

# Sacubitril/valsartan for treatment of chronic heart failure with reduced ejection fraction. Can all patients benefit? A position statement paper of experts of the Heart Failure Working Group of the Polish Cardiac Society

Sakubitril/walsartan w leczeniu przewlekłej niewydolności serca z upośledzoną frakcją wyrzutową. Czy dla wszystkich chorych? Opinia ekspertów Sekcji Niewydolności Serca Polskiego Towarzystwa Kardiologicznego

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## INTRODUCTION

Heart failure (HF) is a huge challenge for cardiology of the twenty-first century. The commonly recognised treatments showing beneficial effects on prognosis, quality of life, and safety apply to patients with heart failure with reduced left ventricular ejection fraction (HFrEF). The treatment of this form of HF is based on the use of beta-blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI) or, if ACEIs are not tolerated, angiotensin-2 receptor blocker (ARB) and, in symptomatic patients with left ventricular ejection fraction (LVEF)  $\leq 35\%$ , mineralocorticoid receptor antagonists (MRA).

In 2015, a new medicinal product was registered in Europe, a combination of valsartan (ARB) and sacubitril (a prodrug that converts into an active neprilysin inhibitor). By now this combination drug is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). The most recent guidelines of the European Society of Cardiology (ESC) on treatment of HF assigned it a high class of recommendation (IB) [1] and make it another milestone in the medical therapy of chronic HFrEF. It is recommended as a replacement for ACEI or ARB in selected patients; however, some discrepancies between the European and American guideline documents make clinicians uncertain

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**Table 1.** Summary of guidelines for the use of sacubitril/valsartan in HFrEF. Based on the reference [1, 6]

Class	Level	Recommendation
<b>ACC/AHA/HFSA 2016</b>		
I	B-R	In patients with chronic symptomatic HFrEF NYHA class II or III, who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
III	B-R	ARNI should not be administered concomitantly with ACEI or within 36 h of the last dose of an ACEI
III	C-EO	ARNI should not be administered to patients with a history of angioedema
<b>ESC 2016</b>		
I	B	Sacubitril/valsartan is recommended as a replacement for an ACEI to further reduce the risk of HF hospitalisation and death in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker, and an MRA
I	A	Treatment with beta-blocker, MRA, and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients)

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin-2 receptor blocker; ARNI — angiotensin receptor neprilysin inhibitor; HF — heart failure; HFrEF — heart failure with reduced left ventricular ejection fraction; MRA — mineralocorticoid receptor antagonists; NYHA — New York Heart Association

in whom and how to start treatment with sacubitril/valsartan in clinical practice.

This position paper provides information on new opportunities for medical therapy of HFrEF using sacubitril/valsartan in daily practice. It presents the position of Polish experts who deal with HF on this ground-breaking therapy and gives practical guidance on implementation, monitoring of effects, and safety of treatment with sacubitril/valsartan composition [2–4].

### SACUBITRIL/VALSARTAN IN GUIDELINES OF VARIOUS MEDICAL ASSOCIATIONS

Sacubitril/valsartan (Entresto™) was first mentioned in the position statement on the implementation of guidelines to clinical practice by the Canadian Cardiovascular Society Heart Failure Companion in 2014 [5]. This information appeared before the drug was registered in Canada, therefore the term “conditional recommendation” was used. The strong position of the drug results from the high-quality data from the PARADIGM-HF study [2]. Sacubitril/valsartan is recommended to replace ACEI or ARB in all patients who, in spite of triple therapy (ACEI or ARB, BB and MRA), remain symptomatic at New York Heart Association (NYHA) functional class II–IV, have LVEF < 40%, increased natriuretic peptide level or HF hospitalisation in the last 12 months, serum potassium level < 5.2 mmol/L, and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. The authors highlight the need to monitor of potassium and creatinine levels during therapy.

Other societies that mention sacubitril/valsartan in the HF guidelines include the ESC [1] and ACC/AHA/ HFSA [6]. The ECS algorithm of pharmacological treatment of chronic HFrEF recommends the use of sacubitril/valsartan in place of ACEI (or ARB) in ambulatory patients with LVEF ≤ 35%, who are still symptomatic at NYHA class II–IV, despite treatment with ACEI (or ARB), BB, and MRA (class I, level of evidence B)

in order to further reduce the risk of HF hospitalisation and death (Table 1).

Depending on indications, sacubitril/valsartan can be combined with ivabradine, electrotherapy (implantable cardioverter-defibrillator, cardiac resynchronisation therapy [CRT]), and diuretics.

In the description of sacubitril/valsartan treatment strategy the ESC guidelines’ authors refer to the PARADIGM-HF study. In accordance with the study inclusion criteria, they recommend using this drug in symptomatic HF subjects at NYHA class II–IV, with decreased LVEF (≤ 35%), elevated serum natriuretic peptide level (B-type natriuretic peptide [BNP] ≥ 150 pg/mL or N-terminal pro B-type natriuretic peptide [NT-proBNP] ≥ 600 pg/mL, and BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL for subjects hospitalised for HF in the past 12 months), and eGFR ≥ 30 mL/min/1.73 m<sup>2</sup>. The candidates should well tolerate ACEI doses equivalent to 10 mg enalapril daily. The target dose of sacubitril/valsartan is 97/103 mg twice daily (97 mg of sacubitril and 103 mg of valsartan). The 2016 ESC guidelines also support the strong position of sacubitril/valsartan therapy in the treatment of ventricular arrhythmias (Table 1) [1].

The American guidelines (ACC/AHA/HFSA) were published simultaneously with the European ones and present an update on HF therapy [6]. Sacubitril/valsartan composition is recommended as an alternative to ACEI or ARB in combination with BB and MRA in patients with HFrEF and LVEF ≤ 40%, NYHA class II and III, who are on a stable dose of ACEI/ARB, in order to reduce morbidity and mortality (Table 1). They also point out safety aspects associated with this treatment, namely the risk of hypotension and (rarely) angioedema. It was also highlighted that, in order to facilitate the initiation of treatment and its optimisation, three dosages of the approved ARNI formulation are marketed, including

one untested in the clinical study in which the target daily dose was  $2 \times 97/103$  mg. They also mention that the clinical experience should provide further information on the tolerability and optimal dose titration strategy.

### MECHANISMS OF ACTION OF SACUBITRIL/VALSARTAN

The new drug is a preparation containing two molecules in the form of sodium salt complex of valsartan and sacubitril acting on two main signalling pathways being activated in HF. It belongs to a new class of drugs — ARNIs — and is so far the only representative.

The first active molecule is well-known **valsartan — angiotensin 2 (AT2) receptor blocker**. AT2 plays a key role in cardiovascular diseases, i.e. hypertension, HF, and diabetes. The impact of AT2 mainly depends on the activation of AT1 receptors (G protein-coupled) located in blood vessels, cardiac muscle, kidneys, and adrenal glands. Their overstimulation typical for HF by AT2 excess leads to unfavourable remodelling of blood vessels (vasoconstriction, wall remodelling) and myocardium (worsening of hypertrophy and fibrosis), as well as deleterious effects on renal and cerebral microcirculation, impaired insulin sensitivity, increased sympathetic activity, and initiation of thrombotic and inflammatory reactions. In view of these negative actions of AT2 excess, blocking AT2 effector by valsartan, namely the AT receptor, leads to a reversal of many of the above-mentioned cardiovascular adverse effects.

The second active agent is **sacubitril**. It inhibits neutral endopeptidase (NEP) decomposing sulphide bonds and thereby destroying the ring structure of natriuretic peptide (NP) molecules. This enzyme is located in the endothelial cells, vascular smooth muscles, neutrophils, epithelial cells of renal tubules, as well as myocardial tissue. HF is associated with an increase of NEP expression and activity resulting in an increased deactivation of NP, thus reducing their beneficial effects. The positive effect of NP depends on the activation of specific receptors (NPR-A/NPR-B). Their activation results in the inhibition of adverse remodelling of myocardial and vascular cells and also antagonises the excessive activation of the renin–angiotensin–aldosterone system. Hence, the use of NEP inhibitor, sacubitril, increases the bioavailability of NP and its favourable cellular effects.

Considering the mechanisms of action of sacubitril/valsartan, it should also be taken into account that NEP is a non-specific endopeptidase that decays many other substances activated in HF, such as bradykinin, adrenomedullin, angiotensin, and endothelin. Consequently, the use of ARNI leads to a multi-cell effect, which translates to a favourable overall effect observed in the clinical trials.

### PARADIGM-HF STUDY

There is little experience with the new class of drugs, ARNI, and, substantially, their first representative, i.e. combination

of valsartan and sacubitril, so far. The PARADIGM-HF study (Prospective comparison of ARNI with ACEI to Determine the Impact on Global Mortality and Morbidity in Heart Failure) was the first study in which the impact of the drug (called LCZ696) on morbidity and mortality was measured in patients with HFrEF.

### PARADIGM-HF methodology

PARADIGM-HF was an international, randomised, double-blind study involving 8442 patients, which compared the efficacy and safety of two treatment strategies — enalapril vs. a combination of sacubitril and valsartan (LCZ696) [7]. Enalapril was chosen as the reference drug for LCZ696 as it was the only ACEI that was proved to reduce mortality in a wide spectrum of patients with HFrEF. Based on the SOLVD-T and CONSENSUS studies, enalapril 10 mg per day was approved by the regulatory authorities as the “gold standard” among ACEIs [8].

Patients meeting the following criteria were enrolled [7]:

- age over 18 years;
  - LVEF  $\leq 35\%$  (originally LVEF  $\leq 40\%$ );
  - clinical signs and symptoms of HF NYHA class II–IV;
  - BNP  $\geq 150$  pg/mL or NT-proBNP  $\geq 600$  pg/mL, and for patients hospitalised for HF in the past 12 months prior to enrolment: BNP  $\geq 100$  pg/mL or NT-proBNP  $\geq 400$  pg/mL;
  - ACEI or ARB in daily doses equivalent to 10 mg of enalapril for at least one month prior to enrolment;
  - BB in stable dose for at least one month prior to enrolment, unless contraindicated or intolerable;
  - considering the use of MRAs with regard to renal function, serum potassium, and tolerability, and the drug dose also had to be stable for at least four weeks prior to enrolment.
- The following exclusion criteria were applied:
- history of intolerance to ACEI or ARB or intolerance of these drugs in doses equivalent to 10 mg of enalapril daily;
  - history of angioedema;
  - decompensated HF requiring the use of intravenous drugs;
  - symptomatic hypotension or systolic blood pressure (SBP)  $< 100$  mm Hg at the first visit (screening), or less than 95 mm Hg during subsequent visits;
  - hyperkalaemia (serum  $K^+ > 5.2$  mmol/L) and/or eGFR  $< 35$  mL/min/1.73 m<sup>2</sup> at the first visit or  $K^+ > 5.4$  mmol/L and/or eGFR reduction by  $> 35\%$  during subsequent visits;
  - acute coronary syndrome, cerebrovascular event or vascular intervention, CRT implantation within three months prior to randomisation, or planned CRT implantation.

Prior to randomisation, all patients underwent sequential, single-blind treatment (run-in phase) with enalapril and LCZ696 to confirm good tolerability of the target doses. From the initially screened 10,521 patients, after completion of the

Table 2. Summary of main results of the PARADIGM-HF study [2]

Outcomes	Hazard ratio (95% CI)	Improvement of risk /result in advantage of LCZ696	p
<b>Primary outcome</b>			
Death from cardiovascular causes or first hospitalisation for worsening heart failure	0.80 (0.73–0.87)	20%	< 0.001
Death from cardiovascular causes	0.80 (0.71–0.89)	20%	< 0.001
First hospitalisation for worsening heart failure	0.79 (0.71–0.89)	21%	< 0.001
<b>Secondary outcomes</b>			
Death from any cause	0.84 (0.76–0.93)	16%	< 0.001
Change in KCCQ clinical summary score at 8 months	1.64 (0.63–2.65)	64%	0.001
New-onset atrial fibrillation	0.97 (0.72–1.31)		NS
Decline in renal function	0.86 (0.65–1.13)		NS

CI — confidence interval; KCCQ — Kansas City Cardiomyopathy Questionnaire

run-in phase, ultimately 8442 subjects were randomised to the study treatment. The study compared the safety and efficacy of sacubitril/valsartan 200 mg twice daily and enalapril 10 mg twice daily [7].

The primary, composite endpoint was cardiovascular death or HF hospitalisation. The secondary endpoints assessed whether sacubitril/valsartan is superior to enalapril using:

- clinical improvement (reduction of severity of HF symptoms assessed by the Kansas City Cardiomyopathy Questionnaire [KCCQ]);
- delay to all-cause mortality (mortality rate);
- delay to new onset atrial fibrillation and/or deterioration of renal function.

The median follow-up period was 27 months, and the patients were treated for up to 4.3 years.

### General patient characteristics

The study group was a typical population with advanced HF. The majority of patients (78%) in the PARADIGM-HF study were males at an average age of 64 years [7, 9]. As many as 93% of patients used BB, and 56% were taking MRA [9]. In nearly 60% of subjects HFrHF was caused by ischaemic heart disease, and 43% had previous myocardial infarction. Hypertension was present in 71%, diabetes in 34%, and atrial fibrillation in 37% of patients. Despite potentially optimal pharmacotherapy, the quality of life of patients enrolled in the PARADIGM-HF study was reduced, primarily due to the ongoing clinical symptoms of HF. The vast majority of patients had a functional capacity of NYHA class II (70%). The average LVEF was 29% and mean NT-proBNP level was 1608 pg/mL [9].

### PARADIGM-HF results

The study was terminated earlier (median follow-up period — 27 months) because of clear benefits of sacubitril/valsartan compared to enalapril (Table 2). The primary endpoint

occurred in 21.8% of subjects in the ARNI group and in 26.5% of the ACEI group, the relative risk reduction was 20% ( $p < 0.001$ ). In the sacubitril/valsartan group the overall mortality was lower (17.0%) as compared to the enalapril group (19.8%). The majority of deaths (80.9%) in the overall population was of cardiovascular aetiology. Among patients who died, cardiovascular death was observed in 13.3% and 16.5% of subjects in ARNI and ACEI group, respectively ( $p < 0.001$ ). The use of sacubitril/valsartan was more effective than enalapril in prevention of both sudden cardiac death (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.68–0.94,  $p = 0.008$ ) and mortality associated with progression of HF (HR 0.79; 95% CI 0.64–0.98;  $p = 0.034$ ) [10].

The use of ARNI was also associated with a 21% reduction in the risk of hospitalisation for HF and clinical improvement (reduction in worsening of symptoms). There were no significant differences in the incidence of new onset atrial fibrillation or end-stage renal failure [2].

The safety analysis showed a higher incidence of hypotension in the ARNI group, while more cases of hyperkalaemia and increased serum creatinine were attributable to enalapril [2]. Eventually the treatment was interrupted due to adverse events in fewer patients receiving sacubitril/valsartan than in those taking enalapril (10.7% vs. 12.3%, respectively;  $p = 0.03$ ), including impaired renal function (0.7% and 1.4%, respectively;  $p = 0.002$ ) [2]. Benign angioedema was observed more frequently in patients treated with LCZ696 than enalapril (19 vs. 10 subjects;  $p = \text{NS}$ ).

The additional analysis of study results showed that an independent risk factor for the primary end point was low LVEF. ARNI effectively reduced the risk of primary outcome in each of the analysed ranges of LVEF [11].

The new drug reduced the risk of hospitalisation for worsening HF (by 23% compared to the enalapril group,  $p < 0.001$ ), the risk of hospitalisation at the intensive care

unit, and the need for intravenous positive inotropes (by 18%,  $p = 0.005$ , and 31%,  $p < 0.001$ , respectively). The benefits of LCZ696 were the same in all pre-specified subpopulations of the PARADIGM-HF study [11–13].

It is worth noting that the ARNI group was observed to show rapid and sustained reduction in biomarkers of myocardial damage: both troponin and NT-proBNP [14].

The results of one of the *post hoc* analyses of the PARADIGM-HF study suggest that the use of sacubitril/valsartan, also in doses lower than the target dose, was more effective in the reduction of risk of cardiovascular death or hospitalisation for HF in comparison with the corresponding lower doses of enalapril [15].

### **Benefits of sacubitril/valsartan treatment**

According to the outcomes of the PARADIGM-HF study, after a median follow-up of 27 months, the incidence of primary outcome was reduced by 20% in the sacubitril/valsartan group. The number needed to treat (NNT), i.e. the number of patients who had to undergo an intervention for a specified period of time to prevent one adverse endpoint, was 21. It means that in order to prevent the occurrence of one cardiovascular death or hospitalisation for HF 21 patients with symptomatic HF need to be treated for 27 months and their clinical and demographic characteristic must be similar to the PARADIGM-HF population. In addition, the analysis of the PARADIGM-HF results also showed that to prevent one death in the HF population a 12-month therapy with sacubitril/valsartan should involve 80.3 patients.

### **TITRATION STUDY**

The PARADIGM-HF study population consisted of patients who had already been treated with optimal doses of enalapril, and it is well known that in clinical practice many patients are not treated with the target doses of ACEI/ARB. Therefore, it was decided to assess the tolerance to various regimens of initiation and titration of sacubitril/valsartan in a wider population than previously studied, being representative for the real-life HF<sub>REF</sub> population. Thus, the TITRATION study included both inpatients and outpatients, also taking small doses of ACEI/ARB or not using these drugs earlier at all. Increased levels of natriuretic peptides on enrolment were not required.

The TITRATION study [16] compared two regimens of sacubitril/valsartan treatment: a conservative regimen for which the patient started on 50 mg twice daily for two weeks, followed by 100 mg twice daily for three weeks, followed by 200 mg twice daily, and condensed titration with an initial dose of 100 mg twice daily for two weeks and the target dose equal to 200 mg twice daily. The randomisation into those regimens was preceded by a five-day open-label run-in phase: the study drug was administered to all subjects at a dose of 50 mg two times per day. The randomised treatment lasted 11 weeks.

On the basis of ACEI/ARB treatment prior to enrolment, the patients were assigned to a low-dose group that was defined as  $\leq 160$  mg valsartan or  $\leq 10$  mg enalapril per day or equivalent doses of other ACEIs or ARBs, including ACEI/ARB-naïve patients.

The results of this study lead to the conclusion that in both regimens a high percentage of patients had a chance to reach a high dose (77.8% in conservative regimen vs. 84.3% for condensed regimen;  $p = 0.078$ ), both hospitalised and outpatient subjects as well as a low-dose group. The prolonged dosing (conservative) regimen can increase the chance of achieving the target dose in patients originally using low doses of ACEI/ARB (84.9% vs. 73.6%, conservative vs. condensed regimens;  $p = 0.03$ ). The tolerability profile of sacubitril/valsartan did not differ from that typically observed in other studies involving approved HF therapies.

### **ADVERSE EFFECTS OF SACUBITRIL/VALSARTAN AND INTERACTIONS WITH OTHER DRUGS**

The adverse reactions are associated with the mechanisms of action of two components of the preparation: sacubitril and valsartan. These include but are not limited to: symptomatic hypotension, compromised renal function, hyperkalaemia, and angioedema (Table 3). The understanding of the mechanism of action and implementation of treatment in optimal patients limit the possibility of predictable adverse effects.

#### **Symptomatic hypotension**

Interference with the renin–angiotensin–aldosterone system may lead to more potent vasodilatory effect and symptomatic hypotension. These adverse effects were mainly observed in subjects  $\geq 65$  years of age, with kidney disease, and those with a relatively low SBP ( $< 112$  mm Hg). Dose reduction, transient discontinuation, or adjustment of other hypotensive drugs is a proper and sufficient management.

In the PARADIGM-HF population, symptomatic hypotension occurred in 14% of patients treated with LCZ696, and it was significantly higher than in patients treated with enalapril (9.2%;  $p < 0.001$ ). Symptomatic hypotension with SBP  $< 90$  mm Hg occurred almost five times less often and affected 2.7% of patients on LCZ696 and 1.4% of patients in the enalapril group ( $p < 0.001$ ). Interpretation of the incidence of this adverse effect must take into account the fact that patients with symptomatic hypotension or SBP  $< 100$  mm Hg at screening ( $< 95$  mm Hg at randomisation) were not included in the study. Most episodes of hypotension did not require discontinuation of therapy.

#### **Deterioration of renal function**

Deterioration of renal function in patients taking sacubitril/valsartan may result from hypotension and impaired renal perfusion. The risk is increased in dehydrated subjects or using non-steroidal anti-inflammatory drugs.

**Table 3.** Adverse effects during treatment with LCZ696(2)A

Adverse effects	Sacubitril/valsartan	Enalapril	p
Symptomatic hypotension	14.0	9.2	< 0.001
Symptomatic hypotension with SBP < 90 mm Hg	2.7	1.4	< 0.001
Increase of serum creatinine $\geq$ 2.5 mg/dL	3.3	4.5	0.007
Increase of serum creatinine $\geq$ 3.0 mg/dL	1.5	2.0	0.10
Increase of serum potassium $\geq$ 5.5 mmol/L	16.1	17.3	0.15
Increase of serum potassium $\geq$ 6.0 mmol/L	4.3	5.6	0.007
Cough	11.3	14.3	< 0.001
Angioedema:			
No treatment or use of antihistamines only	0.2	0.1	0.19
Use of catecholamines or glucocorticoids without hospitalisation	0.1	0.1	0.52
Hospitalisation without airway compromise	0.1	< 0.1	0.31
Airway compromise	0	0	–

SBP — systolic blood pressure

In the population treated with LCZ696 elevated serum creatinine  $\geq$  2.5 mg/dL was observed in 3.3% of subjects — less than among those treated with enalapril (4.5%). It should be highlighted that GFR < 30 mL/min/1.73 m<sup>2</sup> was the study exclusion criterion.

### Hyperkalaemia

Monitoring of serum potassium levels is recommended especially in patients with risk factors for hyperkalaemia, i.e. renal dysfunction, diabetes, hypoaldosteronism, or taking MRAs. It should be noted that hyperkalaemia defined as serum potassium concentration > 5.5 mmol/L was a common phenomenon in the PARADIGM-HF study. It was observed in both sacubitril/valsartan and enalapril subjects, in 16.1% and 17.3% of subjects, respectively. Potassium concentration higher than 6.0 mmol/L was recorded in 4.3% and 5.6% of patients, respectively — significantly more commonly in subjects treated with enalapril ( $p < 0.007$ ).

### Angioedema

Angioedema is one of the most serious but rare adverse effects. Previous experience with omapatrilat, which inhibited as many as three enzymes involved in the degradation of bradykinin (i.e. ACE, aminopeptidase P, and neprilysin), were bad in terms of the risk of angioedema. The action of sacubitril is limited to inhibition of neprilysin and has a negligible impact on the risk of this complication.

Allowing for a 36-h break between the last dose of ACEI and sacubitril/valsartan dose reduces the risk of angioedema. Angioedema involving the face usually resolves without treatment. Angioedema involving the laryngeal oedema can be life-threatening.

Angioedema was observed in single patients in the PARADIGM-HF study — a slightly larger absolute number of

patients treated with LCZ696 compared with enalapril. Symptoms not requiring treatment or requiring only antihistamine therapy were observed in ten (0.2%) patients treated with LCZ696 and five (0.1%) patients on enalapril. Ambulatory use of catecholamines or steroids was required in six (0.1%) and four (0.1%) patients, respectively; and hospitalisation in three (0.1%) and one (< 0.1%) patient, respectively. None of the patients presented significant airway obstruction. It should be underlined that a history of angioedema excluded candidates from enrolment into the study.

### Interactions with other drugs

Interactions resulting in contraindication combined use:

- concomitant use of sacubitril/valsartan and ACEI because inhibition of neprilysin and ACE may increase the risk of angioedema;
- concomitant use of sacubitril/valsartan and direct renin inhibitors such as aliskiren in diabetic patients or in patients with renal impairment (GFR < 60 mL/min/1.73 m<sup>2</sup>) is contraindicated.

### Interactions requiring precautions

Co-administration of drugs potentially increasing serum potassium and creatinine levels requires caution and monitoring of these biomarkers. They include potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid receptor antagonists (spironolactone, eplerenone), potassium supplements, and other medicines containing potassium (e.g. heparin).

Increased risk of worsening renal function occurs also in combining ARNI with non-steroidal anti-inflammatory drugs or selective inhibitors of cyclooxygenase-2. The high-risk groups include patients who are older, dehydrated, or show impaired kidney function at baseline.

Certain aspects concerning drug interactions may be similar to those observed for ACEI or ARB. Currently, in the absence of direct observations of sacubitril/valsartan, this information should certainly be taken into account. The issue of lithium use may be an example. Reversible increase of lithium concentration and its toxicity was documented during its simultaneous use with ACEI or ARB. Such a combination therapy is not recommended; similarly, such concomitant treatment with sacubitril/valsartan is also not recommended. Should such a treatment be necessary, careful monitoring of serum lithium levels is required.

Active metabolites of sacubitril (LBQ657) and valsartan are substrates of the OATP1B1, OATP1B3, OAT1, and OAT3 transporters; valsartan is also a substrate for MRP2. Concomitant administration of inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, cyclosporine), and OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) affect their pharmacokinetics and increase their bioavailability (area under curve [AUC]).

The use of sacubitril/valsartan impacts other drugs that are substrates for OATP1B1 and OATP1B3, e.g. statins. If used with sacubitril/valsartan, a 1.4–2-fold higher concentration of atorvastatin and its metabolites was observed; therefore, a dose reduction may be necessary when using both drugs.

To a limited extent, sacubitril/valsartan is metabolised by CYP450 enzymes, hence it is unlikely to interact with these enzymes.

### Other drug interactions

Concomitant use of sacubitril/valsartan and metformin reduces the bioavailability of metformin (decrease in  $C_{max}$  and AUC by 23%).

Drugs leading to blood pressure drop, e.g. nitroglycerin, phosphodiesterase-5 (PDE-5) inhibitors, may potentiate the hypotensive effect of sacubitril/valsartan.

## TRANSFER OF SACUBITRIL/VALSARTAN RESEARCH BENEFITS TO CLINICAL PRACTICE

Heart failure is an important and difficult issue. In light of the PARADIGM-HF study results and analyses, the new drug sacubitril/valsartan is a promising medication, bringing the first possibility, in many years, of significant improvement of the prognosis of patients with symptomatic HF, who are already on optimal therapy. However, implementation of ARNI in clinical practice may be challenging for physicians. This applies mainly to the possibility of finding appropriate patients in the real world, keeping in mind the PARADIGM-HF criteria. Another issue may be a too cautious approach to modification of existing treatment by clinicians and patients in subjects with stable course of HF. Therefore, it is worth recalling the PARADIGM-HF data showing that even patients with HF and NYHA class II (70%), who were treated with enalapril in the control arm, had significant risk of events. In 15% of these patients the primary endpoint was recorded, and 8% died of cardiovascular causes within 12 months. It also seems that

based on the data showing significant reductions in 30-day hospitalisations and early reduction of sudden death, clinicians should wait until HF becomes worse.

### Practical guidance on how to use sacubitril/valsartan

Starting and optimisation of treatment with sacubitril/valsartan during outpatient care should include the following steps:

- **Candidates for sacubitril/valsartan therapy:**
  - symptomatic HF NYHA class II or III treated on an outpatient basis;
  - optimal medical treatment as per the guidelines;
  - hospitalised for HF within last 12 months;
  - clinical stability for at least one month;
  - LVEF  $\leq$  35%;
  - SBP  $\geq$  95 mm Hg, no symptomatic hypotension related to ACEI or ARB;
  - NT-proBNP  $\geq$  400 pg/mL;
  - creatinine clearance  $\geq$  30 mL/kg/1.73 m<sup>2</sup>.
- **Before initiation of treatment:**
  - check blood potassium level and eGFR;
  - discontinue ACEI and ARB.
- **Initiation of sacubitril/valsartan:**
  - allow at least 36 h from the last ACEI dose. **Do not combine ACEI and sacubitril/valsartan!**
  - administer sacubitril/valsartan 2 × 24/26 mg;
  - gradually increase the dose to 2 × 49/51 mg followed by 97/203 mg while monitoring SBP.
- **Long-term treatment rules:**
  - avoid ACEI, and PDE-5 inhibitors;
  - continue BB, MRA, and ivabradine;
  - unless haemodynamically unstable, do not discontinue sacubitril/valsartan for exacerbation of HF;
  - use NT-proBNP instead of BNP for assessment of clinical status;
  - monitor blood potassium and creatinine levels.

## CONCLUSIONS

Considering the significant risk of events, individuals with HFrEF and NYHA class II or III treated with ACEI/ARB and chronic stable status of the disease should be considered as candidates for conversion to sacubitril/valsartan. Starting with a low dose and gradual up-titration to ensure good tolerance may be relevant in patients treated with low doses of ACEI/ARB or presenting with low SBP. There are no satisfactory data on the benefits and safety of initiating sacubitril/valsartan therapy in patients with worsening HF or *de novo* HF, or in patients not previously treated with ACEI/ARB. The results of a number of ongoing studies on ARNI are expected to increase our experience with this class of drugs.

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### References

- Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members, Document Reviewers, Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; 37(27): 2129–2200, doi: [10.1093/eurheartj/ehw128](https://doi.org/10.1093/eurheartj/ehw128), indexed in Pubmed: [27206819](https://pubmed.ncbi.nlm.nih.gov/27206819/).
- McMurray JJV, Packer M, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014; 371(11): 993–1004, doi: [10.1056/NEJMoa1409077](https://doi.org/10.1056/NEJMoa1409077), indexed in Pubmed: [25176015](https://pubmed.ncbi.nlm.nih.gov/25176015/).
- Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members, Document Reviewers. Wytyczne ESC dotyczące diagnostyki i leczenia ostrej i przewlekłej niewydolności serca w 2016 roku. *Kardiol Pol*. 2016; 74(10): 1037–1147, doi: [10.5603/KP.2016.0141](https://doi.org/10.5603/KP.2016.0141).
- Entresto, INN-sacubitril/valsartan. SUMMARY OF PRODUCT CHARACTERISTICS. 2015. [Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/004062/WC500197536.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004062/WC500197536.pdf)].
- Moe GW, Ezekowitz JA, O'Meara E, et al. Canadian Cardiovascular Society. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. *Can J Cardiol*. 2015; 31(1): 3–16, doi: [10.1016/j.cjca.2014.10.022](https://doi.org/10.1016/j.cjca.2014.10.022), indexed in Pubmed: [25532421](https://pubmed.ncbi.nlm.nih.gov/25532421/).
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2016; 68(13): 1476–1488, doi: [10.1016/j.jacc.2016.05.011](https://doi.org/10.1016/j.jacc.2016.05.011).
- McMurray JJV, Packer M, Desai AS, et al. PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013; 15(9): 1062–1073, doi: [10.1093/eurjhf/hft052](https://doi.org/10.1093/eurjhf/hft052), indexed in Pubmed: [23563576](https://pubmed.ncbi.nlm.nih.gov/23563576/).
- Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991; 325(5): 293–302, doi: [10.1056/NEJM199108013250501](https://doi.org/10.1056/NEJM199108013250501), indexed in Pubmed: [2057034](https://pubmed.ncbi.nlm.nih.gov/2057034/).
- McMurray JJV, Packer M, Desai AS, et al. PARADIGM-HF Committees Investigators. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014; 16(7): 817–825, doi: [10.1002/ejhf.115](https://doi.org/10.1002/ejhf.115), indexed in Pubmed: [24828035](https://pubmed.ncbi.nlm.nih.gov/24828035/).
- Desai AS, McMurray JJV, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J*. 2015; 36(30): 1990–1997, doi: [10.1093/eurheartj/ehv186](https://doi.org/10.1093/eurheartj/ehv186), indexed in Pubmed: [26022006](https://pubmed.ncbi.nlm.nih.gov/26022006/).
- Solomon SD, Claggett B, Desai AS, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. *Circ Heart Fail*. 2016; 9(3): e002744, doi: [10.1161/CIRCHEARTFAILURE.115.002744](https://doi.org/10.1161/CIRCHEARTFAILURE.115.002744), indexed in Pubmed: [26915374](https://pubmed.ncbi.nlm.nih.gov/26915374/).
- Jhund PS, Fu M, Bayram E, et al. PARADIGM-HF Investigators and Committees. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J*. 2015; 36(38): 2576–2584, doi: [10.1093/eurheartj/ehv330](https://doi.org/10.1093/eurheartj/ehv330), indexed in Pubmed: [26231885](https://pubmed.ncbi.nlm.nih.gov/26231885/).
- Kristensen SL, Preiss D, Jhund PS, et al. PARADIGM-HF Investigators and Committees. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail*. 2016; 9(1), doi: [10.1161/CIRCHEARTFAILURE.115.002560](https://doi.org/10.1161/CIRCHEARTFAILURE.115.002560), indexed in Pubmed: [26754626](https://pubmed.ncbi.nlm.nih.gov/26754626/).
- Packer M, McMurray JJV, Desai AS, et al. PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015; 131(1): 54–61, doi: [10.1161/CIRCULATIONAHA.114.013748](https://doi.org/10.1161/CIRCULATIONAHA.114.013748), indexed in Pubmed: [25403646](https://pubmed.ncbi.nlm.nih.gov/25403646/).
- Vardeny O, Claggett B, Packer M, et al. Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail*. 2016; 18(10): 1228–1234, doi: [10.1002/ejhf.580](https://doi.org/10.1002/ejhf.580), indexed in Pubmed: [27283779](https://pubmed.ncbi.nlm.nih.gov/27283779/).
- Senni M, McMurray JJV, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail*. 2016; 18(9): 1193–1202, doi: [10.1002/ejhf.548](https://doi.org/10.1002/ejhf.548), indexed in Pubmed: [27170530](https://pubmed.ncbi.nlm.nih.gov/27170530/).

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