

# Levosimendan in patients with low-output heart failure: lessons from the LIDO trial

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The novel calcium sensitizer levosimendan improves myocardial contractility without causing an increase in intracellular calcium and cyclic adenosine monophosphate concentrations. It also has a vasodilator action due to an opening of the adenosine triphosphate-sensitive potassium channels. In a double-blind clinical trial levosimendan was compared with dobutamine in 203 patients with severe low-output congestive heart failure. A 24-hour infusion of these inotropic drugs was administered to increase the cardiac output by at least 30% together with a decrease in the pulmonary capillary wedge pressure by  $\geq 25\%$ . The pre-defined hemodynamic improvement was achieved in 28% of patients receiving levosimendan compared to only 15% with dobutamine ( $p = 0.022$ ). Levosimendan also reduced the 1- and 6-month mortality more than dobutamine (7.8 vs 17%,  $p = 0.045$  and 26 vs 38%,  $p = 0.029$ , respectively). Levosimendan produced less myocardial ischemia and cardiac arrhythmias than dobutamine.

Calcium sensitizers offer a new therapeutic possibility in patients with decompensated low-output heart failure.

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## Introduction

Cardiac decompensation with severe dyspnea, pulmonary congestion and peripheral vasoconstriction may be the first manifestation of an acute heart disease, such as myocardial infarction or myocarditis, or occur as a rapid clinical deterioration in patients with preexistent chronic heart failure. An ongoing prospective evaluation of patients with acute/decompensated heart failure at the University Hospital in Zurich indicates that about one third of patients present with *de novo* heart failure and two thirds with worsening chronic heart failure<sup>1</sup>. In the latter condition poor compliance and/or medication errors are often the cause of the progressive symptomatology followed by a worsening of the underlying heart disease due to myocardial ischemia or cardiac arrhythmias, mostly atrial fibrillation<sup>2</sup>. Increasing dosages of intravenous diuretics and additional vasodilators are the usual first-line therapeutic measures. If the clinical symptoms and the hemodynamics do not improve and if signs of poor organ perfusion ensue intravenous inotropic drugs are required to reverse the life-threatening condition. Beta-adrenergic agonists and phosphodiesterase inhibitors are currently the main drugs administered in such situa-

tions. The utility of positive inotropic agents has, however, been questioned since the short-term hemodynamic improvements are not associated with a better mid- or long-term outcome<sup>3</sup>.

Calcium sensitizers, such as levosimendan, represent a new type of inotropic and vasodilator drugs which were shown to offer potential advantages in the treatment of patients with severe heart failure. Levosimendan increases myocardial contractility without significant changes in the intracellular calcium ion and cyclic adenosine monophosphate concentrations and does not enhance myocardial oxygen demand<sup>4,5</sup>. By its action on the potassium channels this drug also dilates the coronary and peripheral arteries and exerts an anti-ischemic, anti-stunning effect<sup>6</sup>. Following comparative dose-finding trials in patients with various degrees of cardiac dysfunction<sup>7,8</sup>, levosimendan has also been evaluated in controlled clinical trials. A direct comparison of levosimendan with dobutamine in patients with severe low-output heart failure, the LIDO trial, has shown a better immediate hemodynamic response and a positive influence on survival<sup>9</sup>. In this paper the main findings of the LIDO trial and some additional information not described in the original publication are presented.

## Methods

The patient selection, treatment protocol, endpoints of the study and statistical analysis have been described previously<sup>9</sup>. In short, LIDO was a double-blind, randomized double-dummy multicenter trial performed in 26 European centers to compare the 24-hour infusion of levosimendan and of dobutamine in patients with low-output heart failure requiring intravenous inotropic support. The main hemodynamic inclusion criteria were a cardiac index  $< 2.5$  l/m<sup>2</sup>, a pulmonary capillary wedge pressure  $> 15$  mmHg, and an ejection fraction  $< 35\%$ . Patients with acute myocardial infarction, valvular stenosis, ventricular arrhythmias or conduction disturbances, those with heart rate  $> 120$  b/min and systolic blood pressure  $< 85$  mmHg were excluded as well as patients with severe renal and hepatic failure or septic shock.

**Drug dosage.** Levosimendan was started with a loading dose of 24 µg/kg in 10 min followed by a continuous infusion at 0.1 µg/kg/min. Dobutamine was infused at 5 µg/kg/min. The infusion rate of levosimendan was increased to 0.2 µg/kg/min and that of dobutamine to 10 µg/kg/min after 2 hours if the cardiac index did not increase by more than 30%. During the infusion patients were continuously monitored at an intensive care unit.

The primary endpoint of the study was the frequency of hemodynamic improvement defined as at least a 30% increase in the cardiac index together with a reduction in the pulmonary capillary wedge pressure of 25% without a need for additional intravenous drug therapy with other inotropes, vasodilators or intravenous diuretics. Secondary endpoints included the mortality at 31 days, adverse events and changes in the laboratory val-

ues. A 6-month survival analysis was also carried out at the request of the regulatory authorities.

**Statistical analysis.** Statistical analysis was performed by intention-to-treat with the Mantel-Haenszel test for the primary hemodynamic endpoint and using the Kaplan-Meier technique and the Cox model to compare differences in survival.

## Results

In total, 203 patients were randomized, 100 to dobutamine and 103 to levosimendan. After the drop out of a few patients before the initiation of drug infusion 97 were treated with dobutamine and 102 with levosimendan. The baseline demographic characteristics including age, gender, underlying heart disease and hemodynamic findings as well as concomitant drug treatment were comparable in both patient subsets<sup>9</sup>. The majority of patients suffered from a deterioration of a chronic heart failure despite treatment with diuretics, ACE-inhibitors, beta-blockers and nitrates. Fifteen percent and 18% of the patients respectively were on a heart transplant list. The main presenting symptoms were dyspnea, orthopnea and fatigue, while jugular vein distension, pulmonary rales and signs of peripheral vasoconstriction were the most frequent clinical findings (Table I).

**Hemodynamic response.** The primary endpoint as defined above was reached in 28% under levosimendan compared to 15% under dobutamine (hazard ratio-HR 1.9, 95% confidence interval-CI 1.0-3.3,  $p = 0.022$ ). The main difference was a more marked reduction in the pul-

**Table I.** Clinical presentation.

	Dobutamine (n=100)	Levosimendan (n=103)
Deterioration of congestive heart failure	92 (92%)	86 (84%)
Duration		
Within 1 week	1	8
Within 1 month	28	25
More than 1 month	56	53
Presenting syndrome		
Worsening congestive heart failure	75	74
Fluid retention requiring i.v. diuretics	33	27
Peripheral hypoperfusion	21	21
Acute heart failure	0 (0%)	7 (7%)
Postoperative exacerbation	2 (2%)	4 (4%)
Symptoms and signs of heart failure		
Dyspnea	75/98 (77%)	76/101 (75%)
Fatigue	80/97 (82%)	79/101 (71%)
Unable to tolerate the horizontal position	47/61 (77%)	45/64 (70%)
Jugular vein distension	67/96 (70%)	72/101 (71%)
Pulmonary rales	25/63 (40%)	40/67 (60%)
Coolness of limbs	33/64 (52%)	38/67 (57%)

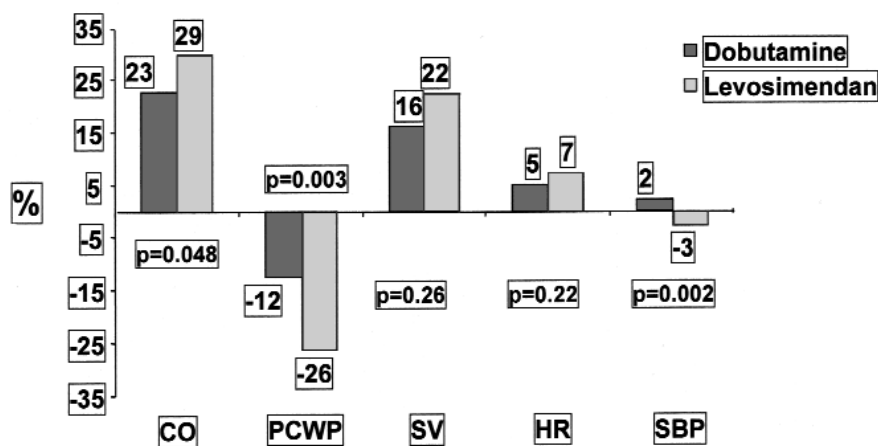
monary capillary wedge pressure following levosimendan therapy (Fig. 1). The changes in stroke volume, heart rate and blood pressure were comparable. To achieve the intended increase in cardiac output, the infusion rate of levosimendan had to be increased after 2 hours in 68.3% of patients with levosimendan compared to 41.2% with dobutamine. Levosimendan infusion had to be interrupted for adverse events in 5.9% compared to 9.2% in patients receiving dobutamine.

An important difference in the drug response was observed in patients who received beta-blockers until the day before or during drug infusion (39% on dobutamine vs 37% on levosimendan). In patients treated with a beta-blocker, a hemodynamic improvement was seen in 10 out of 33 levosimendan- but in only 3 out of 29 dobutamine-treated patients ( $p = 0.056$ , relative risk 2.93, 95% CI 0.97-8.88). Thus, in contrast to the beta-agonist dobutamine the effects of the calcium sensitizer were not reduced by beta-blockade.

**Clinical response.** There was a trend in favor of levosimendan for the improvement of dyspnea and fatigue, the reduction in the jugular venous pressure and the overall assessment of the clinical status by the patients,

but the differences were not statistically significant (Table II).

**Mortality and morbidity.** A main finding in the study was a reduced mortality at 1 month after drug infusion: only 8 (7.8%) of patients in the levosimendan-treated group died compared to 17 (17%) following dobutamine (HR 0.42, 95% CI 0.18-0.98,  $p = 0.045$ ). The mode of death could be evaluated in the majority of patients and the difference was due to a higher rate of progressive left ventricular failure, cardiogenic shock and sudden death in dobutamine-treated patients (Table III). The survival advantage was maintained up to 180 days with 27 (26%) deaths in the levosimendan group and 38 (38%) in the dobutamine group (HR 0.57, 95% CI 0.34-0.95,  $p = 0.029$ ). The long-term outcome was also compared by assessing the median number of days alive and out of hospital during the first 6 months which was 157 days (range 101-173 days) compared to 133 days (range 43-169 days) in the levosimendan and dobutamine groups, respectively ( $p = 0.027$ ). The adverse events and the laboratory changes during the 24-hour infusion period were described in detail in the original publication<sup>9</sup>. The tolerance to levosimendan was better than that to



**Figure 1.** Percent change in hemodynamic variables at 24 hours. CO = cardiac output; HR = heart rate; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; SV = stroke volume.

**Table II.** Effect of treatment on symptoms and signs.

	Much better	Slightly better	No change	Worse
Dyspnea				
Dobutamine	16	28	47	5
Levosimendan	21	32	45	4
p value	0.508			
Jugular venous distension				
Dobutamine	6	13	74	2
Levosimendan	15	15	69	3
p value (prespecified worse rank)	0.508 (adjusted)			
Changes in overall status assessed by the patient				
Dobutamine	17	26	13	4
Levosimendan	24	19	18	5
p value (prespecified worse rank)	0.508 (adjusted)			

**Table III.** The LIDO trial: mortality during the first 31 days.

	Levosimendan (n=103)	Dobutamine (n=100)
Death for any reason	8 (7.8%)	17 (17%)
Mode of death		
Progressive LV failure	5	8
Cardiogenic shock	0	3
HF after HTPL	1	0
Ventricular fibrillation	0	1
Sudden death at home	0	2
Myocardial infarction	1	0
Pulmonary embolism	0	1
Unknown	1	2
Total	8	17

HF = heart failure; HTPL = heart transplantation; LV = left ventricular.

dobutamine with significantly less ischemic chest pain or cardiac arrhythmias. Levosimendan, however, caused more headache due to its vasodilator action. There was also a greater reduction in serum creatinine [-9 (19 to 2)  $\mu\text{mol/l}$ ] under levosimendan compared to [-1 (-12 to 9)  $\mu\text{mol/l}$ ] under dobutamine ( $p = 0.03$ ).

## Discussion

The LIDO trial has shown several advantages of levosimendan over the beta-adrenergic drug, dobutamine: there was a greater hemodynamic benefit, mainly due to a more marked reduction in the pulmonary capillary wedge pressure at the end of treatment. In contrast to dobutamine there were no signs of tachyphylaxis and the hemodynamic effects continued to increase up to 24 hours and persisted up to 6 hours after the infusion was interrupted. An important observation was the good hemodynamic response in the subgroup of patients on beta-blockers in contrast to the expected inhibition by the action of dobutamine. This difference is of considerable practical relevance in view of the increasing use of beta-blockers even in patients with advanced heart failure.

The dosage of both drugs was accurately chosen to achieve the intended rise in cardiac output.

Levosimendan was better tolerated; in particular, the incidence of myocardial ischemia and cardiac arrhythmias was significantly less than under dobutamine. The initial infusion rate of levosimendan at 0.1  $\mu\text{g/kg/min}$  had to be increased in two thirds of patients at 2 hours, but this is not surprising for a drug with a half-life of 1 hour since the time to reach the maximum effects of a given infusion rate would be about 4 hours. A recent pharmacokinetic data analysis in patients of the original US trial indicates that there is a slowly increasing formation of active levosimendan metabolites which have a prolonged duration of action and produce a hemodynamic effect persisting beyond 48 hours<sup>10</sup>.

Therefore, a careful up-titration and an infusion time limited to 24 hours are recommended for the clinical routine to avoid the accumulation of pharmacologically active compounds which could cause a more marked vasodilation with arterial hypotension. The recently published RUSSLAN trial<sup>11</sup> in patients with acute myocardial infarction has also shown that infusion rates of  $> 0.2 \mu\text{g/kg/min}$  may produce an increased risk of a low systolic blood pressure.

The improvement in the long-term outcome associated with levosimendan after a single 24-hour infusion was an unexpected finding. The better prognosis lasting up to 6 months does not seem to be simply due to a relative advantage over dobutamine with increased adverse events. Also the comparison of levosimendan with placebo in the RUSSLAN trial showed a similar positive survival trend<sup>11</sup>. The prevention of further myocardial damage during the acute decompensation related to the anti-stunning and anti-ischemic effects by the potassium channel modifying mechanism could be an important factor. Further trials are ongoing to confirm the positive long-term outcome data.

In conclusion:

- levosimendan given as a short-term infusion has a beneficial hemodynamic effect in patients with decompensated low-output heart failure;
- compared to dobutamine, levosimendan has a more sustained effect (no tachyphylaxis) and is better tolerated;
- levosimendan may have a beneficial effect on mortality and rehospitalizations lasting up to 6 months;
- calcium sensitizers offer a new therapeutic possibility for the treatment of acute cardiac decompensation. Further trials are required to assess the long-term prognostic effects of calcium sensitizers in heart failure.

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