalışması

ÖZET

Giriş: Kalp yetmezliği, optimal medikal tedavi ve cihaz tedavilerine rağmen önde gelen mortalite ve morbidite nedenidir. Birinci jenerasyon bir ilaç olan sakubitril/valsartan'ın yakın zamanda kalp yetmezliği tedavisinde kullanılması onaylandı. Sakubitril/valsartan ile sol ventrikül kasılması arasındaki ilişkiye dair sınırlı sayıda çalışma bulunmaktadır. Çalışmamızda sakubitril/valsartan tedavisi sonrası sol ventrikül ejeksiyon fraksiyonundaki (LVEF) değişiklikleri değerlendirmeyi amaçladık.

Hastalar ve Yöntem: Bu çalışmaya kalp yetmezliği ve düşük ejeksiyon fraksiyonu (KYdEF) olan 52 hasta alındı. Elli iki hastanın başlangıç demografik, klinik ve ekokardiyografik özellikleri Bayes yöntemi kullanılarak karşılaştırıldı.

Bulgular: Kalp yetmezliği ve düşük ejeksiyon fraksiyonu (KYdEF) olan 52 hasta nihai analize dahil edildi (66.2 ± 9.3 yaş, %69.2 erkek). Sakubitril/valsartan başlangıç dozu hastaların %44.2'sinde düşük, %55.8'inde orta düzeydeydi. Düşük başlangıç doz popülasyonunda; mutlak LVEF'deki artış 3.87 (%95 HDI 1.53-6.20) iken orta başlangıç doz popülasyonunda; mutlak LVEF'deki artış 5.89'du (%95 HDI 4.18-7.61). Kadın popülasyonunda; mutlak LVEF'deki artış 5.56 (%95 HDI 3.49-7.63), erkek popülasyonda ise 4.75 (%95 HDI 2.91-6.58) idi.

Sonuç: Bu çalışmada, bazal klinik özelliklerden bağımsız olarak sakubitril/valsartanın artmış LVEF ile ilişkili olduğunu gösterdik.

Anahtar Kelimeler: ARNI; bayesian; ejeksiyon fraksiyonu

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INTRODUCTION

Mortality in patients with heart failure and reduced ejection fraction (HFrEF) has improved over time because of the step-wise introduction of a variety of pharmacological treatments. For years, recommended treatments for patients with HFrEF included the combination of an angiotensin-converting enzyme inhibitor [ACEI; or an angiotensin II receptor blocker (ARB) if an ACEI is not tolerated], a β-blocker (BB), and a mineralocorticoid receptor antagonist (MRA). Despite these recommended treatments being evidence-based, the mortality rate for patients with HFrEF remains high[1-3].

Sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), was recommended as a new treatment option for patients with HFrEF. These recommendations were based on the results of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure), in which sacubitril/valsartan 20% reduction in the risk of cardiovascular death, 21% reduction in the risk of hospitalization for heart failure and 16% reduction in the risk of all-cause mortality comparing to the patients on enalapril treatment[4]. Recent studies have demonstrated that sacubitril/valsartan treatment has favorable effects on the left ventricular ejection fraction (LVEF)[5-8]. In our study, we aimed to investigate by using Bayesian analysis the effect of sacubitril/valsartan treatment on the ejection fraction in HFrEF patients in the cardiology practice in Türkiye.

PATIENTS and METHODS

The study consisted of 56 patients who were diagnosed with HFrEF in three different centers. After the administration of sacubitril/valsartan therapy, we evaluated them with a follow-up phone call. Four patients were lost to follow-up because they could not be reached. The baseline characteristics of the remaining 52 patients were examined and recorded from their hospital files. In addition, clinical characteristics, echocardiographic findings, and drug doses were recorded at the mean follow-up of six weeks. The same transthoracic echocardiography machines [Vivid 3, GE, Norway (in two hospitals) and Vivid 7, GE, Norway (in one hospital)] as previously used were preferred for each patient for follow-up evaluation. The LVEF (%) was determined by using a modified Simpson's method.

Statistics

In this study, we used Bayesian inferential analyses. Continuous variables were demonstrated with mean ± standard deviation (SD), and categorical variables were demonstrated with percent (%). Assuming "p" as the probability of an increase in LVEF after sacubitril/valsartan treatment; null hypothesis (Ho): p= 0 (absence of effect) and alternative hypothesis (H1): p≠ 0 (presence of effect). The prior probability of Ho and H1 were shown as Pr (Ho) and Pr (H1). After combining current data (D) and prior belief, the posterior probability of H0 and H1 were Pr (Ho/D) ve Pr (H1/D). The Bayes factor (BF_{10}) was Pr (H1/D)/Pr (Ho/D). The BF_{10} is a statistical index that quantifies the evidence for a hypothesis, compared to an alternative hypothesis (i.e., BF_{10} equals 10, the data are 10 times more likely under H1 than under H0 or BF_{10} equals 0.2 the data are five times more likely under H0 than under H1). The interpretation of BF_{10} was demonstrated in Table 1. LVEF, mean credible value (±SD) of the actual difference and 95% highest density interval (HDI) as the range were the actual differences before-after sacubitril/valsartan is demonstrated with 95% credibility. We used the Bayesian paired t-test to compare LVEF values before and after sacubitril/valsartan treatment and the Bayesian independent test to compare LVEF changes between male/female and baseline low/intermediate sacubitril/valsartan doses. Inferential analyses were calculated utilizing a Bayesian paradigm by using Markov Chain Monte Carlo (MCMC) methods to evaluate posterior distributions and probabilities and to measure the probability for a coefficient to be positive. The MCMC methods are based upon simulations under specific assumptions, and empirical posterior distributions and probabilities are evaluated for the conclusion. Statistical analyses were done using JASP (0.8.4) and R (3.4.2) packages.

Table 1. Interpretation of the Bayesian factor

BF_{10} factor	Interpretation
>100	Extreme evidence for H1
30-100	Very strong evidence for H1
10-30	Strong evidence for H1
3-10	Moderate evidence for H1
1-3	Anecdotal evidence for H1
1	No evidence
1/3-1	Anecdotal evidence for H0
1/3-1/10	Moderate evidence for H0
1/10-1/30	Strong evidence for H0
1/30-1/100	Very strong evidence for H0
<1/100	Extreme evidence for H0

Table 2. Baseline clinical characteristics of the study population (n= 52)

Age, years	66 (59-75)
Male, n (%)	36 (69.2%)
Diabetes mellitus, n (%)	23 (44.2%)
Hypertension, n (%)	38 (73.1%)
Smoking	23 (44.2%)
Atrial fibrillation, n (%)	10 (19.2%)
Rehospitalization within previous six months, n (%)	35 (67.3%)
Ischemic etiology, n (%)	43 (82.7%)
Medication, n (%)	
Angiotensin converting enzyme inhibitors	39 (75%)
Angiotensin receptor blockers	6 (11.5%)
Beta-blockers	42 (80.8%)
Antiplatelet treatment	41 (78.8%)
Statin	30 (57.7%)
Mineralocorticoid receptor antagonists	22 (42.3%)
Diuretics	41 (78.8%)
Ivabradine	5 (9.6%)
Baseline NYHA, II/III/IV, n (%)	36.5%/50%/13.5%
Baseline creatinine, mg/dL	1.12 (0.90-1.30)
Baseline potassium, mEq/dL	4.2 (3.58-4.83)
Baseline mitral regurgitation, III/IV, n (%)	11.5%/9.6%

RESULTS

We included 52 patients with systolic heart failure (LVEF ranged from 19 to 40%) (66.2 ± 9.3 years, 69.2% male). Overall, 82.7% (n= 43) of the patients had HF with ischemic etiology, and 67.3% (n= 35) had been hospitalized for HF at least once in the last six months. The frequency of patients using ACEI was 75%, the frequency of patients using BB was 80.8%, and the frequency of patients using MRA was 42.3%. Other baseline clinical features are summarized in Table 2.

Low doses of sacubitril/valsartan were administrated to 44.2% of patients and intermediate doses to 55.8%. After adjusting the dose according to blood pressure, creatinine, and potassium levels at follow-up, 7.7% of patients had received low, 36.5% intermediate and 55.8% target doses of sacubitril/valsartan at the end of the study. From April 2017 to November 2017, eight patients using sacubitril/valsartan were re-hospitalized. Of these, five were hospitalized for pneumonia/exacerbation of COPD and urinary infection, and three for decompensated heart failure (one of them had not used sacubitril/valsartan for one month).

The LVEF was 30.8 ± 5.6 (95% HDI 29.1-32.3) before starting sacubitril/valsartan, and 35.8 ± 7.3 (95% HDI 34.0-37.7) 1-3 months after starting sacubitril/valsartan (Figure 1). After initiation of sacubitril/valsartan, patients had a marked increase in LVEF. The Bayesian posterior probability of any increment in LVEF (>0%) after sacubitril/valsartan was 100% and the posterior probability of any decrement in LVEF (<0%) was 0.02% (Figure 2). The absolute increase in LVEF was -5.0% with 95% HDI -7.4, -2.6 (the median effect size was -1.4, 95% HDI -1.80, -0.95, and the BF> 1000) (Figure 3a). The Bayesian sequential analysis in Figure 3b revealed that after about 20 observations, the BF equals 10 and after 30 observations, the BF equals 100. These results indicate that there was extreme evidence against Ho hypothesis when we used different types of prior distribution even in a low sample size.

The increase in absolute LVEF was 3.87 (95% HDI 1.53-6.20) in low initial sacubitril/valsartan doses and 5.89 (95% HDI 4.18- 7.61) in intermediate initial sacubitril/valsartan

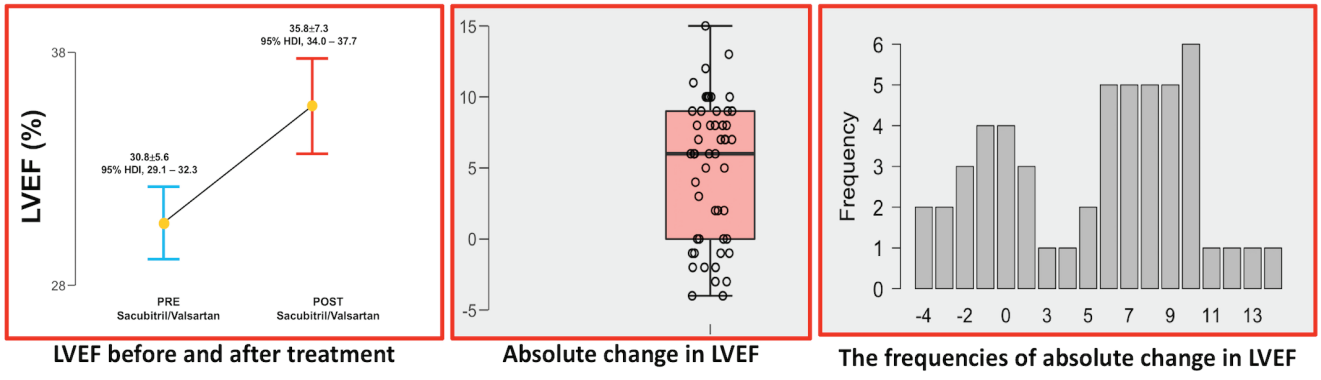

Figure 1. LVEF (mean ± SD and 95% HDI) before and after treatment (left), a boxplot for absolute LVEF changes (middle), and the distribution of frequencies of absolute LVEF changes (right).

LVEF: Left ventricular ejection fraction, HDI: Highest density interval, SD: Standard deviation.

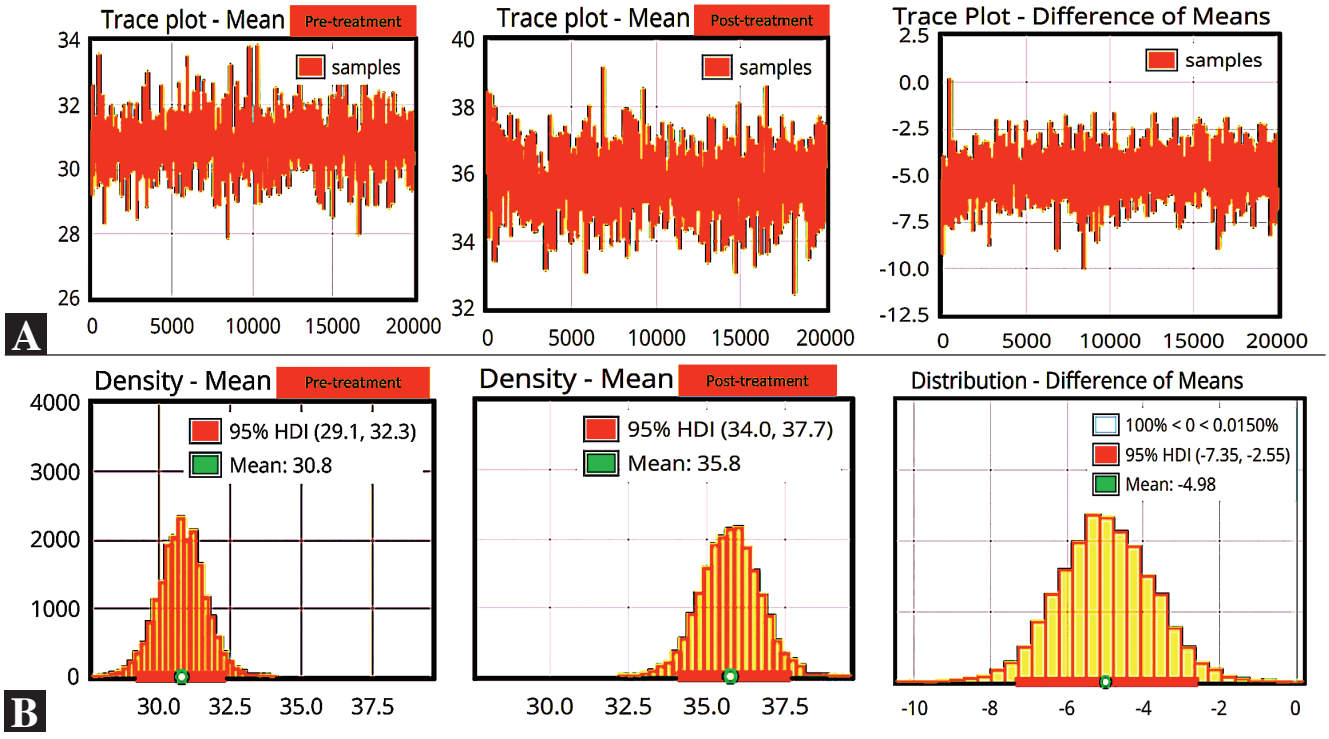

Figure 2. Prior and posterior distribution for the effect size of LVEF changes **(A)** and Bayesian sequential analysis (after about 20 observations the Bayes factor equals 10 and after 30 observations the Bayes factor equals 100) **(B)**.

HDI: Highest density interval.

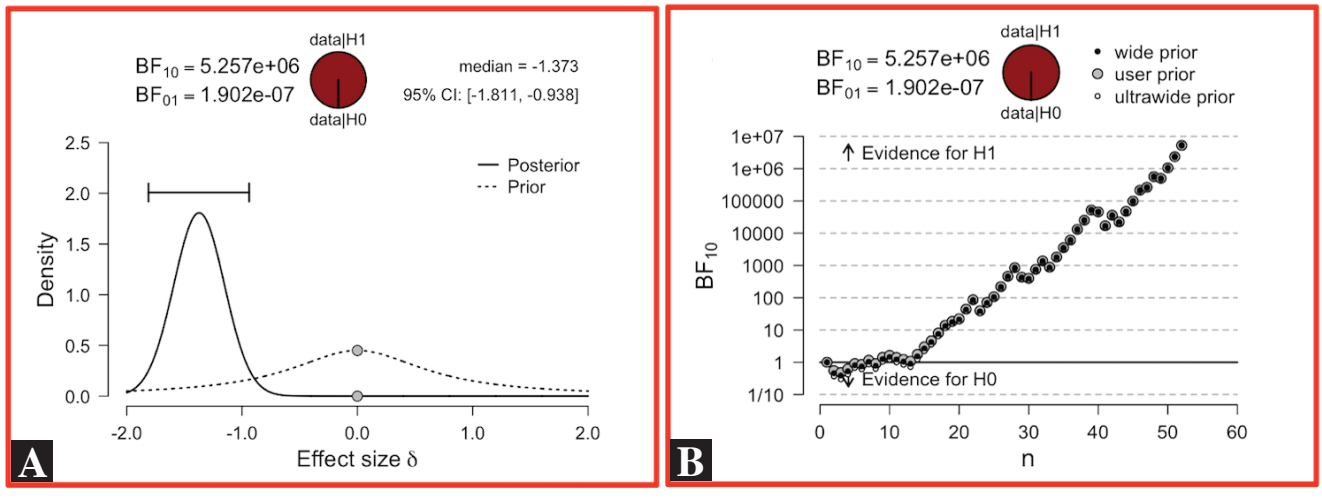

Figure 3. The trace plot for LVEF changes before and after treatment demonstrates the stationary process, which appears to be converged and shows good mixing (fuzzy caterpillar-like trace) and sufficient burn-in period in the Markov Chain Monte Carlo (MCMC) algorithm.

BF: Bayes factor, CI: Confidence interval.

doses (the BF was 0.681 and posterior probability was 92%) (Figure 4a) Similarly, increase in absolute LVEF was 5.56 (95% HDI 3.49-7.63) in women and 4.75 (95% HDI 2.91-6.58) in men (the BF was 0.334 and posterior probability was 72%) (Figure 4b). There was no significant Bayesian correlation between absolute change in LVEF and age (Pearson r= -0.02, 95% HDI -0.28, 0.25, the BF= 0.175, and posterior probability was 22%).

DISCUSSION

The main findings of this study are, i) sacubitril/valsartan increased the LVEF by approximately 5.0%, ii) improvement

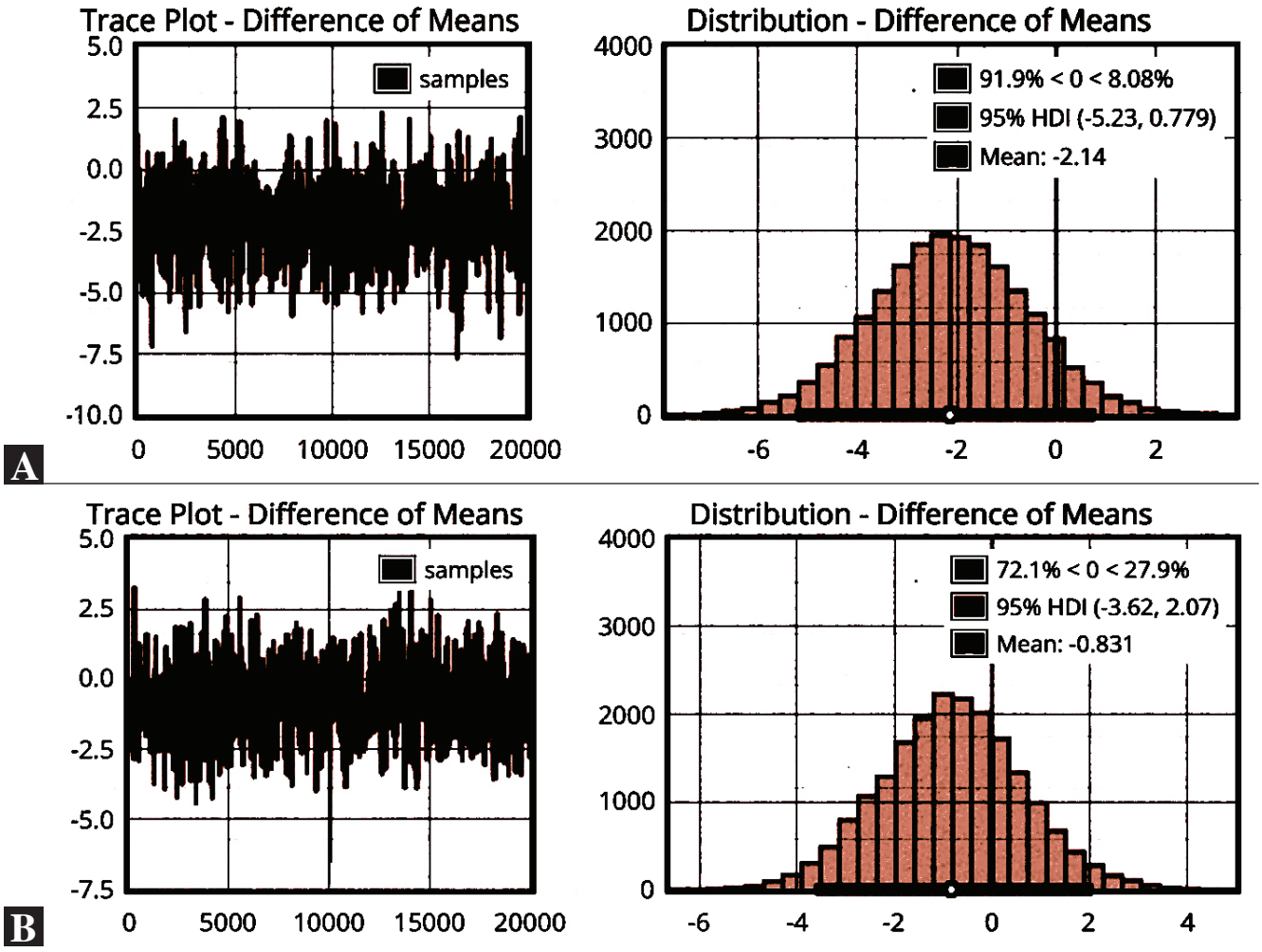

Figure 4. The trace plot for LVEF changes before and after treatment demonstrates the stationary process, which appears to be converged and shows good mixing (fuzzy caterpillar-like trace) and sufficient burn-in period in the Markov Chain Monte Carlo (MCMC) algorithm for initial Sacubitril/Valsartan doses **(A)** and sex **(B)**.

HDI: Highest density interval.

in LVEF is independent from sacubitril/valsartan doses, sex, and age in the Bayesian analyses.

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin[9-11]. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling[12,13]. Combined inhibition of the renin-angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies[4].

Sacubitril/valsartan (LCZ696) offers new hope to patients with HFrEF. The drug secured a high position in the 2016 guidelines on heart failure of the European Society of Cardiology and the American College of Cardiology/American Heart Association[14,15]. These recommendations were based on the findings of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure), which found that sacubitril/valsartan reduced the risk of cardiovascular death by 20%, hospitalization for heart failure by 21%, and all-cause mortality by 16% in the LCZ696 group compared to the enalapril group[4]. Furthermore, the secondary outcomes were the time to death from any cause and the change in clinical summary score from baseline to eight months on the Kansas City Cardiomyopathy Questionnaire (KCCQ)[16]. (On a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure).

Several different effects of sacubitril/valsartan treatment on biochemical and clinical outcomes have been demonstrated.

Patients with diabetes and HFrEF enrolled in PARADIGM-HF who received sacubitril/valsartan had a greater long-term reduction in HbA_{1c} than those receiving enalapril. These data suggest that sacubitril/valsartan might enhance glycemic control in patients with diabetes and HfrEF[13]. In another study, sacubitril/valsartan treatment was more effective than olmesartan in terms of reducing LV mass index. It has been hypothesized that the vasodilatory and antiproliferative effects of the neprilysin inhibitor moiety of sacubitril/valsartan may provide additional benefits to those of the RAS-inhibitor component, further reducing the risks associated with LV remodeling[12]. Furthermore, sacubitril/valsartan reduced cardiac remodeling and dysfunction after experimental MI and inhibited cardiac fibrosis and hypertrophy in vivo and in vitro, which was greater than that achieved by ARB alone[17]. This data may offer novel mechanistic insight into the benefits observed with LCZ696 in clinical studies.

In a study of 77 HFrEF patients, LV functions were assessed using standard and advanced echocardiographic examination. Sacubitril/valsartan was shown to have beneficial effects on LVEF[18]. In addition, in several studies performed with similar patient numbers, it was demonstrated that sacubitril/valsartan treatment significantly improved LV systolic and diastolic functions[5,6]. In a retrospective study examining 501 HFrEF patients with end-stage renal disease, sacubitril/valsartan was demonstrated to significantly increase LVEF[7]. Similarly, in the ARNi-TR study conducted in Türkiye, in which approximately 800 patients were evaluated retrospectively, it was demonstrated that sacubitril/valsartan treatment improved LVEF (34308869). In line with the results of these studies, our study showed that there was an improvement in LVEF with sacubitril/valsartan treatment, and these findings may be associated with positive changes in cardiac remodeling. In addition, these results were defined irrespective of gender, doses of sacubitril/valsartan, and age with Bayesian analysis.

CONCLUSION

The use of sacubitril/valsartan in patients with HFrEF improves left ventricular ejection fraction. This improvement is independent from baseline clinical characteristics.

Limitations of the Study

It was a retrospective study. The analyzed sample size was small, and patients were not treated according to the established protocol. More research and clinical experience are required. Lastly, due to the small number of patients, the Bayesian analysis method, which allows for more flexibility, was preferred.

Ethics Committee Approval: The approval for this study was obtained from Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2022/06-59, Date: 16.05.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - OB, MS; Analysis/Interpretation - PDG, FÖ; Data Collection - OB, PDG, MS; Writing - OB, MS, EA; Critical Revision - EA; Final Approval - All of authors; Statistical Analysis - FÖ; Overall Responsibility - OB.

Conflict of Interest: The authors have no conflicts of interest to declare.

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