

The Impact of Sacubitril/Valsartan on Heart Failure Patient with Reduced Left Ventricular Ejection Fraction: Single Center Retrospective Study in Saudi Arabia

Sultan Al Raddadi¹⁻³, Majed Almutairi^{1,3}, Kholoud AlAamer^{1,3}, Abdulmahsen Alsalman^{3,4}, Maram Albalawi⁵, Meshary Almeshary^{1,3}, Hisham A Badreldin^{1,2,6}, Hind Almodaimegh¹⁻³

¹Department of Pharmaceutical Care, King Abdulaziz Medical City, Ministry of the National Guard-Health Affairs, Riyadh, Saudi Arabia; ²Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; ³Department of Research Office, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; ⁴Department of Cardiology Science, King Abdulaziz Medical City, Riyadh, Saudi Arabia; ⁵Department of Biostatistics and Bioinformatics, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; ⁶Department of Saudi Biobank, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

Correspondence: Sultan Al Raddadi, Department of Pharmaceutical Care, King Abdulaziz Medical City-Riyadh, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia, Email abuibrahim89@yahoo.com

Background: Sacubitril/valsartan (S/V) is used in managing heart failure with reduced ejection fraction (HFrEF), reducing morbidity and mortality while improving symptoms and prognosis. This study aims to evaluate the effectiveness of S/V in patients with reduced left ventricular ejection fraction (LVEF) and its safety.

Methods: This retrospective cohort study included adult patients aged ≥ 18 years diagnosed with HFrEF, receiving S/V, and followed up at a tertiary hospital in Riyadh. Primary outcomes included improvements in LVEF on echocardiography and the number of hospitalizations due to acute decompensated heart failure (ADHF). Secondary outcomes assessed the safety profile of S/V. Multinomial logistic regression analysis was performed with statistical significance set at $P < 0.05$.

Results: The study included 107 patients: 80 with LVEF $< 30\%$ and 27 with LVEF 30–40%. Six-month follow-up, LVEF improvement was categorized into three groups: no improvement, LVEF increased by 1 to < 10 points, and LVEF increased by ≥ 10 points. The LVEF was similar across groups ($P = 0.59$). Although hospitalizations due to ADHF were not significantly different between groups, they numerically decreased after initiating S/V ($P = 0.1$). S/V was generally well tolerated.

Conclusion: This study suggests no significant benefit from S/V regarding LVEF improvement. It is recommended that heart failure clinics assess and titrate S/V to the maximum tolerated dose.

Keywords: heart failure with reduced ejection fraction, left ventricular ejection fraction, angiotensin receptor neprilysin inhibitors, sacubitril/valsartan

Introduction

Heart failure (HF) is a chronic condition that imposes significant medical, economic, physical, and social burdens, leading to poor quality of life.¹⁻⁴ Left ventricular ejection fraction (LVEF) is a critical indicator of disease progression in HF and responds well to medical therapy.⁵ Heart failure patients are often categorized to have heart failure with reduced ejection fraction (HFrEF); (LVEF $\leq 40\%$), mid-range EF; (LVEF 41–49%) or preserved EF; (LVEF $\geq 50\%$).⁶ The incidence and prevalence of HF have increased in recent decades, affecting approximately 64.3 million people worldwide. The prevalence of HF in developed countries estimated by 1–2% of adults.⁷ In the Middle East, the estimated number of HF patients is around 3.75 million, though data are limited.⁸ In Saudi Arabia, the prevalence of HF was estimated to be 1.2% in 2012 among a population of 29 million. A study conducted in 2013 revealed that 20% of patients treated for acute coronary syndrome subsequently developed HF.⁹ These findings highlight the significant burden of heart

failure in Saudi Arabia, with a considerable number of patients developing the condition after acute coronary syndrome. This emphasizes the need for effective preventive measures and improved management strategies to reduce the incidence and impact of heart failure in the country.

Guideline-directed medical therapy (GDMT) for HFrEF includes angiotensin receptor neprilysin inhibitors (ARNIs), ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).¹⁰ These therapies had shown reduction in morbidity and mortality, but ARNIs and SGLT2i appear to further improve symptoms and prognosis.^{10–13} Sacubitril/valsartan (S/V), the first ARNI approved by the FDA for HFrEF treatment, demonstrated significant benefits in the PARADIGM-HF trial.^{10,14} PARADIGM-HF trial was a large multicenter, randomized clinical trial comparing S/V with enalapril in patients with LVEF < 40%. This trial showed 20% reduction in composite Cardiovascular (CV) death (including sudden cardiac death) and hospitalization for HF patients with S/V.¹¹ A recent guideline recommends S/V instead of ACEi or ARB in terms of morbidity and mortality by improving prognosis in HFrEF.¹⁰

Reduced LVEF is associated with cardiovascular events.¹⁵ Different studies have documented the benefit of the GDMTs that blockade renin-angiotensin aldosterone system and beta-adrenergic receptors in terms of their potential impact on ventricular remodeling and therefore lead to improvement in EF.^{16–19} PROVE-HF was an open-label study of 794 patients with chronic HFrEF assigned to S/V and evaluated on echocardiography prior to treatment, at 6 months, and at 12 months; they found the significant reduction by 37% in median NT-proBNP concentration from the baseline 816 pg/mL to 455 pg/mL at 12 months and in the same period, the mean LVEF increased from 28.2% to 37.8% with observed reverse cardiac remodeling.²⁰ Moreover, A single center, prospective blinded study (n = 125) to evaluate the reverse remodeling response of S/V therapy in HFrEF patients, found incremental improvement of 5% in LVEF was noticed after switching therapy from ACEi or ARB to S/V.²¹ Despite the global evidence supporting S/V, data on its impact on EF in Saudi Arabia remain limited. This single-center study aims to evaluate the effectiveness and safety of S/V in patients with reduced LVEF.

Methods

Study Design

In a retrospective cohort study, all patients who received S/V between January 1, 2021, and December 31, 2021, with HFrEF and who met the inclusion/exclusion criteria were included in the study. The investigators collected variables from the electronic record system (BestCare system), and all data were compiled in an electronic data collection sheet. Patients were divided based on LVEF into two groups (LVEF < 30% and LVEF 30% to 40%). Improvement of LVEF due to six-month follow-up from initiating S/V was categorized into three groups (No Improvement, LVEF increased by 1 to <10 points, and LVEF increased by ≥ 10 points). All patients were observed until six months from starting S/V. The study was approved by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (study number: NRC22R/177/04). Participants' confidentiality was strictly maintained throughout the study using the anonymous unique serial number for each subject and restricting data only to the investigators. King Abdullah International Medical Research Center Institutional Review Board waived the informed consent due to the retrospective nature of the study. (Institutional policy ref.# APP 1419-05: Preparation, submission and processing of research proposal, June 2023).

Study Participants and Setting

Patients aged 18 years-old and more were enrolled in the study if they had diagnosed with HFrEF and received S/V starting dose 50 mg oral every twelve hours (Q12hrs) or 100 mg oral Q12hrs. Patients were excluded if they had device known to induce reverse remodeling (eg, Cardiac Resynchronization therapy (CRT)), symptomatic hypotensive patient or Systolic blood pressure (SBP) less than 90 mmHg, serum potassium at baseline >5.2 mmol/l and renal impairment before study by increasing 30% serum creatinine (SrCr) from baseline or estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m².

This study was conducted in adult patients who followed up in King Abdul-Aziz Cardiac Center at King Abdulaziz Medical City, a tertiary-care academic referral hospital in Riyadh, Saudi Arabia.

Data Collection

The follow-up was for six months; patients were evaluated at baseline and within six months after initiating S/V. Demographic data collected at baseline and during follow-up clinic visit blood pressure, heart rate values, presence of comorbidities, echocardiogram LVEF, drug therapy (B-Blocker, MRAs, SGLT2 inhibitors), laboratory parameters: serum creatinine, eGFR, serum potassium, and the number of hospitalization due to ADHF after starting S/V.

Outcomes

This study evaluates the effectiveness of S/V in patients with reduced LVEF: single-center experience. This was done by assessing any improvement in LFEF by 10 points or more in echocardiogram (ECHO)²² and the number of hospitalization due to Acute Decompensated Heart Failure (ADHF) after starting S/V. At the same time, secondary end points include the discontinuation of S/V at any time after initiation due to intolerance. Intolerance is defined by specific criteria encompassing various physiological parameters. These include an SBP measurement falling below 90 mmHg or a Mean Arterial Pressure (MAP) dropping below 60 mmHg. Additionally, intolerance is indicated by elevated serum potassium levels exceeding 5 mmol/l. Renal impairment, a key facet of intolerance, is identified by a substantial increase of 30% or more in SrCr from baseline or an eGFR below 30 mL/min/1.73m².

Data Management and Statistical Analysis

We summarized categorical variables as numbers (percentage) and continuous variables as mean \pm standard deviation. We test the association between two categorical variables by using the Chi-square or Fisher's exact test, we used the Wilcoxon test for association between continuous variables and two-level categorical variables, and we used the Kruskal–Wallis test for association between continuous variables and more than two-level categorical variables. Multinomial logistic regression analysis was performed to test the relationship between the S/V starting dose and S/V maximum tolerated dose. We considered a $P < 0.05$ statistically significant and used SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) for all statistical analyses.

Result

Demographic and Clinical Characteristics

Among 424 patients screened, 107 were included in the study [Figure 1]. Among them, 80 patients have LVEF $< 30\%$. During the study, seven of 107 patients were lost follow-up in regard to repeated ECHO within 6 months. Patient characteristics and demographic data are described in Table 1. Female patients represent (25.23%), and the mean age was 55.25 ± 16.15 years in the whole cohort. The mean SBP is 117.11 ± 17.11 and 119.96 ± 13.18 and estimated eGFR is 82.80 ± 25.74 and 77.22 ± 28.50 for LVEF $< 30\%$ and 30–40% groups, respectively. The most common comorbidities were hypertension (63.64%) and diabetes mellitus (58.88%); hypertension was significantly different between the two groups [Table 1].

A large percentage of the participants, specifically 81.3%, commenced by administering 50 mg of S/V. In contrast, a lesser percentage, precisely 18.69%, was initiated with 100 mg. The distribution of S/V between the groups was similar, and there were no differences [Table 2]. The most common beta-blockers administered were metoprolol succinate (46.7%), followed by bisoprolol (28.03%), and carvedilol (11.2%). Most of the patients received spironolactone (72.9%) and dapagliflozin (71.96%) [Table 2].

Primary Endpoint

The mean ejection fraction improved from $24.10 \pm 8.03\%$ to $32.51 \pm 13.01\%$ at 6 months; $P = 0.74$ [Table 3]. The improvement in LVEF groups was similar between S/V groups; $P = 0.59$ [Table 4]. The number of hospitalizations due to ADHF after starting S/V was numerically reduced by 90.24% ($n=37/41$), 100% ($n=45/45$) and 95.24% ($n=20/21$), but there was no statistically difference between the groups; $P = 0.1$ [Table 4].

Moreover, multinomial logistic regression analysis showed a significant relationship between S/V starting dose and maximum tolerated dose; S/V 100 mg and 200 mg oral every twelve hours (Q12hrs) (maximum tolerated doses) was less likely

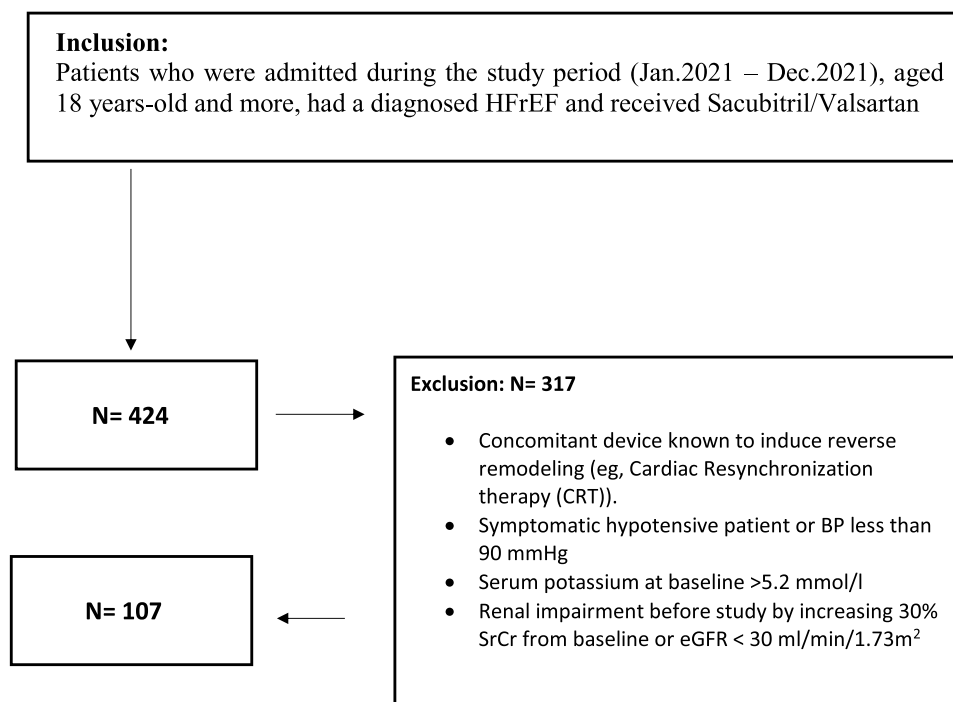


Figure 1 Eligibility criteria flowchart.

to reached compare to S/V 50 mg oral Q12hrs (starting dose) (odds ratio [OR] 0.062; 95% confidence interval [CI], 0.008–0.496; $P = 0.009$) and (odds ratio [OR] 0.063; 95% confidence interval [CI], 0.007–0.563; $P = 0.013$), respectively [Table 5].

Secondary Endpoint

S/V was generally well tolerated. The discontinuation of S/V due to intolerance was similar, and statistically there were no differences regardless of whether doses were used. The main reason for discontinuation was hyperkalemia then

Table 1 Baseline Characteristics

Variables	LVEF		P-value
	<30% (n=80)	30–40% (n=27)	
Age (Years), Mean (SD)	53.95 (15.95)	59.11 (16.42)	0.19 [^]
Gender (Female), n (%)	18 (22.5)	9 (33.33)	0.26 ^{^^}
Weight (kg), mean±SD	77.25 (19.61)	73.63 (14.29)	0.39 [^]
Height (cm), mean±SD	163.70 (8.78)	161.85 (8.18)	0.37 [^]
Systolic Blood Pressure (SBP), Mean (SD)	117.11 (17.11)	119.96 (13.18)	0.25 [^]
Mean arterial pressure (MAP), Mean (SD)	85.98 (12.60)	81.56 (9.04)	0.05 [^]
Heart Rate (HR), Mean (SD)	84.68 (13.46)	79.41 (11.78)	0.06 [^]
Creatinine mmol/l, Mean (SD)	92.37 (27.33)	91.89 (28.21)	0.89 [^]
Estimated Glomerular filtration rate (eGFR) mL/min/m ² , Mean (SD)	82.80 (25.74)	77.22 (28.50)	0.29 [^]
Serum Potassium mmol/l, Mean (SD)	4.30 (0.41)	4.40 (0.34)	0.39 [^]
Co-existing illness, n (%)			
Hypertension	42 (57.53)	21 (80.77)	0.03 ^{^^}
Dyslipidemia	30 (39.47)	16 (66.67)	0.02 ^{^^}
Diabetes mellitus	43 (53.75)	20 (74.07)	0.06 ^{^^}
Coronary Heart Disease	5 (6.25)	3 (11.11)	0.41 ^{^^}
Chronic Kidney Disease	16 (20.51)	6 (22.22)	0.85 ^{^^}

Notes: [^]Wilcoxon rank sum test is used to calculate the P value, ^{^^}Chi-square test is used to calculate the P value.

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation; n (%), total number of patients.

Table 2 Heart Failure Home Medication

	LVEF		
	<30% (n=80)	30–40% (n=27)	P-value
Medication, n (%)			
S/V initial dose (Q12 hrs), 50 mg, n (%)	64(80)	23 (85.19)	0.55
S/V initial dose (Q12 hrs), 100 mg, n (%)	16 (20)	4 (14.81)	0.55
Bisoprolol, n (%)	22 (27.5)	8 (29.6)	
Metoprolol succinate, n (%)	38 (47.5)	12 (44.44)	
Metoprolol tartrate, n (%)	7 (8.75)	2 (7.4)	
Carvedilol, n (%)	9 (11.25)	3 (11.11)	
Spirololactone, n (%)	61 (76.25)	17 (62.69)	
Dapagliflozin, n (%)	64 (80)	13 (48.15)	

Abbreviations: LVEF, Left ventricular ejection fraction; n (%), total number of patients; S/V, Sacubitril/Valsartan; Q12hr, every 12 hour.

Table 3 Echocardiographic Parameters at Baseline and After Starting S/V (Follow-Up)

	Baseline Echocardiographic	Echocardiographic at 6 Months	P-value
LVEF (%), Mean (SD)	24.10 ± 8.03	32.51 ± 13.01%	0.74 ^{^^}

Note: ^{^^} Wilcoxon score is used to calculate the P value.

Abbreviations: S/V, Sacubitril/Valsartan; LVEF, Left Ventricular Ejection Fraction; SD, Standard deviation.

Table 4 Primary Outcomes

Echo Within 6 Month of S/V Maximum Tolerated Dose				
	S/V 50 mg po Q12hrs	S/V 100 mg po Q12hrs	S/V 200 mg po Q12hrs	P-value
No Improvement, n (%)	13 (32.5%)	13 (33.33%)	7 (33.33%)	0.59 ^{^^}
LVEF Improved by 1 to <10 Points, n (%)	17 (42.50%)	13 (33.33%)	5 (23.81%)	0.59 ^{^^}
LVEF improved by ≥ 10 points, n (%)	10 (25%)	13 (33.33%)	9 (42.86%)	0.59 ^{^^}
No. of hospitalization due to ADHF after starting S/V, n (%)				
< 2 times	37/41 (90.24%)	45/45 (100%)	20/21 (95.24%)	0.1 ^{^^}
≥ 2 times	4/41 (9.76%)	–	1/21 (4.76%)	0.1 ^{^^}

Note: ^{^^}Chi-square test is used to calculate the P value.

Abbreviations: S/V, Sacubitril/Valsartan; PO, by mouth; Q12hr, every 12 hour; n (%), total number of patients; LVEF, Left ventricular ejection fraction; <, less than; ≥, more than or equal; ADHF, Acute Decompensated Heart Failure.

Table 5 Multinomial Logistic Regression Analysis

S/V starting dose vs Maximum dose	Odds Ratio (OR) (95% CI)	P-value [^]
50 mg po (Q12hrs) vs 100 mg po (Q12hrs)	0.062 (0.008, 0.496)	0.0088
50 mg po (Q12hrs) vs 200 mg po (Q12hrs)	0.063 (0.007, 0.563)	0.0134

Note: [^] Multinomial logistic regression analysis.

Abbreviations: S/V, Sacubitril/Valsartan; PO, by mouth; Q12hr, every 12 hour.

hypotension, then AKI. An intolerance due to hyperkalemia represents 38.46%, 42.22% and 42.86% in S/V 50 mg, 100 mg and 200 mg groups, P = 0.92, respectively. In addition; discontinuation due to hypotension 26.83%, 17.78% and 9.52% in mentioned S/V groups, P = 0.25 [Table 6].

Table 6 Secondary Outcomes

Safety	S/V 50 mg po Q12hrs	S/V 100 mg po Q12hrs	S/V 200 mg po Q12hrs	P-value
Hypotension, n (%)	11 (26.83%)	8 (17.78%)	2 (9.52%)	0.25 ^{^^}
AKI, n (%)	3 (7.69%)	4 (8.89%)	1 (4.76%)	0.84 ^{^^}
Hyperkalemia; Potassium>5 mmol/L	15 (38.46%)	19 (42.22%)	9 (42.86%)	0.92 ^{^^}

Note: ^{^^}Chi-square test is used to calculate the P value.

Abbreviations: S/V, Sacubitril/Valsartan; PO, by mouth; Q12hr, every 12 hour; n (%), total number of patients; AKI, Acute Kidney injury; >, more than.

Discussion

S/V is a GDMT recommended for all patients with chronic HFrEF with New York Heart Association (NYHA) Functional Classification II–III.²³ Our study is a single-center retrospective cohort of HFrEF patients receiving S/V and treated with another pharmacological therapy, which included BBs, SGLT-2 inhibitors, and MRAs. It aims to evaluate the effectiveness of S/V in improving LVEF by ECHO as well as the safety of S/V. In our cohort, most patients with HFrEF had hypertension, a common risk factor for HFrEF.²⁴ Regarding S/V distribution among LVEF categories, there were no significant differences in our study. However, there was a numeric difference but was not significant in the S/V doses prescribed between the two groups; S/V (initial dose 50 mg) was the most prescribed (LVEF < 30% vs LVEF 30–40%, 64 [80%] vs 23 [85.19%]).

At six months, the study's findings revealed no statistically significant improvement in LVEF with S/V ($P = 0.74$). About 30% of patients showed an improvement of more than 10 points in LVEF. Furthermore, only 19.6% of patients reached the full dose of S/V. Multinomial logistic regression analysis showed a lower likelihood of reaching the maximum tolerated dose of S/V [Table 5]. This finding is consistent with a systematic review of European real-world evidence that showed significant differences in dose achievement between European patients and the PARADIGM-HF population.²⁵ Remarkably, the global approach to S/V titration seems to have a permissive nature. According to statistics from a United States insurance database, a significant proportion (60%) of individuals began their treatment regimen at a dose of 50 mg oral twice daily. Over a period of 6 months, only a minority (24.5%) of patients were able to achieve a dose of 200 mg oral twice daily.²⁶ An additional study had a sample size of 1263 German adults. The prescription rates for S/V are as follows: 62% of patients were prescribed a dose of 50 mg, 31% a dose of 100 mg, and 7% a dose of 200 mg oral twice daily, respectively. Only 14% up titrated to a higher dose within 6 months.²⁷ Since our analysis was retrospective, we are also unable to determine for definite that we did not fail to optimize another medication for heart failure that may have contributed to the lack of improvement in LVEF. Medical therapy based on HF recommendations was frequently delivered at lower dosages than was advised.²⁸ This discrepancy between administered doses and recommended guidelines often results in suboptimal outcomes for patients. The lower doses may have been due to concerns about potential side effects or a lack of awareness regarding the updated guidelines.

This study also measured the percentage reduction in hospitalizations for ADHF after initiating S/V, which ranged from 90.24% to 100% for varied doses of S/V. However, it is important to note that these reductions did not reach statistical significance. These findings suggest that while S/V may lead to a substantial decrease in hospitalizations for ADHF, further research with larger sample sizes is needed to establish statistical significance. Additionally, exploring other factors that could potentially influence these reductions, such as patient demographics or comorbidities, could provide a more comprehensive understanding of the effectiveness of S/V in reducing hospitalizations for ADHF.

Participants generally tolerated S/V well, and there was no statistically significant difference in its safety profile. It was observed that the incidence of discontinuations and adverse events among the participants was low. The findings of our study revealed an elevated incidence of hyperkalemia, along with a decreased occurrence of hypotension and renal failure. These results suggest that S/V may be a safe option for patients, as the lower incidence of adverse events and discontinuations indicates good tolerability. However, the elevated incidence of hyperkalemia should be carefully monitored and managed in clinical practice to ensure patient safety. Considering the missing dose escalation of S/V, these results should be interpreted with caution.

It is important to note that, to the best of our knowledge, this is the first study of its kind on the Saudi population. However, our conclusion can have various limitations. First, the study's retrospective design, single-center data collection, patient heterogeneity, and relatively small sample size all indicate concerns about the study's generalizability. Furthermore, the retrospective design of the study may introduce bias and limit the ability to establish a cause-and-effect relationship between starting S/V and its outcomes. Second, the lack of long-term follow-up data in our study prevents us from assessing the durability of the observed benefits and potential adverse effects of S/V. Finally, because of the character of our study, we cannot be certain that all of our patients were receiving the most optimal dose of another HF medication prior to starting S/V. Confirmation of our findings will require additional well-designed investigations with larger sample sizes.

Conclusion

This study did not suggest a significant benefit from S/V in terms of LVEF improvement within the observed six-months period. However, it did show a non-significant reduction in hospitalizations for ADHF and indicated that S/V was generally well tolerated among patients. Given that only a small proportion of patients achieved the maximum tolerated dose of S/V, it is highly recommended that heart failure clinics carefully assess and titrate S/V to the highest dose patients can tolerate. Addressing the challenges of dose optimization could potentially enhance the therapeutic benefits of S/V. Further, randomized controlled clinical trials with larger sample sizes and longer follow-up periods are required to confirm these results and to explore the long-term efficacy and safety of S/V in diverse patient populations.

Ethical Approval

The study was approved by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (study number: NRC22R/177/04). Participants' confidentiality was strictly observed throughout the study using anonymous unique serial numbers for each subject and restricting data only to the investigators. King Abdullah International Medical Research Center Institutional Review Board waived the informed consent due to the retrospective nature of the study. (Institutional policy ref.# APP 1419-05: Preparation, Submission and processing of research proposal, June 2023). The study was conducted in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (adopted 1964; updated 2013).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

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

Disclosure

We have no conflict of interest to declare.

References

1. Writing Group Members, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2–e220. doi:10.1161/CIR.0b013e31823ac046
2. Díez-Villanueva P, Alfonso F. Heart failure in the elderly. *JGC*. 2016;13(2):115. doi:10.11909/j.issn.1671-5411.2016.02.009
3. Sayago-Silva I, García-López F, Segovia-Cubero J. Epidemiology of heart failure in Spain over the last 20 years. *Revista Española de Cardiología*. 2013;66(8):649–656. doi:10.1016/j.rec.2013.03.012
4. AbuRuz ME, Alaloul F, Saifan A, et al. Quality of life for Saudi patients with heart failure: a cross-sectional correlational study. *Global J Health Sci*. 2016;8(3):49. doi:10.5539/gjhs.v8n3p49
5. Katsi V, Georgiopoulos G, Laina A, et al. Left ventricular ejection fraction as therapeutic target: is it the ideal marker? *Heart Fail Rev*. 2017;22(6):641–655. doi:10.1007/s10741-017-9624-5

6. Uk NA-A, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129–2200. doi:10.1093/eurheartj/ehw128
7. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *Eur J Heart Fai*. 2020;22(8):1342–1356. doi:10.1002/ehf.1858
8. Elasar AA, Alhabeeb W, Elasar S. Heart failure in the Middle East Arab countries: current and future perspectives. *J Saudi Heart Assoc*. 2020;32(2):236. doi:10.37616/2212-5043.1040
9. Tash AA, Al-Bawardy RF. Cardiovascular Disease in Saudi Arabia: facts and the way forward. *J Saudi Heart Assoc*. 2023;35(2):148. doi:10.37616/2212-5043.1336
10. Maddox TM, Maddox TM, Januzzi JL, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am College Cardiol*. 2021;77(6):772–810. doi:10.1016/j.jacc.2020.11.022
11. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi:10.1056/NEJMoa1409077
12. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. doi:10.1056/NEJMoa1911303
13. Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE HF trial. *Circulation*. 2019;140(18):1463–1476. doi:10.1161/CIRCULATIONAHA.119.042929
14. Eadie AL, Brunt KR, Herder M. Exploring the Food and Drug Administration’s review and approval of Entresto (sacubitril/valsartan). *Pharmacol Res Perspect*. 2021;9(3):e00794. doi:10.1002/prp2.794
15. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112(24):3738–3744. doi:10.1161/CIRCULATIONAHA.105.561423
16. Komajda M, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fai*. 2018;20(9):1315–1322. doi:10.1002/ehf.1234
17. Garg R, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273(18):1450–1456. doi:10.1001/jama.1995.03520420066040
18. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293–302. doi:10.1056/NEJM199108013250501
19. Swedberg K, Kjeksus J, CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Am J Cardiol*. 1988;62(2):60A–66A. doi:10.1016/s0002-9149(88)80087-0
20. 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. doi:10.1001/jama.2019.12821
21. Martens P, Beliën H, Dupont M, et al. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther*. 2018;36(4):e12435. doi:10.1111/1755-5922.12435
22. Abramov D, Kittleson MM. The universal definition of heart failure: strengths and opportunities. *J Card Fail*. 2021;27(6):622–624. doi:10.1016/j.cardfail.2021.03.009
23. Heidenreich PA, Bozkurt B, Aguilar D, et al. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 79(17), e263–e421.
24. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275(20):1557–1562. doi:10.1001/jama.1996.03530440037034
25. Giovannazzo S, Carmisciano L, Toma M, et al. Sacubitril/valsartan in real-life European patients with heart failure and reduced ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail*. 2021;8(5):3547–3556. doi:10.1002/ehf2.13547
26. Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of sacubitril/valsartan for the management of patients with heart failure. *Circulation*. 2018;118(2):e004302. doi:10.1161/CIRCHEARTFAILURE.117.004302
27. Wachter R, Klebs S, Balas B, et al. Heart failure signs and symptoms, hospital referrals, and prescription patterns in patients receiving sacubitril/valsartan in primary care and cardiologist settings in Germany. *ESC Heart Fail*. 2020;7(5):2318–2330. doi:10.1002/ehf2.12768
28. Greene SJ, Fonarow GC, DeVore AD, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am College Cardiol*. 2019;73(19):2365–2383. doi:10.1016/j.jacc.2019.02.015

Drug, Healthcare and Patient Safety

Dovepress

Publish your work in this journal

Drug, Healthcare and Patient Safety is an international, peer-reviewed open-access journal exploring patient safety issues in the healthcare continuum from diagnostic and screening interventions through to treatment, drug therapy and surgery. The journal is characterized by the rapid reporting of reviews, original research, clinical, epidemiological and post-marketing surveillance studies, risk management, health literacy and educational programs across all areas of healthcare delivery. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-healthcare-and-patient-safety-journal>