














Jacek Kubica¹, Krzysztof Pstrągowski¹, Aldona Kubica², Tomasz Topoliński¹, Robert Gajda³, Łukasz Pietrzykowski², Ewa Zabielska¹, Tamara Sukiennik¹, Małgorzata Jasiewicz¹, Marzena Wawrzyniak¹, Malwina Barańska¹, Julia M. Umińska⁴, Lidia Manelska¹, Ewa Obońska⁵, Michał Siedlaczek², Piotr Michalski², Ewa Laskowska¹, Klaudyna Grzelakowska¹, Jacek Kryś⁶, Piotr Adamski¹, Piotr Niezgodą¹, Małgorzata Ostrowska¹, Eliano P. Navarese¹

¹Department of Cardiology and Internal Medicine, Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland

²Department of Cardiac Rehabilitation and Health Promotion, Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland

³Gajda-Med Medical Centre, Pultusk, Poland

⁴Department of Geriatrics, Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland

⁵Department of Pharmacology, Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland

⁶Department of Health Economy, Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland

Early administration of LEvosimendan in Patients with decompensated chronic heart failure (ELEPHANT) study. Rationale and protocol of the study

Corresponding author:

Tomasz Topoliński
 Department of Cardiology
 and Internal Medicine, Nicolaus
 Copernicus University in Torun,
 Collegium Medicum,
 9 Curie-Skłodowska St.,
 85–094 Bydgoszcz, Poland;
 e-mail: topol@utp.edu.pl

Medical Research Journal 2023;
 10.5603/MRJ.a2023.0020
 Copyright © 2023 Via Medica
 ISSN 2451-2591
 e-ISSN 2451-4101

ABSTRACT

Dobutamine and levosimendan are both indicated for inotropic support in acute decompensated heart failure (HF).

The study aimed to assess the impact of early administration of levosimendan (first iv therapeutic approach) versus dobutamine (first iv therapeutic approach) on in-hospital treatment expenses and clinical outcomes in patients with decompensated chronic HF.

The ELEPHANT study was designed as a phase III, multicentre, randomized 1:1, double-blind, active-controlled trial that will include patients admitted to the hospital due to HF decompensation. Co-primary endpoints were defined as total in-hospital expenses/survivor and duration of hospitalization/survivor. Secondary efficacy endpoints: on the last day of hospitalization: occurrence of treatment side effects, body weight change during hospitalization, BNP change during hospitalization, in-hospital mortality, additional levosimendan administration due to the ineffectiveness of the initial treatment. Patients will be randomized 1:1 to the active group receiving continuous infusion 24 h of levosimendan 0.1 µg/kg/min or to the control group receiving continuous infusion 24 h of dobutamine 3 µg/kg/min.

After the enrolment of 20 patients, results analysis will be performed (pilot phase — single centre). Based on this analysis conducted according to the intention-to-treat principle, the final population size will be defined. The multicentre phase of the study will be initiated after the pilot phase.

Key words: levosimendan, dobutamine, decompensated heart failure

Introduction

According to European Society of Cardiology guidelines, dobutamine and levosimendan are both indicated for inotropic support in acute decompensated heart failure (HF) [1, 2]. Although dobutamine improves haemodynamics and symptoms in these patients, it has been

associated with an increased risk of death and other cardiovascular events [3]. On the other hand, in the meta-analysis published by Delaney et al. [4] levosimendan was associated with improvements in haemodynamic parameters and reduced mortality compared to dobutamine [odds ratio (OR) 0.75, 95% confidence interval (CI), 0.61–0.92, p = 0.005]. It is not clear, however, whether

levosimendan should be introduced as a first-line drug or only after ineffective treatment with intravenous (iv) inotropes [5–12]. Therefore, the ELEPHANT study was designed to assess the impact of early administration of levosimendan (first iv therapeutic approach) versus dobutamine (first iv therapeutic approach) on in-hospital treatment expenses and clinical outcomes in patients with decompensated chronic HF.

Material and methods

Study design

The ELEPHANT study was designed as a phase III, multicentre, randomized 1:1, double-blind, active-controlled trial that will include patients admitted to the hospital due to HF decompensation.

Study endpoints

Two co-primary endpoints were defined:

- Primary economic endpoint — total in-hospital expenses/survivor,
- Primary efficacy endpoint — duration of hospitalization/survivor.

Patients will be assessed for secondary safety and efficacy endpoints on the last day of hospitalization: any side effect of treatment, body weight change during hospitalization, B-type natriuretic peptide (BNP) change during hospitalization, in-hospital mortality, additional levosimendan administration due to the ineffectiveness of the initial treatment (levosimendan or dobutamine).

Moreover, following parameters will be assessed: blood tests: blood count, K, Na, lactates, troponin I, eGFR, BUN, CRP, AST, ALT, uric acid, total bilirubin, albumin, iron deficiency tests: iron, ferritin, total iron binding capacity (TIBC), TSAT = $(\text{iron}/\text{TIBC}) \times 100\%$; anthropometric data: height [m], waist circumference [cm], hips circumference [cm], waist-hip ratio (WHR), Physical Activity Level indicator (PAL), body fat indicator — Visceral Adiposity Index (VAI), waist to height ratio — WHtR, body adiposity index (BAI), body surface area (BSA); body composition analysis: body weight, body mass index (BMI), fat mass (FM), fatless mass (FFM), fat mass index (FMI), fatless mass indicator (FFMI), skeletal muscle mass (SMM), total body water (TBW), total water content (TBW), extracellular water (ECW), hydration (ECW/TBW), bioelectrical impedance vector analysis (BIVA), reactance, resistance, impedance, phase angle, abdominal fat tissue (VAT), energy demand at rest (REE), total energy demand (TEE), energy stored in the body; haemodynamic data: systolic blood pressure (SBP) [mmHg], diastolic blood pressure (DBP) [mmHg], mean blood pressure (MBP) [mmHg], heart rate (HR), stroke volume (SV), stroke volume index (SI),

cardiac output (CO), cardiac index (CI), cardiac power index (CPI), left ventricle systolic function (GFI), total peripheral resistance (TPR), total peripheral resistance index (TPRI); echocardiographic parameters: left ventricle diastolic diameter (LVDd), left ventricle systolic diameter (LVDs), left ventricular outflow tract diameter (LVOT diam), left ventricular outflow tract velocity time integral (LVOT VTI), ratio between E-wave and A-wave (E/A ratio), right ventricular diameter (RVD), tricuspid annular plane systolic excursion (TAPSE), inferior vena cava diameter (IVC), systolic pulmonary artery pressure (SPAP), left atrium area (LAA), right atrium area (RAA), left atrial volume index (LAVI), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), global longitudinal strain (GLS).

In addition, questionnaire-based tests will be performed during hospitalization and long-term follow-up: Health-Related Quality of Life Questionnaire (HRQoL), The Functioning in the Chronic Illness Scale (FCIS), and The Adherence in Chronic Diseases Scale (ACDS) [13–27] (Tab. 1).

Study population

The study population will consist of patients admitted to the hospital due to heart failure decompensation, who are > 18 and < 80 years old and meet all inclusion criteria, and do not meet any exclusion criteria.

Inclusion criteria

- Patients with INTERMACS level 3 or 4 clinical signs — patients requiring intravenous treatment of heart failure.
- Another (in the last 12 months) incident of decompensation of chronic heart failure requiring intravenous therapy.
- Decreased left ventricular ejection fraction ($\text{EF} \leq 35\%$) in cardiac magnetic resonance imaging or transthoracic echocardiography as assessed by Simpson.
- Increased concentration of natriuretic peptides ($\text{BNP} \geq 1000 \text{ pg/mL}$).

Exclusion criteria

- Contraindications to levosimendan:
 - Known drug hypersensitivity,
 - Dehydration,
 - Systolic blood pressure < 90 mmHg,
 - Resting tachycardia > 100/min,
 - Hypertrophic cardiomyopathy without or with left ventricular outflow tract obstruction or restrictive cardiomyopathy,
 - Severe hepatic impairment (Child-Pugh B and C classification),

Table 1. The ELEPHANT study — important activities and their respective time points during the study period

Action	Enrolment		Observations				
	Visit (V)	Time Point (d)	V0	V1	V2	V3	V4
			Before study treatment Administration	Day 3	Day 7	3 m-th	6 m-ths
<i>Enrolment</i>							
Eligibility Screen			X				
– INTERMACS level 3 or 4 HF			X				
– Previous hospitalization for HF			X				
– EF ≤ 35%			X				
– BNP ≥ 1000 pg/mL			X				
– Exclusion criteria assessment			X				
Informed Consent			X				
Pseudonymisation			X				
Randomization			X				
<i>Assessments</i>							
Blood sampling			X	X	X		
Anthropometric assessment			X	X	X		
Body composition analysis			X	X	X		
Hemodynamic assessment			X	X	X		
Echocardiography			X		X		
HRQoL			X		X	X	
FCIS			X		X	X	
ACDS							X
Central arterial pressure				X		X	
Pulse wave propagation speed				X		X	
Ambulatory BP monitoring				X		X	
Endothelial function				X		X	
Questionnaires				X		X	
Tablets counting					X	X	
<i>Outcome Assessment</i>							
Endpoints				X	X	X	
Side effects monitoring				X	X	X	X

ACDS — The Adherence in Chronic Diseases Scale; BNP — B-type natriuretic peptide; BP — blood pressure; EF — ejection fraction; FCIS — The Functioning in the Chronic Illness Scale; HF — heart failure; HRQoL — Health-Related Quality of Life Questionnaire

- History of torsades de pointes tachycardia.
- Contraindications to dobutamine:
 - Known drug hypersensitivity,
 - Pheochromocytoma,
 - Treatment with MAO inhibitors.
- A severe structural valvular defect that causes heart failure;
- The cause of exacerbation of heart failure is evident
 - infection, dehydration, acute coronary syndrome, arrhythmias, chronic or acute pulmonary embolism;
- PCI or CABG during current hospitalization;
- Chronic dialysis;
- Severe COP;
- Pregnancy;
- End-stage heart failure qualified for palliative treatment;
- Comorbidities with unfavourable prognosis with a predicted short survival period;
- Inability to obtain patient's consent to participate in the study;
- Incapacitated persons.

Treatment protocol

Enrolment in the study is possible up to 36 hours from the beginning of hospitalization. Patients will be randomized 1:1 to the active group (AG) receiving

continuous infusion 24 h of levosimendan 0,1 $\mu\text{g}/\text{kg}/\text{min}$ or to the control group (CG) receiving continuous infusion 24 h of dobutamine 3 $\mu\text{g}/\text{kg}/\text{min}$. Assignment of the patients to group AG or CG will be known only to the persons who blind the drug. None of them will participate in the decision-making process regarding patient therapy or follow-up. During the study, patients will be treated in accordance with the latest medical knowledge and current guidelines of the European Society of Cardiology [1, 2]. On the first day of therapy, an iv loop diuretic will be administered at a dose of $2.5 \times$ the dose previously used (up to a dose of max. 120 mg furosemide or torasemide) or if the patient has not used loop diuretics before, at a dose of 80 mg furosemide or 20 mg torasemide.

Patients will be followed for up to 6 months after hospital discharge with a telephone visit every 3 months [13–27].

Safety monitoring

All patients receiving the infusion (levosimendan or dobutamine) will be continuously monitored. The infusion will be stopped when any of the following occurs: significant, symptomatic and persistent hypotension, severe cardiac arrhythmias (paroxysmal supraventricular tachycardia, nonsustained ventricular tachycardia, including torsade de pointes, ventricular fibrillation, advanced atrioventricular blocks), signs of acute coronary syndrome, and a sudden exacerbation of symptoms of HF.

Ethical issues

The study received approval from the Ethical Committee of the Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland (approval number: KB 629/20190). All enrolled patients will provide written informed consent to participate in this study. This study, which involves human participants, follows the 1964 Helsinki Declaration and its later amendments.

Results

After the enrolment of 20 patients (10 per arm), results analysis will be performed (pilot phase — single centre). Based on this analysis conducted according to the intention-to-treat principle, the final population size will be defined. The multicentre phase of the study will be initiated after the pilot phase.

Discussion

The previously published observational study suggests that the early administration of levosimendan in

patients with decompensated HF is associated with favourable economic and health effects [11]. The authors found a trend towards higher hospital costs and longer in-hospital stays in patients receiving levosimendan as the second choice (after dobutamine) compared to those treated early with levosimendan as the first choice. These observations strongly suggest the positive effect of the early administration of levosimendan on both the clinical and economic outcomes and offer preliminary evidence of its cost-effectiveness while being consistent with some other reports [11, 28–32]. Following the conclusion of the previous, observational study, this randomized trial was designed on the cost-effectiveness of early treatment with levosimendan in patients with decompensated HF.

References

- 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(36): 3599–3726, doi: [10.1093/eurheartj/ehab368](https://doi.org/10.1093/eurheartj/ehab368), indexed in Pubmed: [34447992](https://pubmed.ncbi.nlm.nih.gov/34447992/).
- Kubica J. Heart failure treatment according to the 2021 European Society of Cardiology Guidelines — experiences with SGLT2 inhibitors have changed the treatment strategy. *Medical Research Journal*. 2021; 6(3): 163–165, doi: [10.5603/mrj.2021.0046](https://doi.org/10.5603/mrj.2021.0046).
- Bayram M, De Luca L, Massie MB, et al. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol*. 2005; 96(6A): 47G–58G, doi: [10.1016/j.amjcard.2005.07.021](https://doi.org/10.1016/j.amjcard.2005.07.021), indexed in Pubmed: [16181823](https://pubmed.ncbi.nlm.nih.gov/16181823/).
- 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](https://doi.org/10.1016/j.ijcard.2008.08.020), indexed in Pubmed: [18817994](https://pubmed.ncbi.nlm.nih.gov/18817994/).
- Pollesello P, Parissis J, Kivikko M, et al. Levosimendan meta-analyses: Is there a pattern in the effect on mortality? *Int J Cardiol*. 2016; 209: 77–83, doi: [10.1016/j.ijcard.2016.02.014](https://doi.org/10.1016/j.ijcard.2016.02.014), indexed in Pubmed: [26882190](https://pubmed.ncbi.nlm.nih.gov/26882190/).
- Tycińska A, Gierlotka M, Bartuś S, et al. LEIA-HF Investigators. 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](https://doi.org/10.1016/j.advms.2021.10.001), indexed in Pubmed: [34656873](https://pubmed.ncbi.nlm.nih.gov/34656873/).
- Jaguszewski MJ, Gasecka A, Targonski R, et al. Efficacy and safety of levosimendan and dobutamine in heart failure: A systematic review and meta-analysis. *Cardiol J*. 2021; 28(3): 492–493, doi: [10.5603/CJ.a2021.0037](https://doi.org/10.5603/CJ.a2021.0037), indexed in Pubmed: [33843036](https://pubmed.ncbi.nlm.nih.gov/33843036/).
- 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/KP15551](https://doi.org/10.33963/KP15551), indexed in Pubmed: [32788567](https://pubmed.ncbi.nlm.nih.gov/32788567/).
- Papp Z, Agostoni P, Alvarez J, et al. Levosimendan Efficacy and Safety: 20 years of SIMDAX in Clinical Use. *Card Fail Rev*. 2020; 6: e19, doi: [10.15420/cfr.2020.03](https://doi.org/10.15420/cfr.2020.03), indexed in Pubmed: [32714567](https://pubmed.ncbi.nlm.nih.gov/32714567/).
- Pollesello P, Ben Gal T, Bettex D, et al. Short-Term Therapies for Treatment of Acute and Advanced Heart Failure—Why so Few Drugs Available in Clinical Use, Why Even Fewer in the Pipeline? *J Clin Med*. 2019; 8(11), doi: [10.3390/jcm8111834](https://doi.org/10.3390/jcm8111834), indexed in Pubmed: [31683969](https://pubmed.ncbi.nlm.nih.gov/31683969/).
- Pözl G, Altenberger J, Baholli L, et al. Repetitive use of levosimendan in advanced heart failure: need for stronger evidence in a field in dire need of a useful therapy. *Int J Cardiol*. 2017; 243: 389–395, doi: [10.1016/j.ijcard.2017.05.081](https://doi.org/10.1016/j.ijcard.2017.05.081), indexed in Pubmed: [28571618](https://pubmed.ncbi.nlm.nih.gov/28571618/).
- Siedlaczek M, Pstrągowski K, Ratajczak J, et al. Cost-effectiveness of levosimendan in patients with exacerbation of chronic heart failure — a single-center perspective. *Med Res J*. 2021; 6(2): 114–118, doi: [10.5603/mrj.2021.0027](https://doi.org/10.5603/mrj.2021.0027).
- Kubica A, Kosobucka A, Fabiszak T, et al. Assessment of adherence to medication in patients after myocardial infarction treated with percutaneous coronary intervention. Is there a place for new self-reported questionnaires? *Curr Med Res Opin*. 2019; 35(2): 341–349, doi: [10.1080/03007995.2018.1510385](https://doi.org/10.1080/03007995.2018.1510385), indexed in Pubmed: [30091642](https://pubmed.ncbi.nlm.nih.gov/30091642/).

14. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. *Patient Prefer Adherence*. 2018; 12(4): 333–340, doi: [10.2147/PPA.S150435](https://doi.org/10.2147/PPA.S150435), indexed in Pubmed: [29551891](https://pubmed.ncbi.nlm.nih.gov/29551891/).
15. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. *Curr Med Res Opin*. 2016; 32(8): 1441–1451, doi: [10.1080/03007995.2016.1182901](https://doi.org/10.1080/03007995.2016.1182901), indexed in Pubmed: [27112628](https://pubmed.ncbi.nlm.nih.gov/27112628/).
16. Pietrzykowski Ł, Kasprzak M, Michalski P, et al. Therapy Discontinuation after Myocardial Infarction. *J Clin Med*. 2020; 9(12), doi: [10.3390/jcm9124109](https://doi.org/10.3390/jcm9124109), indexed in Pubmed: [33352811](https://pubmed.ncbi.nlm.nih.gov/33352811/).
17. Kubica A, Gruchala M, Jaguszewski M, et al. Adherence to treatment — a pivotal issue in long-term treatment of patients with cardiovascular diseases. An expert standpoint. *Medical Research Journal*. 2018; 2(4): 123–127, doi: [10.5603/mrj.2017.0016](https://doi.org/10.5603/mrj.2017.0016).
18. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. *Sci Rep*. 2020; 10(1): 12028, doi: [10.1038/s41598-020-68915-1](https://doi.org/10.1038/s41598-020-68915-1), indexed in Pubmed: [32694522](https://pubmed.ncbi.nlm.nih.gov/32694522/).
19. Kubica A. Self-reported questionnaires for a comprehensive assessment of patients after acute coronary syndrome. *Med Res J*. 2019; 4(2): 106–109, doi: [10.5603/mrj.a2019.0021](https://doi.org/10.5603/mrj.a2019.0021).
20. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. *Pharmacology*. 2015; 95(1-2): 50–58, doi: [10.1159/000371392](https://doi.org/10.1159/000371392), indexed in Pubmed: [25592409](https://pubmed.ncbi.nlm.nih.gov/25592409/).
21. Kubica A, Kosobucka A, Michalski P, et al. The adherence in chronic diseases scale—a new tool to monitor implementation of a treatment plan. *Folia Cardiologica*. 2017; 12(1): 19–26, doi: [10.5603/FC.a2016.0105](https://doi.org/10.5603/FC.a2016.0105).
22. Buszko K, Obońska K, Michalski P, et al. The Adherence Scale in Chronic Diseases (ASCD). The power of knowledge: the key to successful patient — health care provider cooperation. *Med Res J*. 2016; 1(1): 37–42, doi: [10.5603/mrj.2016.0006](https://doi.org/10.5603/mrj.2016.0006).
23. Buszko K, Pietrzykowski Ł, Michalski P, et al. Validation of the Functioning in Chronic Illness Scale (FCIS). *Med Res J*. 2018; 3(2): 63–69, doi: [10.5603/mrj.2018.0011](https://doi.org/10.5603/mrj.2018.0011).
24. Kubica A, Michalski P, Kasprzak M, et al. Functioning of patients with post-COVID syndrome — preliminary data. *Med Res J*. 2021; 6(3): 224–229, doi: [10.5603/mrj.a2021.0044](https://doi.org/10.5603/mrj.a2021.0044).
25. Kubica A, Michalski P, Kasprzak M, et al. Two different approaches to assess adherence to medication in Polish cohort of the EUROASPIRE V registry. *Med Res J*. 2022; 7(2): 108–113, doi: [10.5603/mrj.a2022.0015](https://doi.org/10.5603/mrj.a2022.0015).
26. Kubica A. Adherence to medication in elderly patients. *Med Res J*. 2023; 1(8): 93–94, doi: [10.5603/mrj.a2023.0015](https://doi.org/10.5603/mrj.a2023.0015).
27. Kubica A, Kubica J. Functioning in chronic disease — a key factor determining adherence to heart failure treatment. *Med Res J*. 2022; 7(4): 277–279, doi: [10.5603/mrj.2022.0059](https://doi.org/10.5603/mrj.2022.0059).
28. Follath F, Cleland JGF, Just H, et al. Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. 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](https://doi.org/10.1016/s0140-6736(02)09455-2), indexed in Pubmed: [12133653](https://pubmed.ncbi.nlm.nih.gov/12133653/).
29. Fedele F, D'Ambrosi A, Bruno N, et al. Cost-effectiveness of levosimendan in patients with acute heart failure. *J Cardiovasc Pharmacol*. 2011; 58(4): 363–366, doi: [10.1097/FJC.0b013e318224e0a2](https://doi.org/10.1097/FJC.0b013e318224e0a2), indexed in Pubmed: [21697728](https://pubmed.ncbi.nlm.nih.gov/21697728/).
30. de Lissovoy G, Fraeman K, Salon J, et al. The costs of treating acute heart failure: an economic analysis of the SURVIVE trial. *J Med Econ*. 2008; 11(3): 415–429, doi: [10.3111/13696990802291679](https://doi.org/10.3111/13696990802291679), indexed in Pubmed: [19450096](https://pubmed.ncbi.nlm.nih.gov/19450096/).
31. de Lissovoy G, Fraeman K, Teerlink JR, et al. Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study. *Eur J Health Econ*. 2010; 11(2): 185–193, doi: [10.1007/s10198-009-0165-2](https://doi.org/10.1007/s10198-009-0165-2), indexed in Pubmed: [19582491](https://pubmed.ncbi.nlm.nih.gov/19582491/).
32. Nieminen MS, Buerke M, Parissis J, et al. Pharmacoeconomics of levosimendan in cardiology: a European perspective. *Int J Cardiol*. 2015; 199: 337–341, doi: [10.1016/j.ijcard.2015.07.049](https://doi.org/10.1016/j.ijcard.2015.07.049), indexed in Pubmed: [26241640](https://pubmed.ncbi.nlm.nih.gov/26241640/).