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REVIEW ARTICLE

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The inodilator levosimendan: 20 years of experience in various settings of cardiac care

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ABSTRACT

Levosimendan emerged in the 1990s as a first-in-class inotrope and vasodilator that enhances cardiac contractility by sensitizing the contractile response to cardiac troponin C and causes vasodilatation by opening potassium-dependent ATP channels on vascular smooth muscle cells. Since its clinical debut in 2000, it has established itself as a valuable resource in the management of acute decompensated heart failure and is one of very few successful medical innovations of its kind in that field in recent decades. Its pharmacology is notable for delivering inotropy without an increase in myocardial oxygen consumption and for an array of secondary ('pleiotropic') effects that include an anti-ischemic effect, pre-conditioning and post-conditioning and cardioprotective effects and anti-oxidative effects.

Proceeding from those properties it has been proposed that in addition to its use in various scenarios of low cardiac output levosimendan may be beneficial in other conditions associated with acutely decompensated heart failure, including right ventricular failure, subarachnoid hemorrhage, and cardiogenic shock with multi-organ dysfunction. The potential of levosimendan for kidney protection in situations of the cardio-renal syndrome has been identified. Additional lines of investigation include the use of levosimendan for perioperative hemodynamic support, its administration as repeated intermittent infusions to sustain patients with advanced heart failure and its application in a range of critical care settings.

Levosimendan has also provided a template and a starting point for the development of a new generation of cardio-active drugs and is currently being evaluated in advanced clinical trials for the management of pulmonary hypertension in patients with heart failure with preserved ejection fraction.

Key words: inotrope, inodilator, calcium sensitization, adenosine triphosphate-sensitive potassium channels, acute heart failure, advanced heart failure, cardiac surgery, critical cardiac care.

The molecule levosimendan

The use of inotropes for correcting hemodynamic dysfunction in patients with congestive heart failure (HF) has been described over many decades [1]. In the 1990s, a new compound with both inotropic and vasodilatory properties was discovered and developed: the calcium sensitizer and potassium-channel opener levosimendan. This discovery was made possible by new insights into the molecular structure of the protein known to trigger and sustain contraction in cardiomyocytes slow-twitch muscle fibers, i.e. the cardiac isoform of troponin C [2–4], and the main mechanism of action (MoA) of levosimendan derives from its selective binding to this particular molecular target [5–11]. In parallel, other effects of levosimendan were characterized in several non-clinical models and its potassium-channel-opening effect [12] and direct effects on mitochondria [13, 14] were discovered and characterized. Furthermore, inhibition of oxidative stress and apoptosis and modulation of autophagy were suggested to represent one possible mechanisms of protection by levosimendan against cardiac, renal and liver injuries [15]. In addition, a potential role for levosimendan as nitric oxide synthase activator has been described in both endothelial cells and animal models [16, 17].

Finally, an active metabolite of levosimendan was identified and its MoA was characterized, showing similarities with its parent drug both as inotrope and vasodilator [18]. Some years ago, a review authored

by many experts in the field collected and discussed all these MoA data in the light of the pharmacological effect of levosimendan [19].

The pharmacology of levosimendan

The effects of levosimendan have been studied in various cellular, tissue, organ and animal models in vitro, ex vivo and in vivo [20]. Levosimendan was clearly differentiated from other inotropes such as enoximone [21] and milrinone [22, 23]: its unique MoA is at the origin of an inotropic effect [24] that does not entail an increase in oxygen consumption [22, 25–27], and the mechanisms involving the other targets give origin to a vasodilating effect [28-30], an anti-ischemic effect [23, 31], preconditioning, post-conditioning and cardioprotective effects [12, 32–36], anti-remodeling effects [37], anti-oxidative effects [38, 39] and positive signals on animal survival [40]. The pharmacology of OR-1896, the active metabolite of levosimendan, has also been characterized [41, 42]. Finally, the interactions of levosimendan with relevant drugs have been studied and reported [43, 44].

Clinical settings

With a range of pleiotropic effects and consequent multi-faceted pharmacology, levosimendan found clinical use in various settings of acute cardiac care. A general review of its current utility [45] described its use as hemodynamic support in acutely decompensated HF, cardiogenic shock, perioperative settings, critical care settings, weaning from respiratory support, weaning from extracorporeal membrane oxygenation (ECMO), weaning from inotrope support and advanced heart failure (AdvHF). Indeed, a consensus of experts suggested that, in addition to its use in typical scenarios of low cardiac output (CO), levosimendan might be expected to exert favorable effects in various other conditions associated with acutely decompensated HF (Tab. 1). Those additional clinical scenarios (outlined by Farmakis et al. [46]) included: acute coronary syndrome; right ventricular failure; subarachnoid hemorrhage; cardiac surgery, either with preserved organ function or complicated by renal dysfunction; hepatic injury; and cardiogenic shock with multi-organ dysfunction. In the following sections, we will systematically describe the use of levosimendan in those settings.

Acutely decompensated HF

Acute heart failure (AHF) refers to a rapid decline in cardiac pump function requiring urgent medical care. It may arise as a de novo entity in a previously asymptomatic patient or as an acute exacerbation of previously diagnosed chronic HF. AHF may be regarded as an umbrella term describing a complex clinical syndrome that may include the following conditions: worsening or decompensated chronic HF; pulmonary edema; hypertensive AHF; cardiogenic shock; HF relating to acute coronary syndromes; and isolated right-sided HF [47]. Pharmacological interventions must acknowledge these distinct clinical and pathophysiological entities. Intravenous (i.v.) inotropic support may be considered in patients with hypotension, hypoperfusion or shock for the purpose of maintaining peripheral perfusion by increasing CO and blood pressure [48].

Most inotropic drugs currently in clinical use may be described as *calcium mobilizers* that promote cardiac contractility by increasing influx of ionic calcium (Ca^{2+}) into cardiomyocytes. However, cardiomyocyte Ca^{2+} loading is associated with enhanced myocardial oxygen consumption, increased heart rate and greater risk of arrhythmias contributing to higher morbidity and mortality rates [24].

Levosimendan exemplifies an alternative approach of *calcium sensitization*, by which cardiomyocyte sar-

Table 1. Commonly encountered concomitant conditions in Acute Heart Failure patients and corresponding inotrope of choice, according to Bistola et al. [94]

Commonly Encountered Concomitant Conditions in Acute Heart Failure	Inotrope of Choice
Hypotension	Norepinephrine
	Dobutamine
	Dopamine
Beta-blockade	Levosimendan
	Milrinone
Pulmonary hypertension	Levosimendan
	Milrinone
Acute cardiorenal syndrome	Dopamine
	Levosimendan
	Dobutamine
Heart failure of ischaemic aetiology	Levosimendan
	Dobutamine
Cardiopulmonary bypass surgery	Dobutamine
	Levosimendan
	Milrinone
Sepsis-related heart failure	Norepinephrine
	Dobutamine
	Levosimendan

comeres are enabled to contract more powerfully in response to given concentrations of ionic calcium. This strategy is attractive because it offers the prospect of augmented positive inotropy without changes in Ca^{2+} homeostasis and the attendant clinical complications.

Pivotal short-term trials of levosimendan include the LIDO and RUSSLAN studies, both of which documented improvement in short- and mid-term mortality. Findings from the SURVIVE and REVIVE trials were more nuanced but a meta-analysis of all regulatory Phase II and III trials has identified a significant reduction in mortality in critically ill patients treated with levosimendan, and also in those undergoing cardiac surgery [49]. Inter-study population heterogeneity, differences in dosage regimens and the use of concomitant vasodilator or diuretic therapy may have contributed to the discrepant findings between the various levosimendan trials [50].

Despite the identification of several other drugs that operate on conceptually similar principles [24] levosimendan remains the only drug of this kind to have firmly established itself in recent years in the clinical repertoire of treatments for AHF [51]. Proceeding from that success, levosimendan's profile as an inotrope that confers short-term clinical benefits without adverse long-term events has been proposed as the benchmark and minimum standard for any future inotropic or inodilator drug developed for AHF [52], even as a complication of the acute coronary syndrome [53]. Of utmost interest in this context is the data on the effect of levosimendan on the quality of life of AHF patients [54].

Perioperative hemodynamic support

Low cardiac output syndrome (LCOS) in patients undergoing cardiac surgery is a serious complication associated with high mortality rates. Preoperative reduced left ventricular function is a prominent risk factor for LCOS, so there is logic in exploring the potential for perioperative levosimendan-mediated inotropy to try to avert the development of LCOS. [55]. (Conventional adrenergic agents confer a potential risk of increased myocardial oxygen consumption which, in the setting of LCOS, may result in cardiac ischemia, with subsequent damage to hibernating but viable myocardium. By contrast, levosimendan provides positive inotropy with a neutral effect on oxygen consumption and its preconditioning, cardioprotective and anti-ischemic effects may all be advantageous in this situation [56, 57], Meta-analysis of this proposition, reviewed in the context of a pan-European expert overview [55], has provided indications of improved survival plus a reduction in non-fatal adverse outcomes such as postoperative renal failure requiring dialysis, with greatest treatment effect observed in those with the greatest reduction in left ventricular ejection fraction (LVEF) [58]. That expert review [55] identified patients with generally compromised myocardial function (including right ventricular dysfunction) as likely candidates for perioperative levosimendan but emphasized the need for adequate hemodynamic monitoring to anticipate, prevent or treat vasodilatation-related side effects and advised not using bolus doses outside the operating room. The desirability of expanded clinical research in this area was also noted [55].

Later action to address that requirement has included the regulatory double-blind, randomized controlled trial LEVO-CTS (NCT02025621), which aimed to assess the effect of levosimendan in patients with low preoperative LVEF (EF < 35%) undergoing scheduled or urgent cardiac surgery [59].

The LEVO-CTS study confirmed the experience of earlier, smaller investigations that levosimendan is safe and well-tolerated in patients undergoing cardiac surgery with cardiopulmonary bypass who have low LVEF and are at risk of developing postoperative LCOS. Levosimendan decreased the incidence of LCOS and diminished the need for catecholamines when used during coronary artery bypass surgery. In the context of isolated coronary artery bypass grafting (i.e. with no accompanying valve surgery), levosimendan significantly decreased postoperative mortality [60].

No comparable data are available for any other inotropes, which have in fact been associated with detrimental effects on outcome [61]. A recent further exploration of this area has concluded that "Preconditioning with levosimendan, is a cost-effective strategy preventing postoperative low cardiac output in patients with moderate-severe left ventricular systolic dysfunction undergoing elective coronary artery bypass graft surgery" [62].

In critical care settings

The potential of levosimendan as a critical care resource rests substantially on its multi-faceted pharmacology, as already discussed. Applications identified in expert commentaries and supported by preliminary findings [63] include:

- cardiogenic shock;
- septic shock;
- weaning from mechanical ventilation or ECMO;
- pulmonary hypertension and right ventricular dysfunction;
- hemodynamic support in patients with diuretic resistance.

In addition, levosimendan is advocated for inotropic support in Takotsubo syndrome when the option of extracorporeal life support is unavailable [64].

The scale of studies needed for statistically robust outcomes analysis may be a challenge in critical care

(owing to small numbers of eligible patients in very focused sub-settings); or the plurality of criteria that have to be permitted to acquire sufficient numbers of patients may lead to the inclusion of a broad clinical spectrum of participants often subject to extensive polypharmacy and other interventions, all of which may obscure any further effect of the studied intervention. Smaller studies (perhaps conducted at single centers and with closely defined eligibility criteria) may be more effective for revealing positive drug effects, but the influence of their results is likely to be limited. Effective responses to this dilemma may have to include revisions of trial designs for critical care [63].

Effects on renal function

Renal dysfunction is often encountered in HF and in other situations where cardiac function is compromised (e.g. cardiac surgery or sepsis). This combination of morbidities, sometimes characterized as 'cardio-renal syndrome', is a complex pathophysiological interplay in which cardiac dysfunction may adversely affect renal function or vice versa. Renal dysfunction in the context of HF has been strongly linked with poor prognosis in various major clinical trials in HF [65].

Levosimendan's action in opening adenosine triphosphate-sensitive potassium channels in vascular smooth muscle may be a pertinent consideration in the context of renal dysfunction in HF. This action has been linked to organ-preserving effects. In conjunction with levosimendan's effects as a systemic inodilator, this action may mitigate the processes of renal dysfunction through several pathways. Systemic contributions to the renal-protective effect may include central venous and pulmonary artery wedge pressures, thereby alleviating renal vein back-pressure. In addition, levosimendan induces a predominant afferent (preglomerular) renal arteriolar vasodilatation, with accompanying increases in both renal blood flow (RBF) and glomerular filtration rate (GFR). Thus, there are indications that, in patients with HF and impaired renal function, levosimendan may exert renal-protective effects via both an increase in CO and a specific renal vasodilatory influence [65]. (It should be noted that levosimendan causes balanced increases in GFR and renal oxygen delivery. This may be significant because an isolated increase in GFR might endanger the oxygenation of the renal medulla, which is sensitive to ischemia [66].)

Results from several recent detailed pathophysiology studies in patients with HF have supported the view that levosimendan exerts distinctive and theoretically advantageous effects on various aspects of renal hemodynamics, perfusion and function [66]; in particular, while both levosimendan and dobutamine have broadly comparable effects on systemic hemodynamics and RBF, only levosimendan augments GFR [66]. It must be conceded, however, that evidence for a robust clinically favorable impact on renal function in HF is inconsistent: the largest levosimendan HF study (REVIVE I and II) yielded no significant indications of such an effect. The signals from cardiac surgery studies are also inconclusive. Further randomized controlled trials are therefore needed to explore this aspect of levosimendan. HF patients who might derive particular benefit from levosimendan therapy include (a) those with HF of ischemic origins; (b) those with well-sustained systemic blood pressure (systolic blood pressure >100 mmHg) and; (c) those being treated with beta-blockers [66].

Repeated infusion in advanced HF

The later stages of HF are characterized by declining physical capacity, often punctuated (and exacerbated) by acute decompensations that require hospitalization. Patients' symptoms become unresponsive or refractory to maximally tolerated doses of the conventional medical repertoire for HF, making it progressively more difficult to maintain functional capacity and quality of life [67]. At this stage, however, and in contradistinction to end-stage or terminal HF, some reversal of the deterioration in cardiac function and/or symptoms can still be achieved with intensive interventions. In the face of a continuing undersupply of donor hearts for transplantation, options for the management of these patients additional to all usual medications include inotropic support. Goals of therapy at this juncture include the preservation of major organ function in order to optimize patients' prospects for transplantation or implantation of a ventricular-assist device. Repetitive levosimendan therapy may potentially also contribute to a reduction in the need for emergency transplantations, although this possibility has not yet been formally examined [68].

Levosimendan, administered as intermittent i.v. infusions appears to offer preservation, or some improvement in, functional capacity and quality of life in advanced HF, with no adverse impact on life expectancy. A meta-analysis of data from 319 patients in six trials indicated that intermittent use of levosimendan was associated with a significant reduction in the number of re-hospitalizations at 3 months (16% vs. 35%, risk ratio 0.40, 95% confidence interval 0.27–0.59, $p < 0.001$) [69]. That analysis identified methodological limitations in existing studies, however, and its authors emphasized the need for large, high-quality, randomized controlled trials to provide confirmation of their finding [70]. Consideration of the potential of levosimendan in advanced HF by a panel of international experts has highlighted the fact that reliance on symptoms as an objective endpoint in HF trials can be unreliable as a metric of intervention success [70]. Inter alia, reliance

on a composite endpoint may encounter practical obstacles of duration of follow-up and the number of patients required to assure statistical power. Instead, therefore, it is proposed that a study (or studies) might be conducted using a hierarchical endpoint comprising death as a first-tier outcome, with HF-related re-hospitalization and change(s) in natriuretic peptides as lower-tier outcomes [70]. This concept is now being pursued in the LEODOR trial (NCT03437226; www.leodortrial.com) [71].

Criteria for the identification of advanced HF patients for intermittent i.v. levosimendan therapy have been proposed [68]. These comprise:

— Severe systolic dysfunction (LVEF ≤ 35%) and/or
— New York Heart Association class IIIb–IV status and/or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) levels 4–6 and/or
— Repeated hospitalization or emergency department visits (≥2 in the past year);
— All of the above despite optimal treatment for HF.

When used for intermittent i.v. therapy, it is recommended that levosimendan is administered at doses of 0.05–0.2 μg/kg/min for 6–24 h, every 2–4 weeks [68]. Flexibility is emphasized, with a suggestion that treatment may be started at a low dose then increased stepwise during the infusion period, subject to tolerability, hemodynamic stability and broader safety considerations. Use of an initial bolus dose of levosimendan is not recommended and hypokalemia and hypovolemia should be avoided before and during treatment [68]. Intermittent levosimendan therapy may be conducted on an outpatient basis provided the relevant safety dispositions are made.

Intermittent i.v. levosimendan may also have a role in the management of patients with irreversible end-stage HF but has not been formally evaluated for this purpose. In this setting, the goals of therapy differ importantly from those for advanced HF, with emphasis moving towards meeting patients' existential priorities. The well-being of patients and the avoidance of re-hospitalization are key goals, with the extension of life assigned lower priority [67].

Pharmaco-economic perspectives

Various analyses indicate that levosimendan may represent a rational and efficient use of resources due to its effects on length of hospitalization and re-hospitalization rate.

In an early example of this, Lucioni et al. [72] conducted an evaluation of levosimendan versus dobutamine for the treatment of AHF in Italy. Drawing on data from ≈300 patients treated for AHF at a single center in Rome, and with patients followed up for a year, they concluded that the incremental cost of treatment with levosimendan was in effect cancelled by the incremental savings, with the greater part of those savings accruing from a reduction in the average length of stay (LOS), with a further contribution from a lower re-hospitalization rate. In that cost analysis, therefore, levosimendan appeared to be a competitive alternative to dobutamine from the hospital perspective, even when all non-monetary health gains were excluded from consideration.

In a separate investigation, Mardiguian et al. [73] used a two-part Markov model to conduct a cost-benefit comparison (from a hospital perspective) of levosimendan and dobutamine in the perioperative treatment of patients undergoing cardiac surgery who required inotropic support. Cost-benefits were evaluated in terms of costs and bed stays in the German healthcare system using 2014 drug prices and other relevant published information, with a 3% annual discount rate. Key clinical and cost inputs included LOS, mortality, medication and adverse events.

Over a 1-year time horizon (the base-case analysis), fewer adverse events and shorter hospital LOS meant that the use of levosimendan was associated with cost savings of €4787 per patient compared with dobutamine [73].

A broader perspective on this issue is offered by the work of Nieminen and colleagues, who explored the cost-benefit economics of levosimendan therapy for patients hospitalized with AHF in seven European countries representing different economic profiles [74]. Drawing on data from Finland, Germany, Greece, Italy, Israel, Spain and Sweden, and also on extant national data on the costs of medications and the hospitalization cost per day, it was concluded that the use of levosimendan in this scenario yields a net saving to hospitals arising from the reduction in LOS. The saving was mostly modest in size (< €100) but was demonstrated for all the countries considered, ranging from €0.50 in Germany to €354.64 in Sweden [74]. Recently, a pharmaco-economic analysis was performed on the advanced HF patients enrolled in the LION-HEART study, which showed that intermittent ambulatory treatment with levosimendan generated savings for the Spanish national health system [75].

Expert opinions on use and posology

The vasodilating aspects of levosimendan's pharmacological profile are relevant to the drug's application in low-output states such as AHF. Effects that may be anticipated in AHF include improvements in hemodynamics and tissue perfusion and relief of the symptoms

of congestion and fatigue [76, 77]. To the extent that the goals of therapy in advanced HF include hemodynamic stabilization, preservation of functional capacity and mitigation of symptomsa , similar benefit may be expected from levosimendan in this situation. Moreover, the use of levosimendan in repeated intermittent cycles does not appear to be associated with an increase in mortality, contrary to experiences with conventional inotropes [76].

As a general principle, the use of inotropes, when judged appropriate, should be restricted to the lowest dose and the shortest possible period [48]. Within that general prescription, experienced expert opinion asserts that levosimendan should ordinarily be administered without a loading bolus (to mitigate any risk of hypotension). Continuous infusion for up to 24 h may be commenced at infusion rates of 0.05–0.1 μg/kg/min, although some practitioners initiate therapy at a rate of 0.2 μg/kg/min for the first 60 min (in order to reach the desired therapeutic effect more rapidly) before reducing the dose to 0.1 μg/kg/min. The levosimendan infusion rate should be closely monitored and individualized according to tolerability and hemodynamic response [78].

Various lines of evidence suggest that for patients in cardiogenic shock after cardiac surgery who require inotrope support for weaning from temporary extracorporeal life support, levosimendan may be preferable to milrinone and that it may be superior to dobutamine in terms of short-term survival [48]. These preliminary signals are, however, in need of confirmation in good-quality clinical trials.

Levosimendan can exert profound vasodilatory effects and so should be administered with caution in patients with low blood pressure. Hypovolemia should be avoided before and during levosimendan treatment, which possibly should include adjustment of dosage for any i.v. diuretics. Attention should also be paid to maintaining serum potassium levels $\geq$ 4.0 mmol/L during levosimendan infusion, in order to avert hypokalemia [77].

Research in other settings: a future for levosimendan

Levosimendan is currently being evaluated for possible therapeutic benefits in several non-clinical models and in > 30 regulatory or investigator-initiated clinical trials. We will try to describe in this section the main hypotheses and the available data.

Lines of research currently being pursued include the use of levosimendan in pulmonary hypertension and respiratory muscle dysfunction, especially in the context of amyotrophic lateral sclerosis [79]. Trials are also in progress to investigate the effects of i.v. levosimendan on cellular metabolic alterations in patients with septic shock (NCT02963454), on prognosis in acute respiratory distress syndrome (NCT04020003) and on quality of life in patients with pulmonary hypertension and HF with preserved EF (NCT03541603).

At the preclinical stage, investigations are ongoing into the potential of levosimendan for stroke prevention [80] and protection of hepatocytes from liver ischemia/reperfusion injury [81].

In addition to these direct lines of new research with levosimendan, the drug has provided structure–activity information that creates a base for the development of candidate agents such as ORM-3819, which promotes cardiac contractility through Ca^{2+} sensitization in combination with selective phosphodiesterase-III inhibition [82–84].

The discovery and development of novel cardio- and vasoactive drugs for the treatment of acute hemodynamic derangements has been characterized by repeated disappointments in recent decades and new additions to the therapeutic palette would be more than welcome [85–87]. Work proceeding from the structure–activity relations identified during the development of levosimendan provides one starting point for such activities.

Conclusions

Levosimendan emerged from research into new possibilities for inotropic therapy for HF during the 1980 and 1990s. Related lines of enquiry faltered, however, and other novel products either failed to emerge from the laboratory or failed the pragmatic tests applied to new drug therapies. To a notable extent, therefore, levosimendan is one of the few durable innovations of its kind in AHF in several decades [85–87].

This singularity has contributed to levosimendan establishing itself as a prominent addition to the medical armamentarium, aided among other things by the greatly expanded use of beta-blockers in the management of HF: the availability of a calcium-sensitizing inotrope that works by energy-neutral mechanisms not dependent on adrenergic pathways is a tangible advantage and a quality that differentiates levosimendan from conventional inotropes such as dobutamine [88, 89]. Similarly, the ability to administer levosimendan in an outpatient setting and its persistence of effect due to the formation of a long-acting active metabolite has stimulated new interest in the feasibility of ambulatory medical management for patients in the more advanced stages of HF, encouraging hopes that frequency of hospital admission may be reduced for these patients and health-related quality of life preserved. Levosimendan thus occupies a distinctive place in the medical management of AHF and AdvHF, delivering

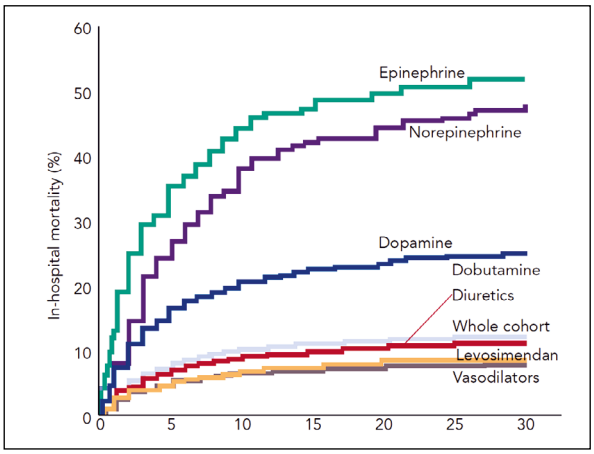

Figure 1. In the ALARM-HF registry, the use of the inodilator levosimendan was linked with a notably lower mortality rate than traditional adrenergic inotropes. Graphic rendition from data by Mebazaa et al. [95]

significant relief of HF symptoms and exerting a variety of potentially favorable effects on a range of hemodynamic, functional and neurohormonal parameters. Proceeding from these experiences, levosimendan is assigned specific roles in current expert guidelines for the treatment of AHF (a IIb recommendation for patients with peripheral hypoperfusion because of low CO) and AdvHF [90, 91].

As might be expected for a drug of its distinctive identity and longevity, clinical curiosity has led to levosimendan being evaluated for a range of applications outside its original central indication [92]. That levosimendan exerts a range of ancillary pharmacologic effects possibly relevant to various cardiovascular and critical care situations has encouraged these lines of enquiry and sustained interest in the drug during the 20 years since it was first approved for clinical use. Further research to clarify the impact of levosimendan in these spheres of use may be anticipated and in several cases is already underway (see, for example, www.leodortrial.com). Most recently, this innovation-directed outlook has seen levosimendan enter advanced clinical trials as a possible therapy for respiratory compromise in patients with ALS [79, 93].

More than 250 clinical trials in the latest 26 years have evaluated levosimendan in therapeutic settings, including perioperative and AdvHF, and an array of meta-analyses have shown a consistent trend towards efficacy and safety: in particular, the increase in mortality often identified with adrenergic inotropes has not been observed with levosimendan [49, 87] (Fig. 1).

Conflict of interest: *In the last 5 years, LT and EG have received grants and honoraria for research and educational events from Orion Pharma, the company responsible for the discovery and development of levosimendan. PP is a full-time employee of Orion Pharma.*

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