ORIGINAL CLINICAL ARTICLE

Real world experience in using Sacubitril /valsartan in heart failure patients with reduced ejection fraction in Cyprus

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Abstract

BACKGROUND

Heart failure is a modern epidemic that affects many people worldwide, has a high mortality, significantly affects patients' quality of life, and has a high economic impact on health systems. Treatment with sacubitril/valsartan has been shown in a large randomized clinical trial (PARADIGM HF) to further improve the effect of medical treatment on morbidity and mortality of heart failure patients. The aim of this study was to assess the use of sacubitril/valsartan in real-world heart failure patients and its effects on their clinical parameters.

METHODS

We have enrolled 21 heart failure patients with reduced ejection fraction who have been switched to sacubitril/valsartan from February 2016 to February 2020. We have recorded their baseline characteristics, clinical and echocardiographic parameters and compared them to the findings at the end of the observation period.

RESULTS

Sixty-six point seven per cent (66,7%) of patients were able to reach the maximum recommended dose. Mean daily dose of sacubitril/valsartan was 157,1 mg. After a mean follow up of 33 months, we observed an improvement in mean NYHA class from 3 to 2. eGFR increased from 67,7 to 69,3 ml/min/173 m^2 and potassium increased from 4,36 to 4,74 mmol/L. Systolic blood pressure decreased from 118,4 to 112,3 mmHg and diastolic blood pressure decreased from 74,1 to 73,7 mmHg. Two patients have discontinued the treatment, both due to renal failure and one patient died. In the subset of patients where echocardiographic indices were measured, LVEF increased from 29,9 to 33,5%, left ventricular end-diastolic diameter decreased from 62,3 to 61,0 mm, left atrial diameter decreased from 46,9 to 43,8 mm and E/e' decreased from 11,1 to 8,1.

CONCLUSION

Use of sacubitril/valsartan in real-world patients is feasible and safe. Even if, in a proportion of patients, it was used in a lower dose than in clinical trials, similar favourable clinical and echocardiographic outcomes were observed.

Introduction

Heart failure is an epidemic affecting 1-2% of the adults in developed countries with about half of them suffering from heart failure with reduced ejection fraction. The total number of patients with heart failure is continuously increasing, mainly due to aging of the population and improvement of survival post diagnosis.[1] Heart failure patients have a high hospitalisation rate leading to a high economic impact on health systems. Furthermore, quality of life of heart failure patients is often poor.[2]

Treatment of heart failure is based on neurohormonal inhibition with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta blockers and mineralocorticoid receptor antagonists (MRAs). Treatment with these classes of medications has been shown in large clinical trials to significantly reduce morbidity and mortality of heart failure patients.[3] Despite the benefit from the above drug classes, morbidity and mortality of heart failure patients remains high. A new drug class has recently emerged aiming to further improve the prognosis and quality of life of heart failure: the combination of an angiotensin receptor blocker with a neprilysin inhibitor (ARNI). Neprilysin inhibition is considered to reduce cleavage of natriuretic peptides as well as other peptides with favourable effects such as vasodilation and natriuresis.[4] The only representative of this class until today, sacubitril/valsartan, has been compared with ACEI enalapril in addition to recommended therapy in a large double-blind randomized study (PARADIGM HF) and was found to significantly reduce the risk of death, hospitalization and improve quality of life of heart failure patients with reduced ejection fraction.[5] The results of this study led to the recommendation of the 2016 guidelines of the European Society of Cardiology (ESC) for management of heart failure to replace ACEIs with sacubitril/valsartan combination in patients who remain symptomatic despite optimal medical therapy and fitting the above-mentioned trial's criteria[6].

Randomized controlled trials (RCTs) provide reliable information on efficacy and safety of treatments and eliminate as much as possible the effect of confounding factors. On the other hand, real world studies are also of great importance since they may include a broader spectrum of patients than the selected per protocol patients of RCTs in various environments. Real world studies can also follow patients for long enough periods to assess benefits and monitor for long term risks.[7] Our study presents our experience in using sacubitril/valsartan in heart failure patients, which is, to our knowledge, one of the longest in Cyprus. We focused on baseline characteristics of patients, dosing titration and effects on symptoms, biomarkers, and echocardiographic indices.

Methods

Study population

Our study is a retrospective cohort of patients with symptomatic (NYHA ≥2) heart failure with reduced ejection fraction (≤35%) who were followed at our practice and were switched from treatment with ACEI or ARB to sacubitril/valsartan from February 2016 until February 2020. Patients were already on maximum tolerated heart failure treatment and were considered suitable for switching to sacubitril/valsartan.

Titration of treatment

Sacubitril/valsartan was initiated at 24/26 mg bd or 49/51 mg bd according to the protocol of PARADIGM HF study[5] and patients were titrated according to clinical judgment based on blood pressure, renal function, electrolytes, and symptoms. The concomitant heart failure medications were managed according to the guidelines.

Patient outcomes

Patients were initially evaluated clinically (including blood pressure measurement) and their NYHA class was defined. Laboratory studies were also performed to measure eGFR, potassium and haemoglobin. Routine echocardiographic measurements were also performed: left ventricular ejection fraction (LVEF) using Simpson's biplane method, left ventricular end-diastolic diameter (LVEDD) and left atrial diameter (LAD) measured at parasternal long axis view, mitral valve inflow E and A wave using pulsed wave doppler, e' velocity of basal lateral wall using tissue doppler and calculation of E/A and E/e' ratios. Pulmonary artery systolic pressure (PASP) was also calculated by adding tricuspid valve systolic peak pressure gradient and right atrial pressure estimated by inferior vena cava diameter and its inspiratory compression. The same outcomes were measured during the follow up period. Natriuretic peptides were not routinely measured since their measurement was not easily accessible during the period when the first patients of the cohort started treatment with Sacubitril/Valsartan.

Statistical analysis

We have performed descriptive analysis of all continuous data using mean and median values and we present categorical data as numbers and percentages. We present differences in outcomes before and after treatment with differences in mean values. The range of the measured values are given in brackets.

Results

Baseline characteristics

The cohort included a total number of 21 patients. Their baseline characteristics are shown in Table 1. Their mean age was 63 years old (34-80). Seventeen (17) patients were male (80,1%). Their mean NYHA class was 3. Their mean LVEF was 29,93% (20-35). 11(52,4%) had heart failure of ischemic aetiology and 10 (47,6%) had non-ischemic heart failure. Thirteen (13) patients (61,9%) had a history of hospitalization for heart failure which was on average at 8,6 (0,5-36) months before switching to sacubitril/valsartan. The mean number of hospitalizations during the last 12 months before switching was 1,4 (1-3). Mean systolic blood pressure at baseline was 118,42 mmHg (80-154) and mean diastolic blood pressure was 74,14 mmHg (58-100). Their baseline renal function was characterized by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation.[8] Mean eGFR was 65,7 ml/min/1,73 m^2 (35-120). Mean baseline potassium level 4,51 mmol/L (3,78-5,72). 3 patients (14,3%) had a history of significant hyperkalemia (K>5,4 mmol/L) before treatment.

Ten (10) patients (47,6%) had a device implanted: 5 patients (23,8%) had an implantable cardioverter defibrillator and 5 (23,8%) had cardiac resynchronization therapy – defibrillator device implanted.

Regarding their baseline medical treatment, 20 patients (95,2%) were on an ACEI (47,6%) or an ARB (47,6%). 19 (90,5%) were on a beta blocker and 18 (85,7%) were on an MRA. All patients who were on an ACEI were receiving ramipril with a median daily dose of 5 mg (2,5-15). Among patients who were on an ARB, 7 (70%) were on valsartan with a median daily dose of 160 mg, 2 (20%) were on candesartan and 1 (10%) was on losartan. 16 (88,9%) patients using MRA were on spironolactone and

2 (11,1%) on eplerenone. Metoprolol was the most frequently used beta blocker (8 patients, 42,2%), followed by carvedilol (7 patients, 36,8%) and bisoprolol (4 patients, 21%).

Considering baseline electrocardiograms (ECGs), 16 (76,2%) patients were in sinus rhythm, and 5 (23,8%) were in atrial fibrillation.

Switching to sacubitril/valsartan

Eleven (11) patients (52,3%) had started with the low starting dose of sacubitril/valsartan (24/26 mg twice daily) while 9 (42,9%) had started with the high starting dose (49/51 mg twice daily). Only 1 patient had started with a lower than the recommended dose (24/26 mg once daily). Sacubitril/valsartan was up titrated to its maximum tolerated dose after a mean duration of 21,33 weeks. 14 patients (66,7%) received the maximum recommended dose of 97/103 mg twice daily, 3 (14,3%) were up titrated to 49/51 mg twice daily and 4 (19%) reached a maximum dose of 24/26 mg twice daily. The mean daily dose of sacubitril/valsartan was 157,1 mg. Two (2) patients (9,5%) had to discontinue the drug due to renal failure while 1 patient (4,8%) died during the follow up period. The outcome of sacubitril/valsartan initiation and up titration is summarized in Table 2.

Clinical outcome

Patients were followed for a mean period of 33 months (6-62). Their clinical outcomes are shown in Table 3. The mean NYHA class improved from a mean value of 3 at baseline to 2 at the end of the follow up period. Mean eGFR had increased from a mean of 67,7 ml/min/1,73m^2 (35-120) to 69.3 ml/min/1,73 m^2 (32-139) (Figure 1). Mean potassium level increased from 4,4 mmol/L (3,78-5,72) to 4,7 mmol/L (3,5-5,5) post treatment. Two (2) patients (9,5%) had significant hyperkalemia (K>5,4 mmol/L) during treatment. Mean systolic blood pressure decreased from 118,42 mmHg (80-154) to 112,33 mmHg (70-165). Mean diastolic blood pressure at baseline was 74,14 mmHg (58-100) and 73,66 (50-127) post treatment. Seven (7) patients (33,3%) were hospitalized during the period of treatment with sacubitril/valsartan.

Echocardiographic outcome

Echocardiographic studies were performed at baseline and at a mean period of 31,9 months (15-50) post switching to sacubitril/valsartan. Echocardiographic outcomes are summarized in Table 4. Besides LVEF which was measured for all patients, the rest parameters were available for a smaller number of participants. Mean LVEF had increased from 29,9% (20-35) to 33,5% post treatment (Figure 2). Mean LVEDD decreased from 63,3 mm (55-74,8) to 61 mm (50-75). Mean LAD decreased from 46,9 mm (41-53,5) at baseline to 43,8 mm (34-50) at the end of the follow up period. Mean baseline PASP was 37,5 mmHg (15-60) and mean post treatment PASP was 36,6 mmHg (35-38,24). E' increased from 5,94 cm/sec (3,1-8,1) to 6,96 cm/sec (5-8,7). Mean E/E' ratio decreased from 11,1 (5,9-14,8) at baseline to 8,1 (5-10,8) post treatment. Finally, E/A ratio had also decreased from a baseline mean of 1 (0,44-1,56) to 0,7 (0,55-0,99) at follow up echocardiography.

Discussion

The study was a retrospective observational study of real life, stable heart failure patients with reduced ejection fraction who were

switched from ACEI or ARB therapy to sacubitril/valsartan at a single centre. All patients were symptomatic (NYHA class at least 2) despite being on optimal medical treatment since over 85% of them were receiving treatment for neurohormonal inhibition with an ACEI or ARB, a beta blocker and an MRA. It should also be noted that 23,8% of them had also a CRT-D device implanted.

An important aim of the study was to investigate whether reaching the maximum dosage of sacubitril/valsartan was feasible in real life patients as in the selected patients of PARADIGM-HF study considering the run-in period of the study which allowed only participants who could tolerate both target doses of enalapril and sacubitril/valsartan to be eligible to enter the study.[5] While randomized controlled trials need to have strict inclusion criteria to limit confounders, real life patients may have different characteristics which are often not represented in these studies.[9] Also, environmental factors including temperature affect blood pressure as well as the outcome of heart failure patients, a fact that is of particular importance in countries with higher temperatures such as Cyprus. In our study, a significant proportion of participants was able to reach maximum dosage of sacubitril/valsartan (66,7%). However, mean daily dose was 157,1 mg which was lower than the respective dose of PARADIGM-HF (375 mg). Lower mean daily dose of sacubitril/valsartan has been also reported by other real-world evidence studies. In a study from Italy, the mean daily dose during follow up was 121,4 mg while 35,8% of patients were able to reach the maximum dosage of 97/103 mg twice daily.[10] On the other hand, in a real- world study from the United Kingdom, 84,5% of patients tolerated the maximum dosage of sacubitril/valsartan and the mean daily dose during the study was 180,3 mg.[11] Both above studies included patients with similar baseline characteristics such as our study besides blood pressure which was slightly higher at the study from the United Kingdom. This could partially explain the higher mean dose achieved at that study.

Regarding the clinical outcome, the results of our study are in concordance with the results of PARADIGM-HF study. This is of particular interest, considering that we have used a lower mean dose of sacubitril/valsartan in comparison with PARADIGM-HF. Mean NYHA class of our cohort has improved post treatment with sacubitril/valsartan while there was a small increase of mean potassium without any patient having to stop the medication due to hyperkalemia. Two (2) cases of significant hyperkalemia (potassium level > 5,4 mmol/L) were managed with adjustment of medications' dosing and reduction of dietary potassium. Also, similarly to PARADIGM-HF study, blood pressure was also reduced after treatment with sacubitril/valsartan.

Considering renal function, our patients had more severe renal dysfunction compared to PARADIGM-HF study with their mean eGFR being 65,7 ml/min/1,73 m2 compared to 70,0 ml/min/1,73 m2. Despite that, the mean eGFR of our patients did not decline during the follow up period (mean eGFR 69,3 ml/min/1,73 m^2). This, in our view, confirms the findings of PARADIGM-HF which showed that treatment with sacubitril/valsartan slowed the decline of renal function in heart failure patients compared to enalapril.[12]

One proposed mechanism explaining the favourable effect of angiotensin receptor-neprilysin inhibition in heart failure is reverse cardiac remodelling. In our study, we have investigated the changes of various echocardiographic parameters in a number of participants after switching to sacubitril/valsartan. Follow up echocardiograms were performed at a mean period of 31,9 months. Our results showed that mean LVEF had increased from 29,9% to 33%. Left ventricular end-diastolic diameter has decreased after treatment with sacubitril/valsartan from 63,3 mm to 61,0 mm. Left atrial diameter and E/e' ratio had also decreased from 46,9 mm to 43,8 mm and from 11,1 to 8,1 respectively indicating a decrease in filling pressures. Echocardiographic markers were also assessed by a prospective study with 12 months of follow up (PROVE-HF), which was designed to investigate the correlation of N-terminal pro-b-type natriuretic peptide (NT-proBNP) changes in cardiac size and function.[13] The echocardiographic results of this study were along the same line with our results. Authors had also shown that there was a correlation of NT-proBNP reduction with favourable changes in echocardiographic indices.

Limitations

Considering the nature of the study (real-world observational data) there are some limitations. Most importantly, there was not a control group. Follow up period of the patients was variable. Echocardiographic data refer only to a subset of participants. Furthermore, natriuretic peptides were not measured.

Conclusion

PARADIGM-HF has shown that sacubitril/valsartan reduced mortality and the risk for hospitalization in heart failure patients with reduced ejection fraction compared to enalapril. Our study shows that the use of sacubitril/valsartan in the recommended dose is feasible in a large proportion of real-world patients. Finally, we have shown that the use of sacubitril/valsartan is safe, with favourable effects on symptoms, renal function, cardiac volume, and hemodynamic indices on the same direction as shown on randomized clinical trial data.

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Conflicts of interest

The authors participate as investigators in studies sponsored by Novartis Pharma Services Inc. Cyprus and Novartis A

Tables

Demographics	
Age at onset (years)	63 (34 – 80)
Male, n (%)	17 (80,1%)
Female, n (%)	4 (19,9%)
Months Follow-up	33 (6 – 62)
Heart failure etiology	
Ischemic n (%)	11 (52,4%)
Non- ischemic n (%)	10 (47,6%)
Clinical Parameters	
NYHA class	3 (2-4)
LVEF (%)	29,9 (20 – 35)
Blood pressure	
Systolic (mmHg)	118,4 (80 – 154)
Diastolic (mmHg)	74,1 (58 – 100)
eGFR (ml/min/1,73 m^2)	65,7 (35 – 120)
Potassium (mmol/L)	4,4 (3,78 – 5,72)
Hospitalization before treatment, n (%)	13 (61,9%)
Last hospitalization (months before treatment)	8,6 (0,5 – 36)
Number of hospitalizations in last 12 months before treatment	1,4 (1 – 3)
Electrocardiogram	
Sinus rhythm, n (%)	16 (76,2%)
Atrial fibrillation, n (%)	5 (23,8%)
ICD, n (%)	5 (23,8%)
CRT-D, n (%)	5 (23,8%)
Hemoglobin (g/dl)	13,1 (9,4 – 16,9)
History of hyperkalemia (K > 5.4 mmol/L) before treatment, n (%)	3 (14,3%)
Medications	
ACEI n (%)	10 (47,6%)
Ramipril, n (%)	10 (47,6%)
Median daily dose (mg)	5 (2,5 – 15)
ARB n (%)	10 (47,6%)
Valsartan, n (%)	7 (70%)

Median daily dose (mg)	160 (80 – 320)
Candesartan, n (%)	2 (20%)
Losartan, n (%)	1 (10%)

MRA, n (%)	18 (85,7%)
Spironolactone, n (%)	16 (88,9%)
Eplerenone, n (%)	2 (11,1%)
Beta-Blocker, n (%)	19 (90,5%)
Carvedilol, n (%)	7 (36,8%)
Bisoprolol, n (%)	4 (21%)
Metoprolol, n (%)	8 (42,2%)
Ivabradine, n (%)	0 (0%)

Table 1. Baseline characteristics of patients

Starting Dose	100 (50 – 200)
50, n (%)	1 (4,8%)
100, n (%)	11 (52,3%)
200, n (%)	9 (42,9%)
Max Achieved Dose	400 (100 – 400)
24/26 mg bd, n (%)	4 (19%)
49/51 mg bd, n (%)	3 (14,3%)
197/103 mg bd, n (%)	14 (66,7%)
Mean average daily dose (mg)	157,1
Weeks to Max Dose	21,3 (0 – 144)
Stopped Treatment	
n (%)	3 (14,3%)
Stopped due to safety n (%)	2 (66,7%)
Renal Failure, n (%)	2 (100%)
Stopped due to Death n (%)	1 (33.3%)

Table 2. Outcome of sacubitril/valsartan initiation and up titration

NYHA class	
Baseline	3 (2-4)
Post Treatment	2 (1-3)

EGFR (ml/min/1,73 m^2)	
Baseline	65,7 (35 – 120)
Post Treatment	69,3 (32 – 139)
(Δ)	3,6 (-66 – 35)
Potassium (K^+) (mmol/L)	
Baseline	4,4 (3,78 – 5,72)
Post Treatment	4,7 (3,5 – 5,5)
(Δ)	0,2 (-0,6 – 4,12)
Systolic blood pressure (mmHg)	
Baseline	118,4 (80 – 154)
Post Treatment	112,3 (70 – 165)
(Δ)	-6,1 (-28 – 47)
Diastolic blood pressure (mmHg)	
Baseline	74,1 (58 – 100)
Post Treatment	73,7 (50 – 127)
(Δ)	-0,4 (-20 – 27)
Hyperkalemia (K^+ > 5.4 mmol/L) during treatment	
n (%)	2 (9,5%)
Hospitalization during treatment	
n (%)	7 (33,3%)

Table 3. Clinical outcomes at baseline and after treatment with sacubitril/valsartan

LVEF (%)	
Baseline	29,9 (20 – 35)
Post Treatment	33,5 (15 – 50)
(Δ)	3,6 (-5 – 20)
LVEDD (mm) (n=8)	
Baseline	63,3 (55 – 74,8)
Post Treatment	61 (50 – 75)
(Δ)	-2,3 (-14,5 – 6,3)
LAD (mm) (n=8)	
Baseline	46,9 (41 – 53,5)
Post Treatment	43,8 (34 – 50)

(Δ)	-3,1 (-7 – 7,7)
PASP (n=2)	
Baseline	37,5 (15 – 60)
Post Treatment	36,6 (35 – 38,24)
(Δ)	-0,9 (-25 – 23,24)
E' (cm/sec) (n=5)	
Baseline	5,9 (3,1 – 8,1)
Post Treatment	7 (5 -8,7)
(Δ)	1,1 (-0,6 – 4,9)
E/E'(n=5)	
Baseline	11,1 (5,9 – 14,8)
Post Treatment	8,1 (5 – 10,8)
(Δ)	-3 (-9,8 – 3,5)
E/A (n=6)	
Baseline	1 (0,44 – 1,56)
Post Treatment	0,7 (0,55 – 0,99)
(Δ)	-0,3 (-0,79 – 0,11)

Time that echo was performed post treatment initiation	
Mean months	31,9 (15 – 50)

Table 4. Echocardiographic parameters at baseline and after treatment with sacubitril/valsartan

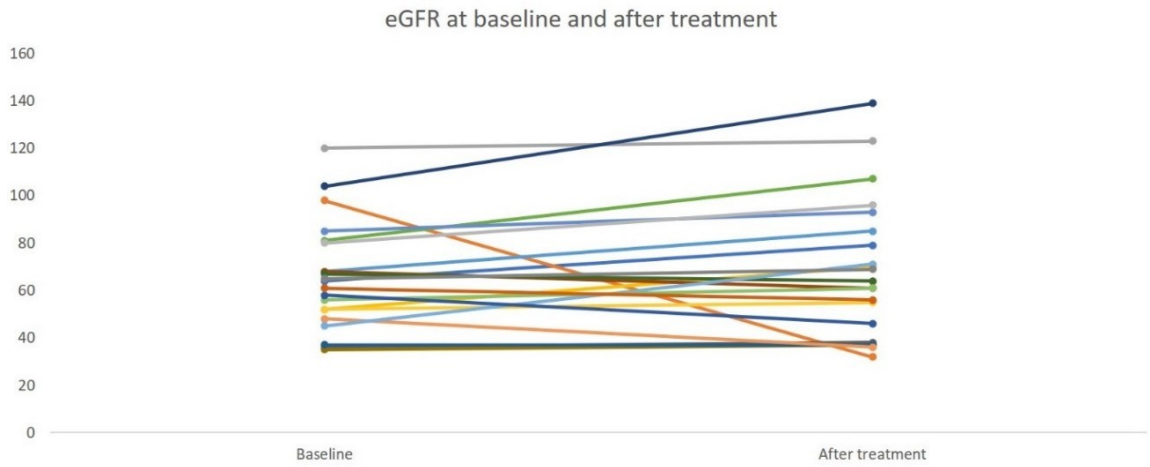

Figure 1. eGFR at baseline and after treatment with sacubitril/valsartan

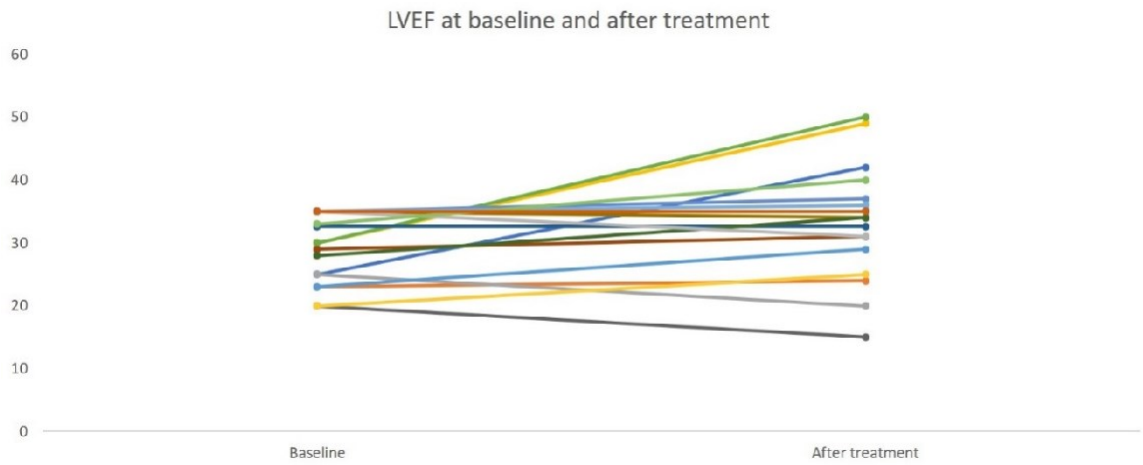

Figure 2. Left ventricular ejection fraction at baseline and after treatment with sacubitril/valsartan

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