

# Multicenter experiences with levosimendan therapy and its safety in patients with decompensated advanced heart failure

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## Abstract

**Background.** Advanced heart failure (AdvHF) is associated with high morbidity and mortality. Patients with this clinical condition are potential candidates for heart transplantation or mechanical circulatory support. Initially, however, they are usually supported with inotropic drugs. Recent studies have suggested that levosimendan, independently of hemodynamic improvements, may lead to outcome benefits.

**Objectives.** To present clinical experiences concerning the indications, effectiveness, tolerance, and safety of levosimendan in the real-life therapy of patients with decompensated AdvHF in 3 cardiac centers in Poland.

**Material and methods.** This is a prospective, observational, three-center study. Forty-nine patients with AdvHF admitted with decompensation were included (88% men, mean age 58 years, 65% ischemic etiology, left ventricular ejection fraction (LVEF) in median 20%) and followed up for an early (3 months) and prolonged period (1 year) after infusion of levosimendan. Patients were analyzed in relation to death.

**Results.** Levosimendan therapy was associated with reduced HF symptoms and signs, New York Heart Association (NYHA) class and level of B-type natriuretic peptide (BNP) at discharge. Five patients died during hospitalization, a further 10 during the three-month follow-up and 3 died during the next nine-month follow-up. During the three-month follow-up, 22 patients were re-hospitalized due to HF and in the next nine-month follow-up 8 were re-hospitalized. A multivariate analysis indicated the QRS duration at discharge (hazard ratio (HR) = 1.02; 95% confidence interval (95% CI) = 1.003–1.03;  $p = 0.018$ ), high-sensitivity C-reactive protein (hsCRP) (HR = 1.01; 95% CI = 1.004–1.02;  $p = 0.002$ ), and simultaneous dobutamine infusion (HR = 6.54; 95% CI = 1.4–30.5;  $p = 0.017$ ) were independent risk factors for death in the one-year follow-up. There were no side effects leading to the interruption of the levosimendan infusion.

**Conclusions.** The use of levosimendan was safe and associated with clinical improvement and reduction in BNP level in AdvHF patients hospitalized due to HF decompensation, although the mortality and re-hospitalization rate during the one-year follow-up remains high.

**Key words:** prognosis, levosimendan, advanced heart failure

## Introduction

Patients with advanced heart failure (AdvHF), which is associated with poor prognosis, comprise an estimated 1% to 10% of the overall heart failure (HF) population and this number is still increasing.<sup>1,2</sup> In acute HF, the estimated in-hospital mortality is 2–17%, a high 30-day mortality of 6.5%, and one-year mortality of up to 45%.<sup>3</sup> On the other hand, the implementation of evidence-based therapies in chronic HF, which improved outcomes,<sup>2</sup> showed improvement in the advanced stage of the disease. Therefore, a growing proportion of patients with AdvHF often need mechanical circulatory support, heart transplantation or palliative care.<sup>1–4</sup> The pharmacotherapy in AdvHF is insignificant. Recent innovative drugs in acute HF reported no evidence of benefit on outcomes.<sup>5</sup> Therapy with classical inotropes, such as dobutamine and milrinone, is able to temporarily improve hemodynamic and reduce symptoms, but long-term prognosis of patients with AdvHF remains unfavorable.<sup>1,2,4,6</sup> In the last (2016) HF guidelines, infusion of classical inotropic agents is limited to patients with signs of hypotension and/or hypoperfusion despite adequate filling status to increase cardiac output, vital organ perfusion and blood pressure (Class IIb).<sup>2</sup> Additional pharmacological options that improve prognosis are still desirable. One such option is levosimendan, a calcium sensitizer. Its inotropic effect is dependent on changes in troponin C conformation during systole, leading to sensitization of the contractile apparatus to calcium ions. Levosimendan also has vasodilator effect related to the activation of ATP-dependent potassium channels.<sup>7,8</sup> There are data and meta-analyses indicating significant benefits from levosimendan therapy in acute HF and AdvHF.<sup>9–16</sup> However, due to high costs and limited access to the therapy, clinical experience with levosimendan is still limited in many countries including Poland. The real-life use of levosimendan remains restricted to high-expertise AdvHF centers in Poland.

Therefore, the aim of this study is to present the clinical experiences concerning the real-life clinical indications, effectiveness, tolerance, and safety of levosimendan in the therapy of patients with AdvHF.

## Material and methods

This prospective, observational multicenter study was conducted between August 2015 and December 2018 at 3 clinical centers in Poland (Gdańsk, Łódź and Poznań) specializing in HF management. Eligible patients were admitted to hospital with decompensation of AdvHF (New York Heart Association (NYHA) class IV and/or signs of congestion) with reduced left ventricular ejection fraction (LVEF) diagnosed at least 3 months before admission and receiving individually optimized HF therapy in accordance with treatment guidelines,<sup>2</sup> which constituted

the inclusion criteria. Advanced HF was recognized according to the updated definition published in 2018.<sup>1</sup>

All 49 included patients received infusion of levosimendan. Mean cumulative drug dose per patient was 12.5 ± 4.7 mg. Twenty-two patients (45%) were treated with simultaneous dobutamine infusion. Median hospitalization duration was 22 days (interquartile range (IQR)) 10–32).

All patients had routinely measured laboratory tests and echocardiograms.

The follow-up after infusion was in early (3 months) and prolonged (1 year) period. The study was approved by the local Ethics Committees (approval No. RNN/231/19/KE, KE/335/20). The paper includes an analysis of the levosimendan safety and tolerability profile and the prognosis (death, hospitalization due to HF).

## Statistical analysis

Quantitative variables are described with mean and standard deviation (SD), or for non-normally distributed variables the median and IQR. Normality of the variables was verified using the Shapiro–Wilk normality test. For categorical variables, the number of observations (N) with the corresponding percentage (%) is given. To compare 2 independent groups, Student's t-test for continuous variables with normal distribution or the non-parametric Mann–Whitney U test for non-normally distributed variables was used.

For qualitative variables, Pearson's  $\chi^2$  test, ML  $\chi^2$  test or  $\chi^2$  test with Yates's correction was applied (regarding the expected counts in the contingency tables). Variables significant in univariate comparisons at  $p < 0.10$  were included in the multivariate stepwise Cox proportional hazards model to determine the independent risk factors of death. The Kaplan–Meier survival curve was also determined.

Missing data were imputed using the missForest algorithm (a multiple imputation procedure). In multivariate analysis, the results were considered statistically significant at  $p < 0.05$ .

To compare 2 dependent groups (i.e., before and after the treatment), the nonparametric Wilcoxon signed-rank test (for quantitative variables) and the McNemar–Bowker test with correction for continuity (for categorical variables) were used.

All the calculations were performed using the statistical packages STATISTICA PL v. 13.3 (StatSoft Inc., Tulsa, USA) and the R environment (the “missForest” package; [www.r-project.org](http://www.r-project.org)).

## Results

Data of 49 patients (43 men, 88%) with median age 58 (IQR = 43–63) years were analyzed. In the majority of patients, ischemic cardiomyopathy was the cause of HF

**Table 1.** Baseline demographic, clinical presentation and laboratory parameters

Variable	Mean $\pm$ SD or median (IQR)
Age [years]	58 (43–63)
BMI [kg/m <sup>2</sup> ]	28.1 $\pm$ 5.4
Number of HF hospitalizations within the last 12 months, N	2 (1–3)
HR [bpm]	82 (76–95)
QRS [ms]	132 (106–159)
BNP [pg/mL]	1838 (823–3271)
Hs-TnT [ $\mu$ g/L]	0.03 (0.02–0.07)
RDW [%]	16 (14.6–17.0)
Ferritin [g/L]	125 (68–254)
Transferrin saturation [%]	11.8 (8.8–20.0)
Serum sodium [mmol/L]	137 (134–139)
Serum potassium [mmol/L]	4.20 (3.7–4.5)
Creatinine [mmol/L]	115 (90–139)
eGFR (MDRD) [mL/min/1.73 m <sup>2</sup> ]	58.5 (40.1–83.0)
hsCRP [mg/L]	9.1 (4.2–13.4)
Total cholesterol [mmol/L]	3.46 $\pm$ 1.18
LDL cholesterol [mmol/L]	2.09 $\pm$ 0.94
HDL cholesterol [mmol/L]	0.85 (0.59–1.14)
Triglycerides [mmol/L]	0.93 (0.74–1.39)
Total bilirubin [ $\mu$ mol/L]	26.93 (18.5–44.5)
AST [IU/L]	39 (29–55)
ALT [IU/L]	30 (22–49)
6MWT [m]	235 $\pm$ 48.9

Data is presented as mean (standard deviation – SD) or median and interquartile range (IQR) related to normal or non-normal distribution. BMI – body mass index; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; hsCRP – high-sensitivity C-reactive protein; hs-TnT – high-sensitivity troponin-T; HR – heart rate; MDRD – modification of diet in renal disease; BNP – B-type natriuretic peptide; NT-pro-BNP – N-terminal-pro B-type natriuretic peptide; RDW – red blood cell distribution width; SBP – systolic blood pressure; LDL – low-density lipoprotein; HDL – high-density lipoprotein; AST – aspartate transaminase; ALT – alanine transaminase; 6MWT – 6-minute walk test

(Table 2) and left ventricular ejection fraction (LVEF) was in median 20% (Table 3) with enlargement of left ventricle, dysfunction of right ventricle (measured by tricuspid annular plane systolic excursion – TAPSE) with high probability of pulmonary hypertension (SPAP – systolic pulmonary arterial pressure – estimated from tricuspid regurgitation flow – Table 3) and concomitant functional mitral regurgitation (FMR; 44 patients, 90%). At admission, systolic blood pressure (SBP) was 107 mm Hg (IQR = 97–115 mm Hg), while diastolic blood pressure (DBP) was 70 mm Hg (IQR = 60–77 mm Hg). The level of B-type natriuretic peptide (BNP) was 1838 pg/mL (IQR = 823–3271 pg/mL).

Baseline demographics, laboratory parameters and clinical presentation are shown in Tables 1 and 2, echocardiographic data in Table 3.

**Table 2.** Etiology, history of HF at admission, concomitant diseases and treatment

Parameter	N (%)
Etiology	
Ischemic	32 (65)
Non-ischemic	17 (35)
Duration of HF	
<1 year	7 (14)
1–5 years	12 (24)
>5 years	30 (62)
Atrial fibrillation at admission	30 (67)
LBBB	10 (20)
RBBB	5 (10)
ICD	8 (16)
CRT-D	4 (8)
Concomitant diseases	
Hypertension	21 (43)
Renal failure	18 (37)
Diabetes mellitus	17 (35)
History of stroke/TIA	7 (14)
History of pulmonary embolism	3 (6)
Chronic obstructive lung disease	1 (2)
Pharmacotherapy	
ACEI/ARB	25 (51)
$\beta$ -blocker	47 (96)
MRA	48 (98)
Diuretic	47 (96)
Ivabradine	7 (14)
ARNI	10 (20)
Digoxin	6 (12)

ACEI – angiotensin-converting-enzyme inhibitors; ARB – angiotensin II receptor blockers; ARNI – angiotensin receptor-neprilysin inhibitors; CRT-D – cardiac resynchronization therapy defibrillator; ICD – implantable cardioverter defibrillator; LBBB – left bundle branch block; MRA – mineralocorticoid receptor antagonists; RBBB – right bundle branch block; TIA – transient ischemic attack; HF – heart failure.

At discharge, a significant reduction in HF symptoms and signs was observed (Fig. 1). At admission, 24 (49%) patients had NYHA class IV, while at discharge only 5/44 (11%) patients had class IV. Also, BNP concentration was significantly reduced from 1838 pg/mL (IQR = 823–3271 pg/mL) at admission to 1654 pg/mL (IQR = 1001–2706 pg/mL) at discharge ( $p = 0.018$ ).

Five (10%) patients died during hospitalization due to worsening HF, but not during the infusion of levosimendan. During the three-month follow-up, 22 of 44 patients (50%) were re-hospitalized for decompensation of HF, and 10 (23%) patients died. The next 3 patients died during the following nine-month observation period and 8 were hospitalized due to HF. During the hospitalization with levosimendan, 5 patients received left ventricular assist device (LVAD) implantation at  $18.2 \pm 18.9$  days, and 2 patients

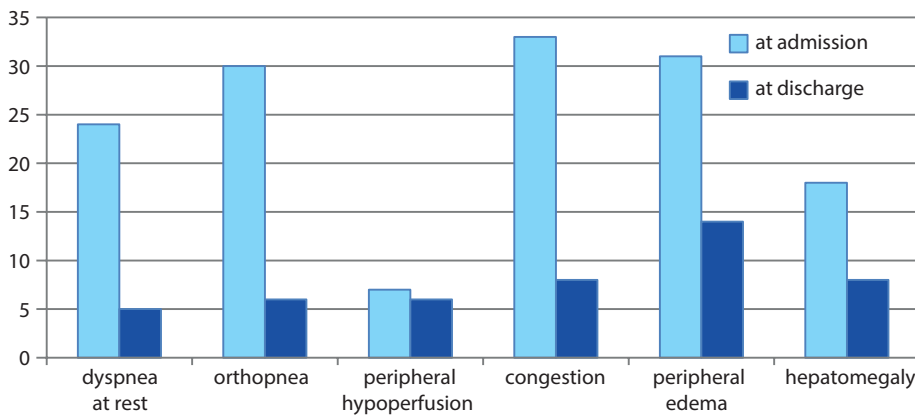


Fig. 1. Clinical improvement in N patients – all  $p < 0.05$  apart from peripheral hypoperfusion and hepatomegaly

Table 3. Echocardiographic data at admission

Parameter	Mean $\pm$ SD or median (IQR)
LVEF [%]	20 (15–26)
TAPSE [mm]	13 (11–15)
LVEDd [mm]	71 $\pm$ 9.9
LVESd [mm]	61.5 (56.0–67.5)
LVEDV [mL]	252 (205–286)
LVESV [mL]	188 (170–240)
VCI [mm]	24.44 $\pm$ 6.08
SPAP [mm Hg]	51.74 $\pm$ 16.10
FMR-VC [mm]	5.94 $\pm$ 1.88
LAVi [mL/m <sup>2</sup> ]	42 (31.0–61.5)

Data is presented as mean (standard deviation – SD) or median and interquartile range (IQR) related to normal or non-normal distribution. FMR-VC – functional mitral regurgitation – vena contracta; LVEDd – left ventricular end-diastolic diameter; LAVi – left atrial volume index; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; LVESV – left ventricular end-systolic volume; LVESd – left ventricular end-systolic diameter; SPAP – systolic pulmonary artery pressure; TAPSE – tricuspid annulus peak systolic excursion; VCI – vena cava inferior.

had heart transplantation at 45 and 97 days after being treated with levosimendan use, respectively.

From univariate analysis, longer levosimendan infusion ( $p = 0.045$ ), lower minimum systolic ( $p = 0.027$ ) and

diastolic ( $p = 0.05$ ) BP during infusion, QRS duration at discharge ( $p = 0.06$ ), and higher high-sensitivity C-reactive protein (hsCRP) ( $p = 0.0001$ ) were associated with death. The differences between analyzed groups related to death from all collected data are presented in Table 4.

Finally, Cox proportional hazards model revealed independent variables for death: QRS duration at discharge (hazard ratio (HR) = 1.02; 95% confidence interval (95% CI) = 1.003–1.03;  $p = 0.018$ ), hsCRP (HR = 1.01; 95% CI = 1.004–1.02;  $p = 0.002$ ) and simultaneous dobutamine infusion (HR = 6.54; 95% CI = 1.4–30.5;  $p = 0.017$ ).

The Kaplan–Meier survival curve is presented in Fig. 2. The probability of survival during the 1<sup>st</sup> year was at 69%.

## Safety and tolerability

Levosimendan infusions were associated with a mean reduction of SBP by  $-13.31$  mm Hg and DBP by  $-9.64$  mm Hg. Due to hypotension, 22 (45%) patients received simultaneous dobutamine infusion and/or a slower levosimendan infusion rate without interruption. There were no episodes of symptomatic hypotension. The other observed potential side effects were ventricular extrasystoles (31%), atrial fibrillation (7%), supraventricular tachycardia (3%), and non-sustained ventricular tachycardia (12%).

Table 4. From all analyzed variables statistical important differences between the studied groups

Parameter	Died (n = 18)	Survived (n = 31)	p-value
	mean $\pm$ SD or median (IQR)	mean $\pm$ SD or median (IQR)	
QRS duration at discharge [ms]	150 $\pm$ 50	128 $\pm$ 22.3	0.0595
hsCRP [mg/L]	34.3 (17–157)	7.6 (3.7–15.5)	0.0001
RDW [%]	17.8 (16.1–22.8)	16.1 (14.6–17)	0.0071
Total bilirubin [ $\mu$ mol/L]	76.95 (39.3–90.6)	22.91 (15.6–33.3)	0.0047
Minimum SBP during infusion [mm Hg]	86.07 $\pm$ 11.95	95.24 $\pm$ 12.43	0.0269
Minimum DBP during infusion [mm Hg]	52.93 $\pm$ 9.4	58.41 $\pm$ 9.03	0.0495
Duration of infusion [h]	30 (25–30)	25 (23–27)	0.0451
Dobutamine infusion [%]	16 (87)	10 (31)	0.0015

DBP – diastolic blood pressure; hsCRP – high-sensitivity C-reactive protein; SBP – systolic blood pressure; SD – standard deviation; IQR – interquartile range.

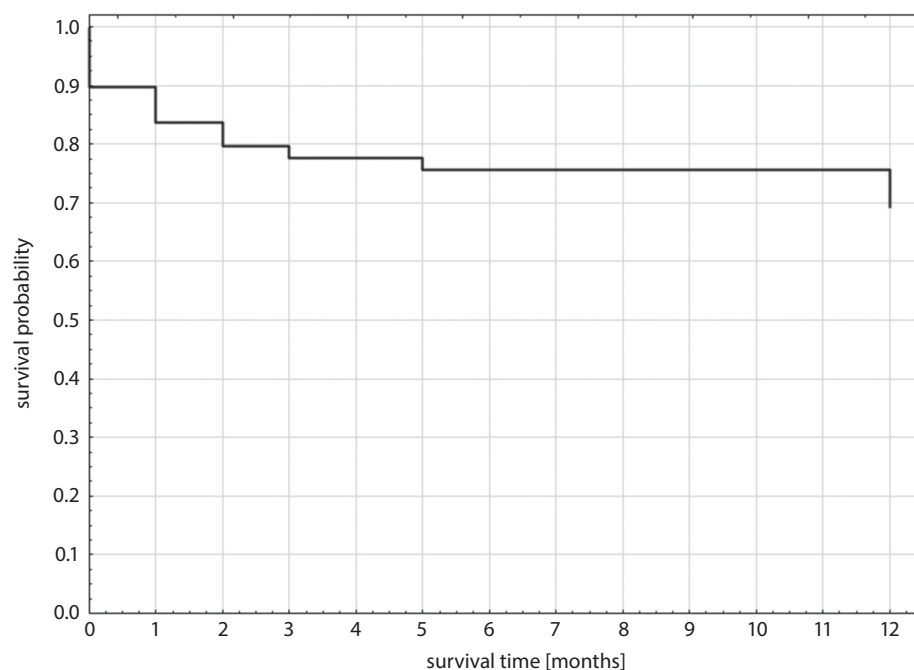


Fig. 2. The Kaplan–Meier survival curve

## Discussion

The paper presents Polish real-life multicenter experiences with levosimendan in the treatment of patients with decompensated AdvHF. According to 2018 updates of the Heart Failure Association, classical inotropic drugs are not recommended as a routine treatment in AdvHF, but may be used in selected patients as short-term therapy, especially as a bridge to mechanical circulatory support or transplantation.<sup>1</sup> Intermittent use of levosimendan may also be useful in such cases to improve clinical outcome and reduction in hospitalizations.<sup>1,17</sup> Despite this recommendation, levosimendan is rarely used in Poland. This limitation is not only due to relatively high cost of the therapy, but also due to concerns about its safety and is related to its little experience in the treatment of AdvHF.

Our study reported high re-hospitalizations rates in short- and long-term period with survival at 69% in a one-year follow-up in a population with AdvHF hospitalized due to HF decompensation. The studied population was in advanced stage of HF with significant dysfunction of LVEF (median 20%), enlargement of LV 71/61.5 mm (left ventricle end-diastolic volume (LVEDV)/left ventricle end-systolic volume (LVESV) 252/188 mL) and dysfunction of the right ventricle (TAPSE in median 13 mm). Among analyzed variables, longer levosimendan infusion, lower minimum SBP and DBP during infusion, and simultaneous dobutamine infusion were associated with mortality. These factors confirm that patients with hypotension and hypoperfusion have a serious prognosis and high mortality rates. Patients requiring simultaneous inotropic support with dobutamine infusion had a very serious clinical status, which is why they died frequently. It is worth noting that low use of angiotensin-converting-enzyme inhibitors

(ACEI), angiotensin II receptor blockers (ARB) and angiotensin receptor-neprilysin inhibitors (ARNI) in the studied group (73%) was related to hypotension and/or worsening renal function.

However, on discharge patients showed improvement in the clinical status, NYHA class and BNP levels after levosimendan therapy. So far, levosimendan has been studied in different clinical situations of acute HF, also showing the reduction of HF clinical signs and symptoms, and improved hemodynamics in patients with acute HF. REVIVE I trial was a pilot study of 100 patients, which showed that acute decompensated HF (ADHF) patients treated with levosimendan saw a significant improvement of clinical signs and symptoms of HF.<sup>15</sup> A 600-patient trial (REVIVE II) comprising of patients with acute decompensated HF with LVEF < 35% revealed that fewer levosimendan patients experienced worsening HF (15% of patients in the levosimendan group and 26% of patients in the control group). In patients with ADHF, levosimendan infusion provided rapid and long-lasting symptomatic relief.<sup>15</sup>

In the double-blind study, levosimendan infusion versus dobutamine (LIDO) in 203 patients with severe low-output acute HF, the hemodynamic improvement defined as an increase of 30% or more in cardiac output and a decrease of 25% or more in pulmonary capillary wedge pressure (PCWP) after 24 h was achieved in 28% of the levosimendan group and 15% in the dobutamine group (HR = 1.9; 95% CI = 1.1–3.3;  $p = 0.022$ ). The defined primary endpoint as the hemodynamic improvement was associated with clinical benefit for mortality in 180 days in levosimendan population (HR = 0.57; 95% CI = 0.34–0.95;  $p = 0.029$ ).<sup>12</sup> Moreover, a post hoc analysis of the LIDO trial showed that hemodynamic effect of levosimendan compared to dobutamine was better in the presence of beta-blockers.<sup>12</sup>



On the other hand, the SURVIVE trial was the first randomized multicenter double-blind, prospective trial to monitor long-term survival in patients with ADHF evaluating 2 inotropic agents, levosimendan and dobutamine. In 1,327 patients with LVEF < 30% not responding to standard therapy, in all-cause mortality, there was no significant difference between the studied groups (levosimendan 26% compared to dobutamine 28%, HR = 0.91 (95% CI = 0.74–1.13);  $p = 0.401$ ).<sup>14</sup> However, the retrospective analysis of the SURVIVE trial revealed that in the presence of  $\beta$ -blockers, mortality was lower for levosimendan than for dobutamine.<sup>18</sup> In another multinational, randomized, double-blind, phase IV study among HF patients in NYHA class III and IV, despite optimal treatment for HF including  $\beta$ -blocker therapy, improvement in hemodynamic parameters like PCWP and cardiac index (CI) with levosimendan was significantly greater compared with dobutamine at 24 h after the start of the infusion, and the effects lasting at 48 h though levosimendan was only administered for 24 h and dobutamine for 48 h.<sup>19</sup> Therefore, levosimendan is perceived as an therapeutic option in ADHF population on optimal medical treatment, requiring inotropic agents.<sup>19</sup> This observation is clinically important, because the majority of patients with HF are receiving  $\beta$ -blockers. In our study at admission with HF decompensation, 96% of patients were treated with  $\beta$ -blockers (in 4% there were side effects as hypotension and/or bradycardia). In contrast to dobutamine, hemodynamic effects of levosimendan are not reduced by a  $\beta$ -blocker use.<sup>20</sup> According to the 2016 European Society of Cardiology (ESC) HF guidelines, levosimendan should be the preferred inotropic agent for a HF decompensated patient with concomitant  $\beta$ -blocker treatment.<sup>1,2</sup>

Important concerns limiting the use of levosimendan in AdvHF are its possible side effects, especially hypotension. Levosimendan should be used with caution in patients with low baseline SBP (<100 mm Hg) or DBP (<60 mm Hg), or those at risk of a hypotensive episode; also, hypovolemia should be corrected prior to levosimendan infusion.<sup>20</sup> Current use of an initial bolus of levosimendan is not recommended in order to minimize the risk of hypotension.<sup>20</sup> Infusion should be started at a dose of 0.1 mg/kg/min or even 0.05 mg/kg/min when SBP is below 100 mm Hg and titrated to 0.2 mg/kg/min if BP remains stable after the first 2–3 h.<sup>20</sup> If patients develop hypotension, one should reduce the infusion rate or co-administer dobutamine or norepinephrine. In our group, the infusion was not initiated with a loading bolus. Due to hypotension, 22 (45%) of our patients received simultaneous dobutamine infusion. However, dobutamine infusion was one of the independent variable for risk of death (HR = 6.54,  $p < 0.01$ ) in our study. Levosimendan infusions were associated with a mean reduction in SBP of –13.31 mm Hg and DBP of –9.64 mm Hg. No serious hypotonic episodes or consequent discontinuation of levosimendan infusion were observed. However, the reduction of BP during infusion

recorded in the meta-analysis by Gong et al.<sup>21</sup> was lower than in our group – in SBP –7.08 mm Hg and DBP –4.75 mm Hg – which is probably related to the studied population.

Other frequent side effects of levosimendan infusion are supra- and ventricular arrhythmias. Also, hypokalemia is mentioned. In the SURVIVE study,<sup>18</sup> patients treated with levosimendan were more likely to experience atrial fibrillation (AF) episodes, but no differences were observed with respect to frequency of ventricular arrhythmias comparing to dobutamine. Similarly, the REVIVE II study also showed that patients treated with levosimendan more frequently had atrial arrhythmias (levosimendan 9% compared to placebo 2%;  $p < 0.001$ ) and also episodes of ventricular tachycardia (25% compared to 17%, respectively,  $p = 0.031$ ).<sup>15,20</sup> In the studied population, there is no data about AF episodes during infusion, because over 2/3 of patients had AF at admission. However, in our opinion, AF episodes in levosimendan patients could also be the sign of advanced stage of HF, not only the side effect of the therapy, similar as for non-sustained ventricular tachycardia (in our population 4 (12%) cases). Although no patient in our group had hypokalemia, it is worth mentioning that the potassium level should be checked before and monitored during infusion of levosimendan, and corrected if low. Because infusion of levosimendan may cause a decrease in the potassium level, increasing it should be considered before infusion even with borderline low potassium. Hypokalemia may also be a trigger of arrhythmia. No episodes of sudden cardiac arrest were observed in our study.

Side effects of levosimendan may be related to more advanced state of HF. Nevertheless, AdvHF patients have a high mortality rate and some of the observed side effects might not be as relevant.

In our study, as seen in multivariate analysis, QRS duration and hsCRP were also independent risk factors for death. A wide QRS complex on the electrocardiography (ECG), especially left bundle branch block (LBBB), indicates interventricular dyssynchrony, and is a well-known marker of poor prognosis in HF.<sup>22–24</sup> C-reactive protein is a biomarker of local and systemic inflammation and its correlation with the severity and prognosis of HF is also well documented.<sup>25,26</sup> Although there are many risk markers (clinical, laboratory, imaging, etc.) and numerous risk scores in patients with AdvHF, clinical history, number of recurrent HF hospitalizations and the physician's experience are still critical.<sup>1</sup>

It is worth noting that LVADs were implanted in 5 described patients and heart transplantations were performed in the other 2 patients during the follow-up. This suggests that infusion of levosimendan may be of value especially in patients waiting for advanced treatment in HF. There was the low rate of device usage at baseline – implantable cardioverter defibrillator and cardiac resynchronization therapy in only 24%. In one-year follow-up the subsequent 20 patients received ICDs and 6 CTRs.

Only 1 patient underwent a Mitraclip procedure 3 years before. These data indicate that there is still a large need for invasive procedures in this population in our country.

Despite the successful treatments for chronic HF in AdvHF, it is still impossible to demonstrate the survival benefit and find the effective pharmacotherapy. The last (2019) expert consensus proposed levosimendan as a safer inodilator option than traditional agents in AdvHF, with prolonged action and pleiotropic properties, including anti-inflammatory and anti-oxidative effects, and as protection not only of myocardial cells, but also of hepatic, renal and neural cells from ischemia/reperfusion injury.<sup>27</sup>

In our study, the patients benefited from levosimendan therapy, as their symptoms, signs of HF and the level of BNP were reduced. Clinical improvement with levosimendan creates an opportunity in AdvHF to bridge therapy to invasive procedures, including LVAD or heart transplantation. Therefore, levosimendan therapy should be used more frequently and earlier in HF journey of patients with HFrEF. The cost of 1 ampulla of levosimendan is about 3,400 PLN, which in the hospitalization rate of E52 group for AdvHF (5,813 PLN) might be well settled. Our results indicate the relative safety of this drug, which may contribute to its greater popularity.

On the other hand, AdvHF represents a severe form of the syndrome, usually worsening over time and, therefore, requiring the frequent administration of inotropes.<sup>30</sup> Levosimendan with its long-lasting effect of active metabolite is the only inodilator in this setting and there is evidence from some studies indicating the benefits of repetitive use of levosimendan in AdvHF.<sup>28</sup> Finally, we still need further clinical experiences with levosimendan therapy in multicenter, prospective trials to establish the impact of levosimendan on mortality in AdvHF.

## Limitations of the study

This was an observational study without a control group and the size of the analyzed group was limited. The observed side effects of levosimendan might be related to more advanced state of HF; however, without a control group, side effects can only potentially be associated with the drug.


## Conclusions

The use of levosimendan in patients with decompensated AdvHF is safe and is associated with clinical benefits, reflected by reduced HF symptoms and signs, NYHA class and BNP level, although mortality and re-hospitalization rates were high during the one-year follow-up. In AdvHF, levosimendan might be used more often as bridge therapy to invasive advanced procedures, such as LVAD or transplantation.

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