

## Efficacy of sacubitril/valsartan in symptomatic heart failure with reduced ejection fraction patients – a case series

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### Abstract

Heart failure with reduced ejection fraction is a medical condition of various etiologies characterized by signs and symptoms of heart failure in the setting of a left ventricular ejection fraction under 40%. The objectives of therapy in patients with this condition are to improve clinical status, prevent rehospitalisation and reduce mortality. Sacubitril/valsartan is a drug combination recommended by current guidelines for the management of patients with heart failure with reduced ejection fraction, in addition to a beta-blocker, mineralocorticoid/aldosterone receptor antagonist and diuretic, as a substitute for the classic angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. We report a case series of patients diagnosed with heart failure with severely reduced ejection fraction of different etiologies, who, under treatment with sacubitril/valsartan, had a favorable evolution. We conclude that, for the current case series, the association of sacubitril/valsartan to standard medical therapy was beneficial.

**Keywords:** heart failure, ejection fraction, sacubitril/valsartan

### Introduction

Current European and American Heart failure (HF) guidelines [1],[2], define heart failure with reduced ejection fraction (HFrEF) as a medical syndrome consisting of symptoms and signs of congestion in the setting of an ejection fraction (EF) under 40%. The etiologies of HFrEF include a wide range of diseases of the myocardium, abnormal loading conditions and tachy- or bradyarrhythmias. Heart failure can have an acute

onset- the first congestive episode- and can eventually become a chronic condition if the etiology is not diagnosed and treated. Currently we use the New York Heart Association (NYHA) classification to group symptomatic patients, according to their functional capacity.

For patients with chronic symptomatic (NYHA class II-IV) HFrEF, guidelines recommend maximum tolerated doses of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB)- if ACE-I is not tolerated, a beta-blocker and a mineralocorticoid/aldosterone (MRA) receptor antagonist as first line therapies, in parallel with diuretic treatment for symptomatic relieve [1, 2].

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Sacubitril/valsartan is a new drug combination of a neprilysin inhibitor (sacubitril) and ARB (valsartan) that has been shown to be superior to enalapril in the prognosis of HFrEF patients in one randomised controlled trial [3]. The drug combination is now recommended as a substitute for ACE-I or ARB in patients with HFrEF who remain symptomatic despite maximal therapy, with a systolic blood pressure (BP) equal to or more than 100 mmHg and a glomerular filtration rate (GFR) more than 30 ml/min/1.73 m<sup>2</sup> [1, 2]. The compound is currently available in three doses: 24/26 mg, 49/51 mg, 97/103 mg. The drug should be administered only after a minimum of 36 hours after the ACE-I (or ARB) has been stopped. The recommended starting dose is 49/51 mg b.i.d with up-titration to the trial recommended dose of 97/103 mg b.i.d for the maximum effect, if the hemodynamic conditions allow it [3, 4].

### Case presentation

We present three cases of patients with heart failure with severely reduced ejection fraction of different etiologies, who were treated according to current guideline recommendations:

### CASE 1

A 53 years old male, smoker, with no significant history of cardiac disease, and a recent viral respiratory infection, presented to the emergency room with acute heart failure symptoms of recent onset. The first medical evaluation revealed a patient with orthopnea, tachypnea, elevated jugular pressure, third heart sound, systolic murmur of mitral insufficiency and pulmonary crepitations. Blood pressure (BP) was 80/60 mmHg, heart rate (HR) 120 beats/min and oxygen saturation (SO<sub>2</sub>) 80%. The electrocardiogram (ecg) showed sinus rhythm with no significant ischemic or arrhythmic changes, no left bundle (LB) or right bundle branch block (RBBB), QRS complex <120 msec. The initial laboratory report showed leukocytosis, elevated C reactive protein, elevated D-Dimers, negative troponin at repeated determinations, elevated NT-proBNP and a glomerular filtration rate (GFR) of 97 ml/min/1.73 m<sup>2</sup>. Transthoracic echocardiography: dilated left ventricle (LV) with an EF of 23% and global hypokinesia, grade 2 diastolic dysfunction, moderate secondary mitral regurgitation (MR) and intermediate probability of pulmonary hypertension (Figure 1).

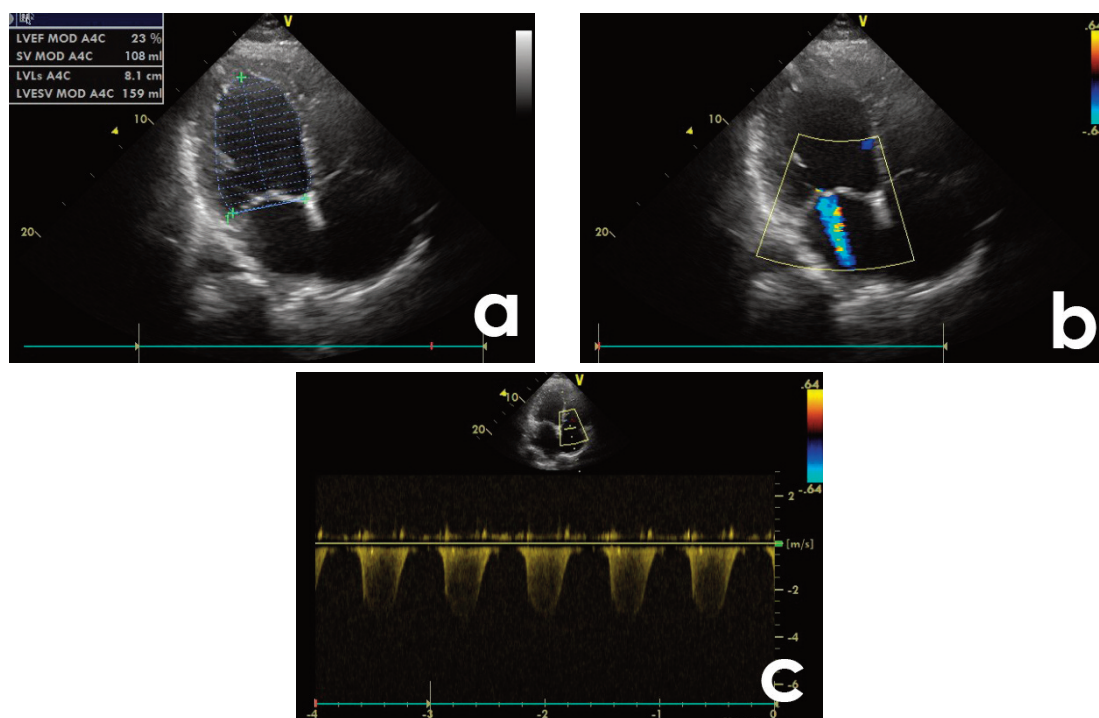


Figure 1.

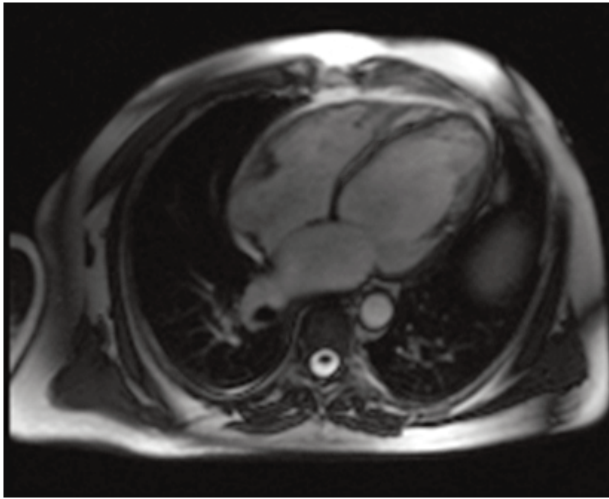


Figure 2.

After the acute phase treatment (hemodynamic and respiratory support), the patient remained with a symptomatic NYHA III class heart failure with reduced ejection fraction, for which, an ACE-I (Perindopril 5 mg/day), beta-blocker (Carvedilol 12.5mg/day), MRA (Spironolactone 50 mg/day) and diuretic (Furosemide 40 mg/day) were started. The etiology of HFrEF was investigated: coronary angiography showed no significant coronary artery disease; the invasive LV end-diastolic pressure was 26 mmHg. There were no signs of pulmonary embolism on CT angiogram and the cardiovascular magnetic resonance (CMR) scan showed a dilated LV with reduced EF (12.9%) with

areas of oedema and sub-epicardial and mid-myocardial enhancement at the level of the interventricular septum, anterior and inferior walls (possible recent myocarditis). There was grade 2 MR secondary to LV dilatation. The right ventricle (RV) was dilated with poor ejection fraction (Figure 2).

After one month of maximal HF treatment with minimal clinical changes, the patient was re-admitted to hospital with NYHA III HFrEF. The control echocardiography showed aggravated LVEF (18% versus the initial 23%), and severe MR. At this point, the ACE-I was stopped and after 3 days sacubitril/valsartan 49/51 mg b.i.d was introduced in addition to the beta-blocker, MRA and diuretic. The dose was well tolerated and, at the first follow-up, 3 weeks after sacubitril/valsartan was introduced, there were minimal symptomatic changes; the follow-up echocardiography showed improved LVEF of 31%. At first, we were not able to up-titrate the dose due to symptomatic hypotension. However, after 6 weeks of therapy with the initiation dose, we were able to up-titrate to 97/103 mg b.i.d. At one month follow-up after the final dose adjustment, the patient was with minimal heart failure symptoms, BP of 110/70 mmHg, HR of 87 beats/minute, normal Nt-proBNP. The echocardiography showed a normal LV with LVEF of 47%, grade 1 diastolic dysfunction, trivial MR and no signs of pulmonary hypertension (Figure 3).

There was no need of diuretic treatment continuation. At one year follow-up the patient was asymptomatic under medical treatment, with good functional status. We continued the HF medication.

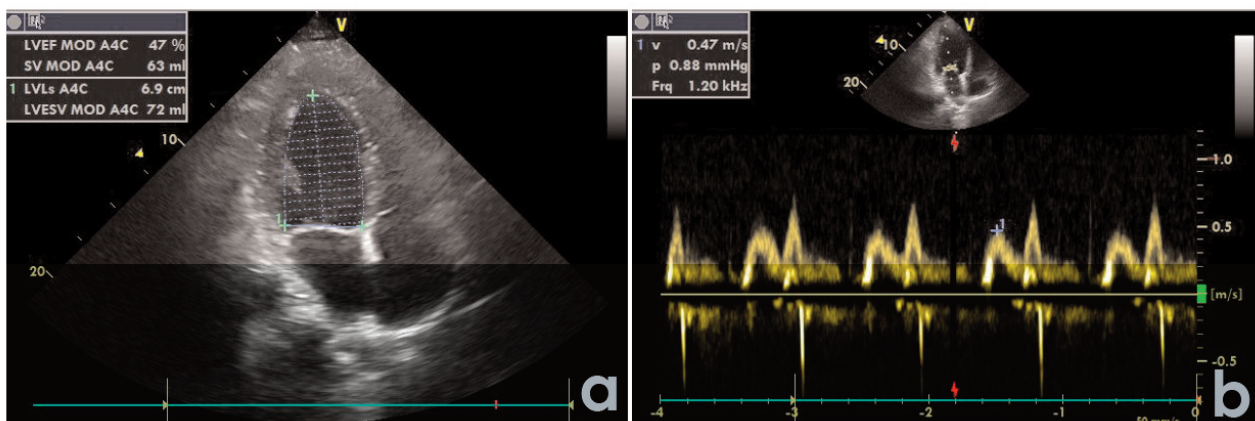


Figure 3.



## CASE 2

A 65 years old male with important history of alcohol consumption, dilated LV (etiology not documented, possible toxic cardiomyopathy) and a mechanical mitral prosthesis for severe MR (operated in 2004), atrial fibrillation (AF) and a permanent VVI pacemaker (implanted in 2014) for low frequencies and symptomatic sinus pauses of more than 3 seconds, with no HF treatment, was referred to our cardiology department for chronic heart failure symptoms with frequent acute decompensations- symptoms aggravated after pacemaker implantation.

The clinical exam at presentation showed: pulmonary crepitations, lower extremity bilateral oedema, normal prosthesis sounds.

BP was 130/80 mmHg, HR 78b/min, ecg: AF, complete LBBB with a QRS duration of 170 msec. Echocardiography: severely dilated LV (89/81 mm) with an EF of 14%, severe global hypokinesia, normal mechanical mitral prosthesis (Figure 4).

We started the recommended treatment for HF: ACE-I (enalapril 10 mg /day), beta-blocker (carvedilol 12.5 mg /day), MRA (spironolactone 25mg/day) and three diuretics for symptom management. We continued oral anticoagulation therapy, with a target INR of 2.5-3.5.

Coronary angiography showed no significant lesions. The VVI pacemaker was upgraded to a CRT-D.

After one year of medical treatment, the patient was rehospitalised with chronic decompensated NYHA

IV HF symptoms and low CRT-D pacing battery, and no positive response to resynchronisation therapy. In this period, there were no arrhythmic ventricular events that needed defibrillation. CRT-D battery was replaced, the diuretic dose was increased, and after 3 days without ACE-I, the patient started treatment with sacubitril/valsartan 24/26 mg b.i.d (low dose start due to low BP). At 3 weeks follow-up, we increased sacubitril/valsartan dose to 49/51 mg b.i.d. and reduced diuretic treatment to furosemide 40 mg/day. We were not able to further up-titrate the drug due to severe symptomatic hypotension, however, at 6 months follow-up the patient was with HF NYHA III class symptoms, and an LVEF of 22%. Systolic BP with the current sacubitril/valsartan dose remained over 100 mmHg.

## CASE 3

A 53 years old female, with history of hypertension and mixed dyslipidemia, seen as an outpatient was diagnosed with angina pectoris CCS class III, after a possible recent non-ST segment elevation myocardial infarction (NSTEMI). The resting ecg showed sinus rhythm, normal HR and negative T waves in the inferior and anterior leads. There was no troponin elevation at the time of visit. Transthoracic echocardiography: dilated LV with wall motion abnormalities of the inferior and anterior walls, LVEF of 30%, grade 1 MR, grade 1 diastolic dysfunction. Coronary angiography showed severe three-vessel disease

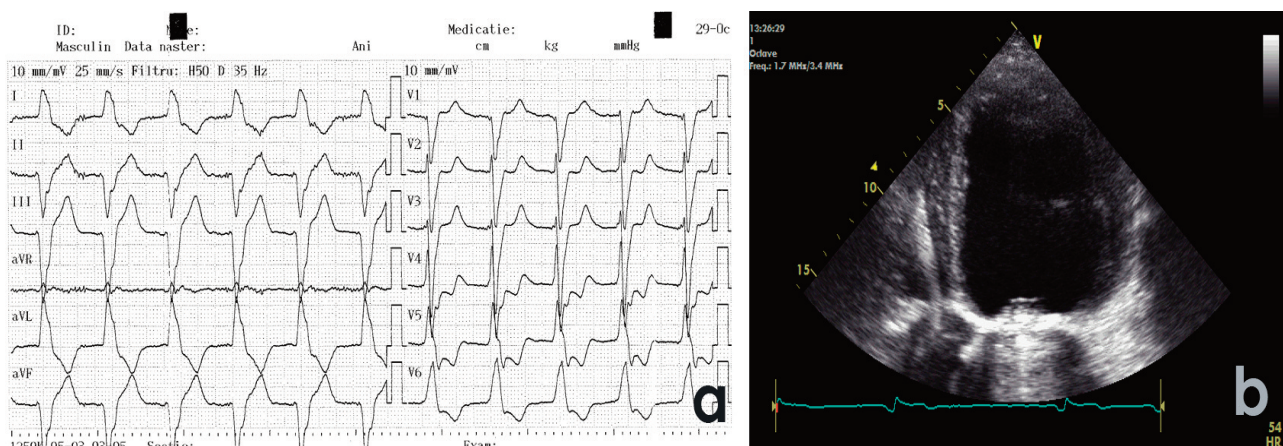


Figure 4.

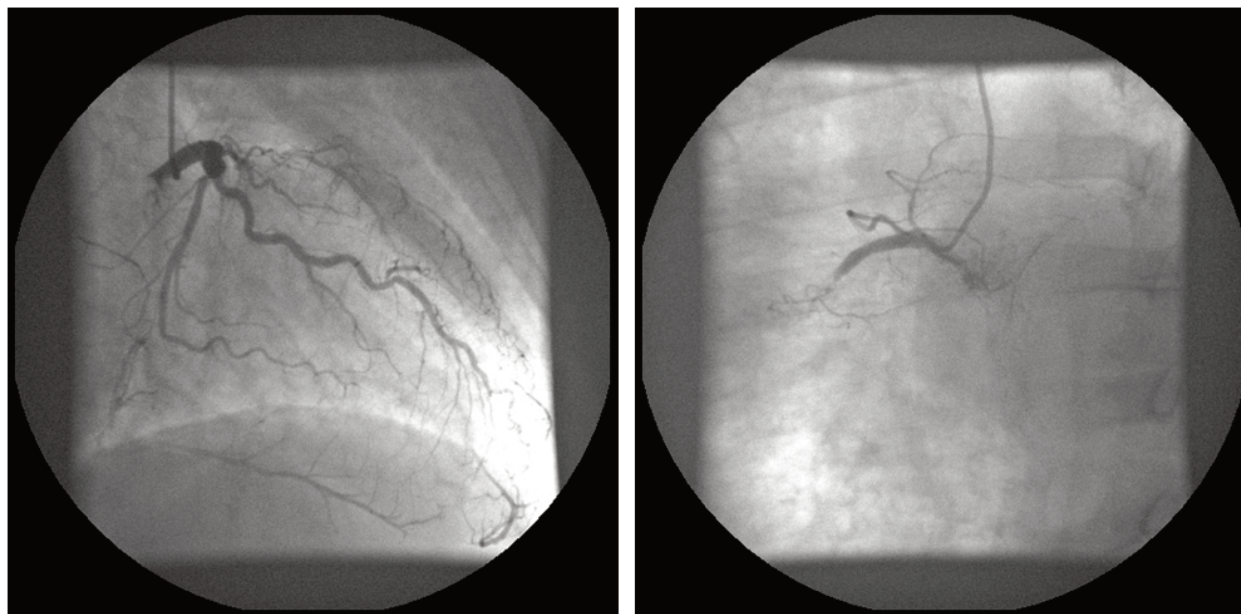


Figure 5.

with a SYNTAX score of 33, a SYNTAX II score favoring coronary artery by-pass grafting (CABG) (Figure 5) and an Euroscore II of 2.07%. The patient refused surgery. A CMR was done in order to assess viability; it showed a dilated LV (end diastolic volume (EDV) =207.7 ml, end systolic volume (ESV) =172.4ml) with a LVEF of 17%, a recent anterior NSTEMI with viable myocardium in the anterior territory.

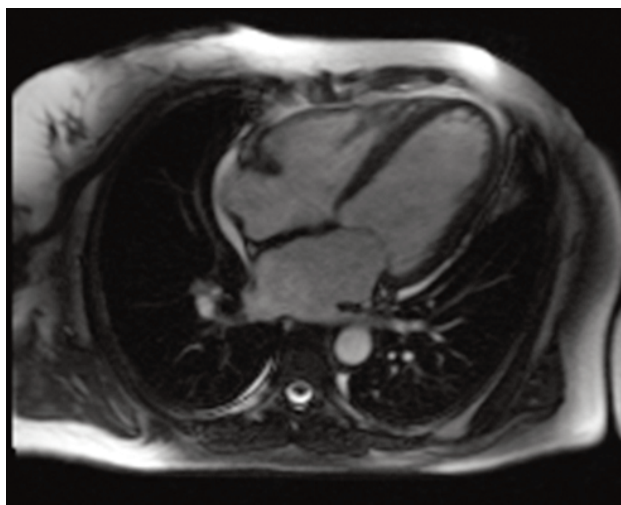


Figure 6.

Percutaneous functional revascularization was performed with drug eluting stents on the right coronary and left anterior descending arteries, with a good angiographic result. The patient was discharged on dual antiplatelet therapy (aspirin 100 mg/day and ticagrelor 180 mg/day), beta-blocker (carvedilol 12.5 mg/day), MRA (spironolactone 50 mg/day) and diuretic (furosemide 20mg/day). After a symptom-free period of four weeks, the patient had a resting BP of 100/70 mmHg, HR of 60 b/min, no ST/T changes on the resting ecg, LVEF at follow-up echocardiography of 37%.

We supplemented the initial treatment with sacubitril/valsartan 24/26 mg b.i.d. (due to low resting BP).

After another month of HF and ischemic treatment, we up-titrated the dose to 49/51 mg b.i.d. There were no adverse events and the patient remained asymptomatic during this period. At future follow-ups we were not able to further increase the dose to the recommended 200 mg/day due to low BP. At 6 months after the procedure, we reevaluated the myocardium using cardiac scintigraphy: LV with normal dimensions, with a necrotic mass of 15 %, LVEF=51%. We decided to continue both HF and ischemic treatment.

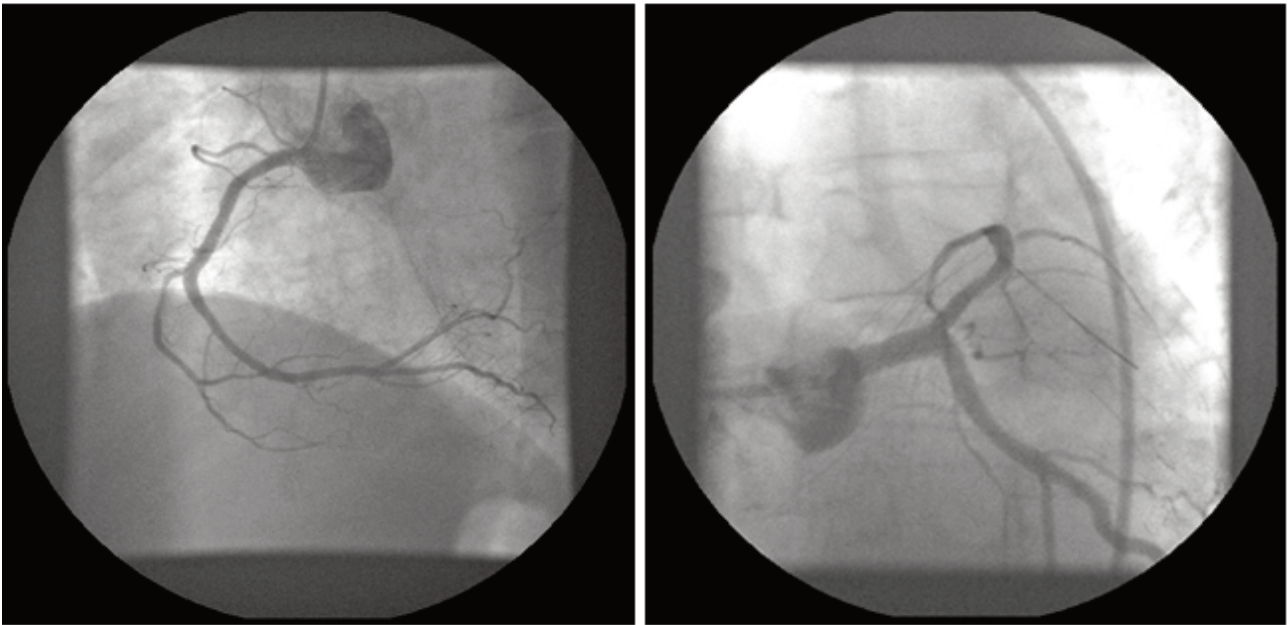


Figure 7.

## Discussion

We presented three patients with HFrEF of various etiologies, from an Eastern European country, who benefitted from sacubitril/valsartan treatment. For the first two patients, sacubitril/valsartan was more useful than the classic ACE-I in restoring functional capacity and improving quality of life. In the first example, we could see a significant change in LV remodeling and function restoration. We are aware of the fact that the drug had regional variations regarding important end-points in the PARADIGM-HF trial [3]. Despite these regional differences, the clinical benefit of sacubitril/valsartan was not affected [5, 6], and the drug proves to be useful in selected real-life settings [7]. For the third patient we decided to start directly with the drug combination, taking into account her personal preferences.

We were not able to reach the recommended trial dose in two of our three patients due to symptomatic hypotension. This is not necessary a concern, as we know from PARADIGM-HF, that hypotension was a frequent adverse event, especially with age [3, 5, 6]. However, those patients who were not able to tolerate recommended doses, still benefited from lower combination doses in comparison with lower ACE-I doses [5]. In terms of other adverse events, we did not see any changes in electrolyte, hepatic or renal function that

would raise concern. Still, we do not know if and when should we retry to up-titrate to target doses.

For the time being, we continued treatment. The question remains: for how long should we continue full HF therapy after a positive response.

## Conclusions

In the current case-series, sacubitril/valsartan in association with a beta-blocker, MRA and diuretic, proved to be beneficial for patients with HFrEF.

## Conflicts of interest

None.

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