Non-comunicable disease

Comparison of the effect of Sacubitril/Valsartan with Losartan and Captopril in improving right ventricular function in patients with right heart failure, a randomized clinical controlled trial

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Keywords

Sacubitril/valsartan • Right ventricle • Right heart failure

Summary

Background. *There is evidence supporting the efficacy of Sacubitril /Valsartan for improving left heart failure, but few studies have examined its effects on right ventricular (RV) dysfunction. The current study aimed to investigate the effects of Sacubitril / Valsartan on RV dysfunction in patients with right heart failure.*
Methods. *The current study was a randomized and parallel clinical trial study. Patients over 18 years with any degree of right heart failure regardless of Left ventricular ejection fraction (LVEF) were included. The included patients were assigned randomly to three study arms using simple random allocation, i.e. the intervention group (Sacubitril Valsartan recipients) and the control groups (Losartan and Captopril recipients). The SPSS software version 19 was used for data analysis.*
Results. *The changes in LVEF, RV FAC, RV diameter, DOE grade, and TAPSE in the Sacubitril/Valsartan group were significantly higher than the other two groups. The severity of RV dysfunction, as well as TR (Tricuspid Regurgitation) severity, decreased significantly three months after the intervention compared to the beginning of the intervention in all groups especially in the Sacubitril/Valsartan group (p: 0.006). The mortality rate in the Sacubitril/Valsartan, Losartan, and Captopril groups, were 2 (6.7%), 2 (11.2%), and 1 (7.7%) respectively (p: 0.83). Also, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose (p: 0.006).*
Conclusions. *Considering the results, it seems that Sacubitril/Valsartan has a positive effect on improving RV dysfunction in patients with right heart disorders.*

Introduction

During the last decade, cardiovascular diseases have become the most important cause of death all over the world; and at least one death out of three deaths is due to cardiovascular diseases [1]. One of the important cardiovascular complications in patients with heart failure with reduced ejection fraction (HFrEF) is right ventricular (RV) dysfunction [2]. During the treatment of HFrEF, right heart dysfunction and improvement of its function should be considered. This disorder is associated with high mortality, especially in patients with congenital heart diseases, valvular diseases, coronary artery diseases, and patients with pulmonary hypertension [3-5].
Losartan potassium, an angiotensin II receptor antagonist, and captopril, an angiotensin-converting enzyme (ACE) inhibitor, have been used in the treatment of heart failure for many years. However, their use often has side effects such as angioedema and hyperkalemia [6]. Sacubitril and valsartan are combination drugs for patients with chronic heart failure. Sacubitril causes vasodilation by inhibiting the degradation of BNP (brain natriuretic peptide) [7]. Valsartan prevents the contraction of blood vessels, which reduces blood pressure and improves blood flow. It was shown that Sacubitril/Valsartan has positive effects in reducing mortality and hospital admission, as well as reducing the hospital lengths of stay in patients with heart failure [8]. Also, this drug is related to improving the quality of life (QoL) and reversing heart reconstruction [9]. The beneficial effects of this drug have been described as improving the systolic function of the right ventricle and reducing its disorders [10, 11]. The improvement of the right ventricular function is associated with the improvement of the patient's clinical outcome and the reduction of hospitalization [12]. Studies have shown that sacubitril/valsartan improves heart function by reducing peripheral vascular resistance, preventing the narrowing of arteries, and reducing cardiac load [13, 14]. Different studies assessed the effects of Sacubitril/Valsartan in cardiovascular patients, however, results about the efficacy have been reported inconsistently [15-17].
Previous studies showed improvements in right ventricular function such as tricuspid annular plane systolic excursion, pulmonary hypertension, and systolic pulmonary arterial pressure after Sacubitril/Valsartan initiation [10, 18]. However, some studies failed to show any beneficial effect of Sacubitril/

Valsartan on improving RV function. Therefore, the effects of Sacubitril/Valsartan on RV dysfunction remain a controversial issue [19]. Therefore, considering the importance of the topic, this study aimed to compare the effect of Sacubitril /Valsartan with Losartan and Captopril in improving biventricular function, including left ventricular ejection fraction, fractional area change, Pulmonary arterial systolic pressure, tricuspid annular plane systolic excursion, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and right ventricular–pulmonary artery coupling.

Materials and methods

The present study was an open-label randomized and parallel clinical trial study.

Inclusion criteria

Inclusion criteria included patients over 18 years of age with any degree of right heart failure regardless of the severity of LV dysfunction (mild, moderate, and severe). Informed consent was obtained from all participants.

Exclusion criteria

The patients with SBP < 100 mmHg, GFR < 30 or Cr > 2.5 or renal artery stenosis, ACEI/ARB intolerance, and history of angioedema, or acute pulmonary embolism were excluded. Sampling was done from patients with right-sided heart failure referring to Hazrat-e Rasoul Akram Hospital who need treatment with ACEi/ARB/ARNI.

Patient allocation

The included patients were assigned randomly to three study arms using simple random allocation, *i.e.* the intervention group (Sacubitril Valsartan recipients) and the control groups (Losartan and Captopril recipients). Graphpad random assignment software was used to generate random sequences. In this way, before using the software and generating the sequence, it was decided to receive the letter (E) of the studied drug, the letter (B) of losartan, and the letter (C) of captopril. Then, using the production sequence software, each letter was placed inside a sealed envelope. To maintain the created sequence, the number was recorded on the outer surface of the envelopes. The patients received the order of referral according to the method inside the envelope. After determining the sequence of patients and the type of intervention, at the beginning of the study, an echocardiography was performed by the fellowship of this field in groups and before the start of the treatments. Then, the intervention group was treated with sacubitril-valsartan drug at a dose of 24/26 mg twice a day, and in subsequent visits, if the patient tolerated this amount, the dose was increased to 97/103 mg twice a day. The control group also received Losartan with a starting dose of 25 mg daily prescribed to patients with any degree of RV dysfunction, and in subsequent visits, if the patient tolerated this amount, the dose was increased to 50mg daily and Captopril drug with the starting dose of 6.25 mg three times daily in patients with any degree of RV dysfunction and subsequent visits, if the patient tolerated this amount, the dose was increased to 50mg three times daily, according to the guidelines for heart failure patients. The intervention continued for three months and during the follow-up period, the patients of all groups were repeatedly evaluated for clinical symptoms. During this period, monthly visits monitored the patients or if they were unable to come to the clinic because of long distances, they were questioned about their functional status, dyspnea grade, daily dose of medication, and compliance by routine phone calls. At the end of the third month, the follow-up echo was repeated. The outcomes that were examined in two echocardiography sessions included: EF, LVESD, LVEDD, E/e', RV size, TAPSE, FAC, PAP, and RV-PA coupling. RV function was assessed by several parameters and each one has its prognostic value. Of the direct indicators of RV function is RVEF, which is the quality of RV muscle contraction and relaxation in apical 4chamber view by eyeball measurement and is classified as normal, mild, moderate, and severe RV dysfunction. The complementary index of RVEF is RV FAC. RV diameter is also important, and directly associated with RV dilation and dysfunction. TAPSE measures RV longitudinal movement by putting M mode on the lateral wall of the RV in an apical 4-chamber view. Tricuspid valve regurgitation (known as TR) is the result of both RV/annulus dilation and tricuspid valve incompetence. It is measured by the percent of the TR jet area occupying the right atrium. TR gradient which is measured by putting CW on TV in apical 4chamber view, is also helpful to define the amount of pressure on RV, and adding RA pressure (which is indirectly estimated by IVC size and collapse) to RVSP is called pulmonary artery systolic pressure (PASP). RA-PA coupling is the relationship between RV contractility and RV afterload. It can be estimated by echo using the ratio between TAPSE and PASP. Other indicators (LVEF, LVESD, LVEDD, E/e') are related to LV systolic and diastolic function and are assessed for considering the effect of drugs on both ventricles. All the data, including the baseline and the data related to the final results, were recorded in the checklist and then entered into SPSS software version 22 to be analyzed according to the objectives of the study (Fig. 1).

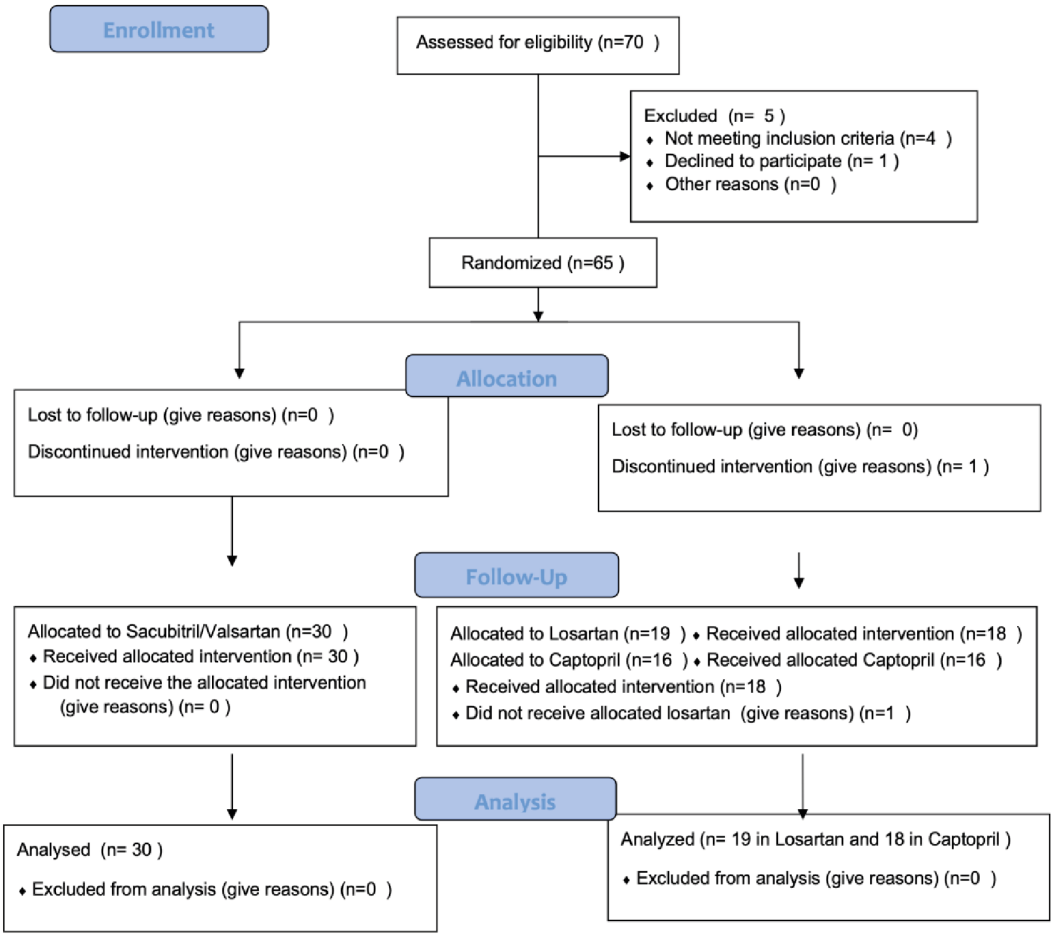
Sample size

All available patients who were willing to participate in the study were selected included in the study and randomly assigned to studied groups.

Data analysis

The results for quantitative variables were expressed as mean and standard deviation (mean ±SD) and for qualitative variables as frequency and percentages. The Chi-square or Fisher's exact tests were used to compare qualitative variables. The continuous variables were analyzed using a one-way ANOVA test. The Bonferroni

Fig. 1. Consort flow chart.



post hoc analysis was used for multiple comparisons. The 5% was considered as a statistically significant level. All analysis was conducted using SPSS software version 22.

Results

Baseline characteristic

Regarding gender, 22 (73.3%), 13 (72.2%) and 12 (75.0%) cases in Sacubitril/Valsartan, Losartan, and Captopril groups were men, respectively (p: 0.59). The mean Age in the Sacubitril/Valsartan, Losartan, and Captopril were 55.93 ± 12.95, 63.66 ± 12.09, and 64.40±13.53 respectively (P: 0.05). Also, the most common type of cardiac disorder in the three studied groups was Biventricular dysfunction (BiV) (p: 0.58). In terms of the history of underlying diseases, 16 (53.3%), 9 (50.0%) and 10 (66.7%) patients in Sacubitril/Valsartan, Losartan, and Captopril groups had a history of IHD (p: 0.44). Other important information is shown in Table I.

Main outcomes

In the Comparison of the mean of changes of different indices between the studied groups, the changes in LVEF, RV FAC, RV diameter, DOE grade, and TAPSE in the Sacubitril/Valsartan group were significantly higher than the other two groups (Tab. II). Regarding the RV dysfunction, most of the cases at the baseline in each group had moderate RV dysfunction (Sacubitril/Valsartan: 66.7%, Losartan: 50%, and Captopril: 75%) and there was no significant difference between the study groups (P: 0.60). But after three months, 68, 13.3 and 50% of cases in the Sacubitril/Valsartan, Losartan and Captopril had mild RV dysfunction respectively. This index had a significant difference between the studied groups three months after receiving the intervention (P: 0.04). Also, the severity of RV dysfunction decreased significantly three months after the intervention compared to the beginning of the intervention in all studied groups (p: 0.006) (Tab. III). The TR (Tricuspid Regurgitation) severity index at the beginning of the study had a significant difference between the studied groups so the most severe cases were in the losartan group (p: 0.03). While this index did not have a significant difference between the studied groups three months after receiving the intervention (p: 0.13). At the baseline, the TR gradient in 3.3, 33.3 and 14.3% of cases in the Sacubitril/Valsartan, Losartan, and Captopril was severe respectively but at the end of the study, 0, 14.3 and 16.7 % of cases in the mentioned groups showed severe TR gradient. These changes were statistically

Tab. I. Basic characteristics of the participants in the studied groups.

Variable	Subgroups		Group			p
			Sacubitril/Valsartan (n:30)	Losartan (n:18)	Captopril (n:16)	
Gender	Males	N	22	13	12	
		%	73.30%	72.20%	75.0%	0.59
Type of heart disorder	BiV	N	27	14	13	0.58
		%	90.00%	77.80%	81.30%	
	RV dysfunction	N	3	4	3	
		%	10.00%	22.20%	18.80%	
History of underlying disease	IHD	N	16	9	10	0.44
		%	53.30%	50.00%	62.5%	
	Other diseases	N	14	9	6	
		%	46.70%	50.00%	37. 5%	
Age		Mean ±SD	55.93±12.95	63.66±12.09	64.40±13.53	0.05

Tab. II. Comparison of the mean of changes of different indices between the studied groups.

Factor	Group	Mean	SD	P
LVEF	Sacubitril/Valsartan *	**0.05**	0.04	**0.001**
	Losartan*	-0.01	0.04	
	Captopril	0.01	0.04	
RV FAC	Sacubitril/Valsartan *	**0.07**	0.04	**0.001**
	Losartan	0.04	0.05	
	Captopril*	0.01	0.04	
PASP	Sacubitril/Valsartan	-6.04	7.68	0.47
	Losartan	-3.64	4.91	
	Captopril	-3.70	6.18	
RV diameter	Sacubitril/Valsartan *	**-0.31**	0.33	**0.007**
	Losartan	-0.13	0.20	
	Captopril*	0.02	0.32	
DOE grade	Sacubitril/Valsartan *	**-1.14**	0.45	**0.009**
	Losartan	-0.67	0.98	
	Captopril*	-0.50	0.52	
TAPSE	Sacubitril/Valsartan *$	**2.75**	2.14	**0.01**
	Losartan*	0.79	2.46	
	Captopril$	0.67	3.14	
LVESD	Sacubitril/Valsartan	-0.32	0.36	0. 15
	Losartan	-0.15	0.40	
	Captopril	-0.10	0.35	
LVEDD	Sacubitril/Valsartan	-0.14	0.28	0.83
	Losartan	-0.16	0.43	
	Captopril	-0.08	0.30	
E/e'	Sacubitril/Valsartan	-3.14	4.61	0.41
	Losartan	-3.03	5.57	
	Captopril	-1.08	3.26	
RV-PA coupling	Sacubitril/Valsartan	0.09	0.09	0.71
	Losartan	0.07	0.12	
	Captopril	0.06	0.15	

* indicates to significant difference according to post hoc test results. $ indicates to significant difference according to post hoc test results. LVEF: Left ventricular ejection fraction, FAC: fractional area change, PASP: Pulmonary arterial systolic TAPSE: pressure, tricuspid annular plane systolic excursion, LVESD: left ventricular end-systolic diameter, LVEDD: left ventricular end-diastolic diameter, RV-PA coupling: Right ventricular–pulmonary artery coupling,

Tab. III. Comparison of RV dysfunction and TR severity between the studied groups.

Group	Baseline				p	Three months later(follow-up)				p	P trend
	RV dysfunction					RV dysfunction					
RV dysfunction (based on RVEF)	Mild	Moderate	Severe	Normal		Mild	Moderate	Severe	Normal		
Sacubitril/Valsartan	6	**20**	4	-	0.60	17	8	0	3	**0.04**	**0.006**
	20.00%	**66.7%**	13.3%	-		68.00%	28.6%	0.00%	10.7%		
Losartan	4	**9**	5	-		2	11	1	1		
	22.2%	**50.0%**	27.8%	-		13.3%	73.3%	6.7%	6.7%		
Captopril	2	**12**	2	-		6	5	1	0		
	12.5%	**75.0%**	12.5%	-		50.0%	41.7%	8.3%	0.00%		
TR severity											
Sacubitril/Valsartan	11	18	1	-	**0.03**	17	11	0	-	0.13	**0.02**
	36.7%	60.0%	3.3%	-		60.70%	39.3%	0.00%	-		
Losartan	7	5	**6**	-		7	5	2	-		
	38.9%	27.8%	**33.3%**	-		25.00%	35.70%	14.3%	-		
Captopril	4	8	2	-		4	6	2	-		
	28.6%	57.1%	14.3%	-		33.30%	50.0%	16.7%	-		

Tab. IV. Comparison reaching to optimum dose between the studied groups.

Group	**Optimum dose**			**P**
	Yes	No	Total	
Sacubitril/Valsartan	8	21	29	**0.006**
	27.60%	72.40%	100.00%	
Losartan	10	6	16	
	62.50%	37.5%	100.00%	
Captopril	1	12	13	
	7.7	92.3%	100.00%	
Total	19	39	58	
	32.8%	67.2%	100.00%	
	50% Optimum dose			
Sacubitril/Valsartan	29	0	29	**0.001**
	100.0%	100.00%	100.00%	
Losartan	15	1	16	
	93.8%	6.30%	100.00%	
Captopril	8	5	13	
	61.5%	38.5%	100.00%	
Total	52	6	58	
	89.7%	10.3%	100	

significant (0.02) (Tab. III). In terms of mortality, 5 deaths occurred, and the incidence of deaths in the Sacubitril/Valsartan, Losartan, and Captopril groups, were 2 (6.7%), 2 (11.2%), and 1 (7.7%) respectively and this difference was not statistically significant (p:0.83). In the comparison of the percentage of reaching the optimum dose as well as 50% of the optimum dose at the end of the study, there was a significant difference between the studied groups. Regarding the reaching optimum dose, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose (p: 0.006). Also, 100, 93.8, and 61.5% of cases in the mentioned groups reached 50% optimum dose (p: 0.001) (Tab. IV).

Discussion

Right ventricular dysfunction is associated with increased mortality in patients with congenital heart diseases, valvular diseases, coronary artery diseases, increased pulmonary blood pressure, and patients with heart failure. Therefore, treatment of right ventricular dysfunction and the presence of an effective treatment regime is one of the main concerns. The improvement of the right ventricular function can lead to improving the patient's clinical outcomes as well as a decrease in mortality and hospital lengths of stay. Considering the importance of the subject, the present study aimed to assess the effectiveness of Sacubitril/Valsartan compared to Losartan and Captopril in patients with RV dysfunction.

Main findings

The results of the current study showed that the increase in LVEF, RV FAC, and TAPSE as well as a decrease in DOE grade and RV diameter in the Sacubitril/Valsartan group was significantly higher than in the Losartan and

Captopril groups. Regarding the RV dysfunction, this disorder in the Sacubitril/Valsartan group improved significantly compared to the Losartan and Captopril groups. Also, the TR gradient change in the Sacubitril/Valsartan group was significantly higher than control groups. Regarding the mortality rate, this amount in the Sacubitril/Valsartan group was lower than in the control groups. Regarding the reaching optimum dose, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose. Also, 100, 93.8, and 61.5% of cases in the mentioned groups reached 50% optimum dose.

Our results showed that Sacubitril/Valsartan improved the TAPSE index. This result is similar to other studies. A meta-analysis which conducted to evaluate the effects of Sacubitril/Valsartan on RV function and PH in patients with HFrEF (Heart Failure with Reduced Ejection Fraction), The results showed that Sacubitril/Valsartan significantly improves TAPSE and S' (functional state of the right ventricle) and reduces sPAP and mPAP (state of pulmonary circulation) (20). The studies conducted in this field indicate the positive effects of these drugs in improving TAPSE in patients with HFrEF with long-term improvement [10]. In another in Italy, the mean TAPSE increased significantly after one year of treatment [11]. In another study that assessed the effect of reversible abnormal TAPSE and patient survival on patients with chronic HFrEF, the results showed that in patients whose TAPSE values were abnormal at the beginning of the study, but these values improved during the treatment, the prognosis of the disease was much better than compared to patients with abnormal TAPSE values [21]. In another study, significant improvement in TAPSE, RVFAC, S', and PASP was observed in patients receiving Sacubitril/Valsartan regardless of NYHA classification, gender, hypertension status, diabetes status, history of MI, and length of follow-up [22]. TAPSE is one of the main indices reflecting RV systolic function [23]. A decrease in TAPSE is associated with a poor prognosis of the disease [24, 25]. The results of the present study showed that Sacubitril/Valsartan has a positive effect in increasing TAPSE and improving the prognosis of the disease.

Our results showed that Sacubitril/Valsartan improved the LVEF, RV FAC, RV diameter, and DOE grade, as well as a decrease in DOE grade and RV diameter. The beneficial therapeutic effects of Sacubitril/Valsartan on improving RV function have also been reported in other studies [26, 27]. A meta-analysis showed significant improvements in LVEF and a reduction in LVEDV in the Sacubitril/Valsartan users [28]. Other studies showed the important therapeutic value of Sacubitril/Valsartan for patients with HFrEF and RV systolic dysfunction [22]. Masarone et al showed that Sacubitril/Valsartan may improve RV-pulmonary artery coupling [10], Landolfo et al. reported a PAsP improvement after S/V therapy [29], and Yenerçağ et al. showed FAC and pulmonary artery stiffness improvement [30].

Right ventricular dysfunction can have three origins, including pressure overload, ischemic heart disease, and cardiomyopathy [31]. The exact mechanisms by which Sacubitril/Valsartan improves the RV function and PH is unknown. However, Sacubitril valsartan may prevent maladaptive RV remodeling in a pressure overload model via amelioration of RV pressure rise, hypertrophy, collagen, and myofiber reorientation, as well as tissue stiffening at both the tissue and myofiber level [31]. Sacubitril/valsartan has dual effects through which it improves right ventricular function. This dual function includes inhibiting neprilysin and inactivating the renin-angiotensin-aldosterone system. This drug leads to natriuresis, vasodilation, and anti-apoptosis by inactivating many neurohormones, such as angiotensin II, aldosterone, and endothelin-1, modulating gene expression, such as transforming growth factor-β1 and promoting re-endothelialization, anti-fibrotic, anti-inflammatory, and anti-thrombotic reactions, as well as reducing cardiac hypertrophy, and ultimately improving the compensation of cardiac damage.

According to the results of this study and other studies conducted in this field, it seems that the evidence supports the effect of Sacubitril/Valsartan as a treatment option for RV dysfunction. The current study had limitations, which include; first, this study was a single-center study that can affect the generalizability of the results. Because the patients included in this study may not be similar in terms of clinical characteristics to all patients with right ventricular disorders, therefore, caution should be used in generalizing the results. Second, the sample size was small and the follow-up period was short, a small sample size can affect the ability of statistical tests to detect differences and lead to non-significant results to be seen. So Further confirmation needs a larger group of patients with longer follow-up periods to have a better perspective of long-term outcomes.

Conclusions

According to the results, it seems that Sacubitril/Valsartan has a positive effect on improving the right ventricular dysfunction in patients with right heart disorders. This effect may be independent of left heart dysfunction. Therefore, this treatment method can be used as an alternative in the treatment of these patients. However, the confirmation of the above findings requires larger studies with more samples.

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Data availability statement

the data set is not publicly available. Requests to access these data sets should be directed to the corresponding author, elahezeinali93@gmail.com

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Iran University of Medical Sciences, Tehran with the ethics code "IR.IUMS.FMD.REC.1401.706."

Irct registration number

The study protocol was registered in the Iranian registry of clinical trials with ID: IRCT20230926059524N1

Transparency statement

The lead author Elahe Zeinali affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

MH and EZ: conceptualization, methodology, and formal analysis. PJ, MP: investigation, data curation. EZ, MH, AND MP: writing - original draft preparation, writing - review and editing. MH: visualization and supervision and project administration. All authors have read and agreed to the published version of the manuscript.

References

[1] Maleki Jamasbi M, Azami H, Samari B, Yousofvand V, Shourcheh E. Epidemiological Survey of Mortality and Morbidity Caused by Cardiovascular Diseases in Patients Admitted to the Cardiac Care Units of Hamadan Educational-medical Hospitals, Hamadan, Iran, in 2017. J Health Res Commun 2019;5:27-38.

[2] Iglesias-Garriz I, Olalla-Gómez C, Garrote C, López-Benito M, Martín J, Alonso D, Rodríguez MA. Contribution of right ventricular dysfunction to heart failure mortality: a meta-analysis. Rev Cardiovasc Med 2012;13:e62-9. https://doi.org/10.3909/ricm0602.

[3] Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol 2008;52:1683-92. https://doi.org/10.1016/j.jacc.2008.08.033.

[4] Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, Seward SB. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838-47. https://doi.org/10.1016/s0894-7317(96)90476-9.

[5] Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107:526-31. https://doi.org/10.1016/0002-8703(84)90095-4.

[6] Wang SJ, Sander GE. Nebivolol/valsartan combination for the treatment of hypertension: a review. Future Cardiol 2021;17:573-83. https://doi.org/10.2217/fca-2020-0079.

[7] Hubers SA, Brown NJ. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation 2016;133:1115-24. https://doi.org/10.1161/CIRCULATIONAHA.115.018622.

[8] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. https://doi.org/10.1056/NEJMoa1409077.

[9] Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ Heart Fail 2017;10:e003430. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003430.

[10] Masarone D, Errigo V, Melillo E, Valente F, Gravino R, Verrengia M, Ammendola E, Vastarella R, Pacileo G. Effects of Sacubitril/Valsartan on the Right Ventricular Arterial Coupling in Patients with Heart Failure with Reduced Ejection Fraction. J Clin Med 2020;9:3159. https://doi.org/10.3390/jcm9103159.

[11] Correale M, Mallardi A, Mazzeo P, Tricarico L, Diella C, Romano V, Ferraretti A, Leopizzi A, Merolla G, Di Biase M, Brunetti ND. Sacubitril/valsartan improves right ventricular function in a real-life population of patients with chronic heart failure: The Daunia Heart Failure Registry. Int J Cardiol Heart Vasc 2020;27:100486. https://doi.org/10.1016/j.ijcha.2020.100486.

[12] Moliner-Abós C, Rivas-Lasarte M, Pamies Besora J, Fluvià-Brugues P, Solé-González E, Mirabet S, López López L, Brossa V, Pirla MJ, Mesado N, Álvarez-García J, Roig E. Sacubitril/Valsartan in Real-Life Practice: Experience in Patients with Advanced Heart Failure and Systematic Review. Cardiovasc Drugs Ther 2019;33:307-14. https://doi.org/10.1007/s10557-019-06858-0.

[13] Triposkiadis F, Xanthopoulos A, Bargiota A, Kitai T, Katsiki N, Farmakis D, Skoularigis J, Starling RC, Iliodromitis E. Diabetes Mellitus and Heart Failure. J Clin Med 2021;10:3682. https://doi.org/10.3390/jcm10163682.

[14] Lee JW, Choi E, Son JW, Youn YJ, Ahn SG, Ahn MS, Kim JY, Lee SH, Yoon J, Ryu DR, Park SM, Hong KS, Yoo BS. Comparison of Blood Pressure Variability Between Losartan and Amlodipine in Essential Hypertension (COMPAS-BPV). Am J Hypertens 2020;33:748-55. https://doi.org/10.1093/ajh/hpaa060.

[15] Lluri G, Lin J, Reardon L, Miner P, Whalen K, Aboulhosn J. Early Experience With Sacubitril/Valsartan in Adult Patients With Congenital Heart Disease. World J Pediatr Congenit Heart Surg 2019;10:292-95. https://doi.org/10.1177/2150135119825599.

[16] Appadurai V, Thoreau J, Malpas T, Nicolae M. Sacubitril/Valsartan in Adult Congenital Heart Disease Patients With Chronic Heart Failure - A Single Centre Case Series and Call for an International Registry. Heart Lung Circ 2020;29:137-41. https://doi.org/10.1016/j.hlc.2018.12.003.

[17] Maurer SJ, Pujol Salvador C, Schiele S, Hager A, Ewert P, Tutarel O. Sacubitril/valsartan for heart failure in adults with complex congenital heart disease. Int J Cardiol 2020;300:137-40. https://doi.org/10.1016/j.ijcard.2019.06.031.

[18] Suematsu Y, Miura S, Goto M, Matsuo Y, Arimura T, Kuwano T, Imaizumi S, Iwata A, Yahiro E, Saku K. LCZ696, an angiotensin receptor-neprilysin inhibitor, improves cardiac function with

the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. Eur J Heart Fail 2016;18:386-93. https://doi.org/10.1002/ejhf.474.

[19] Bayard G, Da Costa A, Pierrard R, Roméyer-Bouchard C, Guichard JB, Isaaz K. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. Int J Cardiol Heart Vasc 2019;25:100418.https://doi.org/10.1016/j.ijcha.2019.100418.

[20] Zhang J, Du L, Qin X, Guo X. Effect of Sacubitril/Valsartan on the Right Ventricular Function and Pulmonary Hypertension in Patients With Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis of Observational Studies. J Am Heart Assoc 2022;11:e024449. https://doi.org/10.1161/JAHA.121.024449.

[21] Dini FL, Carluccio E, Simioniuc A, Biagioli P, Reboldi G, Galeotti GG, Raineri C, Gargani L, Scelsi L, Mandoli GE, Cannito A, Rossi A, Temporelli PL, Ghio S; Network Labs Ultrasound (NEBULA) in Heart Failure Study Group. Right ventricular recovery during follow-up is associated with improved survival in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail 2016;18:1462-71. https://doi.org/10.1002/ejhf.639.

[22] Yang Y, Shen C, Lu J, Fu G, Xiong C. Sacubitril/Valsartan in the Treatment of Right Ventricular Dysfunction in Patients With Heart Failure With Reduced Ejection Fraction: A Real-world Study. J Cardiovasc Pharmacol 2022;79:177-82. https://doi.org/10.1097/FJC.0000000000001162.

[23] Aloia E, Cameli M, D'Ascenzi F, Sciaccaluga C, Mondillo S. TAPSE: An old but useful tool in different diseases. Int J Cardiol 2016;225:177-83. https://doi.org/10.1016/j.ijcard.2016.10.009.

[24] Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, Nikitin NP, Dubois-Randé JL, Hittinger L, Clark AL, Cleland JG. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail 2012;18:216-25. https://doi.org/10.1016/j.cardfail.2011.12.003.

[25] Kjaergaard J, Akkan D, Iversen KK, Køber L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. Eur J Heart Fail 2007;9:610-6. https://doi.org/10.1016/j.ejheart.2007.03.001.

[26] Nederend M, Kiès P, Regeer MV, Vliegen HW, Mertens BJ, Robbers-Visser D, Bouma BJ, Tops LF, Schalij MJ, Jongbloed MRM, Egorova AD. Tolerability and beneficial effects of sacubitril/valsartan on systemic right ventricular failure. Heart 2023;109:1525-32. https://doi.org/10.1136/heartjnl-2022-322332.

[27] Nugara C, Giallauria F, Vitale G, Sarullo S, Gentile G, Clemenza F, Lo Voi A, Zarcone A, Venturini E, Iannuzzo G, Coats AJ, Sarullo FM. Effects of Sacubitril/Valsartan on Exercise Capacity in Patients with Heart Failure with Reduced Ejection Fraction and the Role of Percentage of Delayed Enhancement Measured by Cardiac Magnetic Resonance in Predicting Therapeutic Response: A Multicentre Study. Card Fail Rev 2023;9:e07. https://doi.org/10.15420/cfr.2022.13.

[28] Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc 2019;8:e012272. https://doi.org/10.1161/JAHA.119.012272.

[29] Landolfo M, Piani F, Esposti DD, Cosentino E, Bacchelli S, Dormi A, Borghi C. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. Int J Cardiol Heart Vasc 2020;31:100656. https://doi.org/10.1016/j.ijcha.2020.100656.

[30] Yenerçağ M, Arslan U, Dereli S, Çoksevim M, Doğduş M, Kaya A. Effects of angiotensin receptor neprilysin inhibition on pulmonary arterial stiffness in heart failure with reduced ejection fraction. Int J Cardiovasc Imaging 2021;37:165-73. https://doi.org/10.1007/s10554-020-01973-8.

[31] Lyon RC, Zanella F, Omens JH, Sheikh F. Mechanotransduction in cardiac hypertrophy and failure. Circ Res 2015;116(8):1462-76. https://doi.org/10.1161/CIRCRESAHA.116.304937.

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