Review paper

Levosimendan: a general overview

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Abstract

Heart failure remains a major clinical and public health problem worldwide, associated with high morbidity and mortality, and frequent hospitalizations. Despite advances in pharmacological and device-based therapies, management of acute and advanced heart failure remains challenging, particularly in patients requiring inotropic support. Conventional catecholaminergic inotropes are associated with increased myocardial oxygen consumption, arrhythmias, and adverse prognosis. Levosimendan, a non-catecholaminergic inodilator, has emerged as an alternative therapeutic option. The aim of this review is to summarise current knowledge on levosimendan, with particular emphasis on its pharmacological properties, mechanisms of action, clinical applications, and safety profile. A better understanding of these mechanisms may help optimise the clinical use of levosimendan and identify patient populations most likely to benefit from this therapy.

Introduction

Heart failure remains one of the leading causes of morbidity, mortality, and healthcare expenditure worldwide. Despite significant progress in guideline-directed medical therapy, including neurohormonal blockade and device-based interventions, acute and advanced stages of heart failure continue to pose major therapeutic challenges. Patients presenting with acute decompensated heart failure or advanced chronic heart failure frequently require inotropic support due to low cardiac output and impaired end-organ perfusion. However, the use of conventional inotropic agents remains limited by safety concerns and unfavourable effects on prognosis.

Traditional inotropes, such as catecholamines and phosphodiesterase type 3 inhibitors, increase myocardial contractility primarily by elevating intracellular calcium concentration or cyclic adenosine monophosphate levels. Although these agents can improve short-term haemodynamics, they are associated with increased myocardial oxygen consumption, a higher incidence of arrhythmias, and, in some studies, increased mortality. As a result, their use is generally restricted to short-term, rescue therapy in critically ill patients [1].

Levosimendan represents a novel, non-catecholaminergic inodilator with a unique mechanism of action that distinguishes it from conventional inotropes. By sensitising cardiac troponin C to calcium, levosimendan enhances myocardial contractility without increasing intracellular calcium concentration or myocardial oxygen demand. In addition, it induces vasodilation through activation of adenosine triphosphate–dependent potassium channels in vascular smooth muscle and exerts cardioprotective effects mediated by mitochondrial pathways [1, 2].

Owing to these pharmacological properties, levosimendan has attracted sustained clinical interest over the past 2 decades. It has been investigated across a broad spectrum of clinical scenarios, including acute decompensated heart failure, cardiogenic shock, acute coronary syndromes complicated by heart failure, and advanced heart failure requiring repetitive or intermittent therapy. Furthermore, emerging data suggest potential benefits in selected non-traditional settings, such as Takotsubo syndrome and pulmonary hypertension associated with heart failure. These features continue to position levosimendan as a distinctive therapeutic option in contemporary heart failure management [2].

Objective

The aim of this review is to summarise current knowledge on levosimendan, with particular emphasis on its pharmacological properties, mechanisms of action, clinical applications, and safety profile.

Review methods

This article is a narrative review of the available literature on levosimendan. A comprehensive search of the PubMed and Google Scholar databases was performed to identify relevant publications published between 2000 and 2025. The search strategy included combinations of the terms "levosimendan", "heart failure", "acute heart failure", "inotropic agents", and "inodilators".

The review included original clinical studies, randomised controlled trials, systematic reviews, and meta-analyses, as well as expert consensus statements and position papers issued by international and national cardiology societies, including the European Society of Cardiology and the Polish Cardiac Society. Articles published in English were primarily considered, with selected high-quality publications in other languages included when relevant. Case reports and studies with limited clinical applicability were excluded.

Emphasis was placed on studies addressing the clinical efficacy, haemodynamic effects, safety, and practical use of levosimendan in acute and advanced heart failure, as well as in selected special clinical situations.

Description of the state of knowledge

Pharmacology and mechanism of action of levosimendan

Levosimendan is a non-catecholaminergic inodilator with a unique and multifactorial mechanism of action that distinguishes it from conventional inotropic agents. Its primary pharmacological effect is based on calcium sensitisation of the contractile apparatus rather than an increase in intracellular calcium concentration. Levosimendan selectively binds to cardiac troponin C in a calcium-dependent manner, stabilising the calcium-bound conformation of the protein. This interaction enhances the sensitivity of myofilaments to calcium during systole, resulting in increased myocardial contractility without impairing diastolic relaxation. Importantly, this mechanism does not lead to an increase in intracellular calcium concentration or cyclic adenosine monophosphate levels, thereby avoiding excessive myocardial energy consumption and calcium overload [1, 2]. A key advantage of levosimendan is the absence of a significant increase in myocardial oxygen demand. In contrast to catecholamines and phosphodiesterase type 3 inhibitors, levosimendan improves cardiac performance without exacerbating ischaemia, which is particularly relevant in patients with coronary artery disease or acute coronary syndromes complicated by heart failure [1]. In addition to its inotropic properties, levosimendan exerts vasodilatory effects through activation of adenosine triphosphate-dependent potassium (K_ATP) channels in vascular smooth muscle cells. Opening of these channels leads to hyperpolarisation of the cell membrane and relaxation of vascular smooth muscle, resulting in a reduction of both preload and afterload. Furthermore, levosimendan activates mitochondrial K_ATP channels, which are believed to mediate cardioprotective effects, including ischaemic preconditioning, anti-stunning effects, and protection against apoptosis [2, 3] (Figures 1, 2).

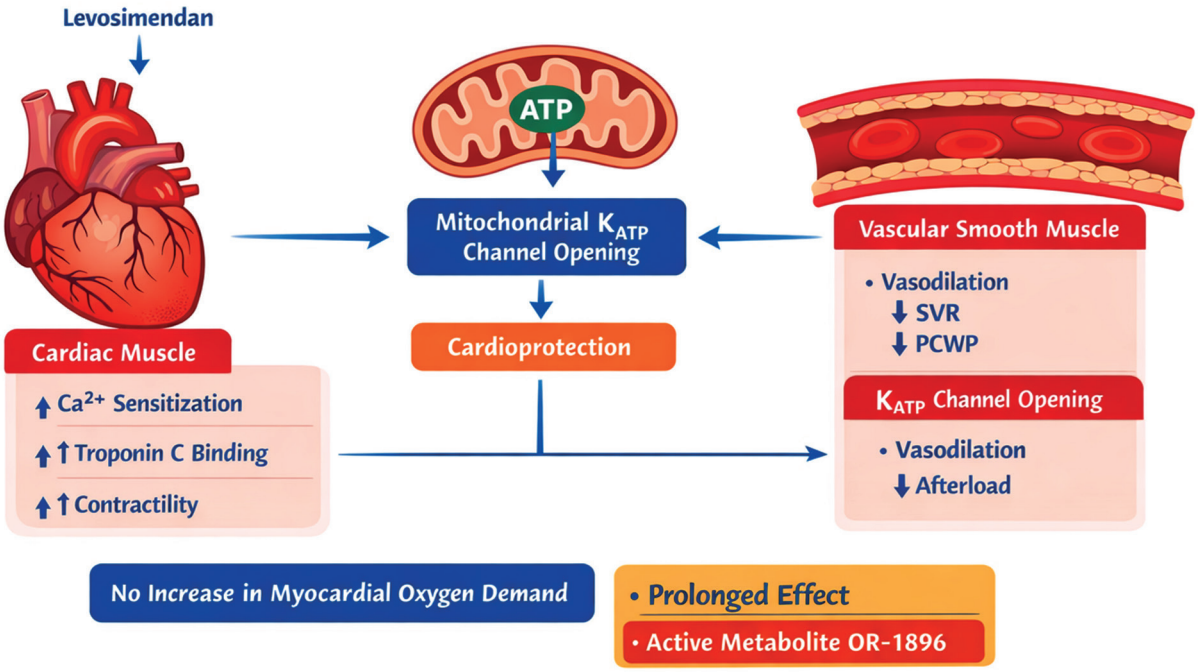

Figure 1. Mechanism of action of Levosimendan

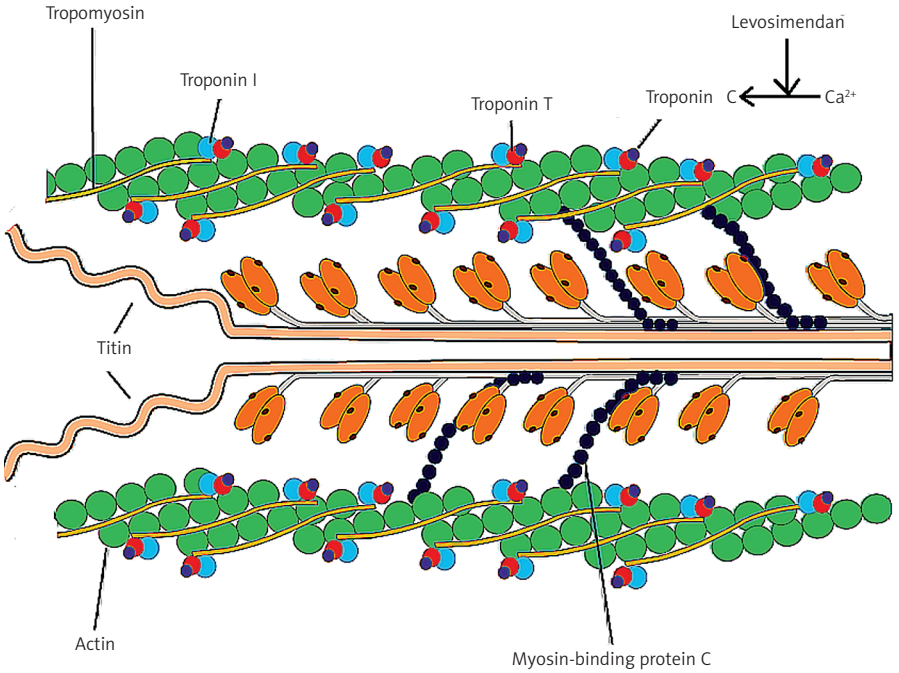

Figure 2. Site of action of Levosimendan in cardiac muscle fibers

Another distinctive pharmacological feature of levosimendan is the formation of an active metabolite, OR-1896. This metabolite has a long elimination half-life and retains the pharmacodynamic properties of the parent compound. As a result, the haemodynamic and clinical effects of levosimendan persist for several days after the termination of a 24-hour infusion, providing sustained therapeutic benefits without continuous drug administration [1, 2].

Haemodynamic and neurohormonal effects

The unique mechanism of action of levosimendan translates into a characteristic haemodynamic profile. Clinical studies consistently demonstrate an increase in cardiac output and stroke volume, accompanied by a reduction in pulmonary capillary wedge pressure and systemic vascular resistance. These effects result from the combined inotropic and vasodilatory actions of the drug, leading to improved ventricular performance and decreased ventricular filling pressures [1, 2]. Levosimendan has also been shown to reduce neurohormonal activation, as reflected by significant decreases in circulating levels of B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide. These reductions correlate with improvements in haemodynamic status, and clinical symptoms and may persist beyond the infusion period due to the prolonged activity of the OR-1896 metabolite [2, 4]. Importantly, levosimendan does not induce pharmacological tolerance. Unlike catecholaminergic inotropes, its haemodynamic effects remain stable during prolonged or repeated administration, which makes it particularly suitable for intermittent or repetitive treatment strategies in patients with advanced heart failure [1].

Clinical applications

Acute heart failure

Levosimendan has been extensively studied in patients with acute decompensated heart failure, particularly those presenting with low cardiac output and signs of hypoperfusion, commonly referred to as the “wet and cold” phenotype. In this clinical setting, levosimendan improves haemodynamics and relieves symptoms without increasing myocardial oxygen demand [3, 4]. An important advantage of levosimendan is its efficacy in patients treated with β-blockers. Because its mechanism of action is independent of β-adrenergic receptor stimulation, levosimendan maintains its inotropic effect in patients receiving chronic β-blocker therapy, unlike catecholamines whose efficacy may be attenuated in this population [3].

Acute coronary syndromes and cardiogenic shock

Levosimendan has been investigated in acute coronary syndromes complicated by acute heart failure, where minimising myocardial oxygen consumption is of paramount importance. By improving cardiac performance without exacerbating ischaemia, levosimendan represents a rational therapeutic option in this high-risk population [5]. In cardiogenic shock, le-

vosimendan is typically administered in combination with vasopressors – most commonly norepinephrine – to maintain adequate arterial pressure while improving cardiac output. This combined approach allows for haemodynamic stabilisation while avoiding excessive vasoconstriction or tachyarrhythmias associated with high-dose catecholamines [5, 7].

Advanced and recurrent heart failure

In patients with advanced heart failure, levosimendan has been evaluated as part of intermittent or repetitive treatment strategies. Cyclic administration aims to stabilise haemodynamics, reduce symptoms, and prevent recurrent hospitalisations. The LEIA-HF study was designed to assess the efficacy and safety of repetitive levosimendan infusions in ambulatory patients with advanced heart failure [8]. Real-life observational data further support the use of levosimendan in this setting, demonstrating symptomatic improvement and acceptable safety profiles even in severely ill patients. These findings suggest a potential role for levosimendan as a bridge to advanced therapies, such as mechanical circulatory support or heart transplantation [9].

Levosimendan in patients undergoing CABG

Several randomised clinical trials have evaluated the efficacy of levosimendan in patients undergoing cardiac surgery, including coronary artery bypass grafting (CABG). The multicentre LEVO-CTS trial included 848 patients with reduced left ventricular ejection fraction undergoing cardiac surgery with cardiopulmonary bypass [10]. In the overall population, levosimendan did not demonstrate superiority over placebo regarding the composite primary endpoint of 30-day mortality, renal replacement therapy, myocardial infarction, or use of mechanical circulatory support. However, a prespecified subgroup analysis of 563 patients undergoing isolated CABG showed significant benefits. Ninety-day mortality was significantly lower in the levosimendan group compared with placebo (2.1% vs. 7.9%; HR = 0.26; 95% CI: 0.11–0.64), and the incidence of low cardiac output syndrome (LCOS) was also reduced (12.0% vs. 22.1%; OR = 0.48; 95% CI: 0.30–0.76) [11]. These benefits were not observed in patients undergoing valve surgery or combined procedures.

In contrast, the French LICORN trial, which included 336 patients with left ventricular ejection fraction ≤ 40% undergoing CABG, did not demonstrate a significant difference between levosimendan and placebo with respect to a composite endpoint of prolonged catecholamine infusion, use of mechanical circulatory support, or renal replacement therapy (52% vs. 61%; $p = 0.15$), nor in mortality during 180-day follow-up [12]. Similarly, the CHEETAH trial, evaluating levosimendan administered after the onset of postoperative cardiac dysfunction in 506 patients requiring haemodynamic support, found no reduction in 30-day mortality (12.9% vs. 12.8%; $p = 0.97$) or differences in duration of mechanical ventilation or length of hospital stay [13].

Overall, the available randomised evidence suggests that levosimendan does not provide consistent benefits in the entire population of cardiac surgery patients. However, subgroup findings indicate that selected high-risk patients – particularly those undergoing isolated CABG with impaired left ventricular function – may derive clinical benefit. Current evidence therefore does not support routine use of levosimendan in all CABG patients, and its administration should be individualised based on the patient's risk profile and degree of ventricular dysfunction.

Special clinical situations

Levosimendan has also been investigated in several specific clinical scenarios. In Takotsubo syndrome, where excessive catecholamine exposure plays a central pathogenic role, levosimendan offers a non-catecholaminergic alternative for inotropic support and has been associated with faster recovery of left ventricular function [14]. In patients with pulmonary hypertension associated with heart failure with preserved ejection fraction, levosimendan has been shown to improve haemodynamics and exercise tolerance, potentially through preferential venodilation and reduction of filling pressures [15]. Additionally, levosimendan may be beneficial in right ventricular failure due to its combined inotropic and pulmonary vasodilatory effects (Table 1).

Safety and adverse effects

Levosimendan is generally well tolerated when administered according to recommended protocols. The most frequently reported adverse effect is hypotension, which is primarily related to its vasodilatory properties and is more likely to occur in patients with low baseline blood pressure or hypovolaemia. Avoidance of a loading bolus and careful dose titration reduce the risk of significant hypotension [3, 9, 16]. Supraventricular arrhythmias, particularly atrial fibrillation, have been reported, but they occur at rates comparable to or lower than those observed with catecholaminergic inotropes. Levosimendan does not appear to increase the risk of malignant ventricular arrhythmias [6]. Electrolyte disturbances, including hypokalaemia, may occur and require routine monitoring. Compared with dobutamine, levosimendan demonstrates a more favourable safety profile, with less tachycardia and a lower risk of myocardial ischaemia, which contributes to its growing acceptance in selected patient populations [3, 6] (Table 2).

Table 1. Main clinical indications for levosimendan

Clinical setting	Rationale for use
Acute decompensated heart failure ("wet and cold")	Improved CO without increased oxygen demand
β-blocker-treated patients	β-adrenergic-independent inotropic effect
Acute coronary syndromes with HF	Reduced risk of ischaemia
Cardiogenic shock	Inotropic support combined with vasopressors
Advanced and recurrent HF	Intermittent stabilisation and symptom relief
Takotsubo syndrome	Non-catecholaminergic inotropic support
PH-HFpEF and RV failure	Reduction of filling pressures and RV support

Table 2. Safety profile of levosimendan

Adverse effect	Frequency	Clinical considerations
Hypotension	Common	Avoid bolus, ensure normovolaemia
Atrial fibrillation	Uncommon	ECG monitoring recommended
Ventricular arrhythmias	Rare	Lower risk than catecholamines
Hypokalaemia	Uncommon	Monitor electrolytes
Myocardial ischaemia	Rare	Lower incidence than dobutamine

Discussion

Despite more than 2 decades of clinical experience, the role of levosimendan in heart failure management continues to be a subject of debate, particularly due to the lack of consistent evidence demonstrating a clear reduction in long-term mortality. However, the absence of unequivocal survival benefit should not be interpreted as a lack of clinical efficacy. In heart failure, many widely accepted therapies primarily aim to improve haemodynamics, relieve symptoms, reduce hospitalisations, and stabilise patients during high-risk periods rather than directly influence mortality. In this context, levosimendan offers clinically meaningful benefits that extend beyond survival endpoints [2]. One of the key advantages of levosimendan is its favourable pathophysiological profile compared with conventional catecholaminergic inotropes. By enhancing myocardial contractility through calcium sensitisation rather than increasing intracellular calcium concentration, levosimendan avoids calcium overload, excessive myocardial oxygen consumption, and tachyarrhythmias. Additionally, its vasodilatory and cardioprotective effects mediated by K_ATP channel activation contribute to improved ventricular-arterial coupling and end-organ perfusion. These mechanisms provide a strong physiological rationale for the observed clinical benefits and distinguish levosimendan from catecholamines and phosphodiesterase inhibitors, which have been associated with adverse prognostic effects [2, 3]. The role of levosimendan must also be considered in the context of contemporary heart failure therapy. Modern guideline-directed treatment includes neurohormonal blockade, sodium–glucose cotransporter 2 inhibitors, and advanced device therapies, which have significantly improved long-term outcomes. Nevertheless, patients with acute decompensated or advanced heart failure continue to experience episodes of haemodynamic instability and low cardiac output, for which short-term inotropic support may be required. Consistent with the European Society of Cardiology heart failure guidelines, inotropic agents may be considered in patients with hypoperfusion and low cardiac output despite optimal therapy. Within this population, levosimendan represents a potentially valuable therapeutic option, particularly for patients on chronic β-blocker therapy, those with ischaemic heart disease, or individuals at elevated risk of arrhythmias [3, 17]. Notably, current recommendations from the American Heart Association and American College of Cardiology do not include levosimendan, largely because the drug has not been approved by the U.S. Food and Drug Administration. This regulatory difference partly explains the divergence between European and North American clinical practice [18]. Accumulating evidence from randomised trials, meta-analyses, and real-life observational studies suggests that levosimendan may reduce rehospitalisations, improve symptoms, and enhance functional capacity, even if its effect on long-term mortality remains neutral or inconsistent. Importantly, intermittent or repetitive administration strategies have emerged as a promising approach in advanced heart failure, aiming to maintain clinical stability and delay disease progression. These strategies reflect a shift from short-term rescue

Table 3. Summary of major meta-analyses on levosimendan indications

Study	Year	Population	Number of patients	Results
LEVOECMO [20]	2026	After weaning from ECMO in cardiogenic shock	Multicentre study	No difference in time to ECMO weaning; no difference in 30- and 60-day mortality
ADHF Meta-analysis [21]	2025	Acute decompensated heart failure	1973 (8 RCTs)	Levosimendan vs. dobutamine: reduction in 30-day mortality (OR = 0.53, 95% CI: 0.31–0.91); hospital stay shortened by 2.4 days
VA-ECMO Meta-analysis [22]	2025	Patients on VA-ECMO	2083 (16 studies)	Improved ECMO weaning (OR = 2.44, 95% CI: 1.72–3.48); reduced 30-day mortality (OR = 0.48, 95% CI: 0.29–0.81); prolonged ECMO support (WMD 2.86 days)
Sepsis meta-analysis [23]	2025	Septic shock with SICM	11 RCTs	Levosimendan vs. dobutamine: reduction in in-hospital mortality (OR = 0.64, 95% CI: 0.47–0.88)
CHEETAH Substudy [24]	2025	LCOS after cardiac surgery	134	No difference in long-term mortality (HR = 1.59, 95% CI: 0.81–3.11); no effect on AKI or ICU stay
Advanced HF Meta-analysis [25]	2024	Advanced heart failure	5137 (41 studies)	Levosimendan superior to milrinone/dobutamine in reducing mortality and improving LVEF; more frequent hypotension

therapy toward proactive haemodynamic support in selected patient populations [2]. Several limitations of the available evidence should be acknowledged. Clinical studies of levosimendan are heterogeneous with respect to patient populations, dosing regimens, use of loading doses, and comparator therapies. Many trials were not powered to assess mortality as a primary endpoint, and differences in study design may partly explain the variability of results [19]. Furthermore, some data derive from observational studies or post hoc analyses, which are inherently subject to bias. These limitations underscore the need for well-designed prospective studies focusing on clearly defined patient subsets and clinically relevant endpoints [6] (Table 3) [20–25].

Conclusions

Levosimendan is an effective non-catecholaminergic inodilator with a unique mechanism of action that combines calcium sensitisation, vasodilation, and cardioprotective effects. Its pharmacological profile distinguishes it from conventional inotropes and underlies its favourable haemodynamic and clinical effects. The drug represents a valuable therapeutic option in selected high-risk patients with acute and advanced heart failure, particularly in those with ischaemic heart disease, ongoing β-blocker therapy, or intolerance to catecholaminergic agents. Although consistent mortality reduction has not been demonstrated, levosimendan provides important clinical benefits, including symptom relief, haemodynamic stabilisation, and potential reduction in hospitalisations. Further prospective, adequately powered studies are warranted to better define the optimal timing, dosing strategies, and long-term role of levosimendan in contemporary heart failure management, including its use in repetitive or preventive treatment regimens.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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