Haemodynamic Balance in Acute and Advanced Heart Failure: An Expert Perspective on the Role of Levosimendan

Piergiuseppe Agostoni,1,2 Dimitrios T Farmakis,3,4 Jose M Garcia-Pinilla,5 Veli-Pekka Harjola,6 Kristjan Karason,7 Dirk von Lewinski,8 John Parissis,4,9 Piero Pollesello,10 Gerhard Pölzl,11 Alejandro Recio-Mayoral,12 Alexander Reinecke,13 Patrik Yerly14 and Endre Zima15

Abstract
Acute and advanced heart failure are associated with substantial adverse short- and longer-term prognosis. Both conditions necessitate complex treatment choices to restore haemodynamic stability and organ perfusion, relieve congestion, improve symptoms and allow the patient to leave the hospital and achieve an adequate quality of life. Among the available intravenous vasoactive therapies, inotropes constitute an option when an increase in cardiac contractility is needed to reverse a low output state. Within the inotrope category, levosimendan is well suited to the needs of both sets of patients since, in contrast to conventional adrenergic inotropes, it has not been linked in clinical trials or wider clinical usage with increased mortality risk and retains its efficacy in the presence of beta-adrenergic receptor blockade; it is further believed to possess beneficial renal effects. The overall haemodynamic profile and clinical tolerability of levosimendan, combined with its extended duration of action, have encouraged its intermittent use in patients with advanced heart failure. This paper summarises the key messages derived from a series of 12 tutorials held at the Heart Failure 2019 congress organised in Athens, Greece, by the Heart Failure Association of the European Society of Cardiology.

Keywords
Acute heart failure, advanced heart failure, cardiorenal syndrome, inotropes, inodilators, levosimendan.

Disclosure: PP is a full-time employee of Orion Pharma. In the past 5 years, all other authors have received honoraria from Orion Pharma for educational lectures. This project did not receive any financial support, apart from logistical expenses related to the organisation of the hands-on tutorials at the annual meeting of the Heart Failure Association of the European Society of Cardiology in Athens, Greece on 26-27 May 2019, which were covered by Orion Pharma. The lecturers and programme were approved by the congress organisers.

Acknowledgement: The authors acknowledge Hughes Associates, Oxford, UK, for assistance in the preparation and editing of the manuscript.

Received: 10 June 2019 Accepted: 9 August 2019 Citation: Cardiac Failure Review 2019;5:8:155–61. DOI: https://doi.org/10.15420/cfr.2019.01.R1

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

The use of IV vasoactive drugs, diuretics, vasodilators and inotropes for correcting haemodynamic dysfunction in patients with decompensated heart failure has been described over many decades. However, data on their effects on prognosis do not offer a convincing picture of clinical benefit. This is particularly true regarding IV inotropes. Clinical data collected on the effects of cardiac glycosides, catecholamines and phosphodiesterase inhibitors indicate an overall increase in mortality risk. Increased cardiomyocyte oxygen consumption in ischaemically jeopardised myocardium, plus a heightened propensity to cardiac arrhythmias, have been proposed as possible explanations for these findings. The calcium sensitiser and potassium channel opener levosimendan has emerged in recent years as potentially a safer inotropic option than the traditional classes of cardio-mobilising drugs by virtue of its different mechanism of action. Levosimendan delivers inotropy via a broadly energy-neutral route, and vasodilation, including reduction of central venous pressure, relief of hepatic congestion and indications of improvement in renal function. Taken in combination with an extended duration of effect ascribable to a long-acting metabolite, this profile identifies levosimendan as a unique inotrope for the management of acute heart failure (AHF) and advanced heart failure (AdHF).
Advanced Heart Failure

This article presents some views on the use of vasoactive drugs in the management of AHF and AdHF that emerged during a series of tutorials held in conjunction with the annual congress of the Heart Failure Association of the European Society of Cardiology (ESC), in Athens, Greece in May 2019. Twelve speakers (from Austria, Cyprus, Finland, Germany, Greece, Hungary, Italy, Spain, Sweden and Switzerland) delivered the tutorials and collaborated in the development of this text.

Levosimendan in Acute Heart Failure

The assessment and management of AHF have been set on a robust practical footing by the most recent ESC guidelines, to which readers are referred for a comprehensive statement on this subject. Summarising broadly, AHF may be described as a situation of rapid onset or worsening of the signs and symptoms of HF. AHF must, inter alia, be characterised as a life-threatening medical condition that requires urgent evaluation and management and frequently leads to hospitalisation.

AHF may present de novo or as a deterioration in chronic HF. Many cases will arise from primary cardiac dysfunction, notably MI, but extrinsic precipitants, such as infection or anaemia, may play a role, along with an extensive range of triggering factors. Other high-risk cohorts include patients with severe aortic stenosis, mitral regurgitation, acute pulmonary embolism or serious cardiac arrhythmias.

An immediate priority in the work-up of a case of suspected AHF is to identify patients with either cardiogenic shock (CS) and/or respiratory failure. These are among the approximately 10% of patients who are critically ill and require intensive care.

Systemic blood pressure is an important guide to the classification and management of AHF. A systolic blood pressure level <90 mmHg is encountered in about 10% of patients, but the occurrence of hypotension of this degree, in conjunction with evidence of inadequate peripheral perfusion, identifies those who are candidates for inotropic therapy and, possibly, vasopressors. These patients usually correspond to the ‘wet and cold’ quadrant of the AHF clinical classification, which is associated with notably poor prognosis. Of course, these remarks should not be regarded as carte blanche for the use of levosimendan or any other specific inotrope. Indeed, it may be argued on the basis of various sources of clinical evidence that inotropes are, in general, overused in AHF, whereas vasodilators are possibly underused. Appreciation of causative pathophysiology is central to correcting this situation. AHF is a phenotype suitable for treatment with vasodilators, as the product of vasoconstriction with increase in venous return, increased left ventricular pressure and fluid redistribution leading to pulmonary congestion. Inotropic therapy is properly confined to AHF arising from a low cardiac output condition. A few observations highlight the need to improve the identification of patients who really need inotropic support (and perhaps the selection of the most appropriate inotrope for any particular case).

However, within that qualifying population, inodilators, such as levosimendan, should be the therapy of preference for patients already receiving beta-blockers, those with MI or ischaemic aetiology and those experiencing cardiorenal syndrome. Aspects of renal function in AHF and AdHF are considered later in this article.

Levosimendan in Acute Heart Failure or Cardiogenic Shock Arising from Acute Coronary Syndromes

AHF in the context of acute coronary syndromes (ACS) is an urgent situation that requires early identification and treatment, not least because AHF can deteriorate into CS. Risk factors for the emergence of AHF in ACS include advanced age, previous MI or chronic HF, diabetes, hypertension and female sex.

More than 40% of cases of AHF were encountered with episodes of ACS in the EuroHeart Failure Survey II, and the combination of ACS with AHF has been associated with very poor survival prospects. The Finnish Acute Heart Failure (FINN-AKVA) study documented an almost twofold higher 30-day mortality in AHF patients with ACS than in non-ACS cases (13% versus 8%; p=0.03). ACS–AHF was also associated with prolonged hospitalisation and with more costly treatment in the intensive care unit. Similar adverse findings for the interplay between ACS and AHF have been recorded in the CardShock study and other investigations.

As evidenced by the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, both the incidence of AHF as a complication of ACS and the mortality associated with ACS–AHF have decreased in recent years: between 1996 and 2008, the incidence of AHF as a sequel to ACS declined from 46% to 28% (p<0.001). This downward trend has been particularly marked in patients with ST-segment elevation MI and is very likely attributable to a more frequent use of primary percutaneous coronary intervention (PCI), which assures early reperfusion and salvage of jeopardised myocardium, thereby averting the emergence of AHF. The use of more high-sensitivity troponin testing to enhance detection of minor evolving ischaemia may also have contributed to this trend.

The results of the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial make a strong case for favouring a culprit-lesion-only strategy in most patients when performing PCI for ACS–AHF. The short-term risks associated with longer procedure times, more complex interventions and higher doses of contrast agents seem to outweigh any potential benefits of a multivessel approach.
There is extensive polypharmacy in ACS–AHF, with widespread use of inotropes, vaspressors and other classes of drugs, but many of these practices are empirical and pragmatic rather than evidence based.20 Formal structured research into the relative merits of different drug therapies in ACS–AHF is lacking and there is insufficient reliable information regarding the comparative efficacy of different agents.20–22

Some broad principles of therapy may nevertheless be identified. Several of these apply with special force to the management of CS, the emergence of which is identified in the 2016 ESC guidelines as a cause of AHF.23–25 The percentage of ACS episodes that progress to CS is relatively low (<10%), but short-term (in-hospital) mortality in CS is exceptionally high (40% in CardShock, higher in other reports) and CS is the leading cause of death in patients with acute MI.21,23,25

The management of CS includes haemodynamic support with inotropes and vasopressors to increase cardiac output and blood pressure in order to restore tissue perfusion. Inotropes as a broad class are endorsed to support the circulation of patients who are demonstrably hypotensive and/or hypoperfused despite adequate filling pressures. This circumscribed indication reflects concerns that conventional adrenergic inotropes (and PDE-3 inhibitors) increase cellular energy demands and oxygen consumption in a situation of ischaemic compromise and may exert undesirable tachycardic or pro-arrhythmic effects. Levosimendan, by virtue of its calcium-sensitising action, does not exert untoward effects of this kind to the same degree and, moreover, exhibits anti-stunning and condition effects that may be relevant and advantageous in states of ischaemia.26–32 The survival benefit of levosimendan in the Randomized Study on Safety and Effectiveness of Levosimendan (SURVIVE) trial supports those considerations, as do the Randomized Study on Safety and Effectiveness of Levosimendan (RUSSLAN) trial and the LIDO study.26–32 Pooled analysis of multiple individual patient data has identified a survival benefit of levosimendan in CS compared with placebo (RR 0.74, 95% CI [0.58–0.93]; p=0.01).21,33,34

The combination of vasopressors plus inodilators may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.

The combination of vasopressors plus inotropes may offer better short-term prognosis than vasopressor therapy alone (HR 0.66, 95% CI [0.55–0.80]). This proposition is based on a pooled analysis from three observational studies and requires confirmation in a suitably powered randomised controlled trial.32 The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, which contributed data to this analysis, indicated within a single dataset of reasonable size (n=4,953) that inodilator as delivered by levosimendan was associated with substantially better survival than inopressors or adrenergic inotropes (Figure 2).32 This identifies, subject to confirmation, a niche for levosimendan, which may be used in combination with noradrenaline as an alternative to dobutamine. Of note in this context, the blood pressure-lowering effect of levosimendan does not appear to require excessive increases in vasopressor dosage in CS.35 Because its inotropic effect is independent of beta-adrenoceptor stimulation, levosimendan is an appropriate haemodynamic support for ACS–AHF or CS patients on chronic beta-blocker therapy.
Levosimendan in AHF and AdHF

Expected to increase in future because of growth in the HF population and improved survival among AdHF patients.

Some published studies and some preliminary observations on the physiological effects of levosimendan in AdHF provide a starting point for an appraisal of the drug’s use in this context. A series of recent studies has examined the impact of levosimendan treatment on the lungs, heart and skeletal muscle. Collectively, these studies provided evidence that single-dose levosimendan administration to AdHF patients was accompanied by:

- improved peak oxygen uptake and amelioration of ventilation efficiency;
- reduced brain natriuretic peptide (BNP);
- increased cardiac output at rest and during exercise;
- improved lung mechanics and diaphragm function;
- restoration of the normal function of alveolar capillary cells (but not of alveolar capillary gas diffusion); and
- improved oxygen delivery to the muscle and muscle oxygen utilisation.

The Heart Failure Association of the ESC reviewed its definition of AdHF in 2018. In our collective opinion, this revised definition provides the best available starting point for a consideration of treatment options, with the proviso that it is not a guideline and that it offers neither classes of recommendation nor formal, structured levels of evidence.

Heart transplantation (HTx) remains the definitive intervention in AdHF and delivers very good outcomes. However, donor shortage limits this option to a minority of patients who must be carefully selected from those who are simultaneously at high risk of dying without a transplant and who may be expected to have good prognosis after receiving a donor heart.

For many patients rendered ineligible for HTx by virtue of age and/or co-morbidities or by the absence of a donor heart, long-term mechanical circulatory support (MCS) with continuous flow left ventricular assist devices (LVADs) may now be a valid alternative destination therapy (DT). About half of the >2,500 LVADs implanted annually in the US are intended as DT measures. Contemporary registries report good survival with LVADs as DT (78% and 68% at 1 and 2 years, respectively between 2013 and 2016 in the International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support [INTERMACS] registry).

Complication rates with MCS remain tangible, but the risk of death, disabling stroke and device reoperation has been substantially reduced with the advent of newer devices.

Many AdHF patients falling outside the parameters for HTx or MCS receive inotropes to stabilise their haemodynamic status and relieve symptoms. Repeated scheduled infusions of drugs, such as dobutamine or PDE-3 inhibitors, should be avoided because of concerns about malignant arrhythmias and increased mortality.

In contrast, the intermittent use of levosimendan has been shown to be safe and well tolerated; neither the LEVO-Rep nor LION-HEART randomised controlled trials produced indications of increases in all-cause mortality or sudden cardiac death during four and six cycles, respectively, of levosimendan therapy. In addition, levosimendan offers persistent haemodynamic improvement thanks to a pharmacologically active metabolite with a long half-life.

A survival effect of intermittent levosimendan has not been demonstrated in a properly powered randomised controlled trial, but the results of the Pulsed Infusions of Levosimendan in Outpatients With Advanced Heart Failure (Levo-Rep) and Intermittent IV Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients (LION-HEART) trials make a persuasive case for further evaluation of levosimendan.
in this context.\textsuperscript{52,54} The Repetitive Levosimendan Infusion for Patients With Advanced Chronic Heart Failure (LeoDOR) trial is currently recruiting patients for this purpose (NCT03437226a). This multicentre randomised controlled trial is designed to explore the safety and efficacy of repetitive levosimendan infusions (seven cycles at 0.2 µg/kg/min for 6 hours every 2 weeks or five cycles at 0.1 µg/kg/min for 24 hours every 3 weeks) administered to AHF patients following a recent HF-related hospitalisation.

As many as 80\% of AHF hospitalisations are the product of acute-on-chronic deterioration in haemodynamic status; this may include cases where AHF is superimposed on AdHF.\textsuperscript{40} As was exemplified in the findings of the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) study, congestion and dyspnoea precede the emergence of AdHF; more generally, haemodynamic congestion precedes symptomatic congestion, which in turn precedes hospitalisation for AHF.\textsuperscript{40} As described by Zile et al. and conceptualised by Adamson, the phase of presymptomatic congestion may precede the emergence of overt clinical symptoms by several days to weeks.\textsuperscript{41,42}

The existence of this period of preclinical decline represents an opportunity for intervention that may avert unplanned hospitalisation due to haemodynamic crisis. Given that repeat hospitalisation for AHF is associated with progressively deteriorating survival prospects, identifying and exploiting this opportunity for pre-emptive treatment is clearly in the interests of patients. Observations on the feasibility of pre-symptomatic intervention to avert hospitalisation add weight to observations in the LEVO-Rep and LION-HEART trials that use of intermittent levosimendan in outpatients with AdHF was associated with marked improvement in event-free survival (LEVO-Rep) or a reduction in HF hospitalisation (LION-HEART).\textsuperscript{53,54,58,59} A recent meta-analysis of six studies of intermittent levosimendan in chronic HF has produced an estimated risk ratio of 0.40 (95\% CI [0.27–0.59]; \textit{p}<0.00001), with consistency of effect in all the contributing studies.\textsuperscript{60}

### Differential Renal Effects of Levosimendan

Kidney dysfunction is encountered in a substantial proportion of patients with AHF or AdHF.\textsuperscript{41} In this setting, it is usually secondary to impaired cardiac function, conforming to the definition of type 1 cardiorenal syndrome (CRS). Various pathophysiological mechanisms contribute to kidney damage in CRS, including hypoperfusion, renal venous congestion and neurohormonal activation.

### Table 1: Molecular Targets and Pharmacological Effects of Levosimendan

| Molecular Targets | Pharmacological Effects |
|-------------------|-------------------------|
| Calcium sensitisation of the contractile apparatus by selective binding to calcium saturated cardiac troponin C | Inotropy without increase of calcium transient and oxygen consumption | Anti-stunning effect |
| Opening of the ATP-sensitive potassium channels on the smooth muscle of the vasculature | Vasodilation (including coronary arteries) | Increase of end-organ perfusion |
| Opening of the mitochondrial ATP-sensitive potassium channels | Cardioprotection and organ protection | Anti-ischaemic effect |

### Table 2: Indications for IV Vasoactive Drugs in Clinical Scenarios in Heart Failure

| Clinical Setting | Agent |
|------------------|-------|
| Increased pulmonary artery pressure | Levosimendan, Milrinone |
| Need for beta-blocker | Levosimendan, Milrinone |
| Hypotension | Dobutamine, Norepinephrine, Dopamine |
| Worsening renal function | Levosimendan, Dobutamine, Dopamine |
| Ischaemic disease | Levosimendan, Dobutamine |

Renal dysfunction has repeatedly been shown to be one of the most adverse prognostic indicators for patients with HF and to be linked with prolonged hospitalisation.\textsuperscript{52–65} Therefore, pharmacological and non-pharmacological interventions for AHF or AdHF need to be shaped by the ambition to preserve or rectify renal perfusion, the deterioration of which underlies the emergence of kidney dysfunction.

The use of inodilators or inotropes to avert or correct CRS may be particularly apt in patients with low blood pressure or hypoperfusion and the specific effects of levosimendan on renal vasculature and haemodynamics highlight its potential in these cases.\textsuperscript{66–69} Those effects include selective vasodilation of the renal glomerular afferent arterioles, thereby enhancing renal filtration directly as well as via its effect on cardiac output.

Lannemyr et al. recently reported that both levosimendan (loading dose of 12 µg/kg for 10 minutes, then infusion at 0.1 µg/kg/min for 65 minutes; \textit{n}=16) and dobutamine (continuous infusion started at 5.0 µg/kg/min for 10 minutes, then 7.5 µg/kg/min for 65 minutes; \textit{n}=16) improve systemic haemodynamics and renal blood flow to a similar extent in patients with chronic HF (mean baseline left ventricular ejection fraction 27\%) and impaired renal function (mean eGFR <80 ml/min/1.73 m\textsuperscript{2}).\textsuperscript{67} However, only levosimendan increased eGFR (Figure 3), supporting the proposition that levosimendan causes selective vasodilation of afferent renal arterioles whereas dobutamine dilates both afferent and efferent vessels. These data indicate that the similarity of effect on systemic haemodynamic indices may not translate into correspondingly favourable effects on renal perfusion and signal that levosimendan may be a preferred inotropic agent for the management of CRS in the setting of low-output AHF or AdHF.

Case studies reviewed at Heart Failure 2019 illustrate that levosimendan may also be appropriate as part of a bridge to transplant strategy for preserving renal function in patients with AdHF and restrictive cardiomyopathy. A series of 35 repeat courses of levosimendan therapy delivered over 20 months was associated with large and sustained improvements in a series of indicators of renal function, including creatinine, N-terminal pro-BNP and the need for oral potassium supplementation. This intervention brought creatinine levels, the most responsive and most quickly reacting indicator of haemodynamic effects on kidney function in CRS, into the normal range for six consecutive months before further clinical deterioration necessitated HTx. These experiences are consistent with an earlier
Advanced Heart Failure

report of long-term improvement in renal function in a prospective study of 40 patients with AdHF treated with levosimendan while awaiting HTx.

Conclusion

The appropriate, effective and successful use of IV vasoactive drugs in AHF and AdHF is founded on accurate assessment of the etiology of decompensation and the broader patient profile. Where congestion or hypertension predominates, and patients present with either fluid accumulation or fluid redistribution, the management emphasis should favor vasodilators and diuretics to unload the heart and mobilize fluid. Inotropes and/or vasopressors are indicated for ‘wet and cold’ patients who exhibit inadequate peripheral perfusion despite adequate filling status. These patients usually present with low blood pressure (systolic <90 mmHg), but it should be kept in mind that hypotension is not synonymous with hypotension; hypotension may not always be followed by significant hypotension, as in the presence of sympathetic overactivity causing peripheral vasoconstriction. Levosimendan is an inotrope with a unique pharmacology (Table 1), and may be appropriate for similar patients with higher blood pressure if they are refractory to vasodilator and diuretic therapy. A series of clinical scenarios warranting the use of inotropes/vasoconstrictors and/or vasopressors is shown in Table 2 and illustrates the wide-ranging utility of levosimendan in these situations.

1. Sinnerberg L, Gizewitz MM. Acute heart failure. Trends Cardiovasc Med 2018;28:729–38. https://doi.org/10.1016/j.tcm.2019.02.007; PMID: 30105522.
2. Rayner Hartley E, Ehrani S, Toma M. Update on the management of acute heart failure. Curr Opin Cardiol 2018;33:225–31. https://doi.org/10.1097/HCO.0000000000000539; PMID: 29196503.
3. Bellatti A, Castro ML, Silvetti S, et al. The effect of inotropes and vasopressors on mortality: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2015;17:1066–70. https://doi.org/10.1002/ejhf.470; PMID: 2597799.
4. Gong W, Peng H, Han J, et al. Levosimendan treatment for heart failure: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2015;39:1415–25. https://doi.org/10.1053/j.jvca.2015.03.033; PMID: 26275522.
5. Tenforch R, Metta M, Zacchi V, et al. Agents with inotropic properties: Effects on patients of acute heart failure syndromes. Traditional agents and beyond. Heart Fail Rev 2019;24:89–99. https://doi.org/10.1007/s10741-018-9513-5; PMID: 29785374.
6. Polletts P, Papp Z, Papp J. Calcium sensitizers: What have we learned over the last 25 years? Eur J Heart Fail 2018;20:165–74. https://doi.org/10.1002/ejhf.1250; PMID: 28403534.
7. Papp J, Blazso I, Orsos G, et al. Levosimendan: mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 2015;189:1–27. https://doi.org/10.1016/j.ijcard.2015.07.022; PMID: 27185460.
8. Nijenhuis MJ, Fratkowski S, Heusmans U, et al. Levosimendan: current data, clinical use and future development. Heart Lung Vasc 2015;10:327–40. https://doi.org/10.1016/j.hlrv.2015.07.007; PMID: 26606437.
9. Najafi S, Esfehmand M, Hage C, et al. Haemodynamic effects of levosimendan in advanced but stable chronic heart failure. J Am Coll Cardiol 2016;67:2129–30. https://doi.org/10.1016/j.jacc.2016.02.052; PMID: 26941772.
10. Altenberger J, Gustafsson F, Harjola VP, et al. Levosimendan in acute and advanced heart failure: An appraisal of the clinical database and evaluation of its therapeutic applications. Int J Cardiol 2017;239:129–36. https://doi.org/10.1016/j.ijcard.2017.06.033; PMID: 28197486.
11. Afdal S, Jorde N. Calcium sensitizers: Effects of calcium sensitizing agents on the heart and other organs: An expert position paper. Int J Cardiol 2016;226:83–102. https://doi.org/10.1016/j.ijcard.2016.07.020; PMID: 27493574.
12. Farimuk D, Ahmrouz S, Jall LB, et al. Tissue supporting therapy in advanced heart failure: Evidence of pleotropic effects on the heart and other organs: An expert position paper. Int J Cardiol 2016;226:83–102. https://doi.org/10.1016/j.ijcard.2016.07.020; PMID: 27493574.
13. Ponikowski P, Vora AS, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:219–30. https://doi.org/10.1002/1524-4539.EJHF13000000001353; PMID: 27204819.
14. Mousa A, Tsiang SW, Fang JC, et al. Clinical assessment identifies homodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2019;74:1177–94. https://doi.org/10.1016/j.jacc.2019.05.039; PMID: 31079300-9; PMID: 31276467.
15. Sabri K, Al-Harbi M, Al-Abdulkady M, et al. Levosimendan meta-analysis: Is there a pattern in the effect on mortality? Int J Cardiol 2016;209:77–83. https://doi.org/10.1016/j.ijcard.2016.06.048; PMID: 27298081.
16. Vora AS, Amin A, Hauptmann S, et al. Clinical assessment identifies homodynamic profiles that predict outcomes in patients admitted with heart failure. Curr Opin Cardiol 2020;35:1177–84. https://doi.org/10.1097/HCO.0000000000001353; PMID: 31276467.
17. Klar M, Al-Tawil F, Al-Rawi S, et al. Levosimendan meta-analysis: Is there a pattern in the effect on mortality? Int J Cardiol 2016;209:77–83. https://doi.org/10.1016/j.ijcard.2016.06.048; PMID: 27298081.
18. Yancy CW, Lopatin M, Stevenson LW, et al. Management of decompensation and the broader patient profile. Where congestion or hypertension predominates, and patients present with either fluid accumulation or fluid redistribution, the management emphasis should favor vasodilators and diuretics to unload the heart and mobilize fluid. Inotropes and/or vasopressors are indicated for ‘wet and cold’ patients who exhibit inadequate peripheral perfusion despite adequate filling status. These patients usually present with low blood pressure (systolic <90 mmHg), but it should be kept in mind that hypotension is not synonymous with hypotension; hypotension may not always be followed by significant hypotension, as in the presence of sympathetic overactivity causing peripheral vasoconstriction. Levosimendan is an inotrope with a unique pharmacology (Table 1), and may be appropriate for similar patients with higher blood pressure if they are refractory to vasodilator and diuretic therapy. A series of clinical scenarios warranting the use of inotropes/vasoconstrictors and/or vasopressors is shown in Table 2 and illustrates the wide-ranging utility of levosimendan in these situations.
50. Tacon CL, McCaffrey I, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med 2012;38:359–67. https://doi.org/10.1007/s00134-011-2165-6; PMID: 22402399.

51. Amstalden E, Kupcinet C, Haddour G, et al. Phosphodieserase III inhibitors for heart failure. Cochrane Database Syst Rev 2010;7:CD002328. https://doi.org/10.1002/14651858.CD002328.pub2; PMID: 15674993.

52. Metra M, Elchion E, Abraham WT, et al. Effects of low-dose oral enoximone on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trial. Eur Heart J 2009;30:3015–26. https://doi.org/10.1093/eurheartj/epn389; PMID: 19700374.

53. Alterberger J, Parrissiot J, Costard-Iassele A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomised trial. Eur Heart J 2014;36:918–931. https://doi.org/10.1093/eurheartj/ehu254; PMID: 24920349.

54. Cramin-Colet I, Mantio N, Segovia-Cubero I, et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur Heart J 2016;37:1298–310. https://doi.org/10.1093/eurheartj/ehw114; PMID: 27084611.

55. Amброси А, Панг П, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J 2018;20:1128–36. https://doi.org/10.1002/ejhf.1145; PMID: 29940039.

56. Z Tie MR, Bennett TO, St John Sutton M, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118:1483–41. https://doi.org/10.1161/CIRCULATIONAHA.107.702546; PMID: 18545758.

57. Adamson PB. Pathophysiology of the transition from chronic compensated to acute decompensated heart failure: new insights from continuous monitoring devices. Circ Heart Fail 2009;2:157–62. https://doi.org/10.1161/CIRCHEARTFAILURE.108.900339; PMID: 19748896.

58. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66. https://doi.org/10.1016/S0140-6736(11)60713-3; PMID: 21371541.

59. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. ACC Heart Fail 2014;6:335–44. https://doi.org/10.1016/j.accf.2013.11.011; PMID: 24654388.

60. Silvetti T, Bellotti A, Fontana A, et al. Repositionalization after intermittent levosimendan treatment in advanced heart failure patients: a meta-analysis of randomized trials. ESC Heart Fail 2017;4:396–406. https://doi.org/10.1002/ejhf.1217; PMID: 28984396.

61. Reid R, Zekeler SJ, Brown PM, et al. The prognostic importance of changes in renal function during treatment for acute heart failure depends on admission renal function. J Clin Oncol 2015;33:183589. https://doi.org/10.123/journal.pone.0138579; PMID: 26380962.

62. Fonarow GC, Adams KF Jr, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. Circ Arrhythm Electrophysiol 2009;2:372–80. https://doi.org/10.1161/CIRCEP.109.904165; PMID: 20031541.

63. Appleton CG, Milsch O, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8. https://doi.org/10.1161/CIRCULATIONAHA.105.580506; PMID: 16418300.

64. Smith GL, Lichstein JH, Bracken ME, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987–96. https://doi.org/10.1016/j.jacc.2005.11.004; PMID: 16973515.

65. Agostoni P, Corti U, Cabigioni G, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MEQIO score: a multiparametric approach to heart failure prognosis. Int J Cardiol 2013;167:2710–14. https://doi.org/10.1016/j.ijcard.2012.06.110; PMID: 22795407.

66. Zager RA, Johnson AC, Lund S, et al. Levosimendan protects against experimental endotoxic acute renal failure. An J Physiol Renal Physiol 2006;290:F1743–52. https://doi.org/10.1152/ajprenal.00845.2005; PMID: 16418300.

67. Reinberg S, Efterri C, Vincent JL, et al. Effects of combined arginine vasopressin and levosimendan on organ function in ovine septic shock. Crit Care Med 2010;38:2016–23. https://doi.org/10.1097/CCM.0b013e3181d44e96; PMID: 20657271.

68. Grossini E, Molinari C, Polisensi P, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. J Pharmacol Exp Ther 2012;342:215–46. https://doi.org/10.1124/jpet.112.199391; PMID: 22466668.

69. Lannemery L, Richetson SE, Rundstedt R, et al. Differential effects of levosimendan and dobutamine on glomerular filtration rate in patients with heart failure and renal impairment: A randomized double-blind controlled trial. J Am Heart Assoc 2018;7:e008455. https://doi.org/10.1161/ JAHN.117.008455; PMID: 30369101.

70. Zemljic G, Bunc M, Zaedanbakhsh AH, et al. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail 2007;13:147–21. https://doi.org/10.1016/j.cardfail.2007.03.005; PMID: 17570504.

71. Bouchez S, Fidele F, Ganiatsoulis G, et al. Levosimendan in acute and advanced heart failure: an expert perspective on pathogenesis and therapeutic applications. Cardiac Drugs Ther 2012;3:61–24. https://doi.org/10.1007/s10557-016-6838-2; PMID: 24048365.

72. Slawsky MF, Colucci WS, Gottlieb SS, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:1022–27. https://doi.org/10.1161/01.CIR.102.18.2222; PMID: 11065969.

73. Nieminen MS, Akkari A, HasERTus G, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2006;48:1903–12. https://doi.org/10.1016/j.jacc.2006.08.057; PMID: 17092463.

74. Filiatr F, Celanad IS, Izur H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the L00 study): a randomized double-blind trial. J Card Fail 2002;306:119–203. https://doi.org/10.1006/jccf.2002.3061; PMID: 11842043.

75. Mabaza A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine in patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297:1883–91. https://doi.org/10.1001/jama.297.17.1883; PMID: 17473298.

76. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. J Am Coll Cardiol 2013;61:103–11. https://doi.org/10.1016/j.jacc.2012.12.004; PMID: 24421834.