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REVIEW

An update on levosimendan in acute cardiac care: applications and recommendations for optimal efficacy and safety

Matthias Heringlake[a], Julian Alvarez[b], Dominique Bettex[c], Stefaan Bouchez[d], Sonja Fruhwald[e], Massimo Girardis[f], Elena Grossini[g], Fabio Guarracino[h], Antoine Herpain[i], Wolfgang Toller[e], Luigi Tritapepe[j] and Piero Pollesello[k]

[a]Klinik Für Anästhesie Und Intensivmedizin, Herz- Und Diabeteszentrum Mecklenburg Vorpommern, Karlsburg, Germany; [b]Department of Anesthesia and Surgical ICU, University of Santiago De Compostela, Santiago De Compostela, Spain; [c]Institute for Anaesthesiology, University Zürich and University Hospital Zürich, Zürich, Switzerland; [d]Department of Anesthesiology, University Hospital, Ghent, Belgium; [e]Department of Anaesthesiology and Intensive Care Medicine, Division of Anaesthesiology for Cardiovascular Surgery and Intensive Care Medicine, Medical University of Graz, Graz, Austria; [f]Struttura Complessa Di Anestesia 1, Policlinico Di Modena, Modena, Italy; [g]Laboratory of Physiology, Department of Translational Medicine, Università Piemonte Orientale, Novara, Italy; [h]Dipartimento Di Anestesia E Rianimazione, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [i]Department of Intensive Care, Erasme University Hospital, Université Libre De Bruxelles, Brussels, Belgium; [j]UOC Anestesia E Rianimazione, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy; and; [k]Critical Care, Orion Pharma, Espoo, Finland

ABSTRACT

Introduction: In the 20 years since its introduction to the palette of intravenous hemodynamic therapies, the inodilator levosimendan has established itself as a valuable asset for the management of acute decompensated heart failure. Its pharmacology is notable for delivering inotropy via calcium sensitization without an increase in myocardial oxygen consumption.

Areas covered: Experience with levosimendan has led to its applications expanding into perioperative hemodynamic support and various critical care settings, as well as an array of situations associated with acutely decompensated heart failure, such as right ventricular failure, cardiogenic shock with multi-organ dysfunction, and cardio-renal syndrome. Evidence suggests that levosimendan may be preferable to milrinone for patients in cardiogenic shock after cardiac surgery or for weaning from extracorporeal life support and may be superior to dobutamine in terms of short-term survival, especially in patients on beta-blockers. Positive effects on kidney function have been noted, further differentiating levosimendan from catecholamines and phosphodiesterase inhibitors.

Expert opinion: Levosimendan can be a valuable resource in the treatment of acute cardiac dysfunction, especially in the presence of beta-blockers or ischemic cardiomyopathy. When attention is given to avoiding or correcting hypovolemia and hypokalemia, an early use of the drug in the treatment algorithm is preferred.

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1. Introduction

Inotropic therapy has a long-established, although not always clearly defined, place in the treatment of heart failure. In the case of acute heart failure (AHF), whether arising de novo as a consequence of a myocardial infarction or as a decompensation of chronic congestive HF, intravenous (i.v.) adrenergic agents have been used for decades and may be regarded as the benchmark for agents of this sort. Experience with these agents has been problematic, however, with extensive reports of adverse events such as the development of cardiac arrhythmias and renal dysfunction [1] and little, if any, reliable indication that these interventions are associated with improved survival. In fact, substantial evidence points toward an increase in mortality when dobutamine is used in AHF [2] or when epinephrine is used in patients with cardiogenic shock (CS) [3]. Even norepinephrine, which is currently preferred to epinephrine in CS or AHF, was not associated with a survival benefit in a large collection of data [4,5].

Other inotropic agents, such as the phosphodiesterase (PDE)-III inhibitors milrinone and enoximone, have proved to be less than fully satisfactory alternatives to dobutamine [6–8], probably because these two drug families share a common denominator, namely that their inotropic action derives from calcium mobilization and hence an increase in myocardial oxygen consumption.

In a separate line of research started in the early 1990s, agents were discovered which enhance cardiac contractility by making cardiac muscle fibers more sensitive to free ionic calcium, instead of relying on increased concentrations of intracellular calcium.

Levosimendan is a product of that research – indeed it might be described as *the* product of that research, since no comparable or similar agent has yet matured into an internationally approved therapeutic with a recognized role in the treatment of AHF, despite several decades of effort and investigation [9]. Since 2000, when i.v. levosimendan (SIMDAX®) was first approved for clinical administration it has become an established part of the inotropic repertoire for AHF. Its pharmacology has been extensively documented, and it has been evaluated in a wide range of other acute situations

CONTACT Piero Pollesello piero.pollesello@orionpharma.com Critical Care, Orion Pharma, PO Box 65, FIN-02101 Espoo, Finland

Article highlights

- The inodilator levosimendan is established in the repertoire of hemodynamic therapies for severe heart failure with various etiologies, and in various clinical settings.
- The unique mechanism of action and pharmacology of levosimendan make it a safe choice for restoring hemodynamic and neurohormonal balance, alleviating symptoms and protecting cardiac tissue.
- In acute cardiac care, the evidence-base for using levosimendan in patients with acutely decompensated chronic heart failure treated with beta-blockers is much stronger than for any other inotrope or inodilator.
- Levosimendan evokes specific vasodilation of the renal afferent (preglomerular) arterioles, allowing the restoration of renal function and reducing the need for renal replacement therapy after cardiac surgery.
- The efficacy of levosimendan has been investigated but is still to be definitely proven in other clinical settings, such as right heart failure, perioperative low cardiac output syndrome, cardiogenic and septic shock, etc. To date, non-regulatory studies have mostly been performed in these areas; properly powered randomized controlled trials are warranted.

characterized by cardiac dysfunction, congestion, and hypoperfusion. In this concise review, we examine the evidence for the use of levosimendan in these various settings and offer some practical guidance on its safe and effective use.

2. Overview of levosimendan pharmacology

The emergence of levosimendan is grounded in research into the molecular structure and functions of the cardiac isoform of troponin C (TnC) [9,10]. The inotropic action of levosimendan derives from its selective binding to TnC [11–13], via which it promotes inotropy without increasing myocardial oxygen consumption [14–16]. This is potentially an important consideration for patients, many of whom may be in a state of precarious myocardial energy balance, and it provides a clear mechanistic differentiation from conventional inotropes, which rely on mobilizing ionic calcium, often at some expense to the cellular energy balance.

The other principal pharmacological effect of levosimendan is the mediation of vascular dilatation via the opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells [17], which causes reductions in preload and afterload and a reduction of vascular resistance in key organs [18,19]. Levosimendan can thus be defined as an inodilator. Of note in this context is a recent paper by Longrois and colleagues that highlighted the advantages of inodilators over inotropes when a less cardiocentric and more integrated framework is considered for the treatment of AHF [20].

As a third mechanism of action, levosimendan has been shown to open the mitochondrial K_{ATP} channels in several organs, including the heart, leading to ischemia-protective effects [17,21,22] as well as to pre- and post-conditioning cardioprotection [23–26], and to anti-remodeling [27]. Additional pharmacological actions of levosimendan have been reported, including activation of nitric oxide synthase [28], inhibition of oxidative stress and apoptosis, and modulation of autophagy [22,25,29–31]. The properties of levosimendan as a modulator of the oxidant/antioxidant balance and its protective effects on mitochondrial function have also been explored in CS/low cardiac output syndrome (LCOS) patients [32]. It has been suggested that these various ancillary actions of levosimendan may be relevant to its clinical profile in various scenarios [17] (Figure 1).

An active metabolite designated OR-1896 with close clinical functional similarities to its parent drug, as both an inotrope and a vasodilator, has been characterized in detail [34,35]. The persistence of this metabolite in the body (for up to a week after an infusion of the parent drug) underwrites the extended duration of effect of levosimendan and has been exploited in clinical practice, especially for the management of advanced HF in ambulatory, non-hospitalized patients.

As a summary, the principal hemodynamic effects of both levosimendan and its metabolite are dose-dependent enhancement of cardiac inotropy and CO and reductions in both right atrial pressure and pulmonary capillary wedge pressure (PCWP) [36]. Systemic vascular resistance is also reduced [37] as is pulmonary vascular resistance (PVR), notably in patients with right HF or pulmonary hypertension [38]. These qualities identify the potential of levosimendan in cases of acutely decompensated HF characterized by low CO and impaired organ perfusion as an intervention that (1) improves hemodynamics and tissue perfusion, (2) relieves symptoms of congestion and fatigue, and (3) normalizes neurohormone levels.

Levosimendan has been shown to exert selective vasodilator effects in the renal vasculature that augment renal blood flow (RBF) and glomerular filtration rate (GFR) and increase urine production [39–41]. These nominally renal-protective actions may also be relevant in the management of AHF, particularly in cases of cardio-renal syndrome, where dysfunction of either organ may induce dysfunction of the other. For completeness, we note that preliminary data have been obtained about effects of levosimendan on the liver [25,42,43] which warrant further exploration in this direction.

3. Levosimendan in acute cardiac care

3.1. Acutely decompensated HF

Levosimendan was pioneered as a treatment for acutely decompensated heart failure/acute heart failure (AHF) and its efficacy and safety in that indication have been demonstrated in randomized controlled trials involving >6000 patients, supplemented by real-world experience. Comparison with other drugs in this indication shows superiority in hemodynamic, neurohormonal, and symptomatic effects, with no signals of an adverse impact on longer-term survival [44]. Findings from meta-analysis aggregating data from >6000 patients, plus a real-world registry involving >5000 patients, are indicative of at least relative long-term survival benefit from levosimendan. At a minimum – and in clear contrast to the use of adrenergic/calcium-mobilizing inotropes such as dobutamine and epinephrine – use of levosimendan does not appear to be associated with increased mortality [4,45], with overall figures showing

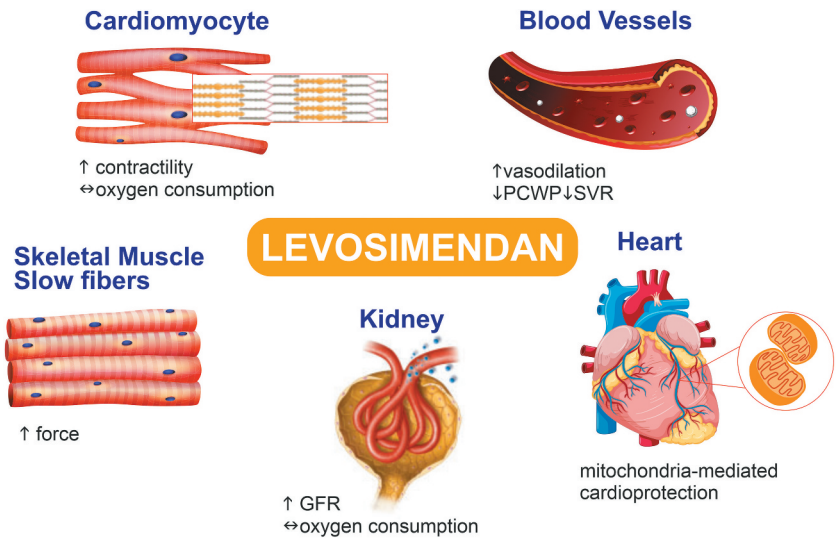

Figure 1. An overview of the pleiotropic actions of levosimendan. Levosimendan acts as an inotrope by enhancing the calcium sensitivity of troponin C in heart muscle, thereby increasing the force of contraction and ensuring an enhancement of cardiac output, without a commensurate increase in the oxygen requirements of the heart. A similar action may occur in the slow skeletal muscle fibers, for instance in the diaphragm, that would be of help in weaning from ventilation or in delaying the need for ventilation in patients with amyotrophic lateral sclerosis. By opening adenosine triphosphate-sensitive potassium channels in the vascular smooth muscle cells of certain vessels, levosimendan causes vasodilation and a reduction in systemic vascular resistance (SVR), which is also seen as a decrease in pulmonary capillary wedge pressure (PCWP), and ensuring an enhancement of cardiac output, in addition to its inotropic actions. A similar action on mitochondrial and sarcolemmal K_{ATP} channels in cardiac myocytes is linked to cardioprotection. Finally, the preferential vasodilation achieved by levosimendan on afferent versus efferent glomerular arterioles increases the glomerular filtration rate (GFR) without increasing renal oxygen demand. (From Kurdi et al. [33] with permission.).

a strong trend – albeit not a significant one – toward an increase in survival (Figure 2). This may be regarded as confirming the proposition that inotropy via calcium sensitization is preferable to that achieved via calcium mobilization, which is associated with enhanced myocardial oxygen consumption, increased heart rate, and greater risk of arrhythmias, which may contribute to worse morbidity and mortality outcomes [46].

Of further note is that the non-adrenergic mechanism of action of levosimendan means that it retains pharmacological and clinical effectiveness in patients pretreated with beta-blockers [49]. This quality has assumed prominence in an era when beta-blockers are widely used in the management of HF and the extant European Society of Cardiology (ESC) guidelines expressly identify the use of levosimendan as an option to 'reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion' [50]. Conceptually, this advantageous feature of bypassing unavailable beta-1-adrenergic receptors could be extrapolated to the common problem of downregulation (desensitization) of beta-1-adrenergic receptors faced in the context of AHF or sepsis, especially after prolonged exposure to dobutamine [51,52].

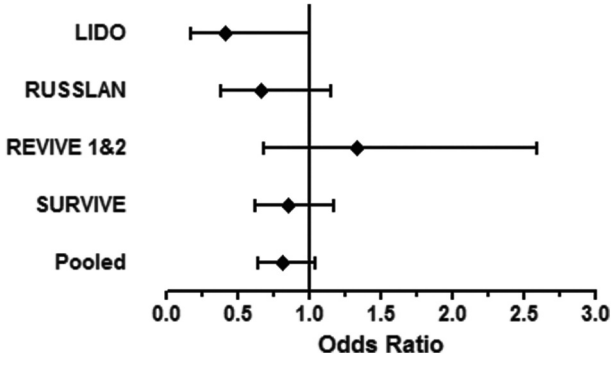

Figure 2. Meta-analysis of the effect of levosimendan on 31-day survival in the four phase III regulatory trials submitted to the authorities for the introduction of levosimendan as a treatment for acutely decompensated heart failure: LIDO (203 patients) [47]; RUSSLAN (504 patients) [48]; REVIVE 1 and 2 (700 patients) [107]; and SURVIVE (1327 patients) [117]. Pooled statistics were calculated using the Cochran–Mantel–Haenszel test, controlling for study. Total events in the pooled levosimendan arms were 167/1519 (11.0%) and total events in the pooled comparator arms were 145/1215 (11.9%). Odds ratio 0.81; 95% confidence interval 0.64–1.04.

More generally, the ESC guidelines frame the i.v. use of levosimendan and other classes of inotropes, including adrenergic agents such as dobutamine and the PDE inhibitors, with the advice that their short-term use 'may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function' [50].

Levosimendan remains the only drug of its kind to have firmly established itself in the clinical repertoire of treatments for AHF [53] and its profile as an inotrope that provides short-term clinical benefits without adverse long-term outcomes has been nominated as a benchmark for future developments [54]. Encouraging reports of the impact of levosimendan on the quality of life of AHF patients are relevant in this context [55].

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 [SBP] >100 mmHg); and (c) those being treated with beta-blockers.

Since its first introduction as a treatment for AHF in 2000, levosimendan has also been used to provide hemodynamic support in perioperative and critical care settings, CS, various forms of weaning (including from inotropic support), and advanced HF [56]. Additional applications identified for further appraisal have been identified and will be examined in this commentary [57].

3.2. Perioperative hemodynamic support

Pre- or peri-operative reduced left ventricular function is a prominent risk factor for LCOS in patients undergoing cardiac surgery, so there is a rationale to investigate the use of levosimendan to avert the emergence of LCOS. Peri-operative use of levosimendan was not associated with a statistically significant impact on overall mortality in three recent trials [58], but a trajectory toward survival benefit was noted in the LEVO-CTS trial, which also produced suggestions of greater clinical benefit in patients with severely reduced (<35%) pre-operative left ventricular ejection fraction (LVEF), especially in isolated coronary artery bypass grafting (CABG) [59]. A lower overall incidence of acute kidney injury (p= 0.02) was also recorded, as well as less need for renal replacement therapy (p= 0.02).

In a single-center study, pre-treatment with levosimendan in patients undergoing surgical myocardial revascularization resulted in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic support, and a shorter length of intensive care unit (ICU) stay [60]. Patients receiving a short infusion of levosimendan before CABG showed evidence of less myocardial damage, suggestive of a preconditioning effect [61] and emphasizing the importance of administering levosimendan as early as possible before surgery.

Several of these findings have been corroborated in a meta-analysis [62] that also identified a reduced risk of post-operative LCOS and reduced mechanical support requirements in patients with pre-operative LVEF <35% (p = 0.05). In a recent meta-analysis by Weber et al. [63] involving 27 randomized controlled trials and 3198 patients, a significant reduction in mortality was shown for prophylactic use of levosimendan in patients with severely impaired LVEF undergoing cardiac surgery (odds ratio [OR] 0.67; 95% confidence interval [CI] 0.49–0.91; p= 0.0087). Furthermore, the incidences of LCOS (OR 0.56, 95% CI 0.42–0.75; p< 0.0001), acute kidney injury (OR 0.63; 95% CI 0.46–0.86; p= 0.0039) and renal replacement therapy (OR 0.70; 95% CI 0.50–0.98; p= 0.0332) were also significantly decreased in the levosimendan group, suggesting beneficial effects from the prophylactic use of levosimendan in patients with severely impaired LVEF undergoing cardiac surgery. No comparable data are available for any other inotropes, several of which have been associated with detrimental effects on outcome [8,58].

Expert commentary on this use of levosimendan emphasizes the need for adequate hemodynamic monitoring to anticipate, prevent or treat vasodilatation-related side effects and recommends avoidance of bolus dosing outside the operating room [64].

3.3. Right ventricular failure and pulmonary hypertension

Right heart dysfunction and failure are frequent complications in patients undergoing cardiac surgery; they are associated with increased mortality and may be aggravated by post-operative pulmonary hypertension after weaning from cardiopulmonary bypass [65,66]. In addition to measures to reduce right ventricular (RV) afterload by administration of inhaled vasodilators and improving systemic perfusion pressure (and, thereby, RV coronary blood flow), augmentation of LV function with inotropic support is one key element in the medical response and levosimendan, which augments myocardial contractility and reduces PVR, is well configured for this application [67]. In addition, it is known that alterations in cellular calcium handling and contractile proteins may contribute to changes in RV inotropic response. Muscle elongation may result in mechanisms that may not support sarcoplasmic reticulum calcium uptake, and a decreased RV homeometric autoregulation is associated with alterations in calcium homeostasis in muscle strips isolated from terminally failing human hearts [68]. Because of its mechanism of action, levosimendan increases RV stroke work without affecting RV myocardial oxygen consumption, leading to an improvement in RV myocardial external efficiency in RV dysfunction [69].

A meta-analysis [70] of responses to levosimendan in patients suffering from acute right HF has identified a reduction in PVR and an increase in RVEF. These findings are complemented by the demonstration that levosimendan exerts multiple nominally beneficial hemodynamic and organ-protective effects in experimental pulmonary hypertension/RV failure [71].

First results of the phase II regulatory randomized controlled trial HELP (Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF) [72] were disclosed at the 2020 Heart Failure Society of America Annual Scientific Meeting [73]. The primary efficacy endpoint of this 37-patient study (PCWP during exercise) did not demonstrate a statistically significant reduction from baseline. However, levosimendan significantly reduced PCWP compared with baseline (p≤ 0.0017) and placebo (p≤ 0.0475) when the measurements at rest, with legs elevated and on exercise were combined. Levosimendan was also associated with a statistically significant improvement in 6-minute walk distance compared with placebo (p= 0.0329) [74].

3.4. Septic shock

Theoretical considerations, experimental research and data from small clinical trials support the expectation of a beneficial impact of levosimendan in septic shock [75]. Against these must be set the findings of the LeoPARDS trial [76], which recorded no clear benefit for prevention of organ dysfunction, albeit that levosimendan infusion was broadly very well tolerated. Reasons have been adduced to explain the negative outcome of the LeoPARDS trial, such as the

liberal inclusion criteria, specifically moderate circulatory failure or the lack of septic cardiomyopathy (SCM) per se to justify the use of an inodilating drug in an already hypotensive patient [77], which leaves open the need for further investigation more specific to sepsis-induced HF.

The currently available clinical evidence in septic shock indicates that: (a) levosimendan may be a viable alternative to dobutamine in severe de novo AHF associated with SCM and may offer additional extra-cardiac effects arising from amelioration of multi-organ failure (MOF); and (b) indiscriminate use of levosimendan (i.e. in patients with hypotension but without evidence of myocardial dysfunction) to prevent the development of MOF is hemodynamically safe but may not deliver clinical benefits. Further insights – if not the definitive answer – may emerge from the observational study GLASSES 1 (Levosimendan and Global Longitudinal Strain Assessment in Sepsis), the protocol of which was published very recently [78].

Further research in SCM is needed to examine possible interplay between the severity of cardiac failure and the timing of treatment. More generally, the risks associated with the use of vasoactive catecholamines make levosimendan a potentially useful substitute in a dobutamine-sparing approach for patients requiring inotropes. Lacking a fully evidenced alternative, however, recent guidelines [79,80] still recommend dobutamine as the first-line inotrope in cases of septic shock, despite various considerations and observations that indicate it may be associated with worse outcomes.

We remind readers that an inodilator should never be used as a first-line drug in septic shock, as reducing SVR further will worsen the hemodynamic imbalance. However, in cases of severe myocardial depression, an inodilator such as levosimendan has a role in augmenting CO. In such cases we recommend use in conjunction with a vasopressor.

3.5. Cardiogenic shock

Acute myocardial infarction (AMI) is the most common etiology of CS but CS may arise from any situation of acute, severe dysfunction in either ventricle of the heart. CS, which most usually (but not invariably) arises as a complication of AMI, is associated with very high mortality [81].

The current standard of care for CS includes primary percutaneous coronary intervention (for the initiating AMI), fluid therapy, vasopressors, inotropes and – in cases of persistent shock and in selected patients – the use of mechanical circulatory support [82–84].

Various small studies have produced indications that levosimendan may be a valid alternative to conventional inotropes for the management of CS. For instance, levosimendan (24 μg/kg bolus, then 0.1 μg/kg/min for 24 h) was superior to dobutamine (initial dose 5 μg/kg/min, with subsequent dose increases to reach the desired hemodynamic effect) for enhancing cardiac power output, even though both drugs evoked similar reductions in PCWP in a trial of 22 consecutive AMI patients who developed CS [85].

In an exploratory randomized controlled study in CS secondary to AMI (n= 32), levosimendan compared favorably with the PDE inhibitor enoximone [86]. Levosimendan (12 μg/kg over 10 min, followed by 0.1 μg/kg/min over 50 min, then 0.2 μg/kg/min for the next 23 h) or enoximone (fractional loading dose of 0.5 mg/kg, then 2–10 μg/kg/min continuously) were administered as add-on therapies to a regimen of revascularization, intra-aortic balloon pump counterpulsation, and conventional inotropes.

Beneficial hemodynamic effects were recorded in both groups but were achieved sooner with levosimendan. In addition, there were no deaths from MOF in the levosimendan group, compared with four in the enoximone group, and there was a significant 30-day survival advantage with levosimendan (69% vs 37%; p= 0.023).

A recent meta-analysis [87] of data from 13 studies (n= 648) about the effect of levosimendan in CS complicating AMI concluded that levosimendan use improved hemodynamic parameters and cardiac function and that there was no indication of an adverse effect on mortality. A separate similar analysis performed under the auspices of the Cochrane Database of Systematic Reviews [88] (13 studies; n= 2001) concluded that, at present, there is no definitive evidence favoring any inotrope or vasodilator over any others with regard to reduction of mortality in hemodynamically unstable patients with CS. The sole exception to this conclusion was an indication of a short-term survival benefit from levosimendan when compared with dobutamine. However, the level of evidence underpinning that finding was considered inconclusive and in need of fuller evaluation in adequately designed and powered prospective controlled trials.

Pending the completion of such trials, the use of levosimendan may be considered in cases of low CO associated with signs of hypoperfusion or deteriorating renal/liver function, especially if beta-blocker use is part of the clinical scenario. It may also be considered as a salvage therapy after dobutamine failure.

3.6. Weaning from respiratory and circulatory support

A substantial proportion of intubated patients in ICUs are difficult to wean from mechanical ventilation, with impacts on morbidity and mortality. Factors thought to contribute to this phenomenon include pulmonary congestion owing to HF and the development of diaphragm weakness. The pathophysiology of diaphragm weakness includes altered calcium sensitivity of the contractile proteins, so it is plausible that levosimendan may improve prospects for successful weaning in some patients [89].

In a prospective observational study in ventilator-dependent difficult-to-wean ICU patients with diminished LVEF (<40%), levosimendan improved cardiac contractility and oxygenation variables and increased the likelihood of successful separation from mechanical ventilatory support [90]. In a recently reported, double-blind, randomized, placebo-controlled trial (NCT01721434) in patients weaning from mechanical ventilation via continuous positive airways pressure, levosimendan increased minute ventilation but no direct effect on diaphragm contractile efficiency was identified [91].

In other research, two retrospective studies of weaning from venoarterial extracorporeal membrane oxygenation (VA-ECMO) [92,93] concluded that use of levosimendan was associated with a substantial improvement in weaning success rates and with lower 30-day mortality (p= 0.016) and better long-term survival [93]. Very recent data [94] show that levosimendan enables weaning from extracorporeal life support without increasing norepinephrine requirements when compared with a control group receiving milrinone. There are also indications that levosimendan may offer further potential benefits in this situation, including improvements in ventriculo-arterial coupling and endothelial function [90,94].

As a side note, recent data were collected on the role of levosimendan in weaning children requiring VA-ECMO after cardiac surgery [95]. In an observational study, 118 eligible children received 145 ECMO runs and, in 55 cases, levosimendan was administered before decannulation. In the controlled analysis, levosimendan was associated with decreased risks of both weaning failure (adjusted relative risk 0.20; 95% CI 0.07–-0.57) and in-hospital mortality (adjusted relative risk 0.45; 95% CI 0.26–0.76).

3.7. Takotsubo syndrome

Levosimendan has also been considered for inotropic support in Takotsubo syndrome when extracorporeal life support is unavailable [96]. Takotsubo syndrome-induced HF and CS are commonly treated with aggressive diuresis, hemodynamic support, and inotropic drugs. The fact that catecholamines are implicated in the pathogenesis of Takotsubo syndrome suggests that levosimendan may be considered as a viable option for inotropic therapy [97]. Supportive clinical data have been presented by Santoro et al. [98] and Yaman et al. [99]. In a very recent review [100], Santoro and colleagues go one step further toward characterizing the use of levosimendan in this therapeutic setting by stating that it may represent an option for Takotsubo patients, but that its use should be limited to patients with impaired systolic function, without left outflow tract obstruction and with systolic arterial pressure ≥90 mm Hg. We agree with Tavazzi et al. [101] that, despite a lack of data on the best treatment strategy for the acute Takotsubo phase, some reports have demonstrated a positive effect of levosimendan in accelerating ventricular function recovery.

4. Renal function effects

There are indications that in patients with HF and associated impaired renal function levosimendan may exert renal-protective effects via both an increase in CO – hence with a proportional increase in RBF – and a specific renal vasodilatory influence evidenced as a net afferent (preglomerular) vasodilatation of renal arterioles, which augments GFR [102]. Of further note, the increase in GFR is matched by an increase in renal oxygen delivery, thus mitigating the risk of under-oxygenation of the renal medulla, which is vulnerable to ischemia.

Pertinently, detailed clinical research has both clarified the effects of levosimendan on the glomerular vasculature and

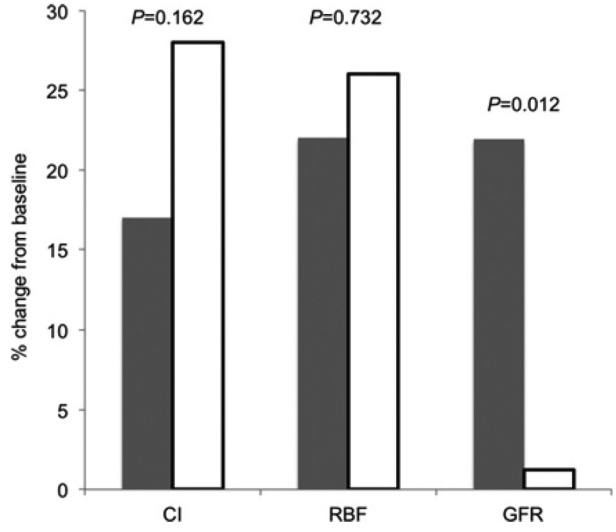

Figure 3. Relative (%) changes in glomerular filtration rate (GFR), renal blood flow (RBF), and cardiac index (CI), after administration of levosimendan (gray) versus dobutamine (white) in the randomized trial (32 patients) reported by Lannemyr et al. [103]. Following treatment, the levosimendan and dobutamine groups displayed similar increases in CI and RBF with no significant differences between groups. In contrast, GFR increased by 22% in the levosimendan group but remained unchanged in the dobutamine group (p= 0.012). Filtration fraction was not affected by levosimendan but decreased by 17% with dobutamine (p= 0.045).

demonstrated that levosimendan-induced augmentation of GFR does not compromise renal oxygenation [41], thus differentiating levosimendan in functionally important ways from agents such as dobutamine and milrinone [103,104] (Figure 3).

In a recent frequentist network meta-analysis [105] levosimendan appeared as a safe renal-protective choice for the treatment of patients undergoing cardiac surgery, especially for those with low systolic function, decreasing the risk of mortality and acute renal injury.

These observations notwithstanding, evidence for a substantive clinical impact on renal function in HF is still to be confirmed by further randomized controlled trials. Some light, however, was recently shed by Guerrero-Orriach and colleagues [106], who reported the results of the FIM-BGC -2014-01 (Renal and Neurologic Benefit of Levosimendan vs Dobutamine in Patients With Low Cardiac Output Syndrome After Cardiac Surgery) clinical trial, in which levosimendan showed a beneficial effect on renal function in LCOS patients after cardiac surgery that was independent from CO and vascular tone.

5. Safety and tolerability data

In the REVIVE-II study, 52.6% of levosimendan-treated patients experienced a reduction in BP, compared with 37.9% in the placebo group (p< 0.001) [107]

The primary endpoint of REVIVE was a composite outcome measuring changes in clinical status during the first 5 days after randomization. Judged by that metric, patients randomized to levosimendan were less likely to deteriorate than those in the control group (p= 0.015), even though intensification of adjunctive therapy occurred more frequently in placebo-treated patients. Conversely, levosimendan was

associated with more frequent hypotension and cardiac arrhythmias during the infusion period and with a numerically greater risk of death (p= 0.29).

Retrospective analyses of the data from that trial identified an association between low baseline arterial BP (BABP; specified as SBP <100 mmHg or diastolic BP [DBP] <60 mmHg) and increased mortality risk in patients treated with levosimendan: mortality was 27% for levosimendan versus 16% in the placebo group. (This excess mortality was incurred entirely during the index admission [15 vs six deaths]; deaths during follow-up were identical in the two groups [n= 29]). Exclusion of patients with low BABP eliminated this early excess mortality: overall mortality in patients with well-supported BP at baseline was then similar (levosimendan, n= 15 [7.9%]; placebo, n= 18 [9.1%]; hazard ratio 0.92; p= 0.81). The study's composite primary endpoint was still positive for levosimendan in the subset of patients with higher BABP.

These findings identified low BABP as a possible risk factor for the use of levosimendan and the current summary of product characteristics advises that levosimendan should be used with caution – and with no bolus dose – in patients with presenting SBP <100 mmHg and/or DBP <60 mmHg, or those with actual pressures above those thresholds but who are deemed to be at risk of developing hypotension. The 2016 ESC HF guidelines [50] consider that these exclusion criteria are likely to apply only to a small proportion of the eligible AHF population. Hypovolemia should be corrected as a precautionary measure, prior to infusion.

An integrated safety data summary from the pivotal placebo-controlled studies of i.v. levosimendan in AHF (prepared by Orion Pharma, which discovered and developed levosimendan and sponsored the studies in question) revealed no difference in the proportions of patients experiencing a reduction in arterial BP in response to levosimendan infusion (23.1% in both groups).

The integrated safety summary also identified a greater likelihood of atrial arrhythmias with levosimendan than placebo (8.2% vs 5.4%; p= 0.024). This difference was slightly more marked than the average in the REVIVE-II study (9% vs 2%; p< 0.001). A statistically significant difference in the incidences of ventricular tachycardia was also noted in REVIVE-II (levosimendan, 25%; placebo, 17%; p= 0.031) but that difference was not replicated in the integrated data (levosimendan, 10.0%; placebo, 11.3%; p= 0.371). There were no statistically significant differences between the levosimendan and placebo groups in respect of cardiac ischemia (7.3% vs 8.9%, p= 0.233), reduction in hemoglobin (2.3% vs 3.8%, p= 0.058), hypokalemia (4.9% vs 7.0%, p= 0.059), or increase in blood glucose (1.6% vs 2.6%, p= 0.117).

The incidences of worsening HF and renal function disturbances, recorded as adverse events, were significantly lower in the levosimendan group than the placebo group (HF events, 15.6% vs 28.4%; p< 0.001; renal events, 6.9% vs 10.4%, p= 0.007). These data are compatible with the potential renal-protective effect of levosimendan addressed earlier in this commentary but are not proof of such an effect.

The safety profile of levosimendan in AHF has also been the subject of a meta-analysis by Gong and colleagues [108] (25 randomized trials, 5349 patients). That analysis indicated increased risks of recurrence of extrasystoles (relative risk [RR] 1.88; 95% CI 1.26–2.81; p= 0.002), headache or migraine (RR 1.94; 95% CI 1.54–2.43; p< 0.00001), and hypotension (RR 1.33; 95% CI 1.15–1.53; p= 0.0001) in patients with HF when levosimendan was compared with combined control therapy of placebo or dobutamine. A separate meta-analysis by Landoni et al. [109] (45 trials, 5480 patients) failed to show any statistically significant increased risks of MI (25 studies; RR 0.786; 95% CI 0.522–1.185; p= 0.3), ventricular arrhythmias (nine studies; RR 0.855; 95% CI 0.611–1.281; p= 0.5), supraventricular arrhythmias (19 studies; RR 1.005; 95% CI 0.782–1.291; p= 0.9), hypotension (22 studies; RR 1.389; 95% CI 0.996–1.936; p= 0.053), or the composite endpoint of hypotension and/or norepinephrine use (25 studies; RR 1.219; 95% CI 0.954–1.558; p= 0.11).

6. Use and posology

As a general principle, the use of inotropes – when judged appropriate – should be restricted to the lowest dose and the shortest possible period [110]. Within that general framework, our collective opinion, based on many years of first-hand experience with levosimendan in clinical settings, is that it should, as a rule, be administered without a loading bolus (to mitigate any risk of hypotension). Exceptions to this guidance may arise in cases of cardiac surgery patients presenting with severe myocardial dysfunction, so as to ensure the administration of an adequate dose before aortic cross-clamping.

Currently accepted good practice is to initiate a continuous infusion (for up to 24 h) at infusion rates of 0.05–0.1 μg/kg/min. Alternatively, therapy may be commenced at a dose of 0.2 μg/kg/min for the first 60 min (to attain the desired therapeutic effect more rapidly) before reducing it to 0.1 μg/kg/min. In either event, the infusion rate should be closely monitored and individualized according to tolerability and hemodynamic response. CO monitoring is highly desirable in order to titrate dosage according to response. After levosimendan is introduced in CS, dobutamine may be weaned depending on the hemodynamic and clinical responses. Established chronic HF treatments should be (re-)introduced promptly after weaning of vasopressors.

Levosimendan can exert profound vasodilatory effects and so should be administered with caution in patients with low BP. Hypovolemia should be excluded using echocardiography and/or advanced monitoring and evaluation of dynamic indices before and during levosimendan treatment; observation of that precaution may extend to dose adjustment for any i.v. diuretics that are being used. Serum potassium levels should be maintained at ≥4.0 mmol/L during infusion, to prevent the emergence of hypokalemia [111].

We agree with the recently published opinion [112] that 'the nearly total absence of evidence of benefit with some of the traditional IV drugs used in acute heart failure [. . .] (such as

the catecholamines or the PDE inhibitors) would warrant their elimination from routine use in favor of treatments where such evidence has been accrued (e.g. for levosimendan).' We concur likewise with the verdict that ' … an earlier use of levosimendan in the therapy of acute heart failure has been shown to be of benefit' [113,114].

7. Expert opinion

Levosimendan has established itself as a valuable resource in the management of acute decompensated HF and is one of very few successful medical innovations of its kind introduced 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 effects that include pre-conditioning and post-conditioning, as well as anti-ischemic, cardioprotective, and anti-oxidative effects. Proceeding from those properties, it has been proposed that, in addition to its use in various scenarios of low CO, levosimendan may be beneficial in other conditions associated with acutely decompensated HF, including RV failure, perioperative hemodynamic support to prevent LCOS, and cardiogenic and septic shock. The potential of levosimendan to protect the kidneys in situations of cardio-renal syndrome has been identified. In addition, current lines of investigation include the administration of levosimendan as repeated intermittent infusions to sustain patients with advanced HF, and its application in a range of critical care settings, including Takotsubo syndrome [115].

The evolution of levosimendan has not, however, been uniformly unproblematic with non-attainment of primary endpoints in several large, controlled trials, including REVIVE II, LICORN, Levo-CTS and LEOPARDS. Particularly in REVIVE II the hazards of hypotension in the context of levosimendan use were clearly apparent and are acknowledged in the extant prescribing information and recommended posology. In the case of trials in cardiac surgery patients with or at risk of LCOS or in sepsis patients, plausible explanations have been put forward to explain the lack of success, but those must nevertheless be recognized as *post hoc* rationalizations for neutral or inconclusive outcomes and new investigations are warranted.

It has also to be recognized that the role and value of levosimendan in pulmonary hypertension is slender and inconclusive and that detailed discrimination between pulmonary hypertension in the context of right ventricular failure as opposed to pulmonary hypertension in the context of lung disease will be needed.

These qualifying remarks themselves must be put in context: a recent update of an online-assisted consensus process identified levosimendan as one of 10 non-surgical interventions that significantly reduce mortality in cardiac surgery and a majority opinion (55% of contributors) recommended its use in low ejection fraction (<35%) patients undergoing CABG to reduce mortality (Grade 1B) [116]. This is a useful illustration of the importance of careful subgroup analysis in reconceptualizing a drug with an intricate pharmacology to address specific, sometimes niche, treatment requirements for complex clinical scenarios. The impact of levosimendan on the risk of acute kidney injury (prespecified in these studies as a secondary endpoint) is another important finding that should not be obscured by the inconclusive primary endpoint results of those studies but which will require further clinical investigations to define the optimal deployment of levosimendan for this purpose.

Overarching these specific considerations is the fact that when compared with conventional adrenergic, calcium-mobilizing inotropes, levosimendan has been shown in multiple assessments to be associated with lower mortality. The deleterious effects of adrenergic inotropes are now too clearly apparent to be easily overlooked and in our opinion the fact that levosimendan can often substitute for those agents with no loss of effectiveness and no adverse impact on survival is sufficient reason to favor its use in many situations. The prominent absence of any signal for increased mortality with levosimendan in the ALARM-HF registry [4] suggests to us that levosimendan is the inotrope least likely to worsen prognosis. Given the scale of the mortality effect recorded with other agents in the ALARM-HF dataset this is a substantial consideration in its own right. More than a decade ago the SURVIVE trial investigators [117] noted that in AHF 'there is a need for agents that at least improve hemodynamics and relieve symptoms *without adversely affecting survival*'. In the intervening years, levosimendan has reliably met that standard for AHF and offers a similar advantageous profile for the other clinical scenarios examined in this review.

As a final recommendation regarding posology, we remind the reader that in the treatment algorithm of acute cardiac dysfunction, early use of levosimendan has been shown to be of benefit especially in the presence of beta-blockers, provided that hypovolemia and hypokalemia are averted.

Declaration of interest

PP is a full-time employee of Orion Pharma. Over the past 5 years, all other authors have received honoraria for educational lectures and/or unrestricted grants for investigator-initiated studies from Orion Pharma, where levosimendan was discovered and developed. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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ORCID

Piero Pollesello http://orcid.org/0000-0001-6994-768X

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