

# The impact of discontinuation of sacubitril–valsartan and shifting to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with heart failure with reduced ejection fraction

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## ABSTRACT

**Objective:** Many trials confirmed the role of sacubitril–valsartan in the treatment of patients with heart failure with reduced ejection fraction (HFrEF). However, there is no sufficient data to register the effect of compulsory discontinuation of sacubitril–valsartan, either because of financial shortage or adverse effects, and shifting to the standard therapy, including angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

**Methods:** The patients with HFrEF (LVEF  $\leq 35\%$ ) were included in the study. They received treatment with sacubitril–valsartan as a replacement for an ACEI or ARB. The patients were divided into two groups: the compliant group (n=111). The non-compliant group (n=82), whose members discontinued sacubitril–valsartan after  $\geq 5$  months but  $< 6$  months since their enrollment in the study.

**Results:** Initially, 199 patients with HFrEF were included in the study. All the patients were started treatment with sacubitril–valsartan in addition to the evidence-based standard therapy of heart failure. Six patients were excluded at the first follow-up visit (at 6 months). The remaining 193 patients showed initial improvement of the New York Heart Association (NYHA) class, the end-diastolic volume (EDV), and the left ventricular ejection fraction (LVEF). Five patients were excluded at the 12 months' follow-up visit. The other 188 patients were divided into two groups: Group I (n=108) patients were compliant on sacubitril–valsartan for 12 months; Group II (n=80) patients were compliant on sacubitril–valsartan for  $\geq 5$  months, but stopped it at  $< 6$  months, and were shifted to ACEI or evidence-based ARB. Group II (n=80) patients showed worsening of their NYHA class, compared to the 6 months' follow-up visit (p=0.001). LVEF and EDV were also shown to be worsened in these patients when we compared them to the values of the 6 months' follow-up appointment with p=0.001 for both parameters.

**Conclusion:** The discontinuation of sacubitril–valsartan in patients with HFrEF leads to deterioration of the LVEF as well as worsening of the functional class. The decline in LVEF and NYHA functional class occurs despite being compliant with the optimal conventional therapy with ACEI or evidence-based ARB.

**Keywords:** sacubitril–valsartan, neprilysin inhibitor, heart failure with reduced ejection fraction

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## Introduction

Sacubitril–valsartan is a combination drug that is used for the treatment of heart failure with reduced ejection fraction (HFrEF). It consists of an angiotensin receptor blocker (ARB) valsartan and a neprilysin inhibitor sacubitril. The guidelines recommended it as a replacement for an angiotensin-converting enzyme inhibitor (ACEI) or an evidence-based ARB in patients with HFrEF (1).

We can use sacubitril–valsartan instead of an ACEI or an ARB in people with HFrEF (2, 3), in conjunction with other standard

therapies [e.g., beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs)] (1, 4). Sacubitril–valsartan decreases the risk of death in those patients who do well with an ACEI or an ARB but still have symptoms (1). If we can shift 100 people from an ACEI or an ARB to sacubitril–valsartan for 2.3 years, we would prevent three deaths, five hospitalizations for heart failure (4).

Neprilysin inhibition results in slowing the rate of degradation of natriuretic peptides, bradykinin, and other peptides. The increased circulating levels of A-type (ANP) and brain-type (BNP) natriuretic peptides result in better diuresis, natriuresis, cardiac

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**HIGHLIGHTS**

- The discontinuation of sacubitril–valsartan in patients with HFrEF leads to deterioration of the LVEF.
- The discontinuation of sacubitril–valsartan in patients with HFrEF leads to worsening of the functional class.
- The decline in LVEF and NYHA functional class occurs despite being compliant with the optimal conventional therapy with ACEI or evidence-based ARB.

relaxation, and anti-remodeling effects (5). Both peptides also reduce renin and aldosterone release. Valsartan blocks angiotensin (AT1) receptors that results in vasodilation, reducing salt and water retention, as well as myocardial hypertrophy (5).

Despite the pathophysiological benefits of sacubitril–valsartan, very few data are available regarding its effect on the left ventricular (LV) function and remodeling; most of the published data are meta-analysis and retrospective data (6, 7).

The wholesale cost of sacubitril–valsartan in Egypt is 28,157 Egyptian pound (EGP) per person per year. In comparison, valsartan costs around 4320 EGP a year. The high cost of the relatively new medication sacubitril–valsartan may lead to compulsory discontinuation of the treatment by some patients, especially in developing countries. Many cardiologists in our country follow the guidelines and start the treatment with sacubitril–valsartan when indicated. However, many patients shift to the standard treatment with ACEI/ARB because of financial shortage. The medical insurance system strictly applies the recommendation of using sacubitril–valsartan only in patients with  $EF \leq 35\%$ . So, when the EF rises above 35%, the medical insurance recommends shifting again to the standard cheaper treatment. We wanted to study the effect of this compulsory discontinuation of sacubitril–valsartan and the shifting to the standard treatment after the initial expected beneficial effect of sacubitril–valsartan. There is no data available till now on the clinical and echocardiographic impact of discontinuation of sacubitril–valsartan and shift to standard therapy, including an ACEI or ARB in those patients.

**Objectives**

This study aimed to register the effect of compulsory discontinuation of sacubitril–valsartan and shifting to an ACEI or ARB in patients with HFrEF because of financial shortage or adverse effects.

**Methods**

This prospective observational study was conducted in two cardiology centers. Initially, 199 patients  $\geq 18$  years old, with HFrEF ( $LVEF \leq 35\%$ ) were included in the study, who remained symptomatic despite optimum management with an ACEI or evidence-based ARB, BB, and MRA. They received treatment with the relatively new medication sacubitril–valsartan as a replacement for an ACEI or ARB. All the patients were candidates for treatment

with the relatively new medication sacubitril–valsartan according to the criteria mentioned in the chronic heart failure guidelines (1). The study protocol was approved by the committees of research and medical ethics of the cardiology departments in June 2018 and July 2018. Informed written consent was obtained from all the patients. All the patients were informed that sacubitril–valsartan was a lifelong treatment, and it should not be discontinued. The patients were switched from an ACEI or ARB to sacubitril–valsartan. A washout period of 36 hours was allowed before the administration of sacubitril–valsartan with a dose of 24/26 mg BID. The dose was doubled every month to target the maintenance dose of 97/103 mg BID as tolerated.

The following patients were excluded from the study:

- 1- Patients with a history of angioedema, symptoms of low blood pressure, hypovolemia, or dehydration.
- 2- Patients with hepatic impairment, bilateral renal artery stenosis, or cardiac outflow obstruction.
- 3- Patients with severe renal impairment [estimated glomerular filtration rate (eGFR)  $< 30$  mL/min/1.73 m<sup>2</sup>] or hyperkalemia ( $> 5.5$  mmol/L).
- 4- Any pregnant lady or was planning to conceive or breastfeeding.
- 5- Patients with a history of revascularization 3 months before the enrollment and during the whole study period.
- 6- Patients with a history of acute myocardial infarction (AMI) or acute coronary syndrome (ACS) 3 months before the enrollment and during the entire study period.
- 7- Patients with symptoms of chronic stable angina during the study period.
- 8- Patients who were not compliant with the evidence-based treatment of heart failure during the 6 months before enrollment in the study.

Eligibility criteria were evaluated, and written, informed consent was obtained from eligible patients at the selection appointment. All the patients were subjected to the following at baseline, at 6 months (first follow-up visit), and at 12 months (second follow-up appointment):

History-taking and clinical examination: to exclude the patients with evidence of any of the exclusion criteria and to assess the New York Heart Association (NYHA) functional class. Routine laboratory test: to exclude patients with renal impairment and hyperkalemia. Transthoracic echocardiography: detailed conventional M-mode and two-dimensional (2D) transthoracic echocardiographic examination and Doppler study using standard parasternal and apical views utilizing an imaging system equipped with a 2–4 MHz transducer, to assess the left ventricular dimensions, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and the ejection fraction (EF) were calculated by the modified Simpson's method, following the recommendations of the European Association of Cardiovascular Imaging (8).

Patients who did not attend all the follow-up visits were excluded from the study. So, the final sample size included only the

patients who participated at the 1-year follow-up visits. Any patient who was not compliant with sacubitril-valsartan for  $\geq 5$  months was also excluded, as shown in Figure 1. Six patients were excluded from the study at the first follow-up visit (6 months after the enrollment) for the following reasons: two patients did not come to the 6 months' follow-up visit. Four patients were compliant with sacubitril-valsartan for  $< 5$  months from the enrollment in the study (stopped the sacubitril-valsartan  $\geq 1$  month before the first follow-up visit): two patients stopped the treatment due to financial reasons after 3 and 4 months, respectively. The other two patients discontinued the treatment after 2 months because of symptoms of hypotension. After the 6 months' follow-up visit, the study included only 193 patients, divided into two groups: the compliant group ( $n=111$ ), whose members were compliant with the treatment. The non-compliant group ( $n=82$ ), whose members discontinued sacubitril-valsartan after  $\geq 5$  months but  $< 6$  months since their enrollment in the study.

### Statistical analysis

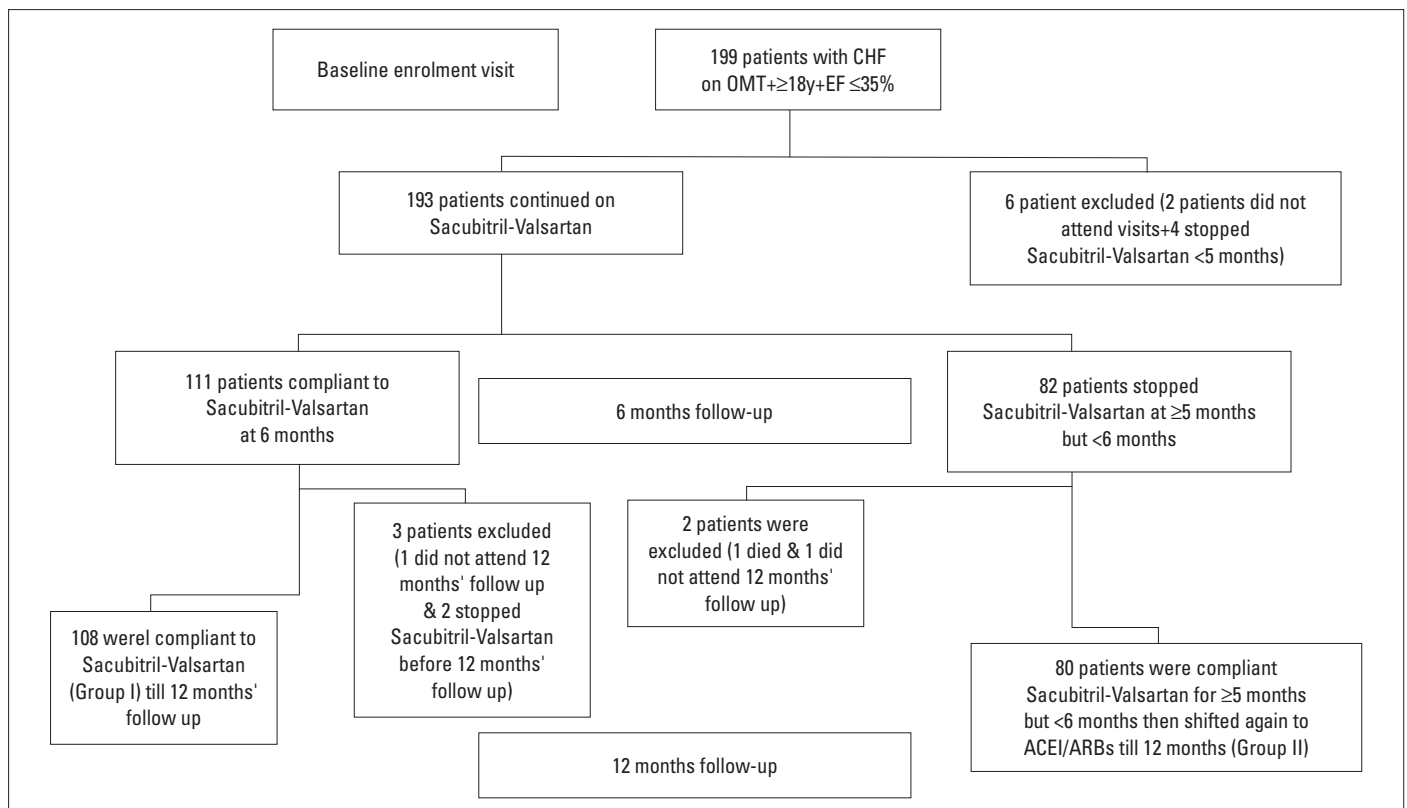
The data were evaluated by using IBM SPSS software package version 20.0. The Kolmogorov-Smirnov test was used for testing the normal distribution of continuous data. Quantitative data were expressed as mean  $\pm$  standard deviation (SD) and range and showed as frequency and percentage. Independent samples t-test was used for normally distributed data, when comparing two means between both groups. Two-way analysis

of variance (two-way ANOVA) was used when comparing more than two means in the same group (baseline, 6 months', and 1-year follow-up). Chi-square ( $X^2$ ) test was used to compare proportions between two qualitative parameters. The significance was evaluated in the form of p-value and classified it into a non-significant  $p > 0.05$  and significant  $p \leq 0.05$ .

### Results

All the 193 patients were followed up at 1 year from the enrollment (the 12 months' follow-up visit); another five patients were excluded from the study at this visit. So, the final sample size was 188 patients.

Three patients were excluded from the compliant group ( $n=111$ ) for the following reasons: two patients stopped sacubitril-valsartan because of financial reasons after 8 and 9 months from the enrollment, and one patient did not turn up at the follow-up. The remaining 108 patients in the compliant group were named as Group I ( $n=108$ ). Two patients were excluded from the non-compliant group ( $n=82$ ): one patient died; he was admitted to the coronary care unit (CCU) with acute pulmonary edema. The other patient did not turn up for follow-up. The remaining 80 patients in the non-compliant group were named as Group II ( $n=80$ ). The flowchart of the study is shown in Figure 1. It was observed that in Group II, 65 of 80 patients were discontinued the treatment because of financial causes, 6 because of decreased



**Figure 1.** Flow chart of our patients

CHF - congestive heart failure, OMT - optimal medical therapy, EF - ejection fraction, ACEI - angiotensin-converting enzyme inhibitor, ARBs - angiotensin receptor blocker

eGFR <30 mL/min/1.73 m<sup>2</sup>, and 9 because of symptomatic hypotension. No statistically significant difference was observed between both the groups in the baseline demographic data in our study, as shown in Table 1. Also, no statistically significant difference was found between both the groups in the baseline NYHA functional class, EF, and EDV, as shown in Table 1.

#### The first follow-up visit (6 months after the enrollment)

A significant improvement was noticed in the patients' NYHA class in both groups ( $p=0.001$ ). No patients were found to be in NYHA class IV or III at this visit. We had found 20 and 90 patients in both groups with NYHA class IV and III, respectively, at the baseline as shown in Table 2 and Figure 2. The mean EF and EDV in Group I at the baseline were 31.7% and 208.8 mL, respectively,

while at 6 months' visit, they were 37.5% and 195.9 mL, respectively. The same was noticed in Group II as well; the mean EF and EDV at the baseline were 32.2% and 207.2 mL, respectively, while at 6 months, they were 38.7% and 193.8 mL, respectively, as shown in Table 3 and Figures 3, 4.

#### The second follow-up visit (12 months after the enrollment)

The patients in group I ( $n=108$ ) showed a sustained improvement in NYHA class, EF, and EDV without significant difference between the findings of first and second follow-up visits:  $p=0.175$ , 0.443, and 0.621 respectively, but with more patients shifted from NYHA class II to NYHA class I. At this visit, 74% of patients were found to be in class I and 26% in class II, while at the 6 months' follow-up visit, 67.6% and 32.4% of patients were found to be in NYHA

**Table 1. The baseline demographic, clinical, and echocardiographic characteristics**

			Range	Mean±SD	t test	P
Age	Group I (n=108)		40-7	58.53±10.24	0.122	0.727
	Group II (n=80)		39-77	58.01±9.80		
Baseline EF (%)	Group I (n=108)		22-37	31.74±3.74	0.908	0.342
	Group II (n=80)		21-37	32.25±3.55		
Baseline EDV (mL)	Group I (n=108)		196-224	208.83±7.04	2.431	0.121
	Group II (n=80)		196-226	207.22±7.02		
			Group I No (108)	Group II No (80)	X <sup>2</sup>	P
Gender	Male	n	77	54	0.393	0.531
		%	71.2%	67.5%		
	Female	n	31	26	0.013	0.909
		%	28.8%	32.5%		
HTN	Yes	n	88	65	0.005	0.941
		%	81.4%	81.25%		
	No	n	20	15	0.358	0.550
		%	18.6%	18.75%		
DM	Yes	n	27	21	0.005	0.941
		%	25.0%	26.25%		
	No	n	81	59	0.358	0.550
		%	75.0%	73.5%		
Smoking	Yes	n	75	53	0.358	0.550
		%	69.4%	66.25%		
	No	n	33	27	0.358	0.550
		%	30.6%	33.75%		
<b>Baseline NYHA class</b>			Group I (n=108)	Group II (n=80)	X <sup>2</sup>	P
II	n	44	34	0.060	0.970	
	%	40.8%	42.5%			
III	n	52	38	0.060	0.970	
	%	48.2%	47.5%			
IV	n	12	8	0.060	0.970	
	%	11.0%	10.0%			

EF - ejection Fraction; EDV - end-diastolic volume; NYHA - New York Heart Association; SD - standard deviation; HTN - hypertension; DM - diabetes mellitus

**Table 2. The NYHA class at the baseline and the follow-up in both groups**

	Range	Mean±SD	F-test		P	
EF%						
Group I (n=108)						
Baseline	22–37	31.7±3.741	65.563	0.001*	P1	0.001*
6 months	25–49	37.6±4.965			P2	0.001*
12 months	26–50	38.0±4.861			P3	0.443
EF%						
Group II (n=80)						
Baseline	21–37	32.2±3.548	72.977	0.001*	P1	0.001*
6 months	27–48	38.7±4.555			P2	0.814
12 months	21–38	32.1±3.675			P3	0.001*
EDV (mL)						
Group I (n=108)						
Baseline	196–224	208.8±7.038	66.972	0.787	P1	0.001*
6 months	175–220	195.9±11.087			P2	0.001*
12 months	174–219	195.2±10.737			P3	0.621
EDV (mL)						
Group II (n=80)						
Baseline	196–226	207.2±7.020	195.117	0.001*	P1	0.001*
6 months	172–216	193.8±10.316			P2	0.918
12 months	195–225	207.1±7.034			P3	0.001*

*P1* comparison between baseline and 6 months. *P2* comparison between baseline and 12 months. *P3* comparison between 6 months and 12 months. \*Significant *P*-value.  
EF - ejection fraction; EDV - end-diastolic volume; SD - standard deviation

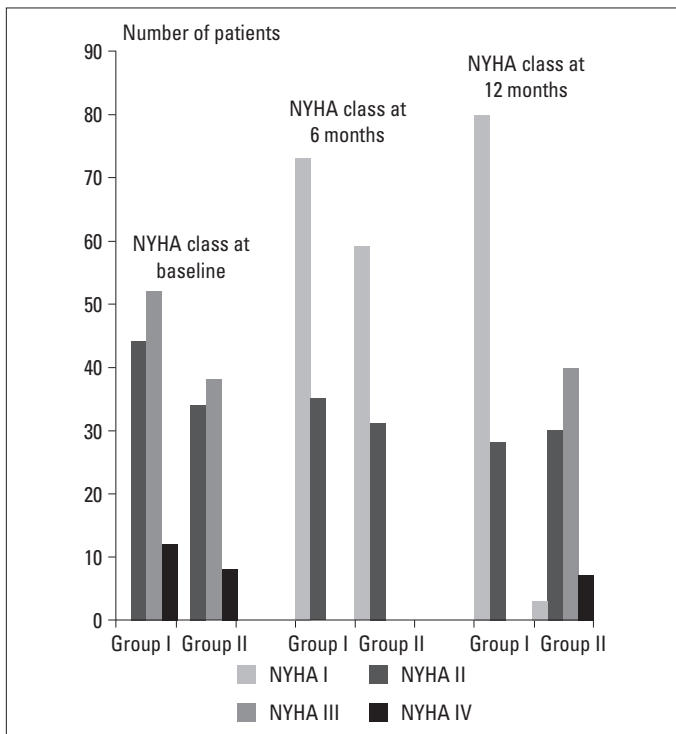
**Table 3. The EF and EDV at the baseline and follow-up in both groups**

	NYHA class		Baseline	6 m	12 m	X <sup>2</sup>	P	P1	P2	P3
Group I (n=108)	I	n	0	73	80	234.426	0.001*	0.001*	0.001*	0.175
		%	0.0%	67.6%	74.0%					
	II	n	44	35	28					
		%	40.7%	32.4%	27%					
	III	n	52	0	0					
		%	48.1%	0.0%	0.0%					
IV	n	12	0	0						
	%	11.2%	0.0%	0.0%						
Group II (n=80)	I	n	0	59	3	157.398	0.001*	0.001*	0.344	0.001*
		%	0.0%	73.75%	3.7%					
	II	n	34	21	30					
		%	42.5%	26.25%	37.7%					
	III	n	38	0	40					
		%	47.5%	0.0%	50.0%					
	IV	n	8	0	7					
		%	10.0%	0.0%	8.6%					

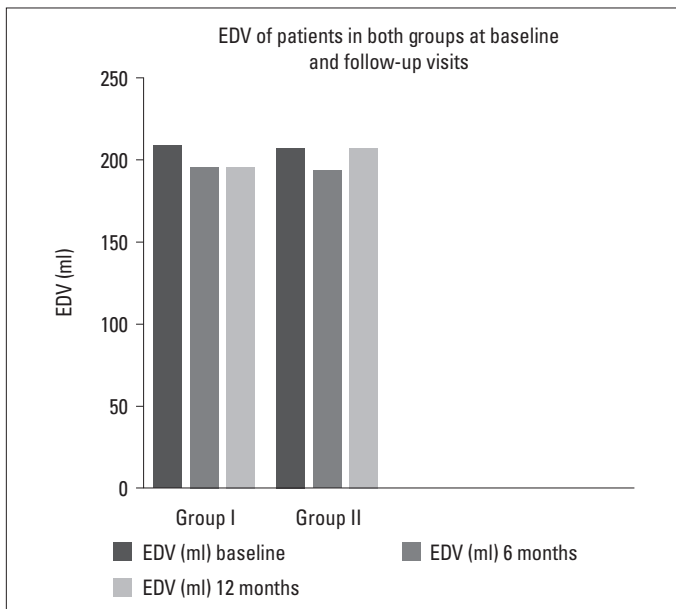
*P1* comparison between baseline and 6 months. *P2* comparison between baseline and 12 months. *P3* comparison between 6 months and 12 months. \*Significant *P*-value.  
NYHA - New York Heart Association

classes I and II, respectively, as shown in Tables 2, 3 and Figures 2-4. The patients in Group II (n=80) were showed worsening of their NYHA class, compared to the 6 months' follow-up visit (p=0.001), as

shown in Table 2 and Figure 2. Worsening of EF and EDV were noticed when compared to the values of the 6 months' follow-up visit (p=0.001) for both the parameters, as shown in Table 3, Figures 3, 4.



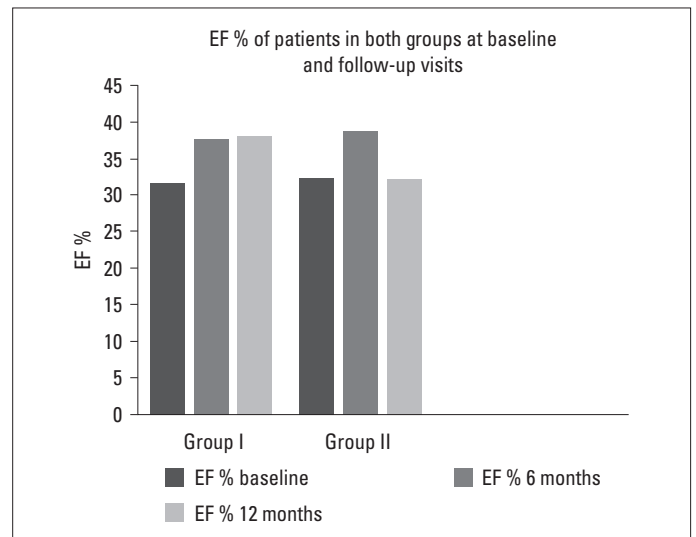
**Figure 2.** EF% at the baseline, 6 months' follow-up and 12 months' follow-up in both groups  
EF - ejection fraction



**Figure 3.** NYHA class of both groups at baseline and follow-up visits  
NYHA - New York Heart Association

### Discussion

This study is a two-center experience. It has been found from the study results that the patients with HFrEF, who used sacubitril-valsartan, had a mean increase in the EF of 6% ( $p=0.001$ ) and a decrease in the mean EDV of 13 mL ( $p=0.001$ ) after 6 months. These



**Figure 4.** EDV at the baseline, 6 months' follow-up and 12 months' follow-up in both group  
EDV - end-diastolic volume

data are matching with that of the single-center study conducted on 52 patients by Bayard et al. (9). Their study found that treatment with sacubitril-valsartan for 3 months resulted in an increase of the mean EF from  $32.6\pm 5\%$  to  $36\pm 6\%$  ( $p<0.001$ ) and a decrease of the mean LVEDV from  $144\pm 37$  mL to  $193\pm 47$  mL ( $p<0.001$ ) (9).

In the PRIME study, the authors found that the combined molecule sacubitril-valsartan had a more beneficial consequence on the ventricular remodeling in comparison with valsartan, with more improvement in the LVEDV index, the effective regurgitant orifice area of mitral regurgitation, and the ratio of the mitral inflow velocity to mitral annular relaxation velocity ( $E/E'$ ) as well as the left atrial volume index. However, no improvement in the LVEF was noticed. The failure to achieve improvement in the LVEF may be explained by the different inclusion criteria because, in this study, they excluded patients with  $LVEF \leq 25\%$ . They included patients only with severe mitral regurgitation (6).

On the other hand, this improvement in the echocardiographic parameters was found to be associated with significant improvement in the patients' NYHA functional class ( $p=0.001$ ). All the patients at 6 months' follow-up visit were either in NYHA class I or II. No patients were found to be in class III or IV, which is matching with the data of the PARADIGM-HF trial that showed a 21% reduction of the first hospitalization and a 20% reduction in the rate of readmission (10). Bayard et al. (9) also found improvement in the NYHA class in their study. Few patients who showed intolerance to sacubitril-valsartan in our study were attributed to the inclusion of patients who were compliant of ACEI or ARB >6 months before enrollment in the study.

In the PARADIGM-HF trial, about 18% of the patients were discontinued sacubitril-valsartan, and they were excluded from the trial (4). Our data showed 42.5% of the patients discontinued sacubitril-valsartan at 12 months' follow-up. However, we did not exclude those patients. We followed them up for 12 months

and found beneficial effects of sacubitril–valsartan on the echocardiographic parameters and the NYHA functional class. They lost these beneficial effects at the 12 months' follow-up with  $p=0.001$  for all the parameters, as shown in Tables 2, 3, Figures 2-4, while the patients in Group I (57.5%) had showed sustained improvement of the echocardiographic parameters and the NYHA functional class. The sustained improvement at the 12 months' follow-up could be explained by the increased concentration of natriuretic peptides. Natriuretic peptides naturally help to balance the hazardous effect resulting from renin–angiotensin–aldosterone system (RAAS) activation and help to restore the hemodynamic balance in patients with HFrEF by improving natriuresis, diuresis, and vasodilation. Natriuretic peptides have also found to have antifibrotic and antihypertrophic effects that improve myocardial remodeling and prevent the progression of heart failure (11). The deterioration of NYHA class and EF that occurred in our study in Group II ( $n=80$ ) at 12 months after discontinuation of sacubitril–valsartan supports that the initial improvement in the symptoms and the echocardiographic parameters at 6 months was independently caused by sacubitril–valsartan. This improvement was not maintained by shifting to ACEI or ARB in addition to the standard therapy of HFrEF.

### Study limitations

Despite the encouraging results presented in our small study, there were significant limitations, including the small sample size and the short-term follow-up after discontinuation of sacubitril–valsartan. We did not study the other causes of discontinuation of sacubitril–valsartan like drug intolerance as our patients were already tolerating the ACEI or ARB, and the leading cause of interruption of therapy was financial.

### Conclusion

The initial improvement of EF and NYHA functional class by sacubitril–valsartan in patients with HFrEF could not be maintained after shifting to ACEI or ARB with the other standard evidence-based treatments such as BB and MRBs.

We recommend against discontinuation of sacubitril–valsartan, especially after the initial improvement in the EF. We should consider sacubitril–valsartan as a lifelong treatment. We recommend this study to be a nucleus for further studies that may present more solid evidence and target extended follow-up period.

**Ethics approval and consent to participate:** The study protocol has been conducted following the Declaration of Helsinki. The study protocol was approved by the Committee of Research and Medical Ethics of the Cardiology Department, Beni Suef University (reference C012018) in June 2018 & the Committee of Research and Medical Ethics of the Cardiology Department, Tanta University in July 2018. Informed written consent was obtained from all the patients.

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**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – O.A.A., A.F.A.; Design – O.A.A., A.F.A.; Supervision – O.A.A., A.F.A.; Fundings – O.A.A., A.F.A.; Materials – O.A.A., A.F.A.; Data collection and/or processing – O.A.A., A.F.A.; Analysis and/or interpretation – O.A.A., A.F.A.; Literature search – O.A.A., A.F.A.; Writing – O.A.A., A.F.A.; Critical review – O.A.A., A.F.A.

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