# A favorable alliance between repetitive use of levosimendan and advanced heart failure: Polish two-centered inpatient perspective in need of validation

Marcin Książczyk[1], Marcin Gruchała[2], Iwona Stopczyńska[2], Małgorzata Lelonek[1]

[1]Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland
[2]1st Department of Cardiology, Medical University of Gdansk, Gdańsk, Poland

**Correspondence to:**
Marcin Książczyk, MD,
Department of Noninvasive Cardiology,
Medical University of Lodz,
Żeromskiego 113,
90–549 Łódź, Poland,
phone: +48 42 639 35 71,
e-mail:
marcin_ksiazczyk@interia.pl



DOI: 10.33963/KP.a2023.0034

**Received:**
November 1, 2022

**Accepted:**
January 27, 2023

**Early publication date:**
February 5, 2023

## INTRODUCTION

The prevalence of advanced heart failure (AdvHF) is estimated to be 1%–10% of heart failure (HF) patients [1]. Although evidence-based therapies improved outcomes in chronic HF [2], in AdvHF patients, they remain poor [3]. The 2021 European Society of Cardiology (ESC) guidelines allow for administering inotropic agents in patients with acute decompensation of HF with hypotonia and hypoperfusion who do not respond to conventional treatment (class IIb) [2]. Levosimendan is an inotrope that augments cardiac contractility by increasing calcium sensitivity, it promotes vasodilatation and cardioprotection [3, 4]. Inotropes without an adrenergic mechanism, such as levosimendan, may be preferred in patients on β-blockers [2, 4].

This study aims to present the first Polish experience on the efficacy and clinical outcomes of repetitive use of levosimendan in AdvHF patients.

## METHODS

We conducted a prospective, observational, real-life study in two Polish cardiology centers (Łódź, Gdańsk) between 2015 and 2018. The institutional review board approved the study (approval No. RNN/231/19/KE, KE/335/20). The study enrolled 46 inpatients meeting the criteria for AdvHF [1, 2]: (1) symptoms of HF in New York Heart Association (NYHA) class III or IV; (2) left ventricular ejection fraction (LVEF) ≤30%; (3) pulmonary or systemic congestion requiring intravenous (IV) diuretics or low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 visit or hospitalization in the last 12 months; (4) severe impairment of exercise capacity of cardiac origin. The exclusion criteria were: (1) age <18 years old; (2) symptomatic hypotonia; (3) estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 $m^2$; (4) non-ischemic liver injury; (5) hypersensitivity to levosimendan; (6) pregnancy or the peripartum period. Patients were receiving appropriate treatments for HF with reduced ejection fraction (HFrEF), including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), or angiotensin receptor/neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA), and, when indicated, diuretics, cardiac devices, and inotropic agents.

All patients received IV infusion of levosimendan with a rate of 0.1 μg/kg/min up to 12.5 mg or the maximum tolerated dose within 24–48 hours. Patients who received a single infusion were defined as non-repetitive, while patients who received >1 infusion were defined as repetitive. Each repetitive infusion was completed during planned hospitalization >2 days and reimbursed by the National Health Found (JGP group: E50, E52, or E53G). The interval between infusions varied from 2 to 4 weeks. The enrolment in the repetitive group was limited to patients who agreed to repetitive infusion within the next 2–4 weeks. A complete history and transthoracic echocardiography were taken before each infusion. A physical examination, lab tests, and electrocardiograms were performed before and after each infusion.

Subjects were followed up via an on-site visit or a phone call every 3 months for 1 year after the first infusion. If a subject did not carry

out the visit as planned, a phone call to his family was made to confirm their death. In total, 95 variables were analyzed.

The endpoint consisted of death or heart transplantation (HTx) or ventricular assist device (VAD) therapy within 1 year of follow-up in the two treatment groups.

### *Statistical analysis*

Baseline characteristics of participants were presented as means with standard deviation (SD) or medians with interquartile range depending on distribution for continuous variables or as numbers of subjects and percentages for categorical variables. The distribution of continuous variables was evaluated using the Shapiro-Wilk test. To compare differences between groups Student's t-test, Welch's t-test, Mann-Whitney U test, Wilcoxon signed rank, and $\chi^2$ tests (Pearson's, Fischer's, McNemar's with Yates' correction if necessary) were used. To identify the influence of treatment regimens on patients' survival time, a survival analysis using Kaplan-Meier curves compared with the Mantel-Cox test was employed. To identify whether baseline parameters could predict the study endpoint, univariate logistic regression was used. A $P$ <0.05 was deemed significant. All analyses were made using Statistica 13 and GraphPad Prism 8 software.

## RESULTS AND DISCUSSION

The baseline patient characteristics in both groups are presented in Supplementary materials, *Table S1*. A total of 30 patients received a single infusion, while 16 patients received >1 infusion (10 patients received 2 infusions, 2 patients received 3 infusions, and 4 patients received 4 infusions).

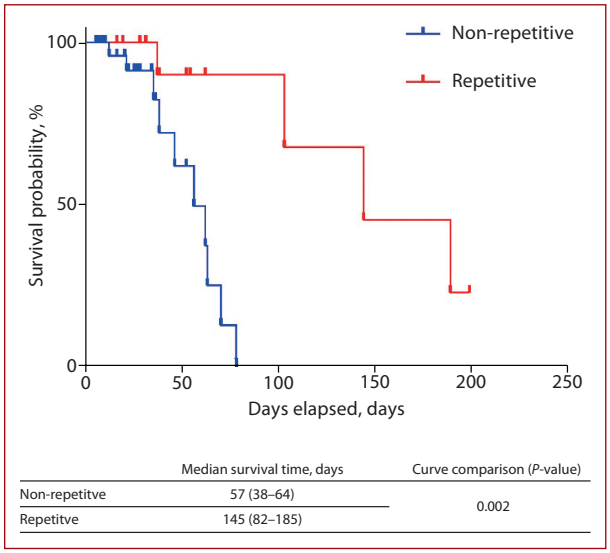
The endpoint occurred in 16 (53%) non-repetitive *vs.* 6 (38%) repetitive patients (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.15–1.82; $P$ = 0.42); during hospitalization in 10 (33%) vs. 4 (25%) patients, respectively.

The survival curve showed that the non-repetitive group was characterized by an over 6-fold higher risk of death compared to the repetitive group (hazard ratio [HR], 6.63; 95% CI, 1.96–22.41; $P$ = 0.002). The median survival time between the repetitive and non-repetitive groups was 145 (82–185) days vs. 57 (38–64) days, respectively (Figure 1).

The results of univariate analysis were shown in Supplementary materials, *Table S2*.

The signs and symptoms of HF, laboratory and electrocardiographic parameters in both groups at baseline and after infusion, and echocardiographic parameters in the repetitive group at baseline and before the last infusion were presented in Supplementary materials, *Tables S3*, *S4,* and *S5*.

In both groups, we observed a reduction in NT-proBNP, while in the repetitive group, we observed a reduction in left ventricular end-diastolic/end-systolic diameters/volumes without an improvement in LVEF.




| | Median survival time, days | Curve comparison (*P*-value) |
|---|---|---|
| Non-repetitve | 57 (38–64) | 0.002 |
| Repetitve | 145 (82–185) | |

**Figure 1.** Kaplan-Meier estimates of survival in the two treatment groups

The study shows that repetitive use of levosimendan does not reduce the risk of death or HTx or VAD, but it increases the probability of 1-year survival in AdvHF and reduces the signs and symptoms of HF.

The pharmacotherapy for HFrEF included the drugs of class I recommendations. Unfortunately, the study was conducted before gliflozins were established as fundamental HFrEF pharmacotherapy [2]. It is worth mentioning that only 60% of patients in the non-repetitive group and 69% in the repetitive group used ACEI/ARB/ARNI, which was limited by hypotension in AdvHF. Although the percentage of patients receiving ACEI/ARB/ARNI did not change significantly after infusion, we observed an increase in ARNI use from 12% to 40% in the repetitive group. The use of MRA was significantly higher in the repetitive group (94% vs. 60%; $P$ = 0.02), which resulted from a higher eGFR in this group.

In our study, pharmacotherapy with beta-blocker, MRA, and diuretic was associated with lower risk of endpoint occurrence.

Levosimendan, compared to other inotropes, reduces the signs and symptoms of HF [3, 5–8], and mortality [5, 7, 8]. However, metanalyses [9, 10] and the SURVIVE study [11] showed that levosimendan does not reduce mortality.

Some trials investigated the repetitive use of levosimendan in AdvHF [12–14]. Both studies, LION-HEART and LAICA, showed that intermittent ambulatory use of levosimendan in AdvHF reduces HF hospitalization [12, 13]. In contrast, the LevoRep study did not show improvements in quality of life or functional capacity after levosimendan use [14]. The doubts about the intermittent use of levosimendan in AdvHF might be cleared up shortly by the new multicenter, randomized, double-blind, placebo-controlled LEIA-HF study that plans to enroll 350 patients with AdvHF [15].

Although the data concerning mortality in patients treated with levosimendan are inconsistent, our study shows that repetitive use of levosimendan might be beneficial in AdvHF.

## Limitations

The study was conducted on small and disproportionate groups of patients, resulting from a small population of AdvHF patients and high levosimendan costs. The real-life protocol makes the study less robust and reliable compared with double-blind and randomized trials. There are missing data on echocardiographic parameters after infusion in the non-repetitive group.

## Supplementary material

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

## Article information

**Conflict of interest:** MG received research and travel grants from Orion Pharma Poland. IS received travel grants from Orion Pharma Poland. Other authors declare no conflict of interest.

**Funding:** None.



## REFERENCES

1. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018; 20(11): 1505–1535, doi: 10.1002/ejhf.1236, indexed in Pubmed: 29806100.
2. 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.
3. Lelonek M, Stopczyńska I, Korościk E, et al. Multicenter experiences with levosimendan therapy and its safety in patients with decompensated advanced heart failure. Adv Clin Exp Med. 2020; 29(11): 1305–1312, doi: 10.17219/acem/126301, indexed in Pubmed: 33269816.
4. Ahmad T, Miller PE, McCullough M, et al. Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials. Eur J Heart Fail. 2019; 21(9): 1064–1078, doi: 10.1002/ejhf.1557, indexed in Pubmed: 31407860.
5. Tycińska A, Gierlotka M, Bugajski J, et al. Levosimendan in the treatment of patients with acute cardiac conditions: an expert opinion of the Association of Intensive Cardiac Care of the Polish Cardiac Society. Kardiol Pol. 2020; 78(7-8): 825–834, doi: 10.33963/KP.15551, indexed in Pubmed: 32788567.
6. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013; 1(2): 103–111, doi: 10.1016/j.jchf.2012.12.004, indexed in Pubmed: 24621834.
7. Follath F, Cleland JGF, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002; 360(9328): 196–202, doi: 10.1016/s0140-6736(02)09455-2, indexed in Pubmed: 12133653.
8. Levy B, Buzon J, Kimmoun A. Inotropes and vasopressors use in cardiogenic shock: when, which and how much? Curr Opin Crit Care. 2019; 25(4): 384–390, doi: 10.1097/MCC.0000000000000632, indexed in Pubmed: 31166204.
9. Belletti A, Castro ML, Silvetti S, et al. The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. Br J Anaesth. 2015; 115(5): 656–675, doi: 10.1093/bja/aev284, indexed in Pubmed: 26475799.
10. Delaney A, Bradford C, McCaffrey J, et al. Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. Int J Cardiol. 2010; 138(3): 281–289, doi: 10.1016/j.ijcard.2008.08.020, indexed in Pubmed: 18817994.
11. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007; 297(17): 1883–1891, doi: 10.1001/jama.297.17.1883, indexed in Pubmed: 17473298.
12. Comín-Colet J, Manito N, Segovia-Cubero J, et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur J Heart Fail. 2018; 20(7): 1128–1136, doi: 10.1002/ejhf.1145, indexed in Pubmed: 29405611.
13. García-González MJ, de Mora-Martín M, López-Fernández S, et al. Rationale and design of a randomized, double-blind, placebo controlled multicenter trial to study efficacy, security, and long term effects of intermittent repeated levosimendan administration in patients with advanced heart failure: LAICA study. Cardiovasc Drugs Ther. 2013; 27(6): 573–579, doi: 10.1007/s10557-013-6476-7, indexed in Pubmed: 23887741.
14. Altenberger J, Parissis JT, Costard-Jaeckle A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. Eur J Heart Fail. 2014; 16(8): 898–906, doi: 10.1002/ejhf.118, indexed in Pubmed: 24920349.
15. Tycińska A, Gierlotka M, Bartuś S, et al. Repetitive use of LEvosimendan in Ambulatory Heart Failure patients (LEIA-HF) - The rationale and study design. Adv Med Sci. 2022; 67(1): 18–22, doi: 10.1016/j.advms.2021.10.001, indexed in Pubmed: 34656873.