Folia Cardiologica 2019
vol. 14, no. 5, pages 516–521

ISSN 2353–7752

# Sacubitril/valsartan predischarge for patient in acute heart failure with reduced ejection fraction of left ventricle — the earlier, the better

## Sakubitril/walsartan dla pacjenta z ostrą niewydolnością serca z obniżoną frakcją wyrzutową lewej komory w okresie przedwypisowym — im wcześniej, tym lepiej

Małgorzata Lelonek

Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland

Artykuł jest tłumaczeniem pracy: Lelonek M. Sakubitril/walsartan dla pacjenta z ostrą niewydolnością serca z obniżoną frakcją wyrzutową lewej komory w okresie przedwypisowym — im wcześniej, tym lepiej. Folia Cardiol. 2019; 14(5): 511–516.
DOI: 10.5603/FC.2019.0103. Należy cytować wersję pierwotną

### Abstract

Based on the results of the TRANSITION and PIONEER-HF trials, the Heart Failure Association of the European Society of Cardiology has reported an expert consensus in 2019 that the initiation of sacubitril/valsartan, rather than an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II type 1 receptor blocker, may be considered for patients hospitalised with new-onset heart failure with reduced ejection fraction (HFrEF) or decompensated chronic HFrEF to reduce the short-term risk of adverse events and to simplify management by avoiding the need to titrate ACE inhibitors first, and then switch to an angiotensin receptor neprilysin inhibitor (ARNI). This paper describes the new data from the two trials, TRANSITION and PIONEER-HF.

Key words: sacubitril/valsartan, acute heart failure, HFrEF, predischarge

Folia Cardiologica 2019; 14, 5: 516–521

Since the announcement in 2016 of the latest guidelines of the European Society of Cardiology (ESC) on heart failure (HF), new data has emerged from subsequent studies using the drug sacubitril/valsartan, indicating the clinical benefits of this drug in an ever-wider population of patients in heart failure with reduced ejection fraction (HFrEF).

The **TRANSITION study** is a multi-centre, randomised, open-label, parallel-group study that compares two strategies of treatment with sacubitril/valsartan in patients with HFrEF who were hospitalised due to acute heart failure (AHF) [1].

The purpose of this study was to demonstrate the safety of sacubitril/valsartan and the tolerance of early incorporation of the drug in patients hospitalised owing to acute HFrEF who were stabilised haemodynamically. The study included patients with pre-existing or newly diagnosed (*de novo*) HF.

The study was conducted among patients taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II type 1 receptor blocker (ARB) at any dose before admission to hospital or patients who were previously not treated with an ACE inhibitor/ARB.

**Address for correspondence:** Małgorzata Lelonek Professor, MD, PhD, FESC, FHFA, Zakład Kardiologii Nieinwazyjnej, Katedra Chorób Wewnętrznych i Kardiologii, Uniwersytet Medyczny w Łodzi, ul. Żeromskiego 113, 90–549 Łódź, Poland, phone 42 639 35 71, fax 42 639 37 30, e-mail: malgorzata.lelonek@umed.lodz.pl

**Table 1.** Inclusion criteria for the TRANSITION study (source [1])

| |
|---|
| Men or women aged ≥ 18 |
| Hospitalised due to an episode of AHF recognised as the primary diagnosis |
| NYHA class II–IV HF diagnosis with reduced EF in screening tests |
| LVEF ≤ 40% in screening tests* |
| Patients who did not receive intravenous vasodilators (except nitrates) or intravenous inotropic drugs in the period between the occurrence of AHF and randomisation |
| Patients stabilised (during hospitalisation) for ≥ 24 h, meeting the following criteria:<br>• no need for intravenous use of diuretics in the last 24 h<br>• SBP ≥ 110 mm Hg from ≥ 6 h prior to randomisation |
| Meeting one of the following criteria:<br>• taking an ACE inhibitor or an ARB at any dose before being admitted to hospital<br>• patients previously not treated with an ACE inhibitor/ARB or not treated with an ACE inhibitor/ARB during ≥ 4 weeks prior to admission |

*If not screened, EF ≤ 40% in any measurement taken locally over the last 12 months; AHF — acute heart failure; HF — heart failure; NYHA — New York Heart Association; EF — ejection fraction; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; ACE — angiotensin-converting enzyme; ARB — angiotensin II type 1 receptor blocker

The inclusion criteria for the TRANSITION study are presented in Table 1.

Two strategies for initiating sacubitril/valsartan treatment were evaluated:

— at least 12 hours before discharge from hospital (*predischarge*) and
— 1–14 days after discharge from hospital (*postdischarge*).

**The primary endpoint** was reaching the target dose of sacubitril/valsartan at 97/103 mg twice a day during week 10 after randomisation in groups in which the treatment was initiated prior to discharge and after discharge from the hospital.

**Secondary endpoints** were:

— reaching and maintaining a dose of sacubitril/valsartan at 49/51 mg or 97/103 mg dose twice a day for at least two weeks leading to week 10 after randomisation (irrespective of any earlier temporary discontinuation of the treatment or dose reduction during the treatment period);
— reaching and maintaining any dose of sacubitril/valsartan for at least two weeks leading to week 10 after randomisation;
— permanent discontinuation of sacubitril/valsartan due to adverse reactions over a 10-week follow-up period.

The characteristics of the TRANSITION study population are shown in Table 2.

**Primary and secondary dose endpoints** were achieved in a comparable percentage of patients whose treatment was initiated before and after discharge, regardless of treatment prior to hospitalisation (ACE inhibitor or ARB, with no ACE inhibitor/ARB treatment). About half of HFrEF patients stabilised after an AHF episode reached a target dose of

**Table 2.** Characteristics of the TRANSITION study population (source [1])

| Assessed parameters | Before discharge N = 497 | After discharge N = 496 | Total N = 993 |
|---|---|---|---|
| Age (average) [years] | 66.7 | 66.9 | 66.8 |
| Male, N [%] | 372 (74.8) | 373 (75.2) | 745 (75.0) |
| Caucasian, N [%] | 484 (97.4) | 480 (96.8) | 964 (97.1) |
| BMI [kg/m$^2$], median (min–max) | 27.9 (17.6–58.8) | 28.8 (17.1–80.9) | 28.4 (17.1–80.9) |
| LVEF [%], mean ± SD | 28.63 ± 7.49 | 28.94 ± 7.62 | 28.79 ± 7.55 |
| Class according to NYHA | | | |
| Class I, N [%] | 0 (0.0) | 3 (0.6) | 3 (0.3) |
| Class II, N [%] | 321 (64.6) | 315 (63.5) | 636 (64.0) |
| Class III, N [%] | 167 (33.6) | 172 (34.7) | 339 (34.1) |
| Class IV, N [%] | 7 (1.4) | 5 (1.0) | 12 (1.2) |
| SBP [mm Hg], mean ± SD | 124 ± 13.7 | 124 ± 14.1 | 124 ± 13.9 |
| eGFR [ml/min/1.73 m$^2$], mean ± SD | 62 ± 20.5 | 62 ± 19.4 | 62 ± 20.0 |
| HF with ischaemic aetiology, N [%] | 219 (44.1) | 239 (48.2) | 458 (46.1) |

N — number of patients; BMI — body mass index; LVEF — left ventricular ejection fraction; SD — standard deviation; NYHA — New York Heart Association; SBP — systolic blood pressure; eGFR — estimated glomerular filtration rate; HF — heart failure

97/103 mg of sacubitril/valsartan two times/day during week 10. More than 86% of the patients in both groups took any dose of the drug for two weeks or more without any discontinuation of the treatment during 10 weeks of observation.

The drug was well tolerated; hypotension was the most common adverse reaction, which occurred in 12.1% of patients subjected to the predischarge strategy and 9% of patients subjected to the postdischarge strategy (p = 0.123). Due to adverse reactions, treatment was permanently discontinued in 7.3% of patients and 4.9% in the pre- and postdischarge groups, respectively (p = 0.117).

**The TRANSITION study documented that the initiation of sacubitril/valsartan soon after an AHF episode during hospitalisation or shortly after discharge from hospital was feasible and well tolerated in a wide population of patients with HFrEF.**

In the TRANSITION study, among the patients starting treatment with sacubitril/valsartan **predischarge, a significant 28% reduction in the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP)** was found as geometric mean ratio at the time of discharge compared to the starting point [0.718, 95% confidence interval (CI): 0.677–0.762, p < 0.0001] [2]. In contrast, in the group of **postdischarge** patients, who were initially treated with standard therapy drugs in HFrEF, there were no significant changes in the NT-proBNP concentration (GMR 0.966, 95% CI: 0.905–1.031, p = 0.293). At the time of discharge from the hospital, the difference between the analysed groups of patients (*predischarge vs. postdischarge*) was statistically significant in terms of the NT-proBNP concentration (p < 0.001). The use of sacubitril/valsartan during hospitalisation was also associated with **a significant reduction in the levels of high-sensitivity troponin T (hsTnT)** from the starting point to discharge from the hospital for predischarge patients, but not for postdischarge patients on a standard HFrEF treatment. A further decrease from the starting point was found in both examined groups for both biomarkers in weeks 4 and 10 with no significant differences between the predischarge versus postdischarge groups [2].

The initiation of predischarge treatment with sacubitril/valsartan in patients hospitalised due to AHF after achieving haemodynamic stability is associated with early and long-term improvement in biomarkers of cardiac wall stress and myocardial damage, indicating pathophysiological benefits in a wide group of people with HFrEF.

**PIONEER-HF** is another study using sacubitril/valsartan in a population of patients with AHF [3]. The most important criteria for inclusion in the study were:

- hospitalisation due to AHF (*de novo* about 1/3 of the population, 2/3 of the population exacerbation of chronic HF);
- LVEF not exceeding 40% in the last six months;
- concentration of NT-proBNP not less than 1,600 pg/mL or B-type natriuretic peptide (BNP) not less than 400 pg/mL;
- haemodynamic stabilisation during hospitalisation defined as:
  - systolic blood pressure (SBP) greater than or equal to 100 mm Hg in the last six hours; without symptomatic hypotension,
  - no increase in the dose of intravenous diuretics in the last six hours,
  - no use of any intravenous vasodilators in the last six hours,
  - not use of any intravenous inotropic drugs in the last 24 hours.

The characteristics of the population are shown in Table 3.

**Table 3.** Characteristics of the PIONEER-HF study population (source [3])

| Assessed parameters | Sacubitril/valsartan (N = 440) | Enalapril (N = 441) |
|---|---|---|
| Age [years] | 61 (50.5–71) | 63 (54–72) |
| Women [%] | 25.7 | 30.2 |
| African origin [%] | 35.9 | 35.8 |
| Prior HF diagnosis [%] | 67.7 | 63.0 |
| LVEF [%], median (25., 75.) | 24 (18–30) | 25 (20–30) |
| Systolic blood pressure, median (25., 75.) [mm Hg] | 118 (110–133) | 118 (109–132) |
| NT-proBNP concentrations, median (25., 75.) [pg/mL] at the time of randomisation | 2,883 (1,610–5,403) | 2,536 (1,363–4,917) |
| ACE inhibitor/ARB treatment [%] | 47.3 | 48.5 |
| Drugs blocking beta-adrenoreceptor activity [%] | 59.6 | 59.6 |

N — number of patients; HF — heart failure; LVEF — left ventricular ejection fraction; ACE — angiotensin-converting enzyme; NT-proBNP — N-terminal pro-B-type natriuretic peptide; ARB — angiotensin II type 1 receptor blocker

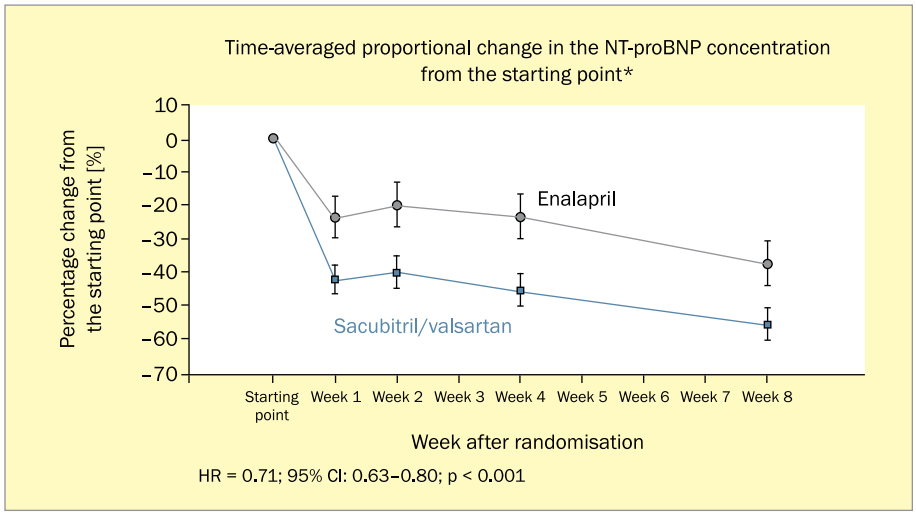


**Figure 1.** Results of the PIONEER-HF study in terms of the primary endpoint (based on [3]); *percentage (%) change from the starting point to the mean value during weeks 4 and 8; NT-proBNP — N-terminal pro-B-type natriuretic peptide; HR — hazard ratio; CI — confidence interval

The comparator in this study, as in the PARADIGM-HF trial, was 10 mg enalapril administered twice a day. The follow-up comprised eight weeks.

The PIONEER-HF study evaluated:

— **the primary endpoint** — time-averaged proportional change in the concentration of NT-proBNP from the starting point to weeks 4 and 8;

— **treatment safety:**
  - worsening of kidney function,
  - hyperkalemia,
  - symptomatic hypotension,
  - angioedema;

— **exploratory clinical evaluation measures: composite endpoint** including major clinical events: death, hospitalisation due to HF, the need to implant a left ventricular assist device (LVAD) or listing for a heart transplant.

During the eight weeks of observation, early and significantly greater reductions in NT-proBNP (Figure 1), and a reduction of endpoints of serious clinical events compared to patients treated with enalapril were documented in the case of patients treated with sacubitril/valsartan (Figure 2) [3].

The drug was well tolerated; among the most common adverse reactions were symptomatic hypotension (15% of patients treated with sacubitril/valsartan vs. 12.7% of patients treated with enalapril), worsening of renal function (13.6% of patients treated with sacubitril/valsartan vs. 14.7% of patients treated with enalapril), and hyperkalemia (11.6% of those treated with sacubitril/valsartan vs. 9.6% of those treated with enalapril) and episodes of angioedema in individual patients (0.2% of those treated with sacubitril/valsartan vs. 1.4% of those treated with enalapril).

**It is safe to initiate predischarge treatment with sacubitril/valsartan in patients hospitalised due to AHF after reaching haemodynamic stabilisation. It has a positive effect on lowering biomarkers of cardiac wall tension and it reduces the risk of serious clinical events.**

Despite the limitations of both studies, which were discussed in the original publications, the results of the TRANSITION and PIONEER-HF studies provide the basis for extending the use of sacubitril/valsartan in HFrEF.

## Conclusion

The results of the TRANSITION and PIONEER-HF studies documented the benefits of initiating treatment with sacubitril/valsartan in patients with HFrEF in the predischarge period due to AHF. The predischarge period and the first few months after the end of hospitalisation due to AHF belong to the vulnerable phase. The vulnerable phase is characterised by a high risk of death, prehospitalisation owing to HF exacerbations and excessive neurohormonal activation [4, 5]. According to the study protocols, **to initiate treatment with sacubitril/valsartan it is necessary to achieve haemodynamic stability of a patient during hospitalisation, *i.e.* for at least six hours without the administration of intravenous diuretics and vasodilators, and 24 hours without the administration of intravenous inotropic drugs, with an additional SBP of at least 100 mm Hg without any symptomatic hypotension.**

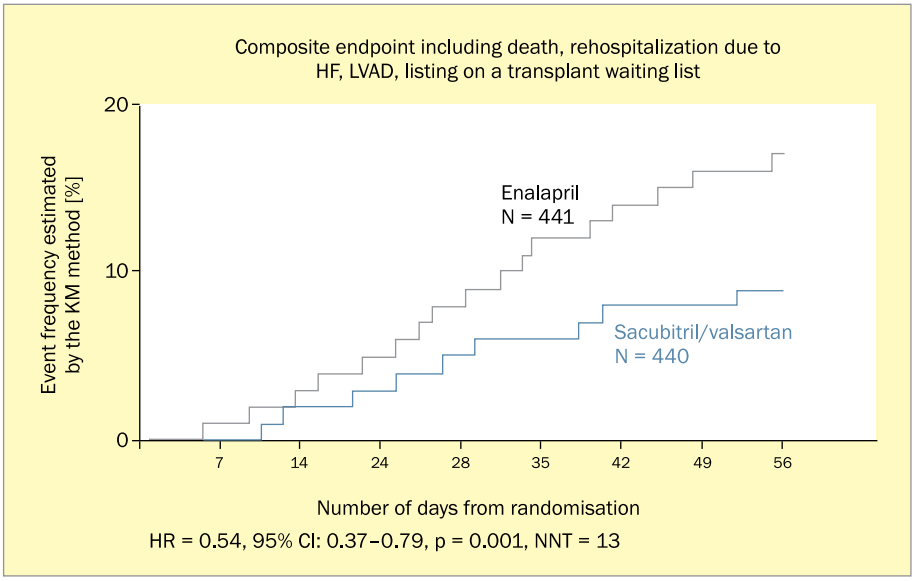


**Figure 2.** Results of the PIONEER-HF study in the exploratory composite endpoint (based on [3]); *the incidence of the exploratory endpoint, including major clinical events, were associated with a reduction in the risk of death and the frequency of re-hospitalisations due to heart failure (HF); LVAD — left ventricular assist device; HR — hazard ratio; CI — confidence interval; NNT — number needed to treat; N — number of patients

The results of the TRANSITION and PIONEER-HF studies were included in the expert report of the Association of Heart Failure ESC in 2019 [6], which indicates that **the initiation of treatment with sacubitril/valsartan can be considered instead of an ACE inhibitor or ARB in patients hospitalised due to acute HF symptoms (de novo or exacerbation of chronic HF)** to improve prognosis in the short term and facilitate treatment [avoiding ACE inhibitor treatment with the principle of increasing doses and switching to an $AT_1$ receptor antagonist for angiotensin II and a neprilysin inhibitor (ARNI)].

Initiating treatment with sacubitril/valsartan does not require NT-proBNP to be tested, because the patient in the predischarge period is at high risk of cardiovascular events.

## Conflict of interest

Participation in LCZ696 clinical trials.


## Streszczenie

Stanowisko eksperckie Asocjacji Niewydolności Serca Europejskiego Towarzystwa Kardiologicznego z 2019 roku wskazuje, że rozpoczęcie terapii lekiem sakubitril/walsartan można rozważyć zamiast inhibitora konwertazy angiotensyny (ACE) czy antagonisty receptora AT1 dla angiotensyny II u chorych hospitalizowanych z powodu ostrej niewydolności serca z obniżoną frakcją wyrzutową (HFrEF) (*de novo* lub zaostrzenia przewlekłej HF) w celu poprawy rokowania w okresie krótkoterminowym i ułatwienia prowadzenia leczenia (uniknięcie leczenia inhibitorem ACE z zasadą zwiększania dawek i zamiany na antagonistę receptora $AT_1$ dla angiotensyny II i inhibitora neprylizyny [ARNI]). Stanowisko to opiera się na wynikach dwóch opublikowanych badań — TRANSITION oraz PIONEER-HF. W poniższym artykule przedstawiono dane z tych badań.


Słowa kluczowe: sakubitril/walsartan, ostra niewydolność serca, HFrEF, okres przedwypisowy

Folia Cardiologica 2019; 14, 5: 516–521

## References


1. Wachter R, Senni M, Belohlavek J, et al. TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019; 21(8): 998–1007, doi: 10.1002/ejhf.1498, indexed in Pubmed: 31134724.
2. Pascual-Figal D, Senni M, Belohlavek J, et al. Short-term effect on cardiac biomarkers of initiation of sacubitril/valsartan in hospitalized patients with heart failure and reduced ejection fraction: results of the TRANSITION study. Poster [Su2183] presented at AHA Congress 2018, Chicago, USA.
3. Velazquez EJ, Morrow DA, DeVore AD, et al. PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019; 380(6): 539–548, doi: 10.1056/NEJMoa1812851, indexed in Pubmed: 30415601.
4. Matyjas K, Lelonek M. Pacjent z niewydolnością serca w okresie vulnerable phase. Folia Cardiol. 2018; 13(1): 71–78, doi: 10.5603//fc.2018.0014.
5. Greene SJ, Fonarow GC, Vaduganathan M, et al. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol. 2015; 12(4): 220–229, doi: 10.1038/nrcardio.2015.14, indexed in Pubmed: 25666406.
6. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 [Epub ahead of print], doi: 10.1002/ejhf.1531, indexed in Pubmed: 31129923.