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Review

Evidence-based use of levosimendan in different clinical settings

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Levosimendan is a new calcium sensitizer and K-ATP channel opener. Compared with other inodilators, it improves myocardial contractility without increasing oxygen requirements and induces peripheral and coronary vasodilation with a potential anti-stunning, anti-ischaemic effect. The documentation regarding levosimendan is one of the largest ever on the safety and efficacy of a new pharmacological agent in acute heart failure syndromes. Recent experiences in small-scale studies and randomized clinical trials have led to greater interest in the use of this drug for the support of impaired cardiac function also in patients with ischaemic heart disease and cardiogenic or septic shock. It is also demonstrated that this drug could be used as bridge therapy for the peri-operative phase of cardiac surgery in both adult and paediatric populations. This review summarizes the evidence from published scientific literature regarding the use of levosimendan in various clinical settings.

Introduction

The role of inotropic therapy in the management of heart failure (HF) has long been a subject of controversy.[1] Although all conventional inotropic agents exert favourable haemodynamic effects, none have produced consistent improvement in symptoms or exercise tolerance, and many have shortened the survival.[2–5] These findings may be related to the fact that these agents increase myocardial concentrations of cAMP, producing an increase in intracellular calcium that possibly leads to myocardial cell death and/or increases lethal arrhythmias.[5]

Over the last few years there has been increasing interest in the pharmacological agents acting on the responsiveness of myofilaments to calcium, the so-called calcium sensitizers. These new agents enhance myocardial contraction with a unique mechanism of action that increases calcium sensitivity with lower intracellular calcium concentration requirements.

Levosimendan is the most thoroughly studied compound of this class of drugs. Its positive inotropic effect appears to be based on stabilizing and prolonging the conformational change that occurs when the drug binds to calcium-saturated cardiac troponin C (cTnC).[6,7] Unlike other calcium sensitizers, this effect of levosimendan was shown to be dependent on the concentration of intracellular ionized calcium.[6,7]

Experimental studies indicated that levosimendan increased myocardial contractility, improved haemodynamics, and dilated both the peripheral and coronary vessels.[8–10] Subsequent experiences in small-scale studies and randomized clinical trials have led to greater interest in the use of this drug for the short-term support of impaired cardiac function in various clinical settings. Recently, two large randomized controlled trials have been presented.

The aim of this review is to summarize the available evidence about the mechanism and use of levosimendan in different clinical situations. We reviewed the peer-reviewed publications identified through searches of MEDLINE from January 1990 through December 2005. Search terms included levosimendan, calcium sensitizer, inotropic agents, HF, ischaemic heart disease, cardiac surgery, and shock. The results of unpublished or ongoing trials were obtained from presentations at national and international meetings and other pharmaceutical industry releases. Bibliographies from these references were also reviewed, as were additional articles identified by content experts. Criteria used for study selection were controlled study design, relevance to clinicians and validity based on the venue of publication and power analysis.

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Pharmacology

Mechanism of action

As described earlier, a stereoselective interaction between levosimendan and the calcium-saturated cTnC forms the basis of the calcium-sensitizing mechanism of levosimendan (*Figure 1*).[11] Its binding site on cTnC was hypothesized at a hydrophobic region of the N-domain of this thin filament regulatory protein.[11–13]

Levosimendan, in common with related compounds, inhibits phosphodiesterases (PDEs) and in particular PDE-III (1300-fold more potently and 90-fold more selectively than enoximone) in human cardiac myocytes that increases calcium influx through sarcolemmal channels.[14,15] In spite of a structural similarity with molecules belonging to the PDE-inhibitor family, levosimendan does not increase intracellular levels of cAMP and thus the amplitude of the intracellular calcium transient in a variety of experimental models.[6] In fact, several reports have stated that levosimendan either did not increase the intracellular calcium at concentrations that are likely to occur *in vivo*,[16–18] or not to levels high enough to explain its positive inotropic effect at therapeutic concentrations.[17,19,20]

In addition to calcium sensitization, levosimendan also stimulates ATP-sensitive K^+ channels that are suppressed by intracellular ATP and acts synergistically with nucleotide diphosphates.[21] This mechanism may contribute to the vasodilator action of this agent (*Table 1*). Similar effects in cardiomyocytes may protect ischaemic myocardium because the activation of ATP-sensitive K^+ channels would likely occur in ischaemic regions in which the intracellular ADP concentration is increased and the intracellular ATP concentration is decreased.[21,22] Finally, levosimendan also opens the cardiac mitochondrial of ATP-sensitive K^+ channels, a potentially cardioprotective mechanism linked to the preconditioning in response to oxidative stress.[22–24]

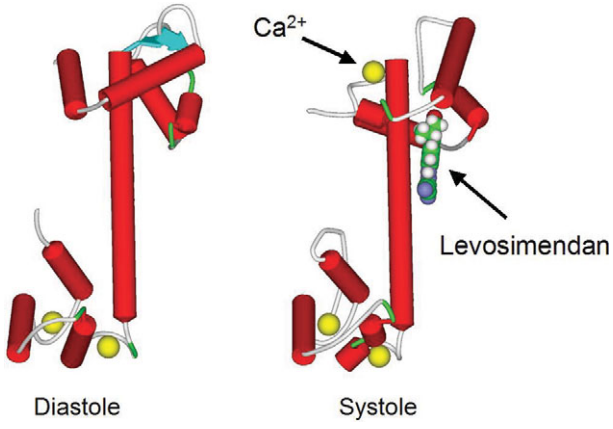

Figure 1 Mechanism of action of levosimendan. Calcium binding to the N-terminal module of troponin C (e.g. during systole) exposes a hydrophobic binding pocket for levosimendan. The binding of levosimendan to troponin C helps stabilize the binding of calcium to troponin C, thereby prolonging calcium binding for a short period of time. In the absence of calcium (e.g. during diastole), the levosimendan binding pocket is not exposed thereby preventing the binding of levosimendan.

Table 1 Dual mechanism of action of levosimendan and possible related effects

• Ca^{2+}-dependent binding to cardiac troponin C
Enhanced myocardial contractility
No impairment of myocardial relaxation
No increased oxygen consumption
• ATP-dependent K^+ channel activation in cardiac myocytes
Anti-stunning effects
Anti-ischaemic effects

Metabolism

Levosimendan is completely metabolized prior to excretion. Approximately 5% of a dose is converted to OR-1855 in the intestines, and then to a highly-active metabolite OR-1896 with an elimination half-life of 75–80 h (compared to 1 h for levosimendan itself). This metabolite reaches a peak plasma concentration about 2 days after the termination of the infusion and exhibits haemodynamic effects similar to those of levosimendan.[25] Because of the long half-life of the active metabolite, these effects last for up to 7 to 9 days after discontinuation of a 24-h infusion of levosimendan.[26]

Levosimendan in patients with HF

The safety and efficacy database on levosimendan is one of the largest for a new pharmacological agent in acute HF syndromes (AHFS). To date, levosimendan is the only drug that appears to produce clinical improvement sustained beyond the period of treatment in patients with AHFS.[27–29] The studies include investigations against placebo and the active comparator dobutamine (*Table 2*).

The recent guidelines on the diagnosis and treatment of AHFS from the European Society of Cardiology,[30] suggested the use of levosimendan in patients with symptomatic low cardiac output HF secondary to cardiac systolic dysfunction without severe hypotension (Class of recommendation IIa, level of evidence B).

Dose-ranging and dose-escalation studies

The first double-blind, placebo-controlled, randomized dose-ranging study analyzed the effects of different doses of intravenous levosimendan compared with placebo and dobutamine in 151 patients with stable NYHA class II–IV HF.[31] Levosimendan was given as a 10 min loading dose of 3, 6, 12, 24 or 36 μg/kg, followed by a 24-h infusion of 0.05, 0.1, 0.2, 0.4, or 0.6 μg/kg/min, respectively. The primary endpoint was the proportion of patients achieving at least one of the following: a ≥15% increase in stroke volume; a ≥40% increase in cardiac output; a ≥25% decrease in pulmonary capillary wedge pressure (PCWP); or a ≥50% decrease in PCWP during two consecutive measures. Levosimendan exerted a dose-dependent effect on cardiac output, stroke volume, and PCWP. At 23–24 h, all doses of levosimendan produced significantly larger decreases in PCWP than dobutamine and infusions of 0.4 and 0.6 μg/kg/min produced significantly larger increases in cardiac output. There were no significant differences in stroke volume changes between the dobutamine and levosimendan groups at any time.[31]

In a double-blind, placebo-controlled, randomized dose escalation study, 146 patients with AHFS and left ventricular (LV) systolic dysfunction were randomized to levosimendan

Table 2 Major clinical studies using intravenous levosimendan in different clinical settings

Study	Patients	Levosimendan dosage	Comparator	Aim	Outcomes
HF					
Nieminem *et al.*[31]	151 with NYHA II–IV	3–36 μg/kg + 0.05–0.6 μg/kg/min	Dobutamine (6 μg/kg /min) and placebo	Effects on haemodynamics	Levosimendan treatment was associated with dose-dependent favourable haemodynamic responses
Slawsky *et al.*[32]	146 with advanced HF	6 μg/kg + 0.1–0.4 μg/kg/min	Placebo	Effects on haemodynamics and symptoms	Levosimendan provided favourable haemodynamic benefit and symptomatic relief
Kivikko *et al.*[26]	146 with decompensated HF	6 μg/kg + 0.1–0.4 μg/kg/min	Placebo	Determine whether the haemodynamic effects of levosimendan are sustained after the discontinuation of drug infusion	The haemodynamic effects of levosimendan were maintained during a 48-h continuous infusion and for at least 24 h after discontinuation of a 24-h infusion
Nanas *et al.*[34]	18 refractory to dobutamine and furosemide	6 μg/kg + 0.2 μg/kg/min as adjunctive therapy	Dobutamine (10 μg/kg/min)	Magnitude and duration of haemodynamic effects of a combined infusion of dobutamine and levosimendan in end-stage HF	The combined treatment improved haemodynamics and symptoms for 24 h
Parissis *et al.*[36]	27 with decompensated advanced HF	6 μg/kg + 0.1–0.4 μg/kg/min	Placebo	Effects on circulating pro-inflammatory cytokines and apoptosis mediators	Levosimendan reduced the levels of IL-6, soluble Fas and Fas-ligand
LIDO Trial[49]	103 with severe HF	24 μg/kg + 0.1 μg/kg/min	Dobutamine (5 μg/kg/min)	Effects on haemodynamics and outcomes	Levosimendan improved haemodynamics and survival at 180 days
CASINO Trial[51]	227 with decompensated low-output HF	16 μg/kg + 0.2 μg/kg/min	Dobutamine (10 μg/kg/min) and placebo	Effects on death and rehospitalization due to HF deterioration	Clear mortality benefit in favor of levosimendan
REVIVE Trial[51,52]	700 with HF and symptoms at rest	0.1–0.2 μg/kg/min (I)	Placebo	Effects on composite clinical endpoints	Levosimendan produced an early greater symptom response and decreased creatinine and BNP levels
SURVIVE Trial[54]	1327 with decompensated HF requiring inotropes	12μg/kg + 0.1–0.2 μg/kg/min	Dobutamine (5–40 μg/kg/min)	Effects on mortality at 180 days	No differences in terms of mortality between levosimendan and dobutamine
CS					
Lilleberg *et al.*[55]	23 after CABG	8 or 24 μg/kg (B)	Placebo	Effects on systemic and coronary haemodynamics and myocardial substrate utilization	Levosimendan improved systemic and coronary blood flow and did not increase myocardial oxygen consumption or change substrate utilization

Labriola *et al.*[57]	11 with severe LV dysfunction after CS	12 μg/kg + 0.1 μg/kg/min	—	Efficacy in low-output syndrome following CS	In eight patients, cardiac index was increased by >30% and PCWP reduced to <18 mmHg within 3 h
Nijhawan *et al.*[58]	18 after CABG	0.2–0.3 μg/kg/min (I)	Placebo	Efficacy after cardio-pulmonary bypass	Increased cardiac output and reduced systemic vascular resistance
Barisin *et al.*[59]	31 after CS	12–24 μg/kg (B)	Placebo	Effects on ischaemic myocardial impairment during and after off-pump CABG	Increase in cardiac output, EF, and decrease in systemic vascular resistances
Plochl and Rajek[56]	10 after CS	0.1–0.2 μg/kg/min (I) as adjunctive therapy	—	Effects on haemodynamics in critically ill post-operative patients	Levosimendan increased cardiac output and stroke volume with decreases in systemic vascular resistance
Ischaemic heart disease					
Sonntag *et al.*[70]	24 with ACS	24 μg/kg (B)	Placebo	Effects LV function after coronary angioplasty	Levosimendan improved the function of stunned myocardium
De Luca *et al.*[72]	26 with AMI	12 μg/kg (B)	Placebo	Effects on haemodynamics and coronary flow velocities after primary angioplasty	Levosimendan improved haemodynamics and coronary flow reserve
Michaelis *et al.*[73]	10 with CAD	24 μg/kg (B)	—	Effects on coronary vasculature, myocardial wall stress and oxygen uptake	Levosimendan exerted vasodilator effects on coronary conductance and resistance arteries, decreasing myocardial oxygen extraction
RUSSLAN Trial[74]	504 LV failure complicating AMI	0.1–0.4 μg/kg/min (I)	Placebo	Effects on composite clinical end-points	Incidence of ischaemia and/or hypotension was similar in all treatment groups. Mortality was lower with levosimendan at 14 and 180 days
Shock					
Delle Karth *et al.*[80]	10 with cardiogenic shock	0.1 μg/kg/min (I)	—	Efficacy in cardiogenic shock following acute ischaemia or cardiac surgery	Levosimendan treatment resulted in a significant increase in cardiac output together with a decrease in systemic vascular resistance
Lehmann *et al.*[81]	10 with cardiogenic shock undergoing emergency surgery	6 μg/kg + 0.2 μg/kg/min	—	Efficacy in high risk patients, with cardiogenic shock and acute ischaemia	8 patients survived without any multiorgan failure
Morelli *et al.*[88]	28 with septic shock	0.2 μg/kg/min (I)	Dobutamine (5 μg/kg/min)	Efficacy in sepsis-induced dysfunction	Levosimendan improvef systemic haemodynamics and regional perfusion

(B), bolus only; (I), infusion only.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CS, cardiac surgery; EF, ejection fraction; HF, heart failure; LV, left ventricle.

or placebo treatment for 6 h.[32] Levosimendan was initiated with a 6 μg/kg bolus and an infusion dose of 0.1 μg/kg/min, with uptitration by 0.1 μg/kg/min increments until a maximum infusion dose of 0.4 μg/kg/min was achieved, or until a dose-limiting adverse event occurred. The primary endpoint was the proportion of patients with an increase in stroke volume or a reduction in PCWP ≥25% at 6 h. The secondary endpoints were the change in stroke volume and PCWP over time and assessments of dyspnea and fatigue by the patient and physician at 6 h. Levosimendan was associated with dose-dependent increases in stroke volume and cardiac index and declines in PCWP that were significantly different from placebo at all doses tested. Heart rate did not increase at the two lowest infusion rates of levosimendan but increased with further uptitration to a maximal increase of 6 ± 1 bpm at 6 h (vs. 1 ± 1 bpm for placebo). Levosimendan also caused a modest decrease in mean arterial pressure, with a maximum decrease of 6 ± 1 mmHg at 6 h (vs. an increase of 1 ± 1 mmHg for placebo).[32] Assessments of dyspnea and fatigue at 6 h demonstrated that levosimendan also provided a significant symptomatic relief compared with placebo ($P = 0.037$).[32]

A series of dose-ranging and tolerability studies of intravenous levosimendan were also conducted in 40 patients with low-output HF as preparation for the Levosimendan Infusion vs. DObutamine (LIDO) study described below.[33] Response rates to levosimendan therapy (defined as >30% increase in cardiac index during administration) were observed in 73–100% of cases (compared with 60% with dobutamine administered at 8–16 μg/kg per minute) with a dose dependence for several haemodynamic parameters.[33] From experience in these studies, it was concluded that the preferred levosimendan dose for the subsequent trial was 12 μg/kg for the bolus, followed by infusion at rates up to 0.2 μg/kg per minute.

Small clinical studies

Several studies explored the effects of intravenous levosimendan on various interesting aspects related to management of HF patients (*Table 2*).

Haemodynamic effects of levosimendan and dobutamine

Because levosimendan sensitizes cTnC to calcium in a calcium concentration-dependent manner, whereas dobutamine increases the intracellular concentration of free calcium, some authors hypothesized that the effects of this drug combination could be beneficial.

Nanas *et al.*[34] added levosimendan (6 μg/kg followed by 0.2 μg/kg/min) to a continuous infusion of dobutamine and furosemide in 18 critically ill patients hospitalized for end-stage chronic HF refractory to dobutamine alone. At 24 h, the combined treatment was associated with a significant increase in cardiac index (mean 0.76 ± 0.78 L/min/m^2) and decrease in PCWP (mean 6.4 ± 7.3 mmHg), compared with dobutamine infusion alone.[34]

In another non-randomized study from the same group, 36 consecutive patients with systolic dysfunction and advanced chronic HF, who were resistant to 24-h continuous dobutamine infusion, received an adjunctive continuous infusion of dobutamine at 10 μg/kg/min for >48 h, followed by weekly intermittent 8-h infusions (or more often if needed), or an adjunctive 6 μg/kg bolus of levosimendan followed by a 24-h infusion of 0.2 μg/kg/min, and other 24-h infusions of 0.2 μg/kg/min every 2 weeks.[35] Importantly, the addition of intermittent levosimendan infusions was associated with improved 45-days survival of these advanced HF patients.[36]

Effects on cytokine levels

The beneficial effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators have been shown in a randomized, placebo-controlled study.[36] Fourty-eight hours after administration, levosimendan was associated with significant reductions of circulating interleukin-6 (IL-6) and soluble Fas and Fas-ligand in 27 patients with systolic LV dysfunction and NYHA functional class III–IV HF.[36] Notably, a significant reduction in serum IL-6 was maintained until 10 days after the drug administration.[37]

Effects on natriuretic peptide levels

Recent clinical and laboratory data suggest that high plasma B-type natriuretic peptide (BNP) plasma concentrations (and plasma BNP precursor forms) are an independent marker for subsequent mortality in patients with chronic HF.[38,39]

Gegenhuber *et al.*[40] reported the favourable time course of invasively measured haemodynamic parameters and of circulating BNP and N-terminal proBNP (NT-proBNP) in 11 patients with decompensated chronic HF as a response to intravenous levosimendan treatment. Also Kyrzopoulos *et al.*[41] observed a significant reduction of NT-proBNP and IL-6 levels with a good correlation between the levosimendan-induced changes in NT-proBNP levels and a concomitant reduction of PCWP in patients with decompensated advanced chronic HF within 72 h after the initiation of treatment.[42] In accordance to these results, other authors demonstrated that levosimendan produces a significant reduction in BNP, IL-6, malondialdehyde, but not TNF-α levels, at 5 days compared with dobutamine in 29 consecutive patients with AHFS.[43]

Parissis *et al.*[44] showed that levosimendan induced a significant decrease in plasma BNP levels in a group of 34 patients with decompensated chronic HF. Interestingly, the percent BNP change was significantly correlated with changes in LV diastolic indexes. Moreover, a greater percent BNP change was correlated with a less severe disease progression, defined as re-hospitalization or death during the 5-month period following levosimendan therapy.[44]

Effects on neurohormones levels

It is well known that elevation of neurohormones in chronic HF has been associated with a worsening prognosis.[45,46] Because two dose-ranging studies conducted in HF patients demonstrated changes in neurohormonal activation immediately after a levosimendan infusion compared with dobutamine,[31,33] some authors specifically studied the effects of this new agent on neurohormonals levels.

Neurohumoral responses (plasma noradrenalin, adrenalin, and atrial natriuretic peptide) at rest and during exercise at two workloads, together with cardiac function and peripheral blood flow have been assessed in 14 healthy young men after administration of two different doses (6.5 or 25 μg/kg) of levosimendan.[47] Of the catecholamines measured, only noradrenalin level was slightly increased

after the higher dose of levosimendan. Therefore, levosimendan seemed to mildly activate the sympathoadrenal system during exercise, possibly secondary to a decrease in blood pressure.

The administration of intravenous levosimendan (0.1–0.4 μg/kg/min for 24 h) has also been associated with a significant reduction in plasma levels of endothelin-1, but not in norepinephrine levels in 79 patients with advanced HF.[48] This degree of reduction in endothelin-1 could have significantly lowered the vascular impedance and made a significant contribution to improved haemodynamics.

Large randomized clinical trials

The effects of levosimendan in patients with low-output HF have been studied in few randomized clinical trials (*Table 2*). Results from these trials indicate that this agent improves haemodynamics and symptoms in patients with HF. In addition, several of these trials suggest that levosimendan provides a survival advantage compared with conventional treatments for HF.

The LIDO study was a double-blind, double-dummy, parallel-group trial that randomized 203 patients with severe low-output HF [defined as LV ejection fraction (LVEF) $<35\%$ within 1 month of study enrollment, cardiac index <2.5 L/min/m^2, and PCWP >15 mmHg] to levosimendan (loading dose of 24 μg/kg followed by an infusion of 0.1 μg/kg/min for 24 h) or dobutamine (started with a continuous infusion of 5 μg/kg/min).[49] The primary endpoint of the trial was the proportion of patients with haemodynamic improvement (defined as $\geq 30\%$ increase in cardiac output and $\geq 25\%$ decrease in PCWP) at the end of the drug infusion. Secondary endpoints included other haemodynamic measures, assessments of symptoms, the number of days alive and out of the hospital, and all-cause mortality at 31 days. A retrospective analyses of the number of days alive and out of the hospital and all-cause mortality at 180 days were also conducted.[49]

Compared with dobutamine, a significantly higher proportion of levosimendan patients experienced haemodynamic improvement with a clear increase in cardiac output and decrease in PCWP (*Figure 2*). Interestingly, a subgroup analysis demonstrated that the use of β-blockers enhanced the haemodynamic effects of levosimendan but reduced the haemodynamic effects of dobutamine. Levosimendan treatment was associated with a significant improvement in overall survival at 31 days.[49] The number of days alive and out of the hospital at 31 days was also reduced, almost entirely related to the lower mortality rate rather than a reduction in re-admissions. Also at 180 days, the retrospective analysis revealed a significant improvement in survival for patients treated with levosimendan compared with dobutamine (*Figure 3*).[49]

The CAlcium Sensitizer or Inotrope or None in Low-Output HF Study (CASINO) was an investigator-initiated randomized, double-blind, double-dummy, parallel-group trial conducted in 299 patients with decompensated low-output HF comparing levosimendan with dobutamine and placebo.[50] The primary endpoint was the composite of death or re-hospitalization due to HF deterioration. The study, not yet published, was designed to recruit 600 patients but it was stopped after 299 patients had been enrolled

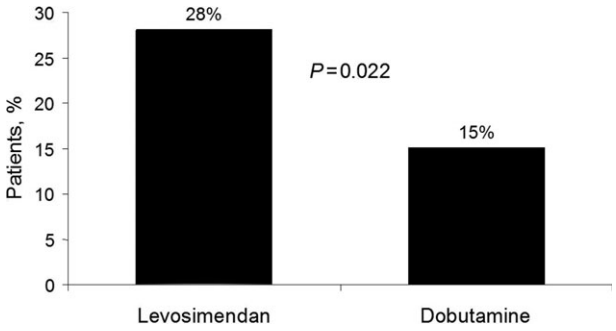

Figure 2 Percentages of patients in both levosimendan and dobutamine groups that reached the primary endpoint in the LIDO trial.[49]

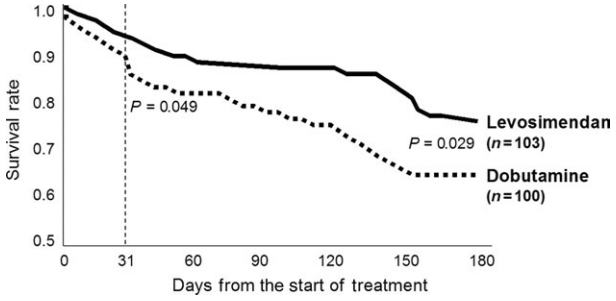

Figure 3 Kaplan–Meier survival analysis in the LIDO trial (modified from Follath *et al.*[49]). The prospective benefit observed at 31 days for levosimendan-treated patients was maintained through the 180-day follow-up period.

because of the survival benefit at 6 months associated with levosimendan treatment (*Figure 4*).

The Randomized multicenter EValuation of Intravenous leVosimendan Efficacy vs. placebo in the short-term treatment of decompensated HF (REVIVE) study was a double-blind, placebo-controlled trial conducted in patients who were hospitalized for AHFS with an LVEF $\leq 35\%$ and dyspnea at rest and requiring intravenous diuretics.[51] Patients were randomly assigned to receive either levosimendan or placebo in addition to standard care. Levosimendan was administered at a loading dose of 12 μg/kg over 10 min followed by an infusion of 0.1 μg/kg/min for 50 min, which if well tolerated was increased to 0.2 μg/kg/min for an additional 23 h. This study consisted of two phases: a pilot study (REVIVE-1) to evaluate the performance characteristics of a new clinical composite endpoint relative to conventional metrics for HF, and a full-scale pivotal trial (REVIVE-2).

The clinical composite endpoint of these studies was a combination of symptoms or clinical status assessment and occurrence of major clinical events.

Data from the REVIVE-1 trial showed a trend toward improvement in the prespecified composite endpoint of improvement at 24 h and 5 days in the levosimendan group. However, when the 6 h time point was also included, the findings reached statistical significance (*Figure 5*), and the endpoint was subsequently modified to include this time point in the REVIVE-2 trial. This endpoint is unique in AHFS trials because it requires improvement both early in the course of treatment as well as persistence of the benefit beyond the acute treatment phase. In addition, REVIVE-1 showed significant reductions in serum BNP levels

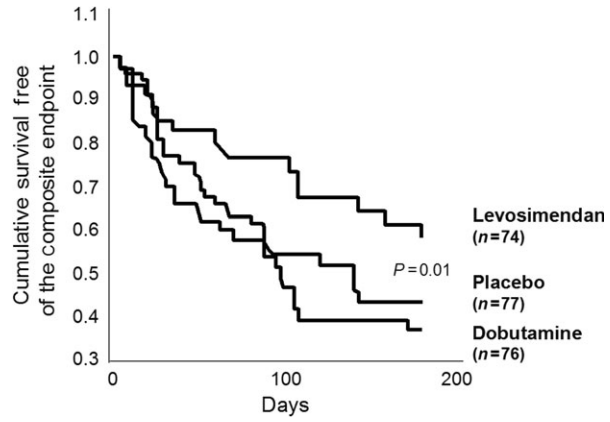

Figure 4 Survival curves for the three treatment arms of the CASINO study before complete follow-up of patients.[50]

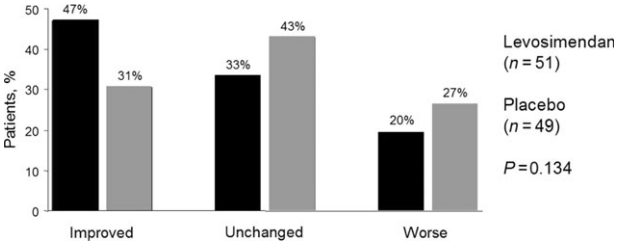

Figure 5 Primary endpoint results from the REVIVE-1 trial.[51] A trend toward improvement in levosimendan group was found across the three categories of patient distribution.

compared to the placebo group (consistent with other studies) and a trend toward a decrease in serum creatinine concentration at 24 h and 5 days in the levosimendan group.[51]

The REVIVE-2 study has recently been completed and the major results were presented in preliminary form at the 2005 Annual Scientific Sessions of the American Heart Association.[52] This study enrolled 600 patients who could receive stable doses of dobutamine, nesiritide and nitroglicerine. Worsening HF requiring rescue IV therapy developed in 15% of patients in the levosimendan group and 26% of patients in the control group. Such therapy was prompted primarily by worsening dyspnea, pulmonary edema, or renal function. The overall composite endpoint was significantly improved in the levosimendan group compared to the control group, as a result of more patients indicating that they were improved and fewer exhibiting deterioration or lack of response at each of the time points. However, the beneficial clinical responses with levosimendan were associated with increased incidences of hypotension (49.2 vs. 35.5%), headache (29.4 vs. 14.6%), episodes of ventricular tachycardia (24.1 vs. 16.9%), ventricular extrasystoles (7.4 vs. 0.2%) and atrial fibrillation (AF)(8.4 vs. 0.2%), and a higher early mortality rate (15.1 vs. 11.6%), although at the prespecified time points of 31 and 90 days, no significant survival differences were present.[52]

The SURVival of Patients with Acute HF in Need of Intra-VEnous Inotropic Support (SURVIVE) study was the first prospective, double-blind, randomized trial utilizing mortality as the primary endpoint in evaluating the efficacy of levosimendan as compared with dobutamine.[53] This trial entered 1327 hospitalized patients with severe AHFS, LVEF $\leq$30% and clinical need for intravenous inotropic support after IV diuretics and/or vasodilators. The primary endpoint of this study was mortality during 180 days after the start of treatment. Secondary endpoints included the number of days alive and out of the hospital during the 180 days of the trial, all-cause mortality during 31 days, cardiovascular mortality during 180 days, and global assessment at 24 h.[53] At 180 days, no differences in mortality have been observed between patients treated with levosimendan and dobutamine [26 vs. 28%, respectively, HR 0.91 (0.74–1.13); $P = 0.401$].[54] However, a trend in favour of levosimendan in the initial phase of treatment [4 vs. 6%, HR 0.72 (0.44–1.16) at 5 days and 12 vs. 14%, HR 0.85 (0.63–1.15) at 31 days], especially among patients with previous episodes of HF [HR 0.58 (0.33–1.01) at 5 days] was present. No significant differences in the incidence of hypotension, cardiac failure, AF, ventricular tachycardia or renal adverse events were found after levosimendan treatment compared with dobutamine.[54]

Levosimendan in the peri-operative phase of cardiac surgery

After cardiac surgery, a low-output syndrome is relatively common and can lead to serious consequences. Therefore, patients with low-output state need treatment aimed at enhancing haemodynamics and cardiac function. Levosimendan has been recently tested as a bridge therapy for the peri-operative phase of cardiac surgery in both adult and paediatric patients.

Adult population

Lilleberg *et al.*[55] first demonstrated that levosimendan improves systemic and coronary haemodynamics without increasing myocardial oxygen consumption or changing myocardial substrate utilization in 23 low-risk patients after coronary artery bypass grafting (CABG). More recently, Plochl and Rajek[56] described a significant increase in cardiac output and stroke volume with decreases in systemic vascular resistance in 10 critically ill post-operative patients. Also Labriola *et al.*[57] evaluated the effects of levosimendan in 11 patients with severely impaired cardiac output and haemodynamic compromise low-output syndrome following cardiac surgery. Of the 11 post-operative patients enrolled, eight showed evidence of combined haemodynamic improvement within 3 h after the start of levosimendan infusion.

In a small randomized study, Nijhawan *et al.*[58] compared the haemodynamic effects of placebo or two doses levosimendan infused for 6 h after a CABG. Fifteen minutes after the end of CABG, levosimendan increased cardiac output and reduced systemic vascular resistance without inducing hypotension or tachycardia. No differences were observed in the two patient groups treated with different dosages of levosimendan.

In another randomized study,[59] 31 patients were treated with a low or a high dose of levosimendan or placebo administered over 10 min and started 20 min before off-pump CABG. All patients also received an initial volume load of 500 mL before levosimendan. After the infusions, cardiac output and LVEF were significantly

higher and systemic vascular resistances were lower in patients receiving levosimendan at both dosages.

These peri-operative and post-operative studies in adult patients indicate that levosimendan is a potentially useful drug to prevent and/or improve haemodynamics and post-operative ischaemic cardiac depression.

Paediatric population

Considering the inotropic proprieties and potent vasodilating effects on pulmonary vasculature, levosimendan may offer the potential as peri-operative therapy for paediatric patients with congenital heart disease and low cardiac output or increased pulmonary artery pressures.

Some reports demonstrated the safety and efficacy in terms of haemodynamics and LV function of this new agent during the pre- or post-surgical phase in infants or children with congenital heart disease.[60,61]

In an open, single-dose study, Turanlahti *et al*.[61] evaluated the pharmacokinetics, haemodynamic effects and safety of levosimendan in 13 children (from 3 months to 7-year-old) with congenital heart disease evaluated for cardiac surgery. All children received levosimendan at 12 μg/kg over 10 min during pre-operative cardiac catheterization. The haemodynamic profile of levosimendan in children was similar to that in adult patients with HF, without any serious adverse event or unexpected adverse drug reactions during the study. However, the changes in haemodynamic variables were not statistically significant compared with baseline, probably because of the small dose administered relative to body surface area.[61]

Levosimendan in patients with ischaemic heart diseases

Positive inotropic agents, especially phosphodiesterase inhibitors and adrenergic agonists such as dobutamine, may be associated with increasing myocardial oxygen demand and the potential to induce myocardial ischaemia or malignant arrhythmias.[1,62–65] On the contrary, by virtue of its dual mechanism of action and its negligible effect on myocardial oxygen demand, levosimendan seems to be better tolerated by patients with ischaemic heart disease.[66–68]

Small clinical studies

An open-label dose-controlled study with three different bolus doses of levosimendan in patients with ST-elevation myocardial infarction (STEMI) demonstrated the safety of this drug in this high-risk population.[69]

In a recent study, 24 patients undergoing a percutaneous coronary intervention (PCI) for an acute ischaemic event were enrolled in a randomized, double-blind, placebo-controlled study.[70] Ten minutes after PCI, the patients were randomized to either levosimendan treatment (24 μg/kg over 10 min), or placebo. Haemodynamics were measured before and 20 min after the start of drug infusion. Levosimendan treatment was associated with a significant reduction in the mean total number of hypokinetic segments. In addition, the pressure–volume area, end-systolic pressure, and volume index were significantly decreased. Also, the index of diastolic relaxation (τ) decreased with levosimendan compared with placebo (*Figure 6*), indicating

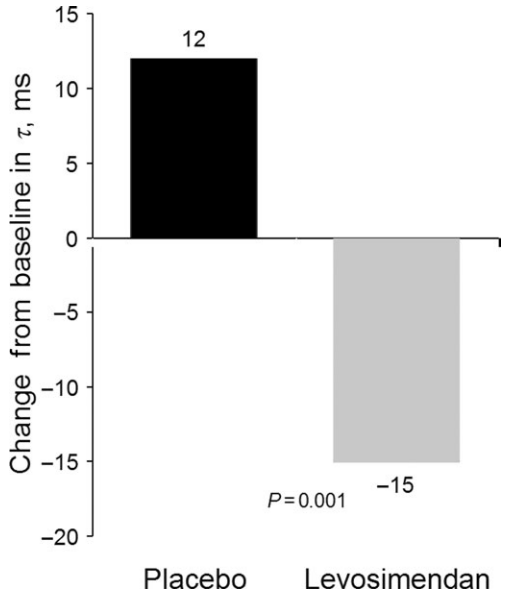

Figure 6 In patients with stunned myocardium, levosimendan does not impair the diastolic function as demonstrated by a significant decrease in τ, an index of early diastolic relaxation.[70]

that levosimendan seems to have improved the systolic performance of stunned myocardium without impairment of diastolic function.[70]

Recent evidence suggests that levosimendan may also exert vasodilator effects on human coronary conductance and resistance arteries. Michaels *et al*.[71] determined the changes in coronary blood flow, myocardial oxygen uptake, and haemodynamics after an intravenous infusion of levosimendan in 10 adult patients undergoing right and left catheterization. After the drug infusion, coronary artery diameter, velocity, and flow increased significantly (*Figure 7*), whereas coronary resistance and myocardial oxygen extraction decreased at 30 min, suggesting an improvement in myocardial efficiency.[71]

Consistent with these findings, we evaluated the acute effects of levosimendan on coronary flow velocities in patients with severe LV dysfunction undergoing PCI for a STEMI.[72] Twenty-six consecutive patients were randomized to intravenous infusion of levosimendan or placebo, 10 min after a primary PCI. After bolus, coronary flow reserve on infarct-related arteries and on reference vessels significantly improved in patients treated with levosimendan (from 1.6 to 2.0 and from 2.1 to 2.4, respectively).[72]

Moreover, after a successful primary angioplasty, we randomized 52 consecutive patients with anterior STEMI to levosimendan or placebo infusion and analyzed the diastolic function, using conventional transmitral Doppler flow and Tissue Doppler Imaging parameters.[73] Twenty-four hours after the index intervention, patients treated with levosimendan showed a significant improvement of the Doppler echocardiographic parameters of LV diastolic function, compared to placebo.[73]

Large randomized clinical trial

The Randomized study on Safety and effectiveness of Levosimendan in patients with LV failure due to an Acute myocardial iNfarct (RUSSLAN) was a double-blind,

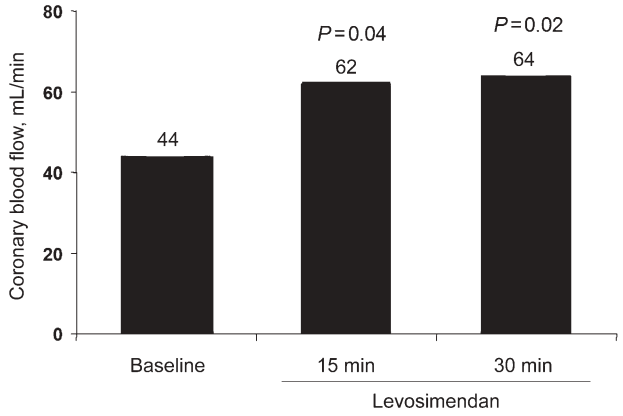

Figure 7 Levosimendan is associated with a significant increase in coronary blood flow after 15 and 30 min of treatment.[71]

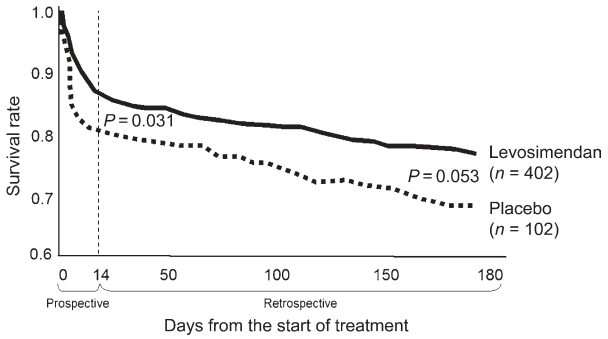

Figure 8 Kaplan–Meier survival analysis in the RUSSLAN trial (modified from Moiseyev *et al.*[74]). The prospective survival benefit of levosimendan compared to placebo at 14 days were maintained through 180 days of follow-up.

placebo-controlled trial conducted in 504 patients who had recently experienced an MI.[74] Patients were randomized to levosimendan at four different loading dose regimens or placebo for 6 h. The primary endpoint addressed the safety of levosimendan and consisted of the incidence of clinically significant hypotension or myocardial ischaemia. Secondary endpoints included the combined risk of death or worsening HF at 6 and 24 h after the start of the infusion, a change in dyspnea and fatigue at the end of the infusion, and all-cause mortality over 14 days. In addition, mortality at 180 days was examined retrospectively.

There were no significant differences among the treatment groups in the proportion of patients who experienced clinically important hypotension or ischaemia. In the secondary endpoints, levosimendan was associated with significantly lower risk of death or worsening HF than placebo at 6 and 24 h after the infusion. Importantly, the all-cause mortality at 14 days was significantly lower with levosimendan treatment than with placebo. This lower mortality persisted at 180 days, though the difference between the two groups did not reach statistical significance (*Figure 8*).[74]

Levosimendan in patients with shock

Cardiogenic shock

In the initial dose finding and therapeutic trials in patients with AHFS, a systolic blood pressure below 90 mmHg was one of the exclusion criteria. In view of its vasodilatory and potential blood pressure lowering effects, levosimendan alone was not a drug of first choice in cardiogenic shock. There are, however, several recent clinical observations indicating that levosimendan can improve haemodynamics even in patients with cardiogenic shock if it is combined with catecholamines to maintain adequate perfusion pressures[75–79] (*Table 2*).

Delle Karth *et al.*[80] administered levosimendan to 10 patients with cardiogenic shock following MI or cardiac surgery who did not improve after revascularization followed by intra-aortic balloon counterpulsation and infusion of catecholamines. Norepinephrine was first given to maintain mean arterial pressure >65 mmHg, then levosimendan infusion was added at a dose of 0.1 μg/kg/min without a bolus and continued for 24 h. To maintain cardiac filling pressures, the patients also received volume administration. Levosimendan treatment resulted in a significant increase in cardiac output together with a decrease in systemic vascular resistance. Four patients could be weaned from catecholamines and all survived up to 6 months.[80] Comparable experiences have been reported by other authors[56,81–83] who described the use of levosimendan patients with cardiogenic shock complicating acute myocardial ischaemia or coronary revascularization.

The above reports suggest that levosimendan may be successfully used in combination with catecholamines to treat cardiogenic shock. Nevertheless, formal controlled and comparative studies are necessary to define the place of levosimendan in such patients.

Septic shock

Animal models[84,85] and case reports[78,86,87] suggested that calcium desensitization could be a potential component in septic myocardial depression.

Recently, 28 patients with persisting LV dysfunction related to septic shock have been randomized to levosimendan or dobutamine after 48 h of conventional treatment including dobutamine (5 μg/kg/min).[88] Data from right heart catheterization, echocardiography, gastric tonometry, laser-Doppler flowmetry, lactate concentrations, and creatinine clearance were obtained before and after the 24 h of drug infusion. Dobutamine did not change systemic or regional haemodynamic variables. By contrast, at the same mean arterial pressure, levosimendan decreased pulmonary artery occlusion pressure and increased cardiac index. Notably, levosimendan decreased LV end-diastolic volume and lactate concentrations, and increased LVEF, gastric mucosal flow, creatinine clearance, and urinary output.[88]

Oral administration

The favourable haemodynamic response with intravenous levosimendan suggested it as an attractive drug for the long-term oral treatment of advanced chronic HF. Recently, a few studies have been conducted to obtain preliminary data for the development of its oral formulation.

In an open-label pilot study, levosimendan was administered orally to 10 patients with severe congestive HF.[90] Each patient received three escalating doses of 1 mg, 2 mg, and 4 mg of levosimendan within 18–24 h. After administration of a 1-mg dose, PCWP decreased by 18% and cardiac output increased by 22%. The 4-mg dose of levosimendan

was associated with a 27% increase in cardiac output and right atrial pressure decreased substantially by 40%.[89]

A phase II study tested the ability of oral levosimendan to wean patients off parenteral inotropic support and to maintain patients without intravenous inotropic support for 10 days in patients with advanced congestive HF.[90] Escalating doses of the oral compound (administered concomitantly with a stable dose of the intravenous inotropic agent for the first 48 h) were instituted every 4 h, beginning at 1 mg for the first 3 doses, before titrating the drug to the maximum tolerated dose, which was then administered every 8 h. Eighty-three percent of patients were successfully weaned from intravenous inotropes and remained off these agents for a minimum of 10 days. Seven patients were maintained on oral levosimendan for >90 days, suggesting that oral levosimendan may be used instead of intravenous inotropic support.[90] However, there was a high incidence of adverse events, including worsening HF, hypotension, and increased ventricular ectopy or ventricular tachycardia affecting almost 50% of the cases. These findings raise concern about the potential for accumulation of the long-lasting active metabolite OR-1896 and the resulting adverse effects.

A randomized, parallel-group, double-blind, placebo-controlled trial explored the pharmacodynamics and pharmacokinetics of oral levosimendan at 2–8 mg daily or placebo in 25 patients with NYHA class III-IV congestive HF for 4 weeks.[91] The 4–8 mg daily doses of oral levosimendan showed moderate inotropic effects. Notably, plasma concentrations of the active metabolite increased in a dose-dependent and time-dependent manner,[91] confirming the potential for accumulation.

Oral levosimendan produces favourable haemodynamic effects, similar to those seen after administration of its intravenous formulation in patients with HF. However, some concerns arise about the pharmacokinetic properties and expediency of the oral compound in severe HF patients. The ongoing double-blind, parallel group, multicentre PERSIST trial that will randomize 300 patients with severe chronic HF to two different doses of oral levosimendan and placebo, will probably clarify these features.

Adverse events

Levosimendan is generally well tolerated in severely ill patients. The most common adverse events associated with the use of levosimendan are hypotension, headache, dizziness, and nausea.[28] One recent analysis indicated that headache induced by levosimendan was seen more frequently in men than in women (8.4% for men compared with 4.9% for women).[92] These adverse events are thought to be secondary to the vasodilatory effects of the drug.

Notably, in the recent REVIVE-2 trial, levosimendan infusion is associated with a higher incidence of ventricular tachycardia and hypotension, compared to placebo.[51] This could be related to the high-sustained infusion, the frequent use of other intravenously active therapies, as well as the more severe ill nature of patients enrolled in this trial.

A slight reduction in red blood cell count, haematocrit, and haemoglobin, as well as small reductions of serum potassium has also been described in some of the patients.[48]

Arrhythmias

Animal studies suggested that a chronic treatment with levosimendan could be beneficial in the presence of congestive HF and arrhythmias resulting from regional myocardial ischaemia.[93]

In patients with severe HF, levosimendan demonstrated little potential to induce life-threatening pro-arrhythmic reactions. As expected from the differences in the mechanisms of action for levosimendan and dobutamine, significantly fewer patients randomized to levosimendan in the LIDO trial experienced heart rate and rhythm disorders (defined as AF, extrasystoles, tachycardia, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, and bradycardia) than those on dobutamine (4 vs. 13%).[48] Also Lilleberg *et al.*[94] assessed the potential of levosimendan to generate cardiac arrhythmias by analysing ECG recordings from clinical studies on intravenously administered levosimendan in HF patients. The database consisted of continuous 1-day recordings, of which 366 were during levosimendan and 142 during placebo comparison. No difference appeared between levosimendan and control groups in the occurrence of AF(12 vs. 13%), supraventricular tachycardia (28 vs. 30%), or ventricular tachycardia (41 vs. 44%).

Singh *et al.*[95] evaluated the electrophysiologic effects of intravenous levosimendan in healthy volunteers and in patients with HF. Levosimendan had no significant effects on heart rate when data were pooled from the 24-h electrocardiograms of patients receiving various dose levels, although increases were noted at high doses. The uncorrected QT interval remained unchanged, but the rate-corrected QT interval was modestly prolonged at doses several-fold higher than that required for therapeutic effect. Atrial and ventricular effective refractory periods in patients with normal heart function were slightly shortened, although the average effect on the ventricles was only 2–5 ms at different pacing rates. No increase in the frequency of non-sustained ventricular tachycardia was found from the analysis of ambulatory electrocardiograph data from a total of 792 1-day recordings pooled from 10 studies that included data from 386 HF patients. In addition, there was no evidence of any increase in the development of new supraventricular or ventricular tachyarrhythmias, including torsade de pointes, in patients who did not exhibit these abnormalities at baseline.[95]

Conclusions

To date, levosimendan has been studied in more than 3000 patients and is registered for clinical use in several countries in Europe, South America, and Asia.

Levosimendan differs from other agents commonly used to treat low-output state in that it has a unique dual mechanism of action: calcium-sensitization through binding to cTnC, and the opening of ATP-sensitive K^+ channels in the vascular smooth muscle.[96] These properties result in significant improvements of haemodynamic parameters and symptoms when compared with placebo or dobutamine in patients with a low-output state associated with different clinical settings.

The REVIVE trial has been the first placebo-controlled study demonstrating that an active treatment may have a

meaningful favourable effects on symptoms in AHFS patients. The overall experience with levosimendan suggests that despite its positive inotropic action, it may not be associated with excess mortality. Nonetheless, these beneficial effects seem to be balanced by the higher incidence of cardiac side effects in critically ill patients who are under aggressive management with other vasoactive agents, when compared to placebo.

Levosimendan may be used instead of dobutamine in patients with a low cardiac output and high LV filling pressures not responding to other therapies. Because levosimendan is a powerful vasodilator and may increase heart rate, it should be avoided in patients with hypotension, especially when concomitant hypotensive therapies are present. Further randomized, placebo-controlled, clinical trials focussed on patients with AHFS are warranted before making any definitive recommendation. The role of levosimendan in the management of patients with AHFS remains to be determined.

Conflict of interest: W.S.C., M.S.N., B.M.M., and M.G. are all consultants for Abbott International.

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