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

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ABSTRACT
Levosimendan is a new inodilator which involves 3 main mechanisms: increases the calcium sensitivity of cardiomyocytes, acts as a vasodilator due to the opening of potassium channels, and has a cardioprotective effect. Levosimendan is mainly used in the treatment of acute decompensated heart failure (class IIb recommendation according to the European Society of Cardiology guidelines). However, numerous clinical trials indicate the validity of repeated infusions of levosimendan in patients with stable heart failure as a bridge therapy to heart transplantation, and in patients with accompanying right ventricular heart failure and pulmonary hypertension. Due to the complex mechanism of action, including the cardioprotective and anti-aggregating effect, the use of levosimendan may be particularly beneficial in acute coronary syndromes, preventing the occurrence of acute heart failure. There are data indicating that levosimendan administered prior to cardiac surgery may improve outcomes in patients with severely impaired left ventricular function. The multidirectional mechanism of action also affects other organs and systems. The positive effect of levosimendan in the treatment of cardiorenal and cardiohepatic syndromes has been shown. It has a safe and predictable profile of action, does not induce tolerance, and shows no adverse effects affecting patients survival or prognosis. However, with inconclusive results of previous studies, there is a need for a well-designed multicenter randomized placebo-controlled study, including an adequately large group of outpatients with chronic advanced systolic heart failure.

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Pharmacodynamics and pharmacokinetics of levosimendan Positive inotropic drugs are classified depending on the mechanism of action into receptor-mediated and non–receptor-mediated drugs. In both cases, an increase in myocardial contractility is secondary to an elevation in intracellular calcium ion concentrations. However, this process is also

associated with adverse effects. Therefore, it would be particularly valuable and important to achieve positive inotropic action independently of the rise in cytoplasmic calcium levels.

Pharmacodynamics Levosimendan has 3 major mechanisms of action: it increases the calcium sensitivity of cardiac muscle cells, activates adenosine triphosphate (ATP)–sensitive potassium (K_{ATP}) channels in vascular smooth muscle (vasodilatory effect), as well as activates K_{ATP} channels in cardiac muscle cells (cardioprotective effect). The drug exerts its therapeutic action by enhancing the calcium sensitivity of cardiac muscle cells rather than by increasing calcium concentrations, which leads to improved myocardial contractile efficiency at lower oxygen consumption. The multidirectional and unique mechanism of action of levosimendan translates into several significant clinical effects (TABLE 1).

Pharmacokinetics The interesting effects of levosimendan are largely due to its pharmacokinetic properties. In terms of therapeutic dosing, the drug is characterized by linear pharmacokinetics and intravenous route of administration. Plasma protein binding is 98% for levosimendan, and only 39% to 42% for its metabolites.[1-3]

The metabolism of levosimendan occurs in several stages. About 5% of the dose is reduced by colonic bacteria to the aminophenolpyridazinone metabolite OR-1855, which is further metabolized by *N*-acetyltransferase-2 enzyme in the liver to form an active metabolite, OR-1896. The acetylation level is genetically determined. The half-life of levosimendan is 1 to 1.4 hours, and of OR-1896, even 75 to 80 hours. Because of these parameters and a significant difference in half-lives between levosimendan and its active metabolite, the clinical effect is observed already after 10 to 20 minutes from the start of the infusion and is maintained for 7 to 9 days after termination of the 24-hour infusion.[4,5] Steady-state concentrations are achieved 4 hours after starting the infusion.[6] The pharmacokinetic properties of levosimendan are not affected by the concomitant administration of a β-blocker or digoxin.[7]

TABLE 1 Levosimendan—the mechanisms of action

Molecular mechanism	Site	Effect
Increased troponin calcium sensitivity	Cardiomyocytes	Increased contractility of cardiomyocytes
Opening the ATP-dependent potassium channels	Cardiomyocytes	Cardioprotection
	Smooth muscle cells of blood vessels	Vasodilatation
		Increasing tissue perfusion

Abbreviations: ATP, adenosine triphosphate

Effect of levosimendan on hemodynamic and echocardiographic parameters in patients with acute heart failure Levosimendan exerts positive inotropic and lusitropic effects, while its vasodilatory action results in reducing left ventricular (LV) preload and afterload. Moreover, animal studies revealed an improvement of LV diastolic function by shortening isovolumic relaxation time and increasing LV filling pressure.[8] In another study, levosimendan was shown to reduce the time constant of isovolumic relaxation and increase peak mitral flow velocity, both at rest and during exercise, which prevented an increase in mean left atrial (LA) pressure and LV end-diastolic pressure.[9] Moreover, the drug improved ventricular–arterial coupling, calculated as the ratio of end-systolic elastance (end-systolic pressure divided by end-systolic volume) to effective arterial elastance (end-systolic pressure divided by stroke volume).[9] This relationship between myocardial contractility and afterload reflects global cardiovascular efficiency. A similar hemodynamic effect was observed in an experimental model of acute right ventricular (RV) failure.

In patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention, levosimendan resulted in a leftward and / or upward shift of the pressure–volume loop, which was associated with a significant improvement in myocardial contractility[10] as well as echocardiographic parameters (reduction in isovolumic relaxation time and the ratio of early diastolic flow to early tissue velocity; increase in the ratio of early to late diastolic flow and early diastolic tissue velocity) already after 24 hours from infusion.[11] Levosimendan also protects the myocardium against ischemia-induced damage or reperfusion injury. In animal studies, the drug induced an increase in coronary blood flow by enhancing nitric oxide release, reduced a tendency to vasospasm by lowering the concentrations of norepinephrine and serotonin in isolated grafts from internal mammary and radial arteries, and showed antiplatelet effects in vitro.[12]

In patients with significant aortic stenosis (aortic valve area <1 cm^2), with reduced LV ejection fraction (LVEF <40%), and a cardiac index of less than 2.2 l/min/m^2, the use of levosimendan for acute decompensated heart failure (HF) led to an increase in the mean (SD) cardiac index of 2 (0.41) l/min/m^2 (P = 0.02), 2.17 (0.4) l/min/m^2 (P = 0.01), and 2.37 (0.49) l/min/m^2 (P = 0.01) at 6, 12, and 24 hours, respectively.[13] A significant reduction in pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (MPAP), and central venous pressure, as well as an increase in stroke volume index, was observed. The improvement in hemodynamic parameters was associated with a significant drop in the levels of N-terminal fragment of

the prohormone brain natriuretic peptide (NT-proBNP) at 24 hours after termination of the infusion.[13] The hemodynamic effects of levosimendan are summarized in TABLE 2.

Levosimendan in acute heart failure Despite a substantial body of evidence from clinical trials, the use of levosimendan in patients with acute HF (AHF) is still controversial, and unequivocal data to support a strong recommendation for this type of treatment is lacking.

The effect of levosimendan on mortality, severity of HF symptoms, and duration of hospital stay was assessed in the following studies: LIDO (Efficacy and Safety of Intravenous Levosimendan Compared with Dobutamine in Severe Low-Output Heart Failure), RUSSLAN (Randomised Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure due to an Acute Myocardial Infarct), REVIVE I and II (Randomized Evaluation of Intravenous Levosimendan Efficacy), and SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support).[14-20] The results of the studies are summarized and shown in Tables III and IV in the extended Polish version of the text (available online as Supplementary material). As the findings are equivocal, levosimendan received class IIb recommendation (level of evidence C) in the European Society of Cardiology guidelines for the diagnosis and treatment of AHF.[21]

One of the more interesting studies assessing the effect of levosimendan in patients with AHF was published by Allou et al,[22] who investigated patients with refractory cardiogenic shock undergoing venoarterial extracorporeal membrane oxygenation (VA-ECMO). This single-center retrospective study yielded intriguing results, especially that it included 150 critically ill patients. Levosimendan was administered according to the following regimen: infusion of 0.2 µg/kg/min for a mean (SD) duration of 3.2 (2.8) days after VA-ECMO implantation. Patients treated with levosimendan showed a significant improvement in LVEF as compared with the control group. Successful weaning from extracorporeal support was reported more often in the levosimendan group than in patients receiving placebo and was associated with a significant improvement in 30-day survival. However, after propensity-score matching, the differences between groups were not significant.[22]

Subsequent meta-analyses of studies including a total of about 6000 patients largely showed a beneficial effect of levosimendan treatment on prognosis in all indications, including HF. A 20% reduction in mortality was shown in comparison with patients receiving not only placebo but also other inotropic drugs, particularly dobutamine.[19,23-26] Similar findings, favoring the use of levosimendan, were reported by the ALARM-HF (Acute Heart Failure Global Survey of Standard Treatment) study. The analysis evaluating the effect of inotropic drugs revealed that levosimendan treatment was associated with significantly lower in-hospital mortality rates.[25]

Another meta-analysis, which included over 3000 patients from 22 trials assessing the effect of levosimendan vs dobutamine, showed that the use of levosimendan was associated with a significant reduction in mortality (19.6% [296 of 1373 patients] vs 25.7% [328 of 1278 patients]; hazard ratio, 0.81; 95% CI, 0.70–0.92; $P = 0.002$). Importantly, the beneficial effect of levosimendan was particularly notable in patients on concomitant therapy with β-blocker (due to a different mechanism of action of the drug).[26] On the other hand, a meta-analysis by Delaney et al,[23] including 3650 patients from 19 studies, did not show a significant reduction in mortality for levosimendan vs placebo.

The discrepancies between clinical trials and meta-analyses are largely due to the use of different regimens. The studies differed not only in terms of the time of drug administration, duration of infusion, or the use of a loading dose but also in terms of the study population, clinical presentation, and disease etiology.

Levosimendan use in patients with advanced chronic heart failure The LAICA (Long-Term Intermittent Administration of Levosimendan in Patients With Advanced Heart Failure),[27] LION-HEART (Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients),[28] and LevoRep (Efficacy and Safety of Pulsed Infusions of Levosimendan in Outpatients with Advanced Heart Failure)[29] studies assessed patients with HF who received repeated doses of levosimendan (summarized and shown in Table IV in the extended Polish version of the text available online as Supplementary material).

TABLE 2 The effect of levosimendan on hemodynamic parameters

Hemodynamic parameter	The effect of levosimendan	Hemodynamic effect
Mean pulmonary artery pressure (mPAP)	Decrease[27,28]	Decrease of left ventricular filling pressure
Pulmonary capillary wedge pressure (PCWP)	Decrease[27,28]	
Time constant for isovolumetric relaxation time (Tau)	Reduction	Positive inotropic and lusitropic effect[17]
Peak flow through mitral valve (dV / dtmax)	Increase	Decrease mean pressure in left atrium (LA) and end-diastolic pressure in LV[19]
End-systolic elasticity (Ees)	Increase	Improvement of ventriculo-arterial coupling. Increase in Ees / Ea ratio
Effective arterial elasticity (Ea)	Decrease	
Cardiac Index (CI)	Increase	Improvement of left ventricular contractivity[26,27,28]
Stroke volume index (SVI)	Increase	

Although the results are varied, the studies have provided interesting and promising data on repeated levosimendan administration. However, in order to obtain the full picture of the drug's efficacy and mechanism of action, studies with a long-term follow-up (lasting several years), larger population, universal regimen that accounts for drug pharmacodynamics, as well as data on adverse events and comprehensive clinical evaluation of patients (including echocardiographic and hemodynamic parameters), are needed. Such an assessment is possible only with a careful patient selection (phenotyping) and constitutes a very promising therapeutic option in patients with AHF.

Levosimendan as a therapeutic option in patients with acute coronary syndrome Due to a complex mechanism of action, including its cardioprotective and antiplatelet effects, levosimendan may be particularly beneficial in patients with ACS, as it may prevent AHF due to increased myocardial wall stiffness, myocardial stunning, reduced contractility, and mechanical complications of myocardial infarction.[30-34] However, only few studies assessing the use of levosimendan for prevention of HF after acute myocardial infarction have been conducted. Moreover, no studies with a clinical endpoint are available.

De Luca et al[11] reported the effects of levosimendan vs placebo in 52 consecutive patients with acute anterior ACS. Patients treated with levosimendan showed improved LV diastolic function after 24 hours from primary angioplasty.

Sonntag et al[10] assessed LV systolic function in 24 patients with ACS treated with percutaneous transluminal coronary angioplasty. The levosimendan group (n = 16) showed a reduction in the mean (SD) number of hypokinetic segments from 8.9 (0.9) to 6.5 (1.1), while in the placebo group (n = 8), an increase from 7.8 (1.0) to 8.5 (1.1) was noted (P = 0.016). Importantly, an improvement in the systolic function of stunned myocardium was reported in 8 patients (50%) in the levosimendan group, as compared with 1 patient (12.5%) in the placebo group.[10]

The use of standard inotropic drugs in patients with ACS is associated with elevated intracellular calcium levels, which leads to increased oxygen demand. This, in turn, is related to higher mortality rates in this population.[25,35] However, studies comparing levosimendan with other therapeutic modalities in patients with AHF in the course of ACS did not have sufficient statistical power to confirm the effect of levosimendan on clinical endpoints.

Shang et al[36] performed a meta-analysis comprising a total of 1065 patients with ACS complicated by AHF, including cardiogenic shock. The levosimendan group included 680 patients, while 385 patients received other treatment modalities. Levosimendan was associated with lower all-cause mortality, lower risk of HF worsening, as well as improvement in hemodynamic parameters (reduced PCWP and systemic vascular resistance; increased cardiac index). The authors suggested that levosimendan should be recommended as routine treatment in patients with AHF complicating ACS.[36]

Despite limited data, the available evidence supports the use of levosimendan in patients with AHF, including cardiogenic shock, in the course of ACS.

Levosimendan in right heart failure Right HF usually develops secondary to LV dysfunction. The less common causes of isolated right HF include RV myocardial infarction or arrhythmogenic RV dysplasia. The onset of symptoms of right HF in patients hospitalized due to AHF was associated with a 2-fold higher risk of death, urgent heart transplant, or the need for mechanical circulatory support.[37]

Levosimendan seems to be beneficial in right HF owing to improvement in RV systolic function and cardiac output, its pulmonary vasodilatory and cardioprotective effects, as well as inhibition of RV hypertrophy.[38] Moreover, the drug improves hemodynamic parameters (increased cardiac output and LVEF; decreased PCWP, mean blood pressure, mean right atrial pressure, and total peripheral resistance). By improving renal blood flow parameters, levosimendan was also shown to improve kidney function.[39]

There have been no clinical trials assessing the effect of levosimendan on isolated right HF. Available data supporting its beneficial action come from a few case reports.[40] Prospective studies showed improved RV systolic function, reduced RV afterload, and improved clinical status.[41-43] Poelz et al[44] administered levosimendan to 18 patients with acute right HF with a LVEF of 30% or lower, cardiac index of 2.5 l/min/m^2 or lower, right atrial pressure of 10 mm Hg or higher, and PCWP of 15 mm Hg or higher. Levosimendan improved RV contractility with no impact on afterload.[44] Yilmaz et al[45] compared levosimendan with dobutamine in 40 patients with acute decompensated HF and moderate to severe RV dysfunction. Both groups showed an improvement in RV systolic function and a reduction in systolic pulmonary artery pressure. However, improvement in tricuspid annular plane systolic excursion as well as 24-hour urine output with creatinine levels was significantly higher in the levosimendan group.

Considering the beneficial effect on pulmonary circulation, such as improved RV systolic function, reduced pulmonary artery pressure, and improved clinical status, levosimendan should be considered as a valuable therapeutic option in patients with right HF.

Levosimendan in pulmonary hypertension

According to the World Health Organization (WHO) functional classification, pulmonary hypertension (PH) is divided into 5 major groups depending on etiology. The pulmonary vasodilatory effect of levosimendan, mediated mainly by the opening of K_{ATP} channels in vascular smooth muscle cells, leads to reduced pulmonary resistance, while the simultaneous improvement of RV systolic function restores normal ventricular–vascular coupling. Randomized trials in patients with left HF confirmed the beneficial hemodynamic effect of levosimendan vs placebo on pulmonary circulation and RV function, with a reduction in PCWP, MPAP, peripheral vascular resistance (PVR) (P <0.001), mean right atrial pressure, and improved RV contractility. The effect was maintained at 6 hours after the initiation of treatment, while no tolerance of the above effects was observed during 48 hours.[42,46,47]

Also experimental research showed that levosimendan improved RV function and reduced PVR and RV afterload by causing vasodilation in the pulmonary vascular bed and improving ventricular–vascular coupling.[48-53] Interestingly, no reduction in PVR was observed in animals with normal pulmonary artery pressure.[54] In a study on the rat model of monocrotaline-induced pulmonary artery hypertension (PAH), levosimendan inhibited pulmonary vascular remodeling by reducing the proliferation of pulmonary arterial smooth muscle cells and RV hypertrophy.[55]

In a randomized placebo-controlled trial, 28 patients with PH of various etiologies (8 patients with PAH, 17 patients with PH associated with left HF, and 3 patients with chronic thromboembolic PH) were randomized in a 2:1 ratio to receive either levosimendan or placebo. Response to levosimendan infusion administered at 2-week intervals was assessed. The first infusion was initiated with a loading dose of 12 µg/kg infused over 10 minutes. The administration was then repeated 4 times as a continuous infusion for 6 hours every 2 weeks. Levosimendan significantly reduced PVR and MPAP, and the effect was maintained during the 2-month follow-up.[56] In a prospective open-label study including 45 hospitalized patients with idiopathic PAH and acute right HF, levosimendan was administered by a continuous infusion of 0.05 µg/kg/min to 0.1 µg/kg/min until the total dose of 12.5 mg was obtained. Levosimendan treatment led to a significant improvement in primary (WHO functional class, Borg dyspnea scores) and secondary endpoints (NT-proBNP levels, 6-minute walk test results). Moreover, echocardiography showed improved RV function after levosimendan infusion, and the drug was well tolerated.[57]

The use of levosimendan may be justified in selected cases of PAH with right HF, especially in patients requiring inotropic drugs, after a careful risk-to-benefit analysis. Caution is needed in patients with PAH and negative bronchodilator response.

Levosimendan in cardiac surgery Patients undergoing cardiac surgery are at higher risk of postoperative complications mostly due to low cardiac output syndrome. Cardiac surgery is associated with induced ischemia and reperfusion, which results in various degrees of myocardial injury in addition to primary heart disease. In its mild form, the injury manifests primarily as myocardial stunning, which requires a temporary use of positive inotropic drugs. The most common cardioprotective strategy is cardioplegia. However, although sufficient in most clinical scenarios, this strategy does not provide full protection.

Levosimendan has a different mechanism of action from other inotropic drugs, thus constituting an interesting additional option for cardiac surgeons. In an experimental study on isolated guinea-pig hearts, levosimendan showed positive inotropic and lusitropic effects, with a simultaneous increase in coronary flow and a minimal increase in oxygen consumption, as compared with milrinone.[58] Levosimendan-perfused hearts showed a significant reduction in the ratio of oxygen consumption to contractility (VO_2/+dP/dt). This effect was in contrast to that of milrinone, which increased coronary flow but was also associated with a higher oxygen consumption, resulting in significantly higher VO_2/+dP/dt ratio.[58]

In a Langerdorff-perfused rabbit heart model of ischemia and reperfusion, levosimendan pretreatment reduced the myocardial infarct size to a similar extent as ischemic preconditioning.[59] The best results were observed for levosimendan pretreatment. These cardioprotective effects were associated with the activation of the RISK pathway.[60] A similar effect was reported for myocytes in a human model of isolated right atrial trabeculae.[61]

Meta-analyses indicate a reduction in perioperative mortality rates in patients receiving levosimendan (odds ratio, approximately 0.65).[62-64] However, available studies supporting the use of levosimendan are scarce and were published before 2015, while recent larger randomized clinical trials provided negative results (CHEETAH [Levosimendan in High Risk Patients Undergoing Cardiac Surgery],[65] LEVO-CTS [Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery on Cardiopulmonary Bypass],[66] and LICORN (Preoperative Levosimendan in CABG Patients With Poor LV Function))[67]. This discrepancy may be caused by the fact that older studies used larger levosimendan doses, usually with an initial bolus dose, which was not used in subsequent studies to avoid hypotension.[63] Second, it seems

that in order to derive potential benefits from the prophylactic use of levosimendan in terms of cardioprotective rather than inotropic effects, the drug would have to be administered prior to the procedure (at least 4 hours before).[68] Finally, the prophylactic use of levosimendan seems to be beneficial in terms of reducing mortality in patients with reduced LVEF.[64,68]

In a study by Levin et al,[69] 250 patients with an ejection fraction lower than 25% (mean, 18%) undergoing coronary artery bypass grafting with cardiopulmonary bypass were randomly assigned to receive pretreatment with levosimendan or placebo. Levosimendan was administered 24 hours before the procedure as a bolus dose of 10 µg/kg for 60 minutes followed by a 23-hour continuous infusion of 0.1 µg/kg/min. Levosimendan outperformed placebo not only in terms of improving hemodynamic parameters but also reducing mortality rates and the incidence of low cardiac output syndrome, systemic inflammatory response syndrome, or atrial fibrillation.

Numerous data indicate that levosimendan pretreatment may improve the outcome of patients with significant LV dysfunction. In current clinical practice, levosimendan is used in patients with a LVEF of less than 25% and in those at risk of complications during the insertion of an intra-aortic balloon pump. To achieve cardioprotective effect, levosimendan infusion should be administered at least 4 hours before the procedure.

Levosimendan in intensive cardiac care Low cardiac output syndrome is a significant challenge in postoperative care. To avoid the unfavorable sequelae, measures to prevent HF in the early postoperative period should be applied. Levosimendan may provide a useful therapeutic option in this setting, although this has not been confirmed by large multicenter trials, such as CHEETAH,[65] LICORN,[70] and LEVO-CTS.[66] The use of levosimendan in cardiac surgery was discussed by a group of experts in intensive cardiac care from 8 European countries during the annual meeting of the European Association of Cardiothoracic Anaesthesiologists in 2017.[71] The council concluded that levosimendan is safe and effective in patients undergoing cardiac surgery and requiring inotropic support by catecholamines.

A well-known indication for levosimendan use is VA-ECMO. It has been postulated that the drug should be administered at initiation and termination of extracorporeal support.

Based on our own observations, it seems that the most important effect of perioperative levosimendan administration is protection against multiple organ damage by improving perfusion (inotropic and vasodilating action), which prevents not only organ dysfunction but also low cardiac output syndrome and, as a result, circulatory centralization. However, this clinical outcome may be achieved only in patients with normal blood volume.

Practical guidelines for the use of levosimendan in patients undergoing cardiac surgery are listed below:

1 Levosimendan should be administered according to the manufacturer's instructions.

2 Infusion lasting more than 24 hours should be terminated before the procedure. During the infusion, continuous electrocardiographic and blood pressure monitoring is required (invasive blood pressure monitoring is recommended). Infusion during the induction of anesthesia may lead to hypotension and necessitate the use of catecholamines already before the start of extracorporeal circulatory support.

3 The dosage of levosimendan infusion should be adjusted to blood pressure but should not be lower than 0.1 µg/kg/min. The patient should have normal blood volume.

4 Hemodynamic parameters should be monitored in the peri- and postoperative period, using the Swan-Ganz catheter, mixed venous blood saturation, and lactate concentrations. The therapy should be optimized according to the hemodynamic status.

5 Levosimendan is not the last-line drug. It does not increase the chances of a positive hemodynamic effect when other therapies have failed.

6 Levosimendan provides cardioprotection in the setting of temporary myocardial ischemia, hypoxia, and cardioplegia. If surgical repair does not improve cardiac hemodynamics, the effect of levosimendan wanes after 7 days and the patient develops low cardiac output syndrome.

Levosimendan and kidney function The most common kidney problem in AHF is prerenal kidney failure due to reduced cardiac output and renal blood flow. Levosimendan is contraindicated (is not recommended) in patients with low blood pressure (<90/<60 mm Hg), while dosing requires blood pressure monitoring. The drug is also contraindicated at a glomerular filtration rate (GFR) of less than 30 ml/min. It is not eliminated by dialysis, and its main active metabolite requires prolonged dialysis sessions due to a low GFR.

However, levosimendan seems to exert beneficial effects in postischemic renal failure, as the opening of K_{ATP} channels may protect against myocardial ischemia–reperfusion injury as well as reduce oxidative stress, inflammatory response, and apoptosis.[72] Levosimendan was shown to induce vasodilation of preglomerular resistance vessels (similarly to renal vasodilation effect of atrial natriuretic peptide), resulting in decreased renal vascular resistance by 18%. This, in turn, led to a significant increase in renal blood flow (by 12%) and GFR (by 21%).[73]

Importantly, an improvement in GFR was not associated with increased renal oxygen consumption, which was also confirmed in patients with HF and renal impairment,[74] including in the DAD-HF (Dopamine in Acute Decompensated Heart Failure) [75] and ROSE studies.[76] This observation may indicate that levosimendan is associated with a lower risk of cardiorenal syndrome in comparison with dobutamine.[77] Of note, levosimendan improves RV function and lowers right atrial pressure, which improves kidney function by reducing renal congestion. Another beneficial mechanism of action may consist in alleviating the angiotensin II-induced contraction of mesangial cells (eg, in sepsis), which improves the glomerular filtration area.

Clinical data on the effect of levosimendan on the kidneys are varied. Most studies indicate improved renal function in patients with AHF (eg, LIDO),[13] but this effect was not supported by the REVIVE study.[15] In patients with AHF with a history of cardiac surgery, the positive effect of levosimendan was particularly notable in individuals with renal dysfunction (eg, CHEETAH).[65] The most recent meta-analysis of 40 randomized trials including over 4000 patients showed a lower risk of mortality (by 44%), acute kidney failure, and need for renal replacement therapy. However, these findings were not confirmed when only 5 studies with highest quality data were included in the analysis.[78]

In hospitalized patients with AHF and renal dysfunction, which is the most interesting population for cardiologists, levosimendan significantly improved estimated GFR. Peak levels were noted at 3 days and the effect was sustained for 14 days.[79] In a prospective randomized trial on 40 patients with acute decompensated HF awaiting heart transplant, the group assigned to receive levosimendan showed improved kidney function parameters in comparison with controls.[80]

A meta-analysis of randomized clinical trials that evaluated levosimendan effects in different populations of critically ill patients, including those undergoing cardiac surgery, showed a 48% reduction in the risk of renal replacement therapy and a lower incidence of acute kidney injury.[81] Renal protective effects of levosimendan were reported, with safety and potential benefits indicated in the settings of cardiogenic or septic shock, cardiorenal syndrome, as well as weaning from extracorporeal membrane oxygenation or mechanical ventilation.[82]

Levosimendan and liver function Liver function abnormalities are a strong and unfavorable predictor of chronic and acute HF.[83-85] The mechanism underlying liver impairment in HF involves 2 processes. In AHF, lower cardiac output with resultant hypotension and hypoperfusion leads to organ ischemia followed by cytolysis of hepatocytes. In acute decompensated HF, hepatic sinusoidal congestion causes compression of the hepatic lobules, including bile ducts and channels, leading to hepatocyte hypertrophy and enhanced bile duct compression. Improved cardiac function, increased cardiac output, and reduced congestion prevent further liver cell damage and improve global liver function.[83]

Liver dysfunction alters the excretion and metabolism of numerous drugs. Levosimendan is excreted mainly be extrahepatic routes (54% in urine and 44% in stool).[2] Importantly, neither the drug itself nor its metabolites inhibit liver enzyme activity (CYP1A1, CYP2A2/A3/A4/A6, CYP2C9/C19, CYP2D6, CYP2E1, and CYP3A).[2] Therefore, the pharmacokinetics of levosimendan is similar in patients with mild or moderate liver dysfunction (Child–Pugh class B) and healthy individuals, except only a slightly longer elimination half-life in liver impairment.[86]

Studies have shown beneficial action of levosimendan on liver metabolism and function. These effects are associated with hemodynamic stability due to inotropic action of the drug in cardiac muscle cells as well as its vasodilatory action.

In experimental research, levosimendan significantly reduced liver cell apoptosis. This action is due to the opening of mitochondrial K_{ATP} channels, which counteracts the loss of mitochondrial membrane potential and reduces mitochondrial permeability transition pore opening, inhibits cytochrome C release, and exerts antiapoptotic and proapoptotic effects by preventing a reduction in Bcl-2 and an increase in Bax protein expression. On the other hand, levosimendan activates interleukin IL-10, which reduces the proinflammatory response (IL-1 and tumor necrosis factor-α levels) and increases Bcl-2 expression. Another potential beneficial effect is increased endogenous nitric oxide synthesis (which has a protective effect on liver cells) as well as improved liver perfusion.[87,88]

The positive effect of levosimendan was also shown in patients with cardiogenic or septic shock. In comparison with dobutamine, levosimendan improved hepatic blood flow through both hepatic artery (increased arterial perfusion and reduced hepatic artery resistance) and portal venous system (increased portal vein flow and reduced portal hypertension).[89,90]

Levosimendan in untypical forms of acute heart failure: Takotsubo syndrome, peripartum cardiomyopathy, and β-blocker or calcium channel blocker toxicity Adrenergic agonists, such as catecholamines or phosphodiesterase inhibitors, are generally contraindicated in cardiogenic shock complicating Takotsubo syndrome.[91] Therefore, apart from temporary mechanical circulatory support, successful treatment options include also levosimendan. Santoro et al[92] reported a case series of 13 patients

with Takotsubo syndrome, with significant LV systolic dysfunction and low LVEF (<35%), who were treated on admission with 24-hour intravenous infusion of levosimendan without a loading dose. The treatment was well tolerated, and all patients showed improvement in clinical condition and LVEF (mean [SD], 51% [8%], P <0.001). The authors concluded that the use of levosimendan in acute Takotsubo cardiomyopathy may be beneficial and safe. Experts from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology listed levosimendan as a potential drug to use in Takotsubo syndrome complicated by cardiogenic shock, particularly in the absence of temporary mechanical support options.[91]

Studies on the use of levosimendan in peripartum cardiomyopathy complicated by AHF provide inconsistent results. Single case reports showed a beneficial effect of levosimendan treatment.[93,94] In a small prospective nonblinded randomized clinical trial including 24 patients with HF complicating peripartum cardiomyopathy, 12 patients were assigned to receive levosimendan in addition to conventional therapy.[95] However, levosimendan did not improve prognosis or LV function in the 20-month follow-up. Currently, levosimendan use in AHF complicating peripartum cardiomyopathy should be based on the individual assessment of the patient's clinical and hemodynamic status.

Levosimendan may be considered in the treatment of cardiogenic shock in cardiovascular depression due to β-blocker or calcium channel blocker toxicity, if the standard treatment with intravenous insulin and glucose infusion, or calcium in the case of calcium channel blocker and catecholamines or phosphodiesterase inhibitors, is ineffective.

Complications and adverse effects of levosimendan treatment The most common adverse effects associated with levosimendan use and its mechanism of action are hypotension and tachycardia, episodes of supraventricular (atrial fibrillation) and ventricular arrhythmia (torsade de pointes), as well as headache and hypokalemia. Adverse effects are summarized in TABLE 3.

To ensure safety during levosimendan treatment, monitoring of blood pressure, heart rate, body mass, as well as sodium, potassium, and creatinine levels during infusion is necessary. Systolic blood pressure ranging from 85 mm Hg to 100 mm Hg does not preclude repeated infusions provided that hypovolemia is excluded or corrected. In the case of significant hypotension, it may be necessary to temporarily reduce the dosage and/or add a vasopressor (eg, norepinephrine). To avoid a sudden drop in blood pressure and kidney function worsening, the morning dose of a diuretic may be missed or reduced before the start of levosimendan treatment.[96]

Levosimendan infusion should not be used in the following scenarios:[97]

1. hypotension (systolic blood pressure <90 mm Hg or <80 mm Hg in the case of repeated infusion or tachycardia);
2. acute kidney or liver injury;
3. significant stenosis that impairs LV filling or emptying;
4. history of torsade de pointes.

A bolus loading dose before the infusion should not be used. Infusion should start at a dose of 0.1 μg/kg/min, and the dose may be uptitrated after 1 to 2 hours or reduced in the case of poor tolerance (hypotension).

In conclusion, levosimendan is safe and well tolerated provided that clinicians follow the recommendations on patient monitoring and dose adjustments according to the clinical status.

TABLE 3 Side effects of levosimendan observed in major studies in acute HF vs placebo (LIDO, RUSSLAN, SURVIVE, REVIVE)

Side effect	Levosimendan, %	Control, %	P value
Hypotension	23.1	23.1	–
Supraventricular arrhythmias	8.2	5.4	0.024
VT	10	11.3	0.371
HF deterioration	15.6	28.4	0.001
Renal impairment	6.9	10.4	0.007
Heart ischemia	7.3	8.9	0.233
Decreased potassium levels	4.9	7	0.059
Hb reduction	2.3	3.8	0.058

Abbreviations: Hb, hemoglobin; HF, heart failure; VT, ventricular tachycardia

SUPPLEMENTARY MATERIAL

The Polish version as well as the extended Polish version of the paper are available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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