# The efficacy and safety of predischarge initiation of angiotensin receptor/neprilysin inhibitor in patients with severe left ventricular dysfunction hospitalized for acute decompensated heart failure: Single-center experience

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## INTRODUCTION

Each episode of acute decompensated heart failure (ADHF) is related to a worsening of prognosis in patients with heart failure (HF) with reduced ejection fraction (HFrEF), which results from developing or progressing dysfunction of vital organs [1]. The period following ADHF and peridischarge days is called the early vulnerable phase. An initiation of optimal medical therapy (OMT) in this phase improves outcomes after ADHF [2]. Thus, the 2021 European Society of Cardiology guidelines highlight the need for OMT in patients with HFrEF and ADHF as soon as possible to reduce mortality and rehospitalization risk [3, 4]. TRANSITION was the first while PIONEEF-HF was the second randomized and multicentre trial to confirm that initiation of angiotensin receptor/neprilysin inhibitor (ARNI) after hemodynamic stabilization in patients with HFrEF and ADHF might be effective and safe [5, 6]. The results of those studies were fundamental in introducing ARNI in patients with HFrEF and ADHF [7].

Our study aimed to assess the efficacy and safety of predischarge initiation of ARNI in patients hospitalized for ADHF, especially in those with severe left ventricular (LV) dysfunction.

## METHODS

We conducted a retrospective observational real-life single-center study that enrolled patients hospitalized and followed in the Department of Noninvasive Cardiology of the Medical University of Lodz between 2019 and 2021. The institutional review board approved the study (approval no. RNN/208/21/KE). The study enrolled 42 patients meeting the following inclusion criteria: (1) hospitalization for ADHF; (2) hemodynamic stability; (3) left ventricular ejection fraction (LVEF) ≤40%; (4) no prior therapy with ARNI. The exclusion criteria were: (1) age <18 years old; (2) estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 $m^2$; (3) serum potassium >5.4 mmol/l; (4) history of angioedema or hypersensitivity to angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB); (5) history of heart transplant (HTx) or ventricular assist device (VAD); (6) significant aortic or mitral valve disease (except for functional mitral regurgitation) or other significant structural heart diseases; (7) postpartum cardiomyopathy; (8) severe pulmonary disease; (9) severe liver disease.

Patients enrolled in the study were receiving HFrEF therapy, including ACEI/ARB, beta-blockers, mineralocorticoid receptor antagonists (MRA), and, when indicated, diuretics and cardiac devices; 2 patients in the studied population were ACEI/ARB naïve.

All patients who achieved hemodynamic stability, defined as no need for intravenous diuretics or inotropes for ≥24 hours and systolic blood pressure (SBP) ≥100 mm Hg, received ARNI ≥12 hours before discharge. ARNI was initiated both for ACEI/ARB-naïve patients and those treated with ACEI/ARB. ACEI/ARB treatment was stopped before ARNI initiation. The starting dose and up-titration to the target dose or maximum tolerated one was as per label recommendations [8].

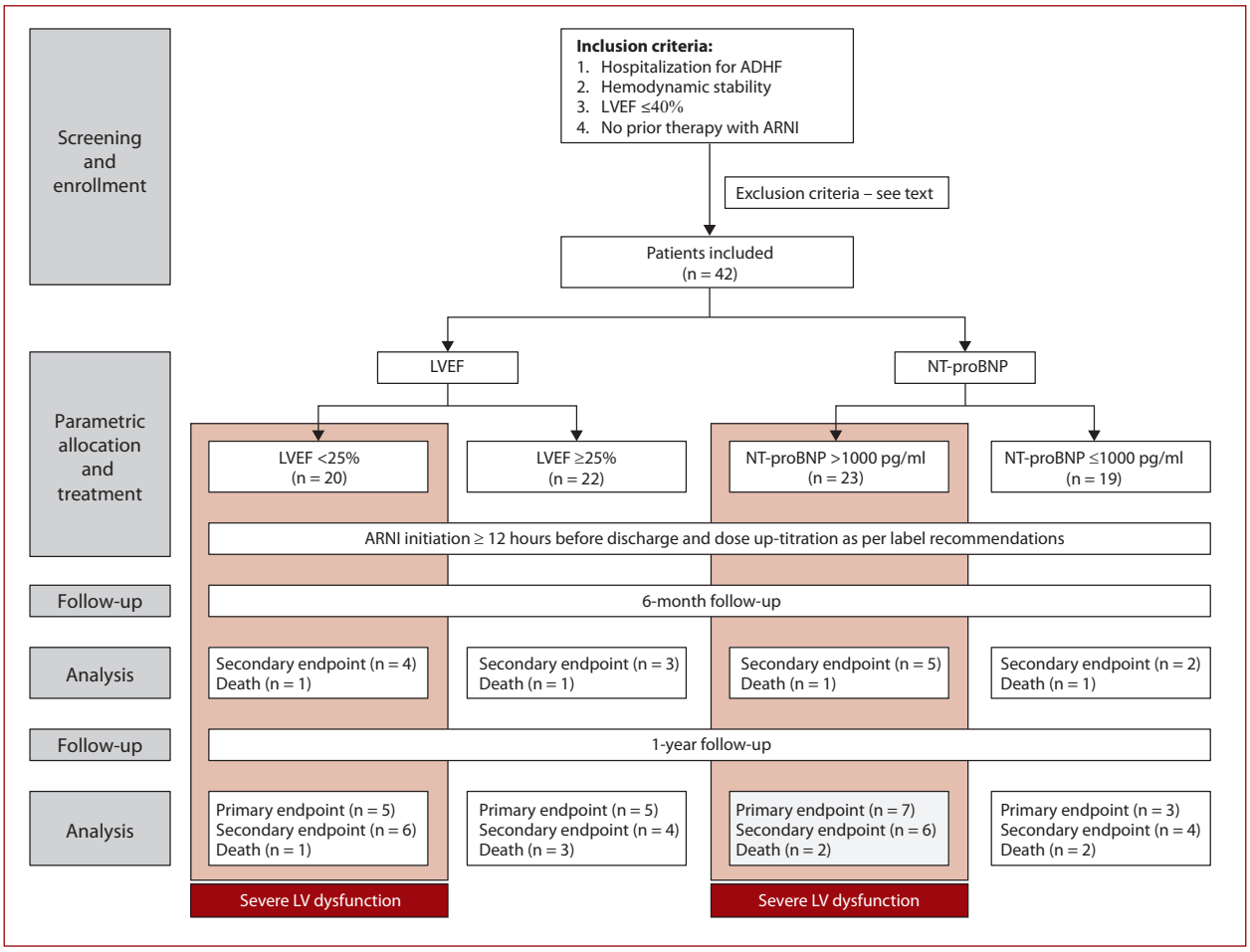


**Figure 1.** Study flowchart

Abbreviations: ADHF, acute decompensated heart failure; ARNI, angiotensin receptor/neprilysin inhibitor; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide

At baseline, a complete history, selected lab tests, electrocardiogram, and transthoracic echocardiography were taken. Subjects were followed for 1 year with mandatory on-site visits at months 6 and 12 and mandatory phone calls or optional on-site visits at months 3 and 9 after discharge. Such events as hospitalization for HF (HHF), acute kidney injury (AKI), HTx, or death were monitored during follow-up. Mortality data were obtained both from a proxy if subjects were lost to follow-up or from the records if subjects died during index HHF.

We aimed to establish the efficacy and safety of predischarge ARNI initiation regarding LVEF and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) values. The cut-off values for severe LV dysfunction were chosen as LVEF <25% [9] or NT-proBNP >1000 pg/ml [10]. Packer et al. [9] and Zile et al. [10] suggest that patients with LVEF <25% or NT-proBP >1000 pg/ml have a higher risk of HHF and death. The LVEF <25% and LVEF ≥25% groups and then the NT-proBNP >1000 pg/ml and ≤1000 pg/ml groups were compared.

The primary endpoint was composed of death or HHF within 1 year of follow-up. A secondary endpoint was composed of ≤50% of the target dose or drug discontinuation within 6 or 12 months of follow-up.

The baseline characteristics of the studied population were compared with the predischarge initiation group in the TRANSITION study.

The study flowchart is shown in Figure 1.

### *Statistical analysis*

Baseline characteristics of participants were presented as means with standard devitions (SD) or medians with interquartile ranges depending on distribution for continuous variables or as numbers of subjects and percentages for categorical variables. Distribution of continuous variables was evaluated using the Shapiro-Wilk test. To compare differences between groups Student's, Welch's, U Mann-Whitney, $\chi^2$, and Fischer's tests were used. A *P*-value <0.05 was deemed significant. All analyses were made using R statistical package version 4.0.2.

## RESULTS AND DISCUSSION

A comparison of participant characteristics between groups at baseline regarding LVEF or NT-proBNP is presented in Supplementary material, *Table S1* and *S2*. Patients with LVEF <25% at baseline had a significantly more frequent history of 1-year HHF, higher Meta-Analysis Global Group in

Chronic Heart Failure (MAGGIC) score and 1-year mortality, NT-proBNP values, LV diameters/volumes, and lower tricuspid annular plane systolic excursion (TAPSE). Patients with NT-proBNP >1000 pg/ml at baseline had significantly more frequent history of 1-year HHF and recorded atrial fibrillation, higher MAGGIC score and 1-year mortality, proximal right ventricular diameter (RVD) and systolic pulmonary artery pressure (SPAP), lower SBP, diastolic blood pressures (DBP), LVEF and TAPSE.

In patients with severe LV dysfunction, we observed a lower frequency of target dose and a higher frequency of medium dose of ARNI achieved during the follow-up. Irrespective of LV dysfunction severity, at least 82% and 76% of all participants achieved the target dose at months 6 and 12, respectively. Interestingly, none of the participants was on dose 24/26 mg at follow-up points. It suggests that a well-tolerated dose of 24/26 mg allowed for its safe up-titration. ARNI dose reduction during the study (permanent or temporary) was observed more often in the group with severe LV dysfunction. The main reason for dose reduction was hypotension, which achieved significance in patients with NT-proBNP >1000 pg/ml ($P = 0.02$).

The frequency of all monitored events was similar irrespective of LVEF or NT-proBNP values, except for HHF. This was more frequent in patients with severe LV dysfunction.

The study endpoint occurrence rate was higher in patients with severe LV dysfunction (Supplementary material, *Tables S3–S4*).

Patients enrolled in the study were at high risk of death and/or HHF related to being in the vulnerable phase [2]. On the other hand, it is well known that use of all fundamental therapy drugs, including ARNI, in populations with severe LV dysfunction might be limited due to the tendency for lower blood pressure, especially after ADHF in the predischarge period [2-4].

A comparison of baseline characteristics between the predischarge initiation group in the TRANSITION study and the studied population is presented in Supplementary material, *Table S5*. The studied population was younger and had lower LVEF, higher New York Heart Association (NYHA) class and eGFR. What is more, in the studied population there were more cases of ischemic HF and higher percentage of HFrEF therapy, including ACEI/ARB, beta-blockers, MRA, diuretics, and cardiac devices. The comparison with the TRANSITION study seems reasonable because both studies involved the European population [5, 11].

Our study shows that ARNI is well tolerated in patients with severe LV dysfunction hospitalized for ADHF, and its initiation before discharge might be effective and safe.

## Limitations

The study was carried out with a proportionate but relatively small group of patients during the 2019 coronavirus disease outbreak. Therefore, univariate or multivariate analyses were not feasible. The real-life and single-center protocol makes the study less reliable compared with randomized trials, i.e. the TRANSITION study. The study was conducted before flozins were established as a fundamental part of OMT in HF patients.

## Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

## Article information

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## REFERENCES

1. Biegus J, Moayedi Y, Saldarriaga C, et al. Getting ahead of the game: in-hospital initiation of HFrEF therapies. Eur Heart J Suppl. 2022; 24(Suppl L): L38–L44, doi: 10.1093/eurheartjsupp/suac120, indexed in Pubmed: 36545227.
2. Gracia E, Singh P, Collins S, et al. The vulnerable phase of heart failure. Am J Ther. 2018; 25(4): e456–e464, doi: 10.1097/MJT.0000000000000794, indexed in Pubmed: 29985824.
3. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.
4. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42: 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
5. Witte KK, Wachter R, Senni M, et al. Rationale and design of TRANSITION: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan. ESC Heart Fail. 2018; 5(2): 327–336, doi: 10.1002/ehf2.12246, indexed in Pubmed: 29239515.
6. DeVore AD, Braunwald E, Morrow DA, et al. 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.
7. 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; 21(10): 1169–1186, doi: 10.1002/ejhf.1531, indexed in Pubmed: 31129923.
8. Entresto, INN-sacubitril/valsartan. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf. First authorisation: 19 Nov 2015. Latest renewal: 25 Jun 2020. Accessed: 7 Mar 2023.
9. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344(22): 1651–1658, doi: 10.1056/NEJM200105313442201, indexed in Pubmed: 11386263.
10. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2016; 68(22): 2425–2436, doi: 10.1016/j.jacc.2016.09.931, indexed in Pubmed: 27908347.
11. Straburzyńska-Migaj E, Dudek M, Kałużna-Oleksy M, et al. Comparison of the population of Polish patients participating in the TRANSITION study with the international population: a post-hoc analysis. Pol Arch Intern Med. 2023 [Epub ahead of print], doi: 10.20452/pamw.16410, indexed in Pubmed: 36633194.