The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 985- 991

Feasibility, Safety, and Efficacy of Sacubitril/Valsartan in Adult Congenital Heart Disease Patients with Systemic Right Ventricular Failure

Fatma A. Taha[1,2]*, Reda Abuelatta[1], Feisel Alnaser[1], Alshimaa Aboalsoud[3], Mohammed H. Sherif[1,2]
[1]Adult Cardiology Department, Madinah Cardiac Center, Madinah, Saudi Arabia
Departments [2]Cardiology and [3]Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
***Corresponding author:** Fatma A. Taha, **Mobile:** (+20) 01142831979,
E-mail: fatmastaha@yahoo.com, **ORCID ID:** https://orcid.org/0000-0002-4450-7167

ABSTRACT

Background: In adult congenital heart disease (ACHD) patients with systemic right ventricle (RV), failure of the morphological RV cannot be avoided. The goal of our study was to examine the feasibility, efficacy, and safety of sacubitril/valsartan (SV) therapy in symptomatic ACHD patients with a failing systemic morphological RV in a biventricular circulation (BVC).

Patients and methods: Sacubitril/valsartan was initiated in all symptomatic patients with failed systemic RV in a BVC after 3-month treatment with heart failure (HF) management. All patients with symptomatic hypotension, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, or serum potassium level >5.4 mmol/L were omitted from the study. Patients' medical records including functional status, six-minute walk test (6-MWT), laboratory investigations, and echocardiography were reviewed and analyzed pre and post treatment (six months) of sacubitril/valsartan.

Results: A total of 22 patients with a mean age of 38.9±8.1 years were included. Fourteen (63.6%) patients had congenitally corrected transposition of the great arteries (ccTGA) and 8 (36.4%) patients had Mustard/Senning procedure for dextro-transposition of the great arteries (d-TGA). After six-month, New York Heart Association functional-class (NYHA-FC) and 6-MWT were significantly improved (P<0.001*). The study displayed significant reductions of the brain natriuretic peptide (BNP) and the N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels (P<0.001*), without change in the potassium level or the renal function (P>0.05). The echocardiographic (ECHO) systemic RV function was significantly improved; ejection fraction (EF), tricuspid annulus plane systolic excursion (TAPSE), fractional area change (FAC), and global longitudinal strain (GLS) (P<0.05*).

Conclusions: Sacubitril/valsartan is a feasible, safe, and efficient treatment in symptomatic ACHD patients with a failing systemic morphological RV in a BVC.

Keywords: Sacubitril/Valsartan, Adult Congenital Heart Disease, Systemic Right Ventricle, Systemic Right Ventricular Failure.

INTRODUCTION

Among adult patients with ACHD are the patients in whom the subaortic systemic ventricle is a morphological RV; patients with ccTGA and patients with Mustard/Senning switch approach for d-TGA. Although the mid-term outcome in such patients is respectable, failure of systemic RV cannot be avoided in the long-term outcome [1,2]. Beyond that, systemic atrioventricular valve (AVV) regurgitation, conduction abnormalities, and cardiac arrhythmias, as well as the lack of myocardial perfusion, all end by HF in those patients [1,2].

In ACHD patients, pharmacological therapy is still the first-line management for HF; the guidelines for HF management approved beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRA) for systemic ventricular dysfunction [3,4]. The guidelines for managing HF in patients with systemic left ventricle (LV) are more detailed than in patients with systemic RV. Systemic morphological RV has unique structural and functional properties, making it difficult to study the effectiveness of pharmaceutical therapy in these patients. Prescriptions for beta-blockers and ACEIs/ARBs are principled on the favorable results of small trials and retrospective studies. Although higher beta-blocker doses have more valuable effects, this may result in hemodynamically significant bradycardia and atrioventricular conduction abnormalities [5-8].

In patients with congenital heart disease (CHD), neurohormonal stimulation is accompanied by the severity of manifestations and systemic ventricular dysfunction [9]. Additionally, there is an association between BNP and systemic RV dysfunction among patients with d-TGA after Mustard/Senning switch operation [10,11]. Also, NT-pro-BNP levels exhibited to anticipate the morbimortality in patients with morphological RV [12,13].

In recent general HF guidelines, the relatively novel angiotensin-receptor neprilysin inhibitor (ARNI) was included [14]. Its mechanism of action relies on the down-regulation of the renin-angiotensin-aldosterone system (RAAS) via the valsartan, combined with the up-regulation of the natriuretic peptide formation via the sacubitril suppression of neprilysin. In addition, sacubitril/valsartan therapy has established significant advances in the reversion of ventricular remodeling, reduction of arrhythmias, alleviation of symptoms, and decrease of HF mortality [15-18].

Currently, sacubitril/valsartan therapy is prescribed in all symptomatic patients with left ventricular HF with diminished EF ≤35% who have already been managed with a beta-blocker (BB) and an

Received: 01/10/2024
Accepted: 03/12/2024

ACEI/ARB [19]. At present, scarce researches have examined the impacts of SV on HF in ACHD patients with systemic morphological RV. Our study aim was to examine the feasibility, efficacy, and safety of SV therapy in symptomatic ACHD patients with a failing systemic morphological RV in a BVC.

PATIENTS AND METHODS

Study design, inclusion, and exclusion criteria:

This was a retrospective cohort study conducted from November 2022 to May 2024. In the current study, all symptomatic ACHD patients with a failing systemic RV in a biventricular circulation, who remained with NYHA-FC II to IV despite at least three months of therapy with the greatest tolerated doses of a BB and an ACEI/ARB had started treatment with sacubitril/valsartan. The failed systemic RV was described as a moderately severe decrease in systolic echocardiographic RV ejection fraction (RVEF) ≤35%. All patients with symptomatic hypotension, serum potassium level >5.4 mmol/L, or eGFR <30 mL/min/1.73m^2 were excluded.

Treatment protocol and follow-up:

Patients' medical records were reviewed and analyzed. Before and six-month after the beginning of SV therapy, the following routine clinical assessments were conducted; functional status evaluation, 6-MWT estimation, laboratory investigations analysis including serum electrolytes, renal function tests (RFTs), hemoglobin, BNP, and NT-pro-BNP levels, and echocardiographic calculations.

The initial dose of SV was 49/51 mg every 12 hours if the patient was on perindopril 5 mg once daily, ramipril 5 mg once daily, lisinopril 20 mg every 24 hours, captopril 25 mg every 8 hours, valsartan 80 mg every 12 hours, or losartan 100 mg every 24 hours, and was 24/26 mg every 12 hours if the former ACEI/ARB dose was lower than these doses [10]. In all patients, the first dose of sacubitril/valsartan was delayed 36 hours following the last dose of ACEI, to overcome the risk of angioedema.

Every 4 weeks of treatment, functional status, and laboratory findings were re-evaluated, and the dose of sacubitril/valsartan was gradually upgraded until it reached the highest tolerable dose.

With any symptomatic hypotension, eGFR decrease to <30 mL/min/1.73m^2, or serum potassium level increase to >5.5mmol/L, the sacubitril/valsartan was planned to be downgraded with the re-follow of the clinical condition, and the laboratory findings after 4 weeks. In any case of decompensation, eGFR decrease to <20 mL/min/1.73m^2, or potassium increase to >6 mmol/L, the medication was planned to be stopped immediately [10].

Echocardiographic assessment:

Echocardiography was performed using PHILIPS-iE33 echocardiography (USA) and was analyzed offline using the Q lab system. RV systolic function was evaluated by (1) RV ejection fraction (RVEF) using the standard M-mode method as in the assessment of the LV, (2) RV TAPSE using the M-mode in the apical four-chamber view with the cursor sited on the lateral surface of the tricuspid valve, (3) Fractional area change (FAC) measured through an optimal RV apical view by subtracting RV end-systolic area (RVESA) from RV end-diastolic area (RVEDA) and dividing the result by RVEDA [FAC = RVEDA – RVESA / RVEDA], and by (4) Speckle tracking RV global longitudinal strain (RVGLS) was used to display the myocardial movement of the RV with an average of the six RV segments strain curves. The sub-pulmonic morphologic LV function was evaluated by the LV ejection fraction (LVEF) and the LV global longitudinal strain (LVGLS).

Ethical approval:

The research protocol followed the 1975 Declaration of Helsinki's ethical principles and was accepted by the institution's human research committee. Madinah Cardiac Center, (Saudi Arabia) Ethics Committee accepted this work. After receiving all of the information, each participant signed their permission. Each patient provided informed written consent for participation and publication.

Statistical analysis

Statistical analysis was achieved using the SPSS Version 25.0. The quantitative statistics were recorded as mean±SD, and the qualitative statistics were reported using numbers and percentages. Differences between the basal and the six-month follow-up data were analyzed by the paired sample t-test for the quantitative data and by the Chi-Square test for the qualitative data. With a 95% confidence interval, a P-value of 0.05 was declared statistically significant*.

RESULTS

The demographic and clinical data:

The demographic and clinical data of the studied patients are displayed in table (1). A total of 22 ACHD patients with systemic morphological RV failure fulfilling the inclusion criteria started treatment with SV. The mean age was 38.9 ± 8.1 years, with 10 (45.5%) of the patients being males. The mean weight was 72 ± 16.8 Kg, the mean height was 1.6 ± 0.1 m, and the mean body surface area was 1.7 ± 0.2 m^2. Fourteen (63.6%) patients had ccTGA and 8 (36.4%) patients underwent Mustard/Senning atrial switch procedure for d-TGA correction.

All patients had ≥ moderate systemic AVV regurgitation [Tricuspid regurgitation (TR)] with 5 (22.7%) patients having previous arrhythmias. Four (18.2%) patients experienced previously implanted permanent pacemakers (PPM), implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT). Ten (45.5%) patients were on regular antiplatelet therapy with no patient was on vitamin K anticoagulant.

Table (1): The demographic and clinical data:

Total number (22)	Baseline
Age (Ys)	38.9 ± 8.1
Gender	
Male	10 (45.5%)
Female	12 (54.5%)
Weight (kg)	72 ± 16.8
Height (m)	1.6 ± 0.1
BSA (m^2)	1.7 ± 0.2
Diagnosis	
ccTGA	14 (63.6%)
Atrial switch for d-TGA	8 (36.4%)
Comorbidities	
Hypertension	7 (31.8%)
Diabetes mellitus	4 (18.2%)
Smoking	2 (9.1%)
Obesity	3 (13.6%)
Stroke	3 (13.6%)
Epilepsy/hypoxic encephalopathy	1 (4.6%)
Chronic respiratory disease	2 (9.1%)
Chronic anemia	2 (9.1%)
Cardiovascular comorbidities	
≥ Moderate systemic AVV regurgitation (TR)	22 (100%)
Arrhythmias	5 (22.7%)
Previous PPM/ICD/CRT	4 (18.2%)
Previous intake of anti-thrombotic	
Antiplatelet	10 (45.5%)
Anticoagulant	0 (0%)
Sacubitril/Valsartan titration to 97/103 mg /12 hours	19/22
Admission during the period of the study	3 (13.6%)
Intervention during the period of the study	2 (9.1%)
Mortality during the period of the study	0 (0%)

AVV: Atrioventricular ventricular valve, BSA: Body surface area, ccTGA: Congenitally corrected transposition of the great arteries, CRT: Cardiac resynchronization therapy, d-TGA: Dextro-transposition of the great arteries, ICD: Implantable cardioverter-defibrillator, PPM: Permanent pacemaker.

Titration of dose:

A maximum dose of 97/103 mg every 12 hours was accomplished in 19 (86.4%) patients, and was not tolerated in 3 (13.6%) patients due to mild symptomatic hypotension; in these patients, a dose of 49/51 mg every 12 hours was sustained. None of the patients developed significant hyperkalemia or impairment of kidney function, and none underwent discontinuation of sacubitril/valsartan management.

Six-month follow-up:

Six-month follow-up of the functional status and laboratory results after the initiation of sacubitril/valsartan therapy is illustrated in table (2). The oxygen saturation and the blood pressure measurements remained stable, with none of the patients displayed worsening throughout the study period. After six months of SV initiation, there was a significant improvement in NYHA-FC (P=0.001*). Before SV intake, 9 (40.9%) patients had NYHA FC-II, 9 (40.9%) patients had NYHA-FC III, and 4 (18.2%) patients had NYHA FC-IV that was improved at a six-month follow-up to record 5 (22.7%) patients with NYHA-FC I, 16 (72.7%) patients with NYHA-FC II, 1 (4.6%) patient with NYHA-FC III, and without any patient remained in NYHA-FC IV. Also, the 6-MWT was significantly improved from a mean of 390 ± 53 m to a mean of 494 ± 63 m (P<0.001*) after a six-month follow-up.

At six-month of SV therapy, the serum potassium level, the blood urea nitrogen (BUN), the serum creatinine, and the eGFR remained unchanged (P>0.05). There were significant rises in the hemoglobin level (P<0.001*), the hematocrit value (P=0.004*), the mean corpuscular volume (MCV) (P=0.005*), and the mean corpuscular hemoglobin (MCH) (P<0.001*). Also, there were significant reductions in the BNP and the NT-pro-BNP levels; from 1104 ± 703.8 ng/L to 684.9 ± 346.9 ng/L and from 754.5 ± 200 ng/L to 527.5 ± 157.6 ng/L respectively (P<0.001*). Six-month reduction of BNP and NT-pro-BNP from the baseline levels are shown in figure 1.

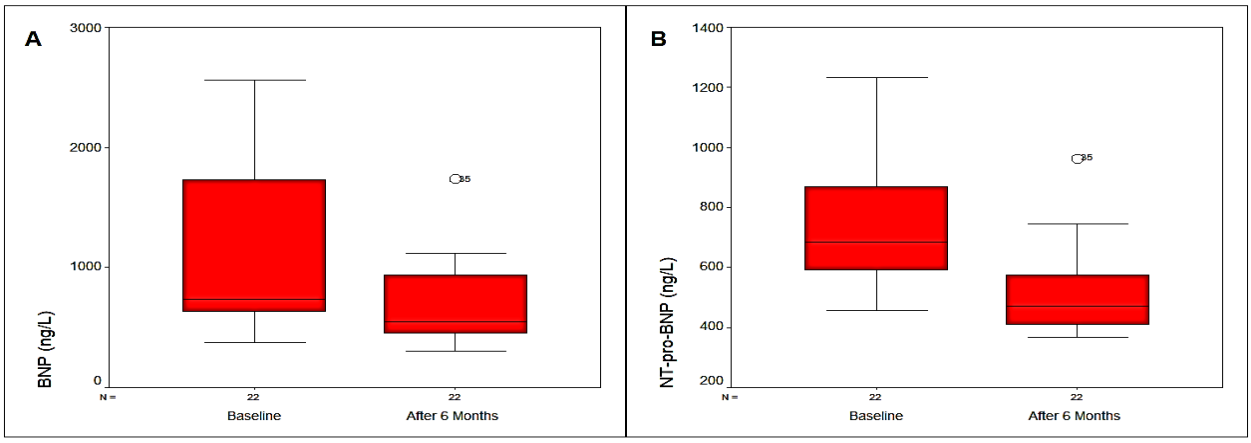

Figure (1): Six-month reduction of brain natriuretic peptide (A) and N-terminal pro-B-type natriuretic peptide (B) from the baseline levels.

Echocardiography follow-up:

Six-month follow-up of the echocardiographic data following the beginning of sacubitril/valsartan therapy is shown in table (2). Systemic RV function was improved as evaluated by the ECHO RVEF (P=0.041*), TAPSE (P=0.004*), RVFAC (P<0.001*), and the echocardiographic RVGLS values (P=0.039*). Also, the RVESA and the RVEDA showed significant diminution with sacubitril/valsartan therapy (P<0.001*). Despite the degree of AVV regurgitation (TR) was reduced in some patients, it did not reach a significant record (P=0.091). The sub-pulmonary LV function remained steady throughout the follow-up (P>0.05). During the follow-up period, 3 (13.6%) patients were admitted, among them 2 (9.1%) patients underwent interventions; 1 (4.6%) patient developed a complete heart block and required PPM implantation, and 1 (4.6%) patient experienced ventricular tachyarrhythmias and required ICD insertion. By the end of the study, no mortality has been reported.

Table (2): Six-month follow-up of the functional status, laboratory findings, and echocardiographic data after the initiation of sacubitril/valsartan therapy

	Total number (23)	Baseline	six-month	P-value
Functional status	**Oxygen saturation (%)**	98.7 ± 1.0	99.0 ± 0.2	0.124
	Systolic blood pressure (mmHg)	128.7 ± 10.6	126.2 ± 7.7	0.103
	Diastolic blood pressure (mmHg)	75.8 ± 12.4	74.6 ± 10.3	0.126
	NYHA-FC			0.001*
	I	0 (0%)	5 (22.7%)	
	II	9 (40.9%)	16 (72.7%)	
	III	9 (40.9%)	1 (4.6%)	
	IV	4 (18.2%)	0 (0%)	
	Six-minute walk test (6-MWT) (m)	390 ± 53	494 ± 63	<0.001*
	Laboratory findings			
Serum electrolytes	Sodium (mmol/L)	136.8 ± 2.6	137.6 ± 2.8	0.195
	Potassium (mmol/L)	3.8 ± 0.4	4.0 ± 0.3	0.211
Renal function tests (RFTs)	BUN (mmol/L)	3.8 ± 0.7	4.2 ± 1.3	0.099
	Creatinine (µmol/L)	72.3 ± 13.4	75.4 ± 16.1	0.091
	eGFR (mL/min/1.73 m^2)	71.2 ± 6.3	69.5 ± 6.2	0.209
Complete blood count (CBC)	Hb (gm/dL)	10.7 ± 1.3	12.4 ± 1.6	<0.001*
	Ht (%)	38.1 ± 4	41.6 ± 4.6	0.004*
	MCV (fL)	78.9 ± 7.7	84.6 ± 5.7	0.005*
	MCH (pg)	25.4 ± 3.1	28.9 ± 3.7	<0.001*
BNP (ng/L)		1104 ± 73.8	684.9 ± 46.9	<0.001*
NT-pro-BNP (ng/L)		754.5 ± 20	527.5 ± 17.6	<0.001*
	Echocardiographic data			
Systemic right ventricular (RV) areas	RVESA (cm^2)	20.9 ± 4.1	18.6 ± 3.9	<0.001*
	RVEDA (cm^2)	27.6 ± 3.8	26.0 ± 3.6	<0.001*
Systemic right ventricular (RV) function	RVEF (%)	31.2 ± 3.2	35.7 ± 4.7	0.041*
	TAPSE (mm)	12.5 ± 2.0	13.7 ± 1.8	0.004*
	RVFAC (%)	23.5 ± 3.4	28.4 ± 2.8	<0.001*
	RVGLS (%)	-12.4 ± 2.2	-14.2 ± 1.9	0.039*
Systemic AVV regurgitation (TR)	Trivial/Mild	0 (0%)	2 (9.1%)	0.091
	Moderate	13 (59.1%)	16 (72.7%)	
	Severe	9 (40.9%)	4 (18.2%)	
Sub-pulmonic LV function	LVEF (%)	56.3 ± 9.5	56.8 ± 10.7	0.317
	LVGLS (%)	-18.6 ± 3.7	-18.6 ± 4.3	0.649

**Statistically significant. 6-MWT: Six-minute walk test, AVV: Atrioventricular ventricular valve, BNP: Brain natriuretic peptide, BUN: Blood urea nitrogen, CBC: Complete blood count, eGFR: Estimated glomerular filtration rate, Hb: Hemoglobin, Ht: Hematocrit, LV: Left ventricle, LVEF: Left ventricular ejection fraction, LVGLS: Left ventricular global longitudinal strain, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, NT-pro-BNP: N-terminal pro–B-type natriuretic peptide, NYHA-FC: New York Heart Association functional class, RFT: Renal function test, RV: Right ventricle; RVEDA: Right ventricular end-diastolic area, RVESA: Right ventricular end-systolic area, RVFAC: Right ventricular fractional area change, RVGLS: Right ventricular, TAPSE: Tricuspid annular plane systolic excursion, TR: Tricuspid regurgitation.*

DISCUSSION

In this cohort, we evaluated the feasibility, efficiency, and safety of SV therapy in adults with systemic morphological RV failure in a biventricular circuit. The value of SV lies in its concomitant effect on the RAAS pathway down-regulation and the natriuretic pathway upregulation. In an animal model, sacubitril/valsartan reduced the RV pressure load in a failing (systemic) RV by decreasing the hypertrophy, and fibrosis [20]. Another study evaluated HF management in adults after an atrial switch operation for d-TGA and demonstrated that the symptomatic patients gained benefits from the HF medications [21]. Thus, making the optimization of the pharmacological therapy for reverse myocardial remodeling of the systemic RV is needed in such symptomatic patients.

In the current study, a maximum dosage of 97/103 mg every 12 hours was not tolerated in 3 (13.6%) patients secondary to mild symptomatic hypotension; in these patients, a dose of 49/51 mg every 12 hours was sustained. This response was in agreement with **Zandstra *et al.* [10],** who stated that symptomatic hypotension was the cause of prevention of dose up-titration in 4 (22%) patients that continued on 49/51 mg twice daily, and the reason for reduction of dose in other 2 (11%) patients who continued on 24/26 mg twice daily. In another retrospective cohort for non-structural cardiac disease patients, the maximally tolerated dose was kept individualized [22]. Also, none of our patients underwent titration cessation or treatment discontinuation due to hyperkalemia or impairment of renal function. Correspondingly, in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF) trial, only a few patients experienced a down-stepping of their treatment doses because of hyperkalemia or renal impairment [23]. In one study, the increase in the potassium level was clinically irrelevant, and the eGFR did not alter significantly [10].

In this study, a six-month follow-up revealed an improvement in the functional condition with an improvement in the 6-MWT. In spite of the lack of controlled studies displaying the benefits of ARNI in systemic RV failure, some cohorts and case series studied SV effect in mixed types of ACHD HF patients and showed functional improvement [24-27].

The case series by **Appadurai *et al.* [26]** stated that the six-month therapy with SV in ACHD HF patients was associated with an improvement in the HF status. Also, the six-month follow-up in a recent group of patients with systemic RV HF who were managed with SV, discovered a marked improvement in the life quality regarding of the cognitive function, and sleep [10]. In patients with systemic RV, the exercise intolerance and the poor 6-MWT performance can be explained by the inadequate contractile reserve and the pressure overload on the systemic RV. Thus, sacubitril/valsartan effect on the contractile reserve, the RV pressure load, and the myocardial fibrosis could improve exercise capacity. In the current study, after six months of SV therapy, the significant improvement in the 6-MWT performance was significantly promising.

In the ongoing study, the hemoglobin, hematocrit, MCV, and MCH levels showed significant improvements; which could be explained by the better elimination of the additional volume, and the consequent improvement of the congested liver.

In consistent with our findings were **Zandstra and coworkers [10]** who also reported a significant improvement in hemoglobin levels. Recognition of patients in the initial stages of systemic RV dysfunction is still challenging because the routine echocardiographic parameters fail to detect subtle RV dysfunction. However, BNP and NT-pro-BNP levels are considered a helpful modality for recognizing subtle ventricular dysfunction in ACHD patients [23].

In the current cohort, there were significant reductions in BNP and NT-pro-BNP levels six-month after SV use (P<0.001*). In agreement with the researches by **Zandstra *et al.* [10] and Nederend *et al.* [27]** who stated that sacubitril/valsartan management led to the improvement in the NT-pro-BNP values in their patients with systemic RV HF. Also, SV therapy was observed to reduce the NT-pro-BNP values by 28% in the PARADIGM-HF trial 8 to 10 weeks after treatment [28].

In this study, there were improvements in the ECHO systemic RV function parameters as assessed by the RVEF (P=0.041*), TAPSE (P=0.004*), RVFAC (P<0.001*), and RVGLS measures (P=0.039*).

In agreement were **Zandstra and colleagues [10],** who revealed an improvement in the ECHO systemic RV function as evaluated by the RVFAC (P<0.001*) and the RVGLS (P=0.014*). Also, **Nederend *et al.* [27]** displayed small reliable echocardiographic improvements in RV systolic function following six months with RVFAC improved from 20% to 26% (P<0.001*) and RVGLS improved from -11.1±0.5% to -12.6±0.7% (P<0.001*). Furthermore, **Correale and coworkers [29]** denoted an ECH improvement in the RV systolic function with the SV therapy in patients with ongoing HF. The Efficacy aNd ToleRability of sacUbitril-valSarTan in adult congenital heart disease patients with heart failure (ENTRUST ACHD HF) is the first long-term, multi-center, prospective registry that evaluated the tolerability, safety, and efficiency of SV in the ACHD HF patients [30].

The current study findings offer a better understanding of the pharmacological potentials for HF treatment in patients with systemic morphological RV. Despite HF management in these patients being still a challenge, optimization of medical therapy, aggressive treatment of cardiac dysrhythmias, proper pacing approaches, resynchronization therapy, and surgical management of systemic AVV regurgitation

(TR) provide the cessation of systemic RV failure. The distinctive anatomic and physiologic features, the detailed surgical history, and the rare numbers of heart donors make this group inappropriate for cardiac transplant. In such patients with systemic RV failure, the destination therapy with the implantation of the ventricular assist devices shows promising results [31].

LIMITATIONS

This is a retrospective study from a single tertiary center with a relatively small study population reflecting the scarcity of the condition. A greater sample of the population and a longer follow-up are required.

CONCLUSION

In conclusion, Sacubitril/valsartan (SV) is a feasible, effective, and safe treatment for symptomatic ACHD patients with a failing systemic morphological RV in a BVC. In addition, SV therapy improves the functional status, 6-MWT, BNP, and NT-pro-BNP, besides an improvement of the systemic RV function.

Acknowledgments: The authors express their gratitude to our center for collaborating on this study and to all of the patients who participated.

Conflict of interest: None.
Financial disclosures: None.

REFERENCES

1. **Vejlstrup N, Sorensen K, Mattsson E *et al.* (2015):** Long-term outcome of Mustard/Senning correction for transposition of the great arteries in Sweden and Denmark. Circulation, 132: 633-638.
2. **Filippov A, Del Nido P, Vasilyev N (2016):** Management of systemic right ventricular failure in patients with congenitally corrected transposition of the great arteries. Circulation, 134: 1293-1302.
3. **Baumgartner H, De Backer J, Babu-Narayan S *et al.* (2021):** 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J., 42(6): 563-645.
4. **Stout K, Daniels C, Aboulhosn J *et al.* (2019):** 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Aassociation task force on clinical practice guidelines. Circulation, 139(14): 698-800.
5. **Bouallal R, Godart F, Francart C *et al.* (2010):** Interest of β-blockers in patients with right ventricular systemic dysfunction. Cardiol Young, 20:615-619.
6. **Dore A, Houde C, Chan K *et al.* (2005):** Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. Circulation, 112:2411-2416.
7. **Tutarel O, Meyer G, Bertram H *et al.* (2012):** Safety and efficiency of chronic ACE inhibition in symptomatic HF patients with a systemic right ventricle. Int J Cardiol., 154:14-16.
8. **van der Bom T, Winter M, Bouma B *et al.* (2013):** Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. Circulation, 127:322-330.
9. **Bolger A, Sharma R, Li W *et al.* (2002):** Neurohormonal activation and the chronic HF syndrome in adults with congenital heart disease. Circulation, 106:92-99.
10. **Zandstra T, Nederend M, Jongbloed M *et al.* (2021):** Sacubitril/valsartan in the treatment of systemic right ventricular failure. Heart, 107(21):1725-1730.
11. **Chow P, Cheung E, Chong C *et al.* (2008):** Brain natriuretic peptide as a biomarker of systemic right ventricular function in patients with transposition of great arteries after atrial switch operation. Int J Cardiol., 127:192-197.
12. **Popelova J, Tomkova M, Tomek J (2017):** NT-proBNP predicts mortality in adults with transposition of the great arteries late after mustard or Senning correction. Congenit Heart Dis., 12:448-457.
13. **Westhoff-Bleck M, Podewski E, Tutarel O *et al.* (2013):** Prognostic value of NT-proBNP In patients with systemic morphological right ventricles: a single-centre experience. Int J Cardiol., 169: 433-438.
14. **Heidenreich P, Bozkurt B, Aguilar D *et al.* (2022):** 2022 AHA/ACC/HFSA Guideline for the Management of HF: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation, 145: 895-1032.
15. **Almufleh A, Marbach J, Chih S *et al.* (2017):** Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in HF with reduced ejection fraction patients. Am J Cardiovasc Dis., 7(6): 108-113.
16. **Januzzi J, Prescott M, Butler J *et al.* (2019):** 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 HF with reduced ejection fraction. J Am Med Assoc., 322(11): 1085-1095.
17. **Martens P, Lambeets S, Lau C *et al.* (2019):** Impact of sacubitril/valsartan on HF admissions: insights from real-world patient prescriptions. Acta Cardiol., 74(2): 115-122.
18. **Martens P, Nuyens D, Rivero-Ayerza M *et al.* (2019):** Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in HF with reduced ejection fraction. Clin Res Cardiol., 108(10): 1074-1082.
19. **McDonagh T, Metra M, Adamo M *et al.* (2021):** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF: Developed by the Task Force for the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology (ESC) with the special contribution of the HF Association (HFA) of the ESC. Eur Heart J., 42(36): 3599. https://doi.org/10.1093/eurheartj/ehab368
20. **Sharifi Kia D, Benza E, Bachman T *et al.* (2020):** Angiotensin Receptor-Neprilysin inhibition attenuates right ventricular remodeling in pulmonary hypertension. J Am Heart Assoc., 9: e015708. doi: 10.1161/JAHA.119.015708.

21. **Woudstra O, Kuijpers J, Jongbloed M *et al.* (2020):** Medication in adults after atrial switch for transposition of the great arteries: clinical practice and recommendations. Eur Heart J Cardiovasc Pharmacother., 8(1): 77-84.
22. **Du A, Westerhout C, McAlister F *et al.* (2019):** Titration and tolerability of Sacubitril/ Valsartan for patients with HF in clinical practice. J Cardiovasc Pharmacol., 73(3): 149-154.
23. **McMurray J, Packer M, Desai A *et al.* (2014):** Angiotensin-neprilysin inhibition versus enalapril in HF. N Engl J Med., 371:993-1004.
24. **Maurer S, Pujol Salvador C, Schiele S *et al.* (2020):** Sacubitril/valsartan for HF in adults with complex congenital heart disease. Int J Cardiol., 300:137-140.
25. **Lluri G, Lin J, Reardon L *et al.* (2019):** Early experience with sacubitril/valsartan in adult patients with congenital heart disease. World J Pediatr Congenit Heart Surg., 10(3): 292-295.
26. **Appadurai V, Thoreau J, Malpas T *et al.* (2020):** Sacubitril/valsartan in adult congenital heart disease patients with chronic HF - a single centre case series and call for an international registry. Heart Lung Circ., 29(1): 137-141.
27. **Nederend M, Kiès P, Regeer M *et al.* (2023):** Tolerability and beneficial effects of sacubitril/valsartan on systemic right ventricular failure. Heart, 109(20): 1525-1532.
28. **Baggen V, Baart S, van den Bosch A *et al.* (2018):** Prognostic value of serial N-terminal pro-B-type natriuretic peptide measurements in adults with congenital heart disease. J Am Heart Assoc., 7:e008349. https://doi.org/10.1161/JAHA.117.008349
29. **Correale M, Mallardi A, Mazzeo P *et al.* (2020):** Sacubitril/valsartan improves right ventricular function in a real-life population of patients with chronic HF: the Daunia HF Registry. Int J Cardiol Heart Vasc., 27:100486. https://doi.org/10.1016/j.ijcha.2020.100486
30. **Appadurai V, Nicolae M, Aboulhosn J *et al.* (2021):** The protocol and rationale for the efficacy aNd ToleRability of sacUbitril-valSarTan in adult congenital heart disease patients with HF (ENTRUST ACHD HF): registry. International Journal of Cardiology Congenital Heart Disease, 3:100096. https://doi.org/10.1016/j.ijcchd.2021.100096
31. **Zandstra T, Palmen M, Hazekamp M *et al.* (2019):** Ventricular assist device implantation in patients with a failing systemic right ventricle: a call to expand current practice. Neth Heart J., 27: 590-593.