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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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LEVOSIMENDAN AS BRIDGING THERAPY IN ADVANCED HEART FAILURE: CURRENT STATE OF KNOWLEDGE AND CLINICAL PERSPECTIVES

Marcin Schulz *(Corresponding Author, Email: mail.schulz.od44@gmail.com)*
II Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland
ORCID ID: 0009-0006-4466-5794

Michał Kulczak
School of Medicine, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0006-4968-3318

Dawid Studziński
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0005-3834-716X

Anna Kołcz
School of Medicine, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0006-1446-2865

Agnieszka Morawa
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0001-2325-7998

Karolina Osińska
Municipal Hospital in Kędzierzyn-Koźle, Kędzierzyn-Koźle, Poland
ORCID ID: 0009-0003-9731-0629

ABSTRACT

Advanced heart failure (AHF) constitutes a terminal expression of cardiovascular disease, associated with severe, refractory symptoms and high mortality despite optimized medical therapy. Levosimendan, a first-in-class inodilator, addresses this challenge, acting as a calcium sensitizer and potassium channel opener. Its unique tripartite mechanism provides positive inotropy independently of the cAMP pathway, critically avoiding increased intracellular calcium or myocardial oxygen demand. The active metabolite, OR-1896, ensures prolonged hemodynamic benefits lasting up to two weeks, supporting intermittent, outpatient bridging strategies. This systematic literature review synthesized current evidence by applying a rigorous search strategy across biomedical databases, resulting in the inclusion of 32 scientific publications encompassing high-level evidence such as meta-analyses, randomized controlled trials (RCTs), and cohort studies. Pooled analyses suggest that repetitive levosimendan administration significantly improves Left Ventricular Ejection Fraction (LVEF), reduces NT-proBNP levels, and is associated with a reduced risk of all-cause mortality (RR 0.60). Furthermore, it confers vital organoprotective effects, notably improving renal function in patients awaiting heart transplantation (HTx), and its preoperative use as a "bridge to transplant" (BTT) is deemed safe. Despite compelling data from small RCTs (e.g., LION-HEART), the field requires larger, definitive studies—such as the ongoing LEIA-HF trial—to establish the precise role of levosimendan in contemporary AHF management.

KEYWORDS

Levosimendan, Advanced Heart Failure, Bridging Therapy, Calcium Sensitizer, Inodilator

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1. Introduction

Advanced heart failure (AHF) represents the terminal stage of diverse cardiovascular diseases [Abbate et al., 2018] and constitutes a major global health challenge [García-González et al., 2021]. It corresponds to ACC/AHA Stage D [Cui et al., 2020, Książczyk et al., 2023] and advanced HFA-ESC categories [Codina et al., 2023, Książczyk et al., 2023, Altenberger et al., 2018]. Patients typically exhibit severe, refractory symptoms (NYHA IIIb–IV) [Silvetti et al., 2024, Książczyk et al., 2023, Altenberger et al., 2018], marked functional limitation [Silvetti et al., 2024, Altenberger et al., 2018], and end-organ dysfunction [Silvetti et al., 2024], despite optimized guideline-directed medical therapy (OMT) [García-González et al., 2021, Altenberger et al., 2018, Silvetti et al., 2024]. Although representing only 1–10% of the overall HF population [Cui et al., 2020, Książczyk et al., 2023, Lelonek et al., 2020, Guzman-Bofarull et al., 2025], these patients experience profound reductions in quality of life [García-González et al., 2021, Pölzl et al., 2017] and frequent hospitalizations [García-González et al., 2021, Silvetti et al., 2024, Książczyk et al., 2023, Pölzl et al., 2017], with particularly high readmission and mortality rates in the early "vulnerable phase" after discharge [Pölzl et al., 2023, Papp et al., 2020].

Despite substantial therapeutic advances, many patients progress to AHF [Lelonek et al., 2020, Bouchez et al., 2018] and become unable to tolerate maximally titrated therapies [Bouchez et al., 2018], highlighting the limitations of conventional pharmacological management [Lelonek et al., 2020, Altenberger et al., 2018]. Classical intravenous inotropes (e.g., dobutamine, milrinone) provide symptomatic relief [Abbate et al., 2018, Lelonek et al., 2020] but increase intracellular Ca^{2+} and myocardial oxygen consumption [Altenberger et al., 2018, Ráduly et al., 2023, Sumanaru et al., 2019], contributing to arrhythmias and higher long-term mortality [Abbate et al., 2018, von Scheidt et al., 2016, Reis et al., 2023]. Accordingly, guidelines limit their use to short-term stabilization in hypotension, hypoperfusion, or as temporary support before definitive therapies [Bouchez et al., 2018, Lelonek et al., 2020].

Advanced therapeutic options—mechanical circulatory support (e.g., LVAD) [Cui et al., 2020, García-González et al., 2021] and heart transplantation [Cui et al., 2020]—remain the most effective interventions [García-González et al., 2021, Cui et al., 2020], but their availability is frequently restricted by organ shortage, advanced age, and comorbidities [García-González et al., 2021]. Consequently, intravenous inotropes are integral to bridging strategies, including bridge to transplant (BTT), bridge to LVAD (BTLVAD) [Guzman-Bofarull et al., 2025, Milwidsky et al., 2022, Reis et al., 2023], and bridge to recovery (BTR) [Reis et al., 2023]. For non-eligible patients, intermittent inotropic therapy may serve as destination therapy for symptom relief and morbidity reduction [Reis et al., 2023, Dobarro et al., 2023, Codina et al., 2023].

Levosimendan, introduced in 2000 [Papp et al., 2020], has emerged as a potentially safer inodilator [Altenberger et al., 2018, Reis et al., 2023, Lelonek et al., 2020] due to its tripartite mechanism: Ca^{2+} sensitization of cardiac troponin C [Lelonek et al., 2020, Altenberger et al., 2018, Cui et al., 2020, Papp et al., 2020, Bouchez et al., 2018], KATP-mediated vasodilation [Lelonek et al., 2020, Papp et al., 2020, Bouchez et al., 2018, Altenberger et al., 2018], and mitochondrial protection [Papp et al., 2020, Lelonek et al., 2020, Altenberger et al., 2018, Bouchez et al., 2018]. Unlike conventional inotropes, it does not increase intracellular Ca^{2+} [Reis et al., 2023] or oxygen demand [Altenberger et al., 2018, Sumanaru et al., 2019, Pölzl et al., 2017, Bouchez et al., 2018], and remains effective in patients on beta-blockers [Altenberger et al., 2018]. Its prolonged haemodynamic effect derives from its active metabolite OR-1896, lasting up to approximately two weeks [Reis et al., 2023, Altenberger et al., 2018, Bouchez et al., 2018, Guzman-Bofarull et al., 2025].

This review aims to synthesise contemporary evidence and future perspectives on intermittent intravenous levosimendan as a targeted therapeutic modality and bridging strategy in AHF management [Pölzl et al., 2017, Abbate et al., 2018, Papp et al., 2020].

2. Methodology

This systematic literature review was undertaken with the primary objective of synthesizing the existing clinical evidence regarding the utility of levosimendan as a targeted therapeutic modality and bridging strategy in the management of patients with advanced heart failure (AHF). A rigorous, systematic search strategy was implemented across key biomedical literature databases to identify pertinent research publications.

Selection Criteria and Study Flow The initial search and screening process led to the identification of 52 publications for subsequent review. Each identified record was independently assessed against predefined criteria for relevance and methodological quality. Following this detailed process, 20 publications were ultimately excluded from the final scientific synthesis. The rationale for these exclusions was meticulously documented to ensure transparency and methodological integrity. Specifically, ten articles had to be rejected due to a lack of full-text access, rendering in-depth methodological evaluation and reliable data extraction impossible. A further three publications were excluded because they were categorized as review articles, which synthesize existing data rather than presenting primary clinical findings, and three were identified as letters to the editor, which generally lack original data. Additionally, two publications were deemed ineligible as they represented expert opinions. One paper was excluded because its focus was strictly limited to the ethical considerations of the drug's application, while another was excluded because it concentrated solely on the economic analysis of the treatment regimen.

Data Extraction and Included Study Designs The stringent application of the inclusion and exclusion criteria resulted in a final corpus of 32 scientific publications incorporated into the definitive review. These studies provided primary clinical evidence that directly addressed the objectives of this analysis. The included papers represented a wide methodological scope, encompassing high-level evidence such as meta-analyses, various forms of experimental studies, including rigorous randomized controlled trials (RCTs) and non-randomized designs, cohort studies, and case-control studies. This diverse inclusion strategy ensures a comprehensive synthesis of the evidence base related to levosimendan's effectiveness and safety profile across different clinical settings in AHF.

3. Pharmacological Basis for the Use of Levosimendan in Bridging Therapy

Mechanism of Action and Pharmacokinetics

Levosimendan is a first-in-class inodilator characterized by a distinctive three-pronged mechanism of action, which renders it an attractive option for bridging therapy in advanced heart failure (AdHF) [Bouchez et al., 2018, Altenberger et al., 2018]. Its pharmacological profile is defined predominantly by calcium sensitization and the activation of adenosine triphosphate (ATP)-dependent potassium (KATP) channels [Bouchez et al., 2018, Altenberger et al., 2018, Książczyk et al., 2023, Papp et al., 2020]. The principal pathway involves enhancement of the sensitivity of cardiac troponin C (cTnC) fibres to ionic calcium within cardiomyocytes, thereby generating a positive inotropic effect that is entirely independent of the cyclic adenosine monophosphate (cAMP) signalling cascade [Bouchez et al., 2018, Altenberger et al., 2018, Książczyk et al., 2023, Papp et al., 2020, Cui et al., 2020, Lelonek et al., 2020, Sumanaru et al., 2019, Teixeira et al., 2025]. Molecular modelling studies support this mechanism by demonstrating binding of levosimendan to calcium-saturated human cTnC [Papp et al., 2020].

Crucially, because levosimendan functions as a calcium sensitizer rather than a calcium mobilizer, it does not increase myocardial oxygen consumption, thereby avoiding the pro-ischemic burden associated with conventional inotropes [Cui et al., 2020, Sumanaru et al., 2019, Teixeira et al., 2025, Bouchez et al., 2018, Papp et al., 2020, Altenberger et al., 2018]. The remaining two components of its mechanism comprise opening of KATP channels on vascular smooth muscle cells, which induces systemic and pulmonary vasodilation [Bouchez et al., 2018, Altenberger et al., 2018, Książczyk et al., 2023, Papp et al., 2020, Cui et al., 2020, Lelonek et al., 2020, Teixeira et al., 2025], and activation of KATP channels in cardiac mitochondria, conferring cytoprotective effects against ischemia–reperfusion injury [Bouchez et al., 2018, Altenberger et al., 2018, Teixeira et al., 2025, Papp et al., 2020].

The pharmacological profile of levosimendan is additionally defined by distinctive pharmacokinetic properties that support its use in intermittent infusion protocols [Bouchez et al., 2018, Altenberger et al., 2018]. Although the parent compound is cleared relatively quickly, with an elimination half-life of approximately 1 hour [Sumanaru et al., 2019], its clinical effects are prolonged through the generation of two active metabolites, OR-1896 and OR-1855 [Papp et al., 2020, Teixeira et al., 2025, Sumanaru et al., 2019, Bouchez et al., 2018]. OR-1896 is produced in the intestine via a reduction–acetylation pathway [Papp et al., 2020] and retains the calcium-sensitising and vasodilatory properties of the parent drug [Papp et al., 2020]. Importantly, OR-1896

exhibits a much longer half-life, with peak plasma levels occurring approximately 2–3 days after the initial infusion [von Scheidt et al., 2016]. As a consequence, therapeutically relevant concentrations persist for several days, extending the haemodynamic benefits for roughly 1–2 weeks following discontinuation of intravenous levosimendan [Altenberger et al., 2018, Papp et al., 2020, Sumanaru et al., 2019, Silvetti et al., 2017, Bouchez et al., 2018, Guzman-Bofarull et al., 2025, Reis et al., 2023, Teixeira et al., 2025]. This prolonged duration of action provides a clear pharmacological rationale for the use of repeated or intermittent dosing regimens in bridge-to-therapy strategies [Altenberger et al., 2018, Silvetti et al., 2017, Bouchez et al., 2018].

Comparison with Classical Inotropes (Dobutamine, Milrinone)

The selection of an inotropic agent in advanced heart failure (AdHF) is pivotal, as conventional inotropes that act via adrenergic stimulation or phosphodiesterase (PDE) inhibition are generally linked to unfavourable long-term outcomes [Reis et al., 2023, Abbate et al., 2018, Najjar et al., 2018, von Scheidt et al., 2016]. Classical β-adrenergic agonists such as dobutamine, and PDE inhibitors such as milrinone, exert their positive inotropic effects by increasing intracellular cyclic adenosine monophosphate (cAMP) levels, thereby augmenting myocardial Ca^{2+} transient currents [Abbate et al., 2018, Papp et al., 2020, Ráduly et al., 2023]. Although this mechanism affords prompt symptomatic improvement and haemodynamic stabilisation, sustained administration has been associated with heightened risks of arrhythmogenesis and mortality [Abbate et al., 2018, Najjar et al., 2018, von Scheidt et al., 2016]. Indeed, meta-analyses of trials involving traditional inotropes, including dobutamine and PDE inhibitors, frequently indicate a detrimental impact on mid- to long-term prognosis [Papp et al., 2020]. This concern is exemplified by findings from the FIRST trial, where continuous intravenous dobutamine therapy was associated with increased mortality in patients with AdHF [Najjar et al., 2018, Guzman-Bofarull et al., 2025].

In marked contrast, the pharmacodynamic profile of levosimendan—based on calcium sensitisation without elevating intracellular calcium concentrations or myocardial oxygen consumption—supports its consideration as a comparatively safer inodilator [Sumanaru et al., 2019, Bouchez et al., 2018, Altenberger et al., 2018]. Unlike dobutamine, levosimendan retains its efficacy in patients receiving concurrent beta-blocker therapy, which is a cornerstone of optimal heart failure management [Książczyk et al., 2023, Altenberger et al., 2018, Bouchez et al., 2018, Lelonek et al., 2020]. Comparative clinical studies, including the LIDO and SURVIVE trials, have directly evaluated levosimendan against dobutamine in individuals with severe low-output HF [Najjar et al., 2018, Lelonek et al., 2020, Zheng et al., 2023, Książczyk et al., 2023, Lannemyr et al., 2018, Papp et al., 2020, Altenberger et al., 2018, von Scheidt et al., 2016]. While large randomized controlled trials have yielded mixed results regarding a definitive survival advantage over comparators [Bouchez et al., 2018], pooled analyses suggest that levosimendan may be the only inotrope associated with improved survival and a reduced risk of HF worsening [Altenberger et al., 2018, Papp et al., 2020]. Additionally, levosimendan has demonstrated superiority over dobutamine in improving selected physiological parameters, notably renal function [Lannemyr et al., 2018].

Effect on Organ Perfusion (Kidneys, Liver, Microcirculation)

Levosimendan, owing to its potent inodilatory properties, is particularly beneficial in low-output heart failure (HF) states complicated by organ hypoperfusion [Altenberger et al., 2018, Papp et al., 2020]. One of its most clinically relevant advantages, consistently observed in both clinical and preclinical investigations, is its favourable impact on renal function, suggesting a reno-protective profile [Bouchez et al., 2018, Altenberger et al., 2018]. This is especially important given that renal dysfunction is common in HF and is strongly associated with adverse outcomes [Bouchez et al., 2018].

The proposed reno-protective action of levosimendan appears to extend beyond simple improvement in systemic haemodynamics [Bouchez et al., 2018, Altenberger et al., 2018]. Physiological studies indicate that levosimendan exerts organ-specific effects, notably via selective vasodilation of the glomerular afferent arterioles [Bouchez et al., 2018, Lannemyr et al., 2018, Altenberger et al., 2018]. This targeted vasodilation leads to increased renal blood flow (RBF) and enhancement of glomerular filtration rate (GFR), in contrast to agents such as dopamine or dobutamine, which typically dilate both afferent and efferent arterioles [Bouchez et al., 2018]. In a randomized, double-blind controlled trial in HF patients with impaired renal function, GFR increased by 22% in the levosimendan group, whereas it remained unchanged in those treated with dobutamine [Lannemyr et al., 2018, Papp et al., 2020, Elsaeidy et al., 2024]. Furthermore, levosimendan has been shown to improve renal function in patients with advanced HF awaiting heart transplantation [Lannemyr et al., 2018, Zheng et al., 2023, Altenberger et al., 2018, Elsaeidy et al., 2024].

Beyond its renal effects, the vasodilatory action of levosimendan enhances global peripheral perfusion [Altenberger et al., 2018]. It has also been proposed as a valuable option for patients on the heart transplant

waiting list who present with marked hepatic or renal impairment [Zheng et al., 2023]. In experimental models, levosimendan has demonstrated protective effects against ischemia–reperfusion injury in both the kidney and liver [Papp et al., 2020, Bouchez et al., 2018, Altenberger et al., 2018]. This multi-organ perfusion benefit underpins its role as a stabilizing bridge therapy, potentially limiting end-organ damage that could otherwise preclude eligibility for advanced interventions such as heart transplantation or ventricular assist device (VAD) implantation [Reis et al., 2023].

Anti-apoptotic and Cytoprotective Action – Potential Effect on Cardiac Remodeling

The clinical utility of levosimendan extends beyond immediate haemodynamic stabilisation and encompasses a range of favourable pleiotropic effects, particularly anti-apoptotic and cytoprotective actions that may attenuate adverse cardiac remodelling [Cui et al., 2020, Bouchez et al., 2018, Comín-Colet et al., 2018].

A central element of its cytoprotective profile is the opening of KATP channels in cardiac mitochondria, which confers protection against ischemia–reperfusion injury and contributes to a reduction in infarct size [Bouchez et al., 2018, Altenberger et al., 2018, Papp et al., 2020, Teixeira et al., 2025]. This mitochondrial mechanism is a key feature differentiating levosimendan from conventional inotropes [Papp et al., 2020]. In preclinical models of hypertension-induced heart disease, levosimendan has been shown to limit myocardial apoptosis and unfavourable structural remodelling [Cui et al., 2020, Bouchez et al., 2018].

In clinical settings, repeated administration of levosimendan has been associated with improvements in left ventricular function and modulation of neurohormonal activation [García-González et al., 2021, Silvetti et al., 2016, Altenberger et al., 2018, von Scheidt et al., 2016]. Enhanced cardiac performance is consistently reflected by significant increases in left ventricular ejection fraction (LVEF) [Cui et al., 2020, Reis et al., 2023, Elsaeidy et al., 2024], and meta-analytic data from randomized controlled trials support a meaningful improvement in LVEF with levosimendan therapy [Cui et al., 2020]. In parallel, treatment with levosimendan has been shown to significantly reduce circulating N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations [Comín-Colet et al., 2018, Cui et al., 2020, Reis et al., 2023, Elsaeidy et al., 2024, Najjar et al., 2018, Visco et al., 2024, Teixeira et al., 2025]. Lower NT-proBNP levels indicate a reduction in wall stress and neurohormonal activation, suggesting partial reversal of pathophysiological processes that drive disease progression in advanced HF [Comín-Colet et al., 2018].

Moreover, when compared with dobutamine, levosimendan has been shown to attenuate oxidative damage and decrease circulating pro-inflammatory cytokines and soluble mediators of apoptosis in patients with decompensated AdHF [Pölzl et al., 2017]. Collectively, these findings imply that the anti-apoptotic and anti-inflammatory properties of levosimendan may help disrupt the vicious cycle of ongoing myocardial injury, thereby contributing to clinical stabilisation and functional recovery—an essential prerequisite when used as a bridge to advanced therapies. This global benefit is often conceptualised as a reduction in the "neurohormonal burden" characteristic of advanced HF [Comín-Colet et al., 2018].

In essence, levosimendan's influence on myocardial biology—enhancing contractile performance while simultaneously providing cytoprotection and limiting adverse remodelling—resembles a stabilising support that preserves function without imposing additional energetic strain or structural harm, rendering it particularly well suited for preparing the failing myocardium for subsequent advanced interventions.

4. Application of Levosimendan in Various "Bridge Therapy" Strategies

The pharmacological profile of levosimendan, and in particular the sustained effects mediated by its long-acting active metabolite OR-1896, makes it especially well suited for intermittent administration beyond the acute hospital setting and thus for a range of advanced heart failure (AdHF) "bridge therapy" applications [Silvetti et al., 2017, Codina et al., 2023, Reis et al., 2023]. Such strategies are typically employed in patients with severe, persistent symptoms (most often New York Heart Association [NYHA] class IIIb or IV) who require ongoing inotropic support to alleviate symptom burden and preserve end-organ perfusion [Silvetti et al., 2024, Książczyk et al., 2023, Abbate et al., 2018, Altenberger et al., 2018]. In this context, intermittent inotropic therapy (IIT) with agents such as levosimendan is widely used as a bridge to heart transplantation (HTx), a bridge to left ventricular assist device (LVAD) implantation, or as a bridge to recovery or decision (including destination therapy and palliative care approaches) [Codina et al., 2023, Milwidsky et al., 2022, Pölzl et al., 2017, Reis et al., 2023].

4.1. Bridge to Transplant (BTT)

For patients with AdHF, heart transplantation remains the definitive treatment standard [Zheng et al., 2023]. Given the scarcity of donor organs and extended waiting times, inotropic support is often necessary to stabilize the patient's hemodynamic status and functional parameters while awaiting transplantation [Zheng et al., 2023, Lelonek et al., 2020, Reis et al., 2023]. Intermittent levosimendan infusion is utilized as a BTT strategy [Milwidsky et al., 2022, Reis et al., 2023].

Review of Studies Assessing Pre-Transplant Use

Pre-transplant administration of levosimendan has been evaluated with particular attention to its impact on critical postoperative complications and end-organ function. In a retrospective analysis of heart transplant recipients, levosimendan was associated with improved renal function in patients with chronic advanced heart failure awaiting cardiac transplantation [Zheng et al., 2023, Altenberger et al., 2018]. This is clinically important, as concomitant hepatic and renal dysfunction is common in heart failure and is a well-recognised predictor of poor prognosis after transplantation. In another retrospective study of patients with severe hepatic and renal impairment listed for HTx, preoperative treatment with levosimendan yielded mortality rates comparable to those observed in patients receiving dobutamine or dopamine, suggesting that levosimendan may represent a valuable option in this particularly high-risk population [Zheng et al., 2023].

Impact on Hemodynamic Stabilization and Waiting Time

The principal function of levosimendan as a bridge to transplant (BTT) is to achieve haemodynamic stabilisation and symptomatic relief through its potent inodilatory properties [Abbate et al., 2018, Lelonek et al., 2020]. By improving circulatory status, levosimendan infusions can create a therapeutic window that enables safe transition to invasive interventions such as heart transplantation (HTx) [Lelonek et al., 2020]. In this context, the overarching aim of inotropic therapy with agents like levosimendan is to preserve end-organ perfusion and augment cardiac output until transplantation can be performed [Abbate et al., 2018]. Notably, in one case series, a patient who received four cycles of levosimendan infusion improved to such an extent that removal from the transplant waiting list was deemed appropriate [Silvetti et al., 2024].

Safety and Tolerance

A major concern surrounding the use of inotropes in the transplant setting is the potential for increased post-transplant complications, particularly vasoplegia and primary graft dysfunction (PGD) [Guzman-Bofarull et al., 2025]. In a recent retrospective, multicentre observational study of 598 heart transplant recipients, the safety of levosimendan administered within one month prior to HT was specifically evaluated; 94 patients in this cohort received levosimendan [Guzman-Bofarull et al., 2025]. The investigators found that pre-HT levosimendan use was not associated with a higher incidence of post-transplant vasoplegia (40.0% vs. 39.2%, OR 0.99, p=0.98) or severe PGD (10.6% vs. 10.3%, OR 1.25, p=0.63) [Guzman-Bofarull et al., 2025]. Moreover, short-term post-transplant mortality did not differ significantly between patients who received levosimendan and those who did not (HR 0.78, p=0.37), supporting the conclusion that preoperative levosimendan administration represents a safe strategy in the context of heart transplantation [Guzman-Bofarull et al., 2025].

4.2. Bridge to LVAD (Mechanical Circulatory Support)

Mechanical circulatory support (MCS), most commonly via implantation of a left ventricular assist device (LVAD), is an increasingly utilised strategy in patients with advanced heart failure (AdHF), serving either as destination therapy or as a bridge to transplantation [Milwidsky et al., 2022, García-González et al., 2021]. Within this context, levosimendan has been employed as a pharmacological bridge to LVAD implantation [Milwidsky et al., 2022, Pölzl et al., 2017, Tycińska et al., 2021, Pölzl et al., 2019].

Clinical Data on Hemodynamic and Organ Perfusion Improvement

From a clinical standpoint, optimisation of haemodynamic status and preservation of end-organ perfusion before LVAD surgery are critical determinants of prognosis [Reis et al., 2023, Abbate et al., 2018]. Levosimendan, by enhancing cardiac contractility and overall performance, is used to limit renal and hepatic dysfunction prior to device implantation [Reis et al., 2023, Lelonek et al., 2020]. In line with this rationale, one study demonstrated that preoperative optimisation with levosimendan was associated with improved outcomes following LVAD implantation [Papp et al., 2020].

Examples of Studies and Registries

Evidence from clinical trials and registries further underscores this bridging role. Studies evaluating repetitive levosimendan dosing frequently include ventricular assist device (VAD) implantation as a key adverse event within hierarchical composite endpoints [Pölzl et al., 2017, Pölzl et al., 2019, Silvetti et al., 2024, Papp et al., 2020]. For example, the original design of the LeoDOR trial (and the recommended framework for future studies) defined the primary outcome—Tier 1 of the global rank endpoint—as time to death, urgent heart transplantation (HTx), or VAD implantation [Pölzl et al., 2017, Pölzl et al., 2019, Silvetti et al., 2024, Papp et al., 2020]. This structure reflects the clinical reality that levosimendan is often used to stabilise patients whose only immediate alternative may be urgent mechanical support [Pölzl et al., 2019]. Similarly, the Polish LEIA-HF study incorporated hospitalization for implantation of a permanent MCS system into its composite primary endpoint [Tycińska et al., 2021]. Together, these data highlight the ongoing need for haemodynamic stabilisation prior to VAD surgery and support the role of levosimendan as a valuable bridging therapy in this setting.

4.3. Bridge to Recovery / Bridge to Decision

In patients with advanced heart failure (AdHF) for whom heart transplantation (HTx) or LVAD implantation are not immediately indicated or desired, repeated administration of levosimendan may be employed as a bridge to recovery, a bridge to decision, or as a palliative destination therapy [Codina et al., 2023, Pölzl et al., 2017, Reis et al., 2023, Elsaeidy et al., 2024].

Repeated Infusions as an Element of Patient Stabilization

The core therapeutic concept is the use of intermittent intravenous levosimendan infusions [Silvetti et al., 2017, Pölzl et al., 2017], leveraging the prolonged haemodynamic effect of its active metabolite OR-1896, which sustains clinical benefit for approximately two weeks after cessation of the infusion [Silvetti et al., 2017, Reis et al., 2023]. Across published studies, treatment protocols vary considerably with respect to infusion duration (6–24 hours), dosing interval (weekly to monthly), and total treatment period (up to 12 months) [Silvetti et al., 2017, García-González et al., 2021, Silvetti et al., 2015, Pölzl et al., 2019].

Several key randomized controlled trials (RCTs)—notably LevoRep, LION-HEART, and LAICA—provide evidence for this strategy [García-González et al., 2021, Bouchez et al., 2018, Książczyk et al., 2023, Altenberger et al., 2018, Guzman-Bofarull et al., 2025]. In the multicentre LION-HEART trial, six cycles of intermittent outpatient levosimendan significantly reduced NT-proBNP levels and attenuated the neurohormonal burden characteristic of AdHF [Altenberger et al., 2018, Comín-Colet et al., 2018]. The need to stabilise patients during the early post-discharge "vulnerable phase" is further underscored by the design of the LeoDOR trial, which was conceived to assess the impact of initiating intermittent levosimendan therapy shortly after hospitalisation for acute heart failure [Reis et al., 2023, Papp et al., 2020, Pölzl et al., 2023**].**

Impact on Quality of Life and Reduction in Hospitalizations

A substantial body of evidence indicates that intermittent levosimendan infusion exerts a favourable impact on clinical status and quality of life (QoL) in this highly compromised patient population [Pölzl et al., 2017, Bouchez et al., 2018]. More broadly, studies of intermittent inotropic therapy suggest consistent improvements in functional class and QoL measures [Milwidsky et al., 2022].

One of the most consistently documented benefits of this strategy is the reduction in hospitalizations and unplanned healthcare contacts:

- In the LION-HEART trial, intermittent levosimendan was associated with a significant decrease in hospital admissions for decompensated heart failure [García-González et al., 2021, Altenberger et al., 2018, Visco et al., 2024].
- Data from the RELEVANT-HF registry demonstrated a statistically significant reduction in both the number and cumulative duration of HF-related hospitalizations during the six months following initiation of intermittent levosimendan therapy [García-González et al., 2021].
- In the LEVO-D registry, ambulatory, periodically administered levosimendan infusions significantly reduced HF events at one year [Codina et al., 2023]. The proportion of patients experiencing HF hospitalization or unplanned HF visits fell from over 80% in the preceding year to 56% in the year after treatment initiation, corresponding to a 33% reduction in total HF hospitalizations and a 50% reduction in unplanned visits [Dobarro et al., 2023].
- A meta-analysis reported that intermittent levosimendan significantly improved left ventricular ejection fraction (LVEF), reduced BNP levels, and lowered all-cause mortality (RR 0.60 [95% CI 0.40–0.90], P=0.01) [Elsaeidy et al., 2024]. However, no statistically significant effect on all-cause rehospitalization was

observed (RR 0.75 [95% CI 0.46–1.22], P=0.25), and heterogeneity for this outcome was substantial (I^2=70%) [Elsaeidy et al., 2024].

Intermittent levosimendan has also been shown to enhance functional capacity. In one single-centre series, the proportion of patients in NYHA class IV declined from 52.2% at baseline to 12.5% at six-month follow-up [Reis et al., 2023, Teixeira et al., 2025]. Improvements have likewise been reported in exercise performance parameters, including peak oxygen uptake (pVO_2) and the VE/VCO_2 slope [Reis et al., 2023, Teixeira et al., 2025]. In the LION-HEART study, patients receiving levosimendan experienced a smaller deterioration in QoL scores assessed by the EQ-5D Visual Analogue Scale (VAS) [Visco et al., 2024].

Thus, the clinical application of intermittent levosimendan as a bridging strategy extends beyond simple life-prolongation. It seeks to enhance health-related QoL in patients with limited therapeutic options, stabilising their condition to optimise the time available for potential recovery or, alternatively, to improve comfort within a palliative framework [Reis et al., 2023]. The observed sustained benefits—improved LVEF, reductions in NT-proBNP, and fewer HF-related hospitalizations—support its role in maintaining clinical stability through critical phases of advanced disease [Reis et al., 2023, Elsaeidy et al., 2024].

5. Clinical Evidence: Review of Studies

The investigation of levosimendan as a bridging or destination therapy in advanced heart failure (AdvHF) is supported primarily by studies evaluating its intermittent, repeated intravenous administration in outpatient settings, building on earlier evidence from trials in acute heart failure (AHF) [Comín-Colet et al., 2018, Altenberger et al., 2017, Pölzl et al., 2019]. Levosimendan is classified as a first-in-class inodilator and calcium sensitizer and may offer several advantages over conventional inotropes, including sustained haemodynamic effects after a single infusion, compatibility with beta-blocker therapy, and the absence of increased myocardial oxygen consumption [Altenberger et al., 2017, Pölzl et al., 2017, Najjar et al., 2018].

Overview of Key Clinical Trials

Several pivotal randomized controlled trials (RCTs) and large acute HF studies have shaped current understanding of levosimendan's role in cardiac dysfunction.

LION-HEART Trial

The LION-HEART (Levosimendan Intermittent administration in Outpatients: effects on Natriuretic peptides in advanced chronic HEART failure) study was a multicentre, double-blind, randomized, parallel-group, placebo-controlled trial designed to assess the efficacy and safety of intermittent intravenous levosimendan in outpatients with advanced chronic HF [Comín-Colet et al., 2018, Altenberger et al., 2017, Dobarro et al., 2022]. Eligible patients had advanced chronic HF, typically defined as NYHA class III/IV for at least four weeks and a left ventricular ejection fraction (LVEF) <35% [Altenberger et al., 2017]. Participants received six cycles of intermittent levosimendan infusions (0.2 µg/kg/min over 6 hours) or placebo every two weeks [Comín-Colet et al., 2018, Pölzl et al., 2017, García-González et al., 2021].

The trial met its primary endpoint, demonstrating a significant reduction in N-terminal pro–B-type natriuretic peptide (NT-proBNP) with levosimendan compared with placebo (P<0.001) [Comín-Colet et al., 2018, Altenberger et al., 2017, Visco et al., 2024]. It also showed favourable effects on key secondary endpoints, including a significant reduction in HF hospitalizations (P=0.002) and in the composite endpoint of all-cause death or HF hospitalization (P=0.022) [Altenberger et al., 2017, Visco et al., 2024]. Additionally, the decline in HF-related quality of life at six months was less pronounced in the levosimendan group than in the placebo group (20% vs. 64%, P=0.022) [Altenberger et al., 2017, Visco et al., 2024].

LevoRep Trial

The LevoRep (Levosimendan in outpatients with advanced heart failure) study was one of the earliest and largest multicentre randomized trials specifically investigating intermittent levosimendan in outpatients with advanced HF [Silvetti et al., 2017, Tycińska et al., 2021, Pölzl et al., 2019]. This double-blind trial enrolled 120 patients with severe systolic dysfunction (LVEF <35%) and NYHA class III or IV symptoms persisting for at least three months [Altenberger et al., 2017, von Scheidt et al., 2016]. The intervention consisted of pulsed levosimendan infusions (0.2 µg/kg/min for 6 hours) administered in four cycles at 2-week intervals [Pölzl et al., 2017, García-González et al., 2021].

Although LevoRep did not achieve statistical significance for its ambitious primary composite endpoint focused on functional capacity and clinical status, it did yield encouraging results in secondary analyses. Notably, levosimendan significantly reduced NT-proBNP levels at 8 weeks (P=0.006) and improved event-free survival (Hazard Ratio 0.39, 95% CI 0.15–0.98, P=0.037) compared with placebo [Altenberger et al., 2017].

LAICA Study

The LAICA (Levosimendan Administration in Advanced Chronic Heart Failure Patients) study was a randomized, double-blind, placebo-controlled multicentre trial designed to evaluate repeated levosimendan administration in patients with advanced HF [Altenberger et al., 2017, Abbate et al., 2018, Silvetti et al., 2017]. Unlike LION-HEART and LevoRep, LAICA used a lower infusion rate delivered over a longer period (0.1 μg/kg/min intravenously for 24 hours), repeated monthly for up to 12 months [Silvetti et al., 2017, García-González et al., 2021].

Premature termination and limited recruitment (99 patients) rendered the trial underpowered to definitively address its primary endpoint of HF hospitalization [Altenberger et al., 2017, García-González et al., 2021]. Nonetheless, the results numerically favoured levosimendan, with a lower cumulative incidence of acute HF decompensation and/or death at 1 and 3 months and a significantly higher survival probability as a secondary endpoint [Ferreira Reis et al., 2022, García-González et al., 2021].

LeoDOR Trial

The LeoDOR (Repetitive Levosimendan Infusion for Patients with Advanced Chronic Heart Failure) trial is a more recent multinational RCT that evaluated intermittent levosimendan therapy during the particularly vulnerable post-discharge phase following hospitalization for acute HF exacerbation [Pölzl et al., 2023, Pölzl et al., 2019]. Patients were randomized to levosimendan or placebo for 12 weeks, receiving either 6-hour infusions every 2 weeks or 24-hour infusions every 3 weeks [Pölzl et al., 2023, Pölzl et al., 2019].

The primary efficacy outcome was a hierarchical global rank endpoint comprising three tiers: (1) time to death or urgent heart transplantation/ventricular assist device (VAD) implantation, (2) time to non-fatal HF events requiring intravenous vasoactive therapy, and (3) time-averaged proportional change in NT-proBNP [Pölzl et al., 2023, Pölzl et al., 2019, Papp et al., 2020]. The trial ultimately demonstrated that intermittent levosimendan did not significantly improve post-hospitalization clinical stability based on this global rank score over 14 weeks [Pölzl et al., 2023]. The investigators suggested that the heterogeneity of the enrolled population (spanning advanced to end-stage HF with diverse aetiologies and phenotypes) may have contributed to the neutral results compared with smaller, more homogeneous earlier studies [Pölzl et al., 2023].

SURVIVE and REVIVE II Trials

The SURVIVE and REVIVE II trials were landmark large-scale RCTs investigating levosimendan in acute decompensated heart failure (ADHF) [Comín-Colet et al., 2018, Lelonek et al., 2020, Papp et al., 2020]. SURVIVE compared levosimendan with dobutamine and did not show a significant difference in all-cause mortality in the overall study population [Comín-Colet et al., 2018, Altenberger et al., 2017, von Scheidt et al., 2016]. However, a pre-specified subgroup analysis suggested a potential benefit of levosimendan over dobutamine in patients receiving baseline beta-blocker therapy [Najjar et al., 2018, Lelonek et al., 2020].

In REVIVE II, which enrolled patients with ADHF and LVEF <35%, levosimendan treatment was associated with fewer episodes of worsening HF (15% vs. 26% in the control group) and produced rapid, sustained symptomatic improvement [Lelonek et al., 2020].

LEVO-CTS Trial

The LEVO-CTS trial evaluated levosimendan in a distinct high-risk cohort: patients with left ventricular dysfunction undergoing cardiac surgery [Abbate et al., 2018, Papp et al., 2020]. Although focused primarily on the prevention and management of perioperative low cardiac output syndrome rather than on AdvHF as a bridge-to-transplant or destination therapy, LEVO-CTS remains an important study supporting the safety and haemodynamic efficacy of levosimendan in a critical care setting [Abbate et al., 2018].

Analysis of Meta-Analyses and Observational Studies on Cyclic Infusions

Despite the mixed results of individual RCTs on repetitive levosimendan—most notably the neutral outcome of LeoDOR—a considerable body of meta-analytic and observational evidence from real-world practice suggests that cyclic administration is associated with clinically relevant benefits [Ferreira Reis et al., 2022; Silvetti et al., 2024; Silvetti et al., 2015].

Impact on Mortality and Rehospitalizations

Meta-analyses have repeatedly indicated a favourable effect of intermittent levosimendan on survival in advanced HF (AdvHF) [Silvetti et al., 2024; Silvetti et al., 2015; von Scheidt et al., 2016]. A systematic review and meta-analysis of seven randomized trials including 438 patients reported that intermittent levosimendan was associated with a significant reduction in mortality at the longest available follow-up (Odds Ratio [OR] 0.54, 95% CI 0.32–0.91, P=0.02) [Silvetti et al., 2015]. In line with this, a more recent meta-analysis of 15 RCTs comprising 1181 patients found that intermittent levosimendan significantly reduced all-cause mortality (Risk Ratio [RR] 0.60, 95% CI 0.40–0.90, P=0.01) [Milwidsky et al., 2024].

With respect to rehospitalizations, the LION-HEART trial demonstrated a significant reduction in HF-related hospital admissions [Altenberger et al., 2017; Visco et al., 2024]. Similar findings emerged from large observational registries, such as LEVO-D, which enrolled an elderly, high-risk cohort. In LEVO-D, the proportion of patients experiencing HF hospitalization or unplanned HF visits fell from over 80% in the year preceding treatment to 56% in the subsequent year, corresponding to a 33% reduction in total HF hospitalizations and a 50% reduction in unplanned HF visits [Dobarro et al., 2022; Abbate et al., 2018; Codina et al., 2023]. In contrast, pooled data on the broader outcome of all-cause rehospitalization are less consistent: a recent meta-analysis found no statistically significant difference between levosimendan and placebo for this endpoint (RR 0.75, 95% CI 0.46–1.22, P=0.25), with substantial heterogeneity (I^2=70%) [Saad Elsaeidy et al., 2024].

Impact on Symptoms and Biomarkers

Intermittent levosimendan also appears to exert beneficial effects on surrogate markers and symptoms in AdvHF [Comín-Colet et al., 2018; Altenberger et al., 2017; Ferreira Reis et al., 2022; Visco et al., 2024]. Both LION-HEART and LevoRep documented significant reductions in NT-proBNP levels with levosimendan therapy [Comín-Colet et al., 2018; Altenberger et al., 2017]. These findings are supported by meta-analyses indicating that intravenous levosimendan can significantly lower BNP/NT-proBNP concentrations and increase LVEF in advanced HF populations [Saad Elsaeidy et al., 2024; Cui et al., 2020]. For example, one meta-analysis of RCTs reported that levosimendan significantly improved LVEF compared with placebo (Mean Difference 6.39; 95% CI 3.04–9.73; P=0.002) [Saad Elsaeidy et al., 2024].

Symptomatic benefits are evident in observational data, which show a reduction in the proportion of patients in the most severe functional class. In one single-centre experience, the proportion of NYHA class IV patients declined from 52.2% at baseline to 12.5% at follow-up, accompanied by significant gains in exercise capacity, including peak oxygen uptake [Ferreira Reis et al., 2022]. The improvement in symptoms and QoL is generally attributed to the haemodynamic effects of levosimendan together with its pleiotropic actions, notably mitigation of neurohormonal burden [Comín-Colet et al., 2018; Papp et al., 2020]. Polish real-world multicentre data similarly documented clinical improvement and BNP reduction in decompensated AdvHF patients receiving levosimendan, although 1-year mortality and rehospitalization rates remained high, reflecting the severity of the underlying disease [Lelonek et al., 2020].

Differences Between HFrEF and HFpEF Populations

The current evidence base for intermittent levosimendan as a bridging strategy in advanced heart failure (AdvHF) is concentrated almost exclusively on patients with heart failure with reduced ejection fraction (HFrEF) [Altenberger et al., 2017; Silvetti et al., 2017]. The major multicentre trials—LevoRep, LION-HEART, LAICA, and LeoDOR—specifically enrolled cohorts with marked systolic impairment, typically defined as LVEF <35% or LVEF ≤30% [Pölzl et al., 2023; Altenberger et al., 2017; Ferreira Reis et al., 2022]. Consequently, the reported benefits in terms of mortality reduction, NT-proBNP lowering, and LVEF improvement observed in meta-analyses predominantly pertain to the HFrEF population [Saad Elsaeidy et al., 2024].

By contrast, data on repetitive levosimendan administration in advanced heart failure with preserved ejection fraction (HFpEF) in the ambulatory AdvHF setting are extremely limited. Nonetheless, the HELP trial—although not designed to study chronic intermittent use in AdvHF—showed that levosimendan improved haemodynamics and exercise tolerance in patients with pulmonary hypertension associated with HFpEF (PH-HFpEF) [Silvetti et al., 2024]. These findings suggest that the vasodilatory and lusitropic properties of levosimendan may be advantageous in conditions characterised by elevated pulmonary pressures or impaired diastolic function, and they point toward a potential future role in advanced HFpEF. However, dedicated studies are needed to establish the efficacy and safety of intermittent levosimendan in the specific context of AdvHFpEF [Abbate et al., 2018].

6. Safety Profile and Methodological Limitations of Levosimendan Therapy in Advanced Heart Failure

Although accumulating data indicate that repetitive or intermittent levosimendan may provide meaningful clinical benefits in advanced heart failure (AdHF)—including symptomatic relief, reductions in natriuretic peptides, and improvements in left ventricular ejection fraction (LVEF) [Ferreira Reis et al., 2022; Saad Elsaeidy et al., 2024; Cui et al., 2020]—careful consideration of its safety profile and of the limitations of the available evidence is crucial when defining its role as a bridging therapy.

Adverse event profile: hypotension, tachycardia, and arrhythmias

Levosimendan is generally regarded as a comparatively safe inodilator relative to conventional inotropes, largely because its mechanism of action—calcium sensitisation without increasing intracellular calcium or myocardial oxygen demand—differs fundamentally from catecholamines and phosphodiesterase inhibitors [Bouchez et al., 2018; Altenberger et al., 2017; Abbate et al., 2018]. In contrast to agents such as dobutamine and milrinone, which augment myocardial Ca^{2+} transients via cAMP-dependent pathways and are clearly associated with increased arrhythmic risk and mortality [Abbate et al., 2018; Najjar et al., 2018], levosimendan's cAMP-independent inotropic effect appears inherently less arrhythmogenic [Bouchez et al., 2018; Ferreira Reis et al., 2022; Saad Elsaeidy et al., 2024]. In the LION-HEART trial, the intermittent levosimendan regimen was safe and well tolerated, with no significant between-group differences in the overall incidence of adverse events, serious or non-serious, compared with placebo [Comín-Colet et al., 2018]. A recent meta-analysis likewise reported no increase in overall adverse events with levosimendan versus placebo (Risk Ratio [RR] 1.00, 95% CI 0.73–1.37, I^2=0%) [Saad Elsaeidy et al., 2024].

Despite this favourable global profile, several specific adverse effects are recognised, most of which are related to vasodilation [Bouchez et al., 2018]. Hypotension is the most prominent and well-documented complication, particularly when a loading bolus is administered [Bouchez et al., 2018; Comín-Colet et al., 2018; Lelonek et al., 2020]. Accordingly, current expert recommendations advocate starting levosimendan without a bolus dose to reduce the risk of abrupt blood pressure drops [Lelonek et al., 2020]. A recent meta-analysis reported a statistically significant increase in hypotension with levosimendan (RR 2.01, 95% CI 1.06–3.82, I^2=0%) [Saad Elsaeidy et al., 2024]; however, this did not translate into higher all-cause mortality [Saad Elsaeidy et al., 2024]. In the LeoDOR trial, clinically relevant hypotension (systolic blood pressure ≤80 mmHg) occurred in 9.7% of infusions in the levosimendan arm versus 11.1% in the placebo group, a non-significant difference (p=0.564) [Pölzl et al., 2023]. In LAICA, hypotension occasionally necessitated a reduction in infusion rate. From a practical standpoint, careful volume assessment, correction of hypovolemia before infusion, and, if needed, infusion-rate adjustment or concomitant vasopressor support are recommended to manage this risk [Lelonek et al., 2020].

With respect to tachycardia and rhythm disturbances, the calcium-sensitising, non–calcium-mobilising mechanism of levosimendan would theoretically be expected to confer a lower propensity for ventricular arrhythmias [Saad Elsaeidy et al., 2024; Milwidsky et al., 2022]. Nonetheless, earlier acute HF trials, such as REVIVE II and SURVIVE, reported higher rates of atrial arrhythmias (notably atrial fibrillation) and episodes of ventricular tachycardia in levosimendan-treated patients compared with control or dobutamine groups [Bouchez et al., 2018; Lelonek et al., 2020]. By contrast, LION-HEART did not show any relevant differences in rhythm parameters or new-onset atrial fibrillation during the first infusion cycle [Comín-Colet et al., 2018], and in LeoDOR only a non-significant trend toward more tachycardia, new atrial fibrillation, and non-sustained ventricular tachycardia was observed with levosimendan compared to placebo (2.7% vs. 0.8%; p=0.070) [Pölzl et al., 2023]. Importantly, a comprehensive recent meta-analysis did not identify a significant difference in tachycardia events between levosimendan and control (RR 0.86, 95% CI 0.38–1.96, I^2=3%) [Saad Elsaeidy et al., 2024].

Other adverse effects reported with levosimendan include headache and hypokalaemia, both of which are generally manageable with standard supportive measures [Bouchez et al., 2018; Lelonek et al., 2020; Zheng et al., 2023]. Overall, while vigilance for hypotension and arrhythmias remains essential—especially in frail, multi-morbid AdvHF patients—the available evidence supports a safety profile that is at least comparable, and often superior, to that of traditional inotropes when levosimendan is used in carefully selected patients and with appropriate dosing strategies.

Interactions with Other Inotropic and Vasopressor Agents

Levosimendan is particularly favoured in patients already receiving optimal guideline-directed medical therapy, especially those treated with beta-blockers, because its mechanism of action remains fully effective despite beta-adrenergic blockade—unlike traditional catecholamine-based inotropes [Bouchez et al., 2018; Altenberger et al., 2017; Książczyk et al., 2023]. This characteristic is of central importance in the management of advanced heart failure [Bouchez et al., 2018].

In cases where significant hypotension develops during levosimendan infusion, current management recommendations indicate that concomitant administration of dobutamine or norepinephrine may be required to stabilise blood pressure [Lelonek et al., 2020]. This underscores that, in emergency situations—particularly when the vasodilatory effect of levosimendan is pronounced—temporary combination with conventional inotropes or vasopressors may be necessary [Lelonek et al., 2020]. In a Polish observational study of

decompensated AdHF, 45% of patients received dobutamine simultaneously because of hypotension [Lelonek et al., 2020]. Notably, in the same cohort, dobutamine infusion emerged as an independent predictor of increased mortality (HR 6.54, $p<0.01$) [Lelonek et al., 2020], further emphasising the safety gap between traditional inotropes and levosimendan. Levosimendan has also been compared with, or used sequentially to, milrinone—another inotropic drug whose chronic use is constrained by excess mortality and a substantial pro-arrhythmic burden [Abbate et al., 2018; Milwidsky et al., 2022; Guzman-Bofarull et al., 2025].

Importantly, the prolonged haemodynamic effect of levosimendan—mediated by its long-acting active metabolite OR-1896—extends for several days after the infusion has ended [Bouchez et al., 2018], meaning that both its therapeutic impact and any potential interactions continue well beyond the actual administration period.

Limitations of Clinical Trials in Advanced Heart Failure

Despite encouraging evidence that intermittent levosimendan may reduce mortality and hospitalizations in patients with advanced heart failure (AdHF) [García-González et al., 2021; Silvetti et al., 2015], the clinical evidence base underpinning its systematic use remains constrained by important methodological limitations [Abbate et al., 2018; Pölzl et al., 2017; Tycinska et al., 2021].

Small sample sizes and limited statistical power

A major limitation is the paucity of large, adequately powered randomized controlled trials (RCTs) specifically designed for populations with advanced, yet clinically stable, chronic HF [Comín-Colet et al., 2018; Abbate et al., 2018; Pölzl et al., 2017]. Many of the available studies—particularly earlier ones—were characterised by small sample sizes, single-centre or open-label designs, and consequently limited internal validity [Silvetti et al., 2017; Tycinska et al., 2021; Pölzl et al., 2018].

For example, LION-HEART was powered primarily to detect changes in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and therefore analyses of clinical events, symptoms, and patient-reported outcomes were exploratory rather than definitive [Comín-Colet et al., 2018]. The LAICA trial was terminated prematurely for logistical reasons, with recruitment restricted to 99 patients, which substantially reduced its ability to meet its primary endpoint [García-González et al., 2021]. Although these and other smaller studies have generated promising signals—such as improvements in LVEF, reductions in BNP, and lower mortality—these findings, often derived from secondary endpoints in underpowered trials, must be interpreted with considerable caution [Comín-Colet et al., 2018; Saad Elsaeidy et al., 2024; García-González et al., 2021].

Heterogeneity of study designs and patient populations

Interpretation of meta-analytic data is further complicated by marked heterogeneity among the included trials [Silvetti et al., 2017; Silvetti et al., 2024]. Variability is evident across multiple dimensions:

- Comparators: Control arms have ranged from placebo to active comparators such as dobutamine, furosemide, and prostaglandin E1 [Silvetti et al., 2024].
- Dosing regimens: Infusion protocols differ substantially, from 6-hour infusions every 2 weeks (LION-HEART) to 24-hour infusions every 30 days (LAICA), alongside the alternative schedules evaluated in LeoDOR [Saad Elsaeidy et al., 2024; García-González et al., 2021; Pölzl et al., 2019]. The use or omission of a loading bolus also varied among studies [Saad Elsaeidy et al., 2024].
- Clinical status at inclusion: Many studies historically enrolled heterogeneous cohorts, combining patients with acute decompensated HF and those with relatively stable AdHF [Pölzl et al., 2023]. Notably, the recent LeoDOR trial, focused specifically on the "vulnerable post-discharge period" after acute HF hospitalization, failed to show that intermittent levosimendan improved clinical stability in this highly unstable phase, indicating that its role in this setting remains uncertain [Pölzl et al., 2023].

Despite repeated calls for a definitive trial [Comín-Colet et al., 2018; Abbate et al., 2018; García-González et al., 2021; Silvetti et al., 2015], a key unmet need remains: a large, rigorously designed, adequately powered RCT that can conclusively establish the long-term safety of intermittent levosimendan (particularly regarding hypotension, arrhythmias, and mortality versus placebo) and validate the suggested benefits on hard clinical outcomes [Comín-Colet et al., 2018; Silvetti et al., 2017]. Current initiatives such as the LEIA-HF trial, which aims to randomize approximately 350 patients, represent important steps towards generating the robust, conclusive evidence required to define the precise role of levosimendan in AdvHF bridging strategies [Tycinska et al., 2021].

7. Future Research Directions

Future research is essential to define more precisely the clinical role of levosimendan as a bridging therapy in advanced heart failure (AdHF) and to clarify how it should be integrated with contemporary management strategies.

Need for large randomized trials in advanced heart failure

Although early studies have reported encouraging improvements in surrogate endpoints and reductions in rehospitalization with intermittent levosimendan, there remains a pressing need for large, adequately powered randomized controlled trials (RCTs) specifically targeting the AdHF population [Comín-Colet et al., 2018; Silvetti et al., 2017; Silvetti et al., 2015]. Pilot studies such as the multicentre LION-HEART trial suggested that intermittent levosimendan can reduce N-terminal pro–B-type natriuretic peptide (NT-proBNP), improve health-related quality of life (HRQoL), and lower heart failure hospitalization rates [Comín-Colet et al., 2018; Bouchez et al., 2018].

By contrast, the more recent multinational LeoDOR trial, which evaluated intermittent levosimendan during the highly vulnerable phase immediately after acute HF hospitalization, did not demonstrate a significant difference versus placebo in its primary efficacy endpoint, the Global Rank Score (GRS), at 14 weeks [Pölzl et al., 2023]. This discrepancy between earlier positive signals and later neutral findings highlights the need for more definitive evidence [Pölzl et al., 2023].

Addressing this gap, the ongoing LEIA-HF (LEvosimendan In Ambulatory Heart Failure Patients) trial is a prospective, multicentre, randomized, double-blind, placebo-controlled study planned to enrol 350 patients. It will assess the effect of repeated 24-hour levosimendan infusions administered every four weeks for 48 weeks on a composite primary endpoint of all-cause death or unplanned HF hospitalization [Tycinska et al., 2021; Książczyk et al., 2023]. Such rigorously designed studies are crucial to provide a comprehensive understanding of both the effectiveness and safety profile of long-term intermittent levosimendan therapy [Tycinska et al., 2021].

Integration with newer generation therapies (SGLT2i, ARNI, MRA)

Another key research priority is defining how intermittent levosimendan fits within modern Guideline-Directed Medical Therapy (GDMT), particularly alongside sodium–glucose co-transporter 2 inhibitors (SGLT2i), angiotensin receptor–neprilysin inhibitors (ARNI) and mineralocorticoid receptor antagonists (MRA). Because levosimendan exerts its inotropic effect without adrenergic stimulation and remains effective in beta-blocked patients, it is conceptually well suited to complement these newer agents [Bouchez et al., 2018; Altenberger et al., 2017].

However, many existing real-world datasets, including the LEVO-D registry, reflect treatment patterns from the pre–SGLT2i era [Dobarro et al., 2022]. LEIA-HF has been specifically designed to overcome this limitation by incorporating pre-specified subgroup analyses in patients receiving ARNI and/or SGLT2 inhibitors, thereby assessing outcomes in the context of contemporary background therapy [Tycinska et al., 2021]. These analyses will be crucial to determine whether levosimendan's benefits are additive to, or modified by, these newer drug classes.

Potential for remotely guided / home-based ambulatory infusions

Levosimendan's pharmacokinetic properties—particularly the prolonged haemodynamic effect of its active metabolite OR-1896, lasting up to approximately 10 days—make it inherently suitable for intermittent outpatient or ambulatory administration [Bouchez et al., 2018; Altenberger et al., 2017; Pölzl et al., 2018]. Future studies should therefore explore optimized delivery models, including remotely guided home-based infusions.

Advanced remote monitoring technologies such as CardioMEMS, which provide continuous pulmonary artery pressure (PAP) and haemodynamic data, offer a means to individualize the timing and need for levosimendan infusions [Visco et al., 2024]. This strategy contrasts with fixed-interval protocols (e.g., every 15 or 28 days) used in earlier studies such as LION-HEART or the Ortis et al. experience [Visco et al., 2024]. Preliminary data suggest that haemodynamic-guided administration may optimize drug use, reduce the overall number of levosimendan vials required, shorten HF-related hospital stays, and improve organizational efficiency at the health-system level [Visco et al., 2024]. Validation of such dynamic, data-driven protocols represents an important future direction.

Biomarkers and prediction of treatment response

Identifying robust biomarkers of response will be crucial for tailoring intermittent levosimendan therapy to those AdHF patients most likely to benefit. NT-proBNP remains the principal biomarker in this setting, reflecting neurohormonal burden and ventricular wall stress. Multiple studies, including LION-HEART, have

shown consistent and clinically meaningful reductions in NT-proBNP with intermittent levosimendan [Comín-Colet et al., 2018; Visco et al., 2024]. Its importance is reflected in the LeoDOR trial design, where NT-proBNP change constitutes Tier 3 (the lowest hierarchical level) of the composite Global Rank Score (GRS) [Pölzl et al., 2023; Pölzl et al., 2018].

Beyond generic prognostic tools, dedicated response scores are emerging. The LEVO-D score, developed from the large real-world LEVO-D registry, was created to predict "responder" status—defined as survival without urgent HF hospitalizations or unplanned visits at one year [Dobarro et al., 2022]. In this cohort, LEVO-D outperformed more general risk models, such as the MAGGIC score, for predicting outcomes in advanced HF patients considered for intermittent levosimendan [Dobarro et al., 2022].

Continued work is required to validate and refine such specialized tools, potentially incorporating markers of advanced HF severity (e.g., prior inotrope use, progression of right ventricular dysfunction) to better delineate the phenotypes most likely to derive meaningful benefit [Codina et al., 2023]. Ultimately, the convergence of biomarker-driven risk stratification, modern GDMT, and remote haemodynamic monitoring may enable a more precise, personalized deployment of levosimendan in AdHF bridging strategies.

8. Discussion

The strategic deployment of levosimendan offers a compelling pharmacological alternative within the complex management landscape of advanced heart failure (AHF). As a first-in-class inodilator, its unique tripartite mechanism functions via calcium sensitization and potassium channel opening, yielding positive inotropy independently of the cAMP pathway [Papp et al., 2020; Altenberger et al., 2018; Reis et al., 2023; Lelonek et al., 2020; Pölzl et al., 2017; Bouchez et al., 2018]. Crucially, this action avoids the increase in myocardial oxygen demand and the heightened arrhythmic risk associated with conventional calcium-mobilizing inotropes [Papp et al., 2020; Lelonek et al., 2020; Altenberger et al., 2018; Bouchez et al., 2018; Reis et al., 2023; Sumanaru et al., 2019; Pölzl et al., 2017; Cui et al., 2020; Sumanaru et al., 2019; Teixeira et al., 2025; Książczyk et al., 2023; Abbate et al., 2018; Najjar et al., 2018; Ferreira Reis et al., 2022; Saad Elsaeidy et al., 2024]. The prolonged action conferred by its active metabolite, OR-1896, which sustains hemodynamic benefits for up to two weeks, provides the essential foundation for viable intermittent and outpatient bridging strategies (BTT, BTLVAD, BTR) [Reis et al., 2023; Altenberger et al., 2018; Bouchez et al., 2018; Guzman-Bofarull et al., 2025; Pölzl et al., 2017, Abbate et al., 2018, Papp et al., 2020]. Repetitive levosimendan administration has been consistently associated with favourable clinical signals, including significant improvements in Left Ventricular Ejection Fraction (LVEF), reduction in NT-proBNP concentrations, and, in pooled analyses, a reduced risk of all-cause mortality (RR 0.60) [Milwidsky et al., 2024; Altenberger et al., 2017; Visco et al., 2024; Saad Elsaeidy et al., 2024; Ferreira Reis et al., 2022]. Its specific organoprotective effects, notably improved renal function, further enhance its utility in stabilizing high-risk patients awaiting heart transplantation [Lannemyr et al., 2018; Papp et al., 2020; Elsaeidy et al., 2024; Zheng et al., 2023; Altenberger et al., 2018]. Despite compelling data from meta-analyses, the field is hampered by the heterogeneity and small scale of many trials [Silvetti et al., 2024; Saad Elsaeidy et al., 2024; García-González et al., 2021; Pölzl et al., 2019; Comín-Colet et al., 2018; Abbate et al., 2018; Pölzl et al., 2017; Silvetti et al., 2017; Tycinska; et al., 2021; Pölzl et al., 2018]. The neutral primary outcome of the LeoDOR trial highlights that the role of levosimendan in the unstable, post-discharge phase remains uncertain [Comín-Colet et al., 2018, Lelonek et al., 2020, Papp et al., 2020; Altenberger et al., 2017, von Scheidt et al., 2016]. Consequently, larger, definitive studies, such as the ongoing LEIA-HF trial, are indispensable to define optimal dosing, confirm long-term safety, and establish the precise integration of levosimendan with contemporary optimal medical therapy, including SGLT2 inhibitors and ARNIs [Tycinska et al., 2021; Bouchez et al., 2018; Altenberger et al., 2017; Dobarro et al., 2022].

9. Summary and Conclusions

Advanced heart failure (AdHF) remains a high-mortality syndrome marked by recurrent hospitalisations, with mechanical circulatory support or heart transplantation as the only definitive options for a minority of patients [Ferreira Reis et al., 2022; Pölzl et al., 2017; Lelonek et al., 2020]. In this setting, repetitive intravenous levosimendan has emerged as a promising approach for bridge therapy and long-term palliation [Ferreira Reis et al., 2022; Pölzl et al., 2017; Silvetti et al., 2023]. Its dual mechanism—calcium sensitisation and potassium-channel opening—distinguishes it from conventional inotropes, providing inotropy without increasing oxygen demand and retaining efficacy despite beta-blockade [Bouchez et al., 2018; Altenberger et al., 2017; Ferreira Reis et al., 2022].

Across trials and registries, repeated levosimendan infusions improve haemodynamics (cardiac output, stroke volume, LVEF) [Altenberger et al., 2017; Najjar et al., 2018; Papp et al., 2020; Saad Elsaeidy et al., 2024] and reduce neurohormonal activation, reflected by substantial NT-proBNP/BNP declines [Comín-Colet et al., 2018; Ferreira Reis et al., 2022; Saad Elsaeidy et al., 2024]. Patients typically experience symptomatic relief and improved functional capacity/HRQoL [Comín-Colet et al., 2018; Apostolo et al., 2021]. Meta-analyses indicate a modest but significant LVEF gain (~6.4 percentage points) and a reduction in all-cause mortality (risk ratio 0.60–0.62) at longest follow-up [Saad Elsaeidy et al., 2024; Silvetti et al., 2023; Silvetti et al., 2015].

Levosimendan may also exert renal benefits by increasing renal perfusion and glomerular filtration [Bouchez et al., 2018; Altenberger et al., 2017], with observational data suggesting improved renal function pre-transplant and no increase in post-transplant complications [Zheng et al., 2023; Guzman-Bofarull et al., 2025]. Safety profiles remain favourable, with no excess arrhythmias versus placebo [Saad Elsaeidy et al., 2024].

Despite encouraging signals, the evidence base is heterogeneous and dominated by small pilot RCTs and registries often underpowered for hard endpoints [Comín-Colet et al., 2018; Pölzl et al., 2017; von Scheidt et al., 2016]. Robust, well-powered trials are needed to refine dosing strategies, optimise infusion intervals, and identify responders [Silvetti et al., 2023; Pölzl et al., 2018]. Emerging tools such as LEVO-D scores and biomarkers may help predict benefit, yet distinguishing true “super-responders” remains unresolved [Dobarro et al., 2022]. The neutral LeoDOR results highlight the importance of patient selection and clinical context, reinforcing the relevance of ongoing evaluation in stable ambulatory populations (e.g., LEIA-HF) [Pölzl et al., 2023; Tycinska et al., 2021].

REFERENCES

1. Abbate, A., & Van Tassell, B. W. (2018). Levosimendan in Advanced Heart Failure: Where Do We Stand?. *Journal of cardiovascular pharmacology*, *71*(3), 127–128. https://doi.org/10.1097/FJC.0000000000000539
2. Altenberger, J., Gustafsson, F., Harjola, V. P., Karason, K., Kindgen-Milles, D., Kivikko, M., Malfatto, G., Papp, Z., Parissis, J., Pollesello, P., Pölzl, G., & Tschöpe, C. (2018). Levosimendan in Acute and Advanced Heart Failure: An Appraisal of the Clinical Database and Evaluation of Its Therapeutic Applications. *Journal of cardiovascular pharmacology*, *71*(3), 129–136. https://doi.org/10.1097/FJC.0000000000000533
3. Apostolo, A., Vignati, C., Della Rocca, M., De Martino, F., Berna, G., Campodonico, J., Contini, M., Muratori, M., Palermo, P., Mapelli, M., Alimento, M., Pezzuto, B., & Agostoni, P. (2022). Why Levosimendan Improves the Clinical Condition of Patients With Advanced Heart Failure: A Holistic Approach. *Journal of cardiac failure*, *28*(3), 509–514. https://doi.org/10.1016/j.cardfail.2021.10.009
4. Bouchez, S., Fedele, F., Giannakoulas, G., Gustafsson, F., Harjola, V. P., Karason, K., Kivikko, M., von Lewinski, D., Oliva, F., Papp, Z., Parissis, J., Pollesello, P., Pölzl, G., & Tschöpe, C. (2018). Levosimendan in Acute and Advanced Heart Failure: an Expert Perspective on Posology and Therapeutic Application. *Cardiovascular drugs and therapy*, *32*(6), 617–624. https://doi.org/10.1007/s10557-018-6838-2
5. Codina, P., Dobarro, D., de Juan-Bagudá, J., De Frutos, F., Lupón, J., Bayes-Genis, A., Gonzalez-Costello, J., & Spanish LEVO-D registry Collaborators (2023). Heart failure risk scores in advanced heart failure patients: insights from the LEVO-D registry. *ESC heart failure*, *10*(5), 2875–2881. https://doi.org/10.1002/ehf2.14400
6. Comín-Colet, J., Manito, N., Segovia-Cubero, J., Delgado, J., García Pinilla, J. M., Almenar, L., Crespo-Leiro, M. G., Sionis, A., Blasco, T., Pascual-Figal, D., Gonzalez-Vilchez, F., Lambert-Rodríguez, J. L., Grau, M., Bruguera, J., & LION-HEART Study Investigators (2018). Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. European journal of heart failure, 20(7), 1128–1136. https://doi.org/10.1002/ejhf.1145
7. Dobarro, D., Donoso-Trenado, V., Solé-González, E., Moliner-Abós, C., Garcia-Pinilla, J. M., Lopez-Fernandez, S., Ruiz-Bustillo, S., Diez-Lopez, C., Castrodeza, J., Méndez-Fernández, A. B., Vaqueriza-Cubillo, D., Cobo-Marcos, M., Tobar, J., Sagasti-Aboitiz, I., Rodriguez, M., Escolar, V., Abecia, A., Codina, P., Gómez-Otero, I., Pastor, F., … Gonzalez-Costello, J. (2023). Intermittent inotropic support with levosimendan in advanced heart failure as destination therapy: The LEVO-D registry. *ESC heart failure*, *10*(2), 1193–1204. https://doi.org/10.1002/ehf2.14278
8. Elsaeidy, A. S., Abuelazm, M., Ghaly, R., Soliman, Y., Amin, A. M., El-Gohary, M., Elshenawy, S., Seri, A. R., Abdelazeem, B., Patel, B., & Bianco, C. (2024). The Efficacy and Safety of Levosimendan in Patients with Advanced Heart Failure: An Updated Meta-Analysis of Randomized Controlled Trials. *American journal of cardiovascular drugs : drugs, devices, and other interventions*, *24*(6), 775–790. https://doi.org/10.1007/s40256-024-00675-z

9. Ferreira Reis, J., Valentim Gonçalves, A., Ilhão Moreira, R., Pereira da Silva, T., Timóteo, A. T., Pombo, D., Carvalho, T., Correia, C., Santos, C., & Cruz Ferreira, R. (2023). Levosimendan in outpatients with advanced heart failure: Single-center experience of 200 intermittent perfusions. *Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology*, *42*(4), 335–343. https://doi.org/10.1016/j.repc.2022.03.006
10. García-González, M. J., Aldea Perona, A., Lara Padron, A., Morales Rull, J. L., Martínez-Sellés, M., de Mora Martin, M., López Díaz, J., López Fernandez, S., Ortiz Oficialdegui, P., & Jiménez Sosa, A. (2021). Efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients: the LAICA study. *ESC heart failure*, *8*(6), 4820–4831. https://doi.org/10.1002/ehf2.13670
11. Giannini, C., Petronio, A. S., Fiorelli, F., Liga, R., Spontoni, P., De Carlo, M., Marraccini, E., Pieroni, A., & Guarracino, F. (2017). Effects of levosimendan in patients with severe functional mitral regurgitation undergoing MitraClip implantation. *Journal of cardiovascular medicine (Hagerstown, Md.)*, *18*(9), 679–686. https://doi.org/10.2459/JCM.0000000000000537
12. Guzman-Bofarull, J., Martín-Centellas, A., Couto-Mallon, D., Borràs, R., Arenas-Loriente, A., Rivas-Lasarte, M., Segovia-Cubero, J., Crespo-Leiro, M. G., García-Álvarez, A., & Farrero, M. (2025). Impact of Pre-Heart Transplant Levosimendan Administration on Post-Transplant Vasoplegia and Primary Graft Dysfunction. *Clinical transplantation*, *39*(10), e70327. https://doi.org/10.1111/ctr.70327
13. Książczyk, M., Gruchała, M., Stopczyńska, I., & Lelonek, M. (2023). A favorable alliance between repetitive use of levosimendan and advanced heart failure: Polish two-centered inpatient perspective in need of validation. *Kardiologia polska*, *81*(3), 287–289. https://doi.org/10.33963/KP.a2023.0034
14. Lannemyr, L., Ricksten, S. E., Rundqvist, B., Andersson, B., Bartfay, S. E., Ljungman, C., Dahlberg, P., Bergh, N., Hjalmarsson, C., Gilljam, T., Bollano, E., & Karason, K. (2018). Differential Effects of Levosimendan and Dobutamine on Glomerular Filtration Rate in Patients With Heart Failure and Renal Impairment:A Randomized Double-Blind Controlled Trial. *Journal of the American Heart Association*, *7*(16), e008455. https://doi.org/10.1161/JAHA.117.008455
15. Lelonek, M., Stopczyńska, I., Korościk, E., Straburzyńska-Migaj, E., & Gruchała, M. (2020). Multicenter experiences with levosimendan therapy and its safety in patients with decompensated advanced heart failure. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University*, *29*(11), 1305–1312. https://doi.org/10.17219/acem/126301
16. Milwidsky, A., Frydman, S., Laufer-Perl, M., Sadeh, B., Sapir, O., Granot, Y., Hochstadt, A., Korotetski, L., Ketchker, L., Topilsky, Y., Banai, S., & Havakuk, O. (2022). Intermittent inotropic therapy with levosimendan vs. milrinone in advanced heart failure patients. *ESC heart failure*, *9*(2), 1487–1491. https://doi.org/10.1002/ehf2.13807
17. Najjar, E., Stålhberg, M., Hage, C., Ottenblad, E., Manouras, A., Haugen Löfman, I., & Lund, L. H. (2018). Haemodynamic effects of levosimendan in advanced but stable chronic heart failure. *ESC heart failure*, *5*(3), 302–308. https://doi.org/10.1002/ehf2.12272
18. Papp, Z., Agostoni, P., Alvarez, J., Bettex, D., Bouchez, S., Brito, D., Černý, V., Comin-Colet, J., Crespo-Leiro, M. G., Delgado, J. F., Édes, I., Eremenko, A. A., Farmakis, D., Fedele, F., Fonseca, C., Fruhwald, S., Girardis, M., Guarracino, F., Harjola, V. P., Heringlake, M., … Pollesello, P. (2020). Levosimendan Efficacy and Safety: 20 Years of SIMDAX in Clinical Use. *Journal of cardiovascular pharmacology*, *76*(1), 4–22. https://doi.org/10.1097/FJC.0000000000000859
19. Pölzl, G., Allipour Birgani, S., Comín-Colet, J., Delgado, J. F., Fedele, F., García-Gonzáles, M. J., Gustafsson, F., Masip, J., Papp, Z., Störk, S., Ulmer, H., Vrtovec, B., Wikström, G., & Altenberger, J. (2019). Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period. *ESC heart failure*, *6*(1), 174–181. https://doi.org/10.1002/ehf2.12366
20. Pölzl, G., Altenberger, J., Baholli, L., Beltrán, P., Borbély, A., Comin-Colet, J., Delgado, J. F., Fedele, F., Fontana, A., Fruhwald, F., Giamouzis, G., Giannakoulas, G., Garcia-González, M. J., Gustafsson, F., Kaikkonen, K., Kivikko, M., Kubica, J., von Lewinski, D., Löfman, I., Malfatto, G., … Pollesello, P. (2017). Repetitive use of levosimendan in advanced heart failure: need for stronger evidence in a field in dire need of a useful therapy. *International journal of cardiology*, *243*, 389–395. https://doi.org/10.1016/j.ijcard.2017.05.081
21. Pölzl, G., Altenberger, J., Comín-Colet, J., Delgado, J. F., Fedele, F., García-González, M. J., Gustafsson, F., Masip, J., Papp, Z., Störk, S., Ulmer, H., Maier, S., Vrtovec, B., Wikström, G., Zima, E., Bauer, A., & LeoDOR Investigators (2023). Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period: The multinational randomized LeoDOR trial. *European journal of heart failure*, *25*(11), 2007–2017. https://doi.org/10.1002/ejhf.3006
22. Ponz de Antonio, I., de Juan Bagudá, J. S., Rodríguez Chaverri, A., García-Cosío Carmena, M. D., Arribas Ynsaurriaga, F., & Delgado Jiménez, J. F. (2020). Levosimendan as bridge to transplant in patients with advanced heart failure. *Revista espanola de cardiologia (English ed.)*, *73*(5), 422–424. https://doi.org/10.1016/j.rec.2019.10.026

23. Ráduly, A. P., Tóth, A., Sárkány, F., Horváth, B., Szentandrássy, N., Nánási, P. P., Csanádi, Z., Édes, I., Papp, Z., & Borbély, A. (2023). Omecamtiv mecarbil augments cardiomyocyte contractile activity both at resting and systolic Ca^{2+} levels. *ESC heart failure*, *10*(2), 1326–1335. https://doi.org/10.1002/ehf2.14300
24. Silvetti, S., & Nieminen, M. S. (2016). Repeated or intermittent levosimendan treatment in advanced heart failure: An updated meta-analysis. *International journal of cardiology*, *202*, 138–143. https://doi.org/10.1016/j.ijcard.2015.08.188
25. Silvetti, S., Belletti, A., Fontana, A., & Pollesello, P. (2017). Rehospitalization after intermittent levosimendan treatment in advanced heart failure patients: a meta-analysis of randomized trials. *ESC heart failure*, *4*(4), 595–604. https://doi.org/10.1002/ehf2.12177
26. Silvetti, S., Pollesello, P., & Belletti, A. (2024). Repeated Levosimendan Infusions in the Management of Advanced Heart Failure: Review of the Evidence and Meta-analysis of the Effect on Mortality. *Journal of cardiovascular pharmacology*, *83*(2), 144–157. https://doi.org/10.1097/FJC.0000000000001506
27. Sumanaru, D., Josseran, L., Essid, A., Mbieleu, B., Haegy, I., & Bergounioux, J. (2019). Levosimendan as Rescue Therapy for Acute Heart Failure in a Patient with Duchenne Muscular Dystrophy. *Pediatric cardiology*, *40*(3), 668–670. https://doi.org/10.1007/s00246-019-02072-9
28. Teixeira, A. R., Barbas de Albuquerque, F., Pereira-da-Silva, T., Gonçalves, A. V., Ilhão Moreira, R., Timóteo, A. T., Alves, J., Barquinha, S., Mata, R., Dias, M., Cacela, D., & Cruz Ferreira, R. (2025). Hemodynamic effect of outpatient levosimendan infusion assessed daily using the CardioMEMS™ invasive remote monitoring system. *Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology*, *44*(5), 281–288. https://doi.org/10.1016/j.repc.2024.11.014
29. Tycińska, A., Gierlotka, M., Bartuś, S., Gąsior, M., Główczyńska, R., Grześk, G., Jaguszewski, M., Kasprzak, J. D., Kubica, J., Legutko, J., Leszek, P., Nessler, J., Pacileo, G., Ponikowski, P., Sobkowicz, B., Stępińska, J., Straburzyńska-Migaj, E., Wojakowski, W., Zawiślak, B., Zymliński, R., … LEIA-HF Investigators (2022). Repetitive use of LEvosimendan in Ambulatory Heart Failure patients (LEIA-HF) - The rationale and study design. *Advances in medical sciences*, *67*(1), 18–22. https://doi.org/10.1016/j.advms.2021.10.001
30. Visco, V., Esposito, C., Rispoli, A., Di Pietro, P., Izzo, C., Loria, F., Di Napoli, D., Virtuoso, N., Bramanti, A., Manzo, M., Vecchione, C., & Ciccarelli, M. (2024). The favourable alliance between CardioMEMS and levosimendan in patients with advanced heart failure. *ESC heart failure*, *11*(5), 2835–2848. https://doi.org/10.1002/ehf2.14838
31. von Scheidt, W., Pauschinger, M., & Ertl, G. (2016). Long-term intravenous inotropes in low-output terminal heart failure?. *Clinical research in cardiology : official journal of the German Cardiac Society*, *105*(6), 471–481. https://doi.org/10.1007/s00392-016-0968-y
32. Zheng, Q., Lan, H., Guo, Q., Li, C., Xiong, T., Zhang, J., Wang, G., Dong, N., & Shi, J. (2023). Preoperative Levosimendan Administration in Heart Transplant Patients with Severe Hepatic and Renal Impairment: A Retrospective Study. *The heart surgery forum*, *26*(4), E346–E357. https://doi.org/10.59958/hsf.5433