

Considerations on the efficacy and safety of levosimendan in ischemic heart failure

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Levosimendan is a new vasodilator agent with properties which improve cardiac contractility by calcium sensitization. Its dose-related efficacy and prolonged action have been documented in several major studies both against placebo and dobutamine. Out of 997 patients, 837 (84%) had acute or stable heart failure due to coronary heart disease. Therefore, it would be most interesting to analyze the efficacy and safety of levosimendan in heart failure due to ischemic heart disease.

The dose-finding study included 98 patients who were given intravenous levosimendan at different doses and 20 patients treated with dobutamine. All patients had heart failure due to coronary heart disease. The other major trial included 500 acute myocardial infarction patients with heart failure and was placebo-controlled. In other levosimendan vs placebo or dobutamine comparative trials 50-60% of patients had ischemic heart disease and severe heart failure.

Levosimendan significantly improves the cardiac index by 30-39% at bolus doses of 6-24 µg/kg/min followed by infusion doses of 0.05-0.2 µg/kg/min and reduces the wedge pressure by 20-25% to optimal levels (from 15-20 mmHg). There is a lesser blood pressure reduction and some heart rate increase. However in patients with an acute myocardial infarction the rate of ischemia or hypotension were similar in levosimendan- and placebo-treated patients and in the dobutamine controlled trials no major adverse effects were seen or they were more frequent in dobutamine patients. There is no increase in mortality either compared to placebo or to dobutamine. Rather, the opposite seems to be true. No increase in arrhythmias is seen.

The hemodynamic effects of levosimendan are dose-dependent and the current recommended doses are safe. No increase in mortality or any life-threatening arrhythmias have been observed.

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Introduction

This review will outline the current experience regarding levosimendan therapy in heart failure patients with ischemic heart disease. As a background we can acknowledge that heart failure is one of the most important causes of mortality and morbidity in the western world. It is estimated that 4 to 5 million persons in the United States¹ and 10 million persons in countries that are represented by the European Society of Cardiology suffer from heart failure². The prevalence of symptomatic heart failure is estimated to range from 0.4 to 2% in the overall European population³. In the United States nearly 500 000 patients are diagnosed with heart failure annually and about the same number in the European Union as well. This disorder accounts for 12 to 15 million medical visits and for 6.5 million hospital days. In the United States, heart failure, as the primary or secondary diagnosis, annually accounts for approximately 900 000 and 2.6

million hospitalizations respectively⁴. Heart failure accounts for 2-3% of hospital admissions^{5,6}.

Acute heart failure is a medical emergency. Thus effective management requires accurate assessment of the underlying cause, hemodynamic stabilization, relief of pulmonary congestion, and the improvement in tissue oxygenation whilst minimizing the length of hospitalization and preventing readmission. Oxygen, morphine, intravenous diuretics and oral/intravenous nitrates are effective and have withstood the tests of time and clinical observation⁷⁻¹¹. In case these treatment modalities are not sufficient, the short-term use of intravenous inotropic agents is usually commenced. Agents which have additional properties such as vasodilation and the augmentation of the renal circulation are more efficacious in medical emergencies.

The major issue of chronic heart failure is that most of the patients have coronary heart disease as a causative or complicating

factor. In a UK study, the investigators submitted all patients with advanced heart failure to angiography and found that a stenosis of $\geq 70\%$ was observed in 60% of the patients. In the EuroHeart Failure survey 68% of patients had known coronary heart disease¹². The in-hospital mortality rate in patients with an acute myocardial infarction (AMI) complicated by heart failure is 24%¹³. Thus, the safety of new agents to be used for acute heart failure has to be evaluated in coronary patients. Pathophysiology of ischemia is illustrated in figure 1.

Levosimendan is a new therapeutic option, a calcium sensitizer that has been introduced into clinical practice for the treatment of acutely decompensated advanced heart failure. By virtue of its dual mechanism of action, levosimendan induces peripheral and coronary vasodilation, by opening the adenosine triphosphate-sensitive potassium channels¹⁴ and enhances cardiac contractility through myofilament calcium sensitization¹⁵. Levosimendan binds to troponin C¹⁶, thereby sensitizing the contractile proteins to intracellular calcium without increasing the influx of calcium into the cardiac myocytes¹⁷. As a result, the cardiac performance is improved with no significant increase in oxygen consumption¹⁸. In contrast to other agents with calcium-sensitizing properties, the effects of levosimendan are calcium-dependent, facilitating normal diastolic relaxation. Moreover, by mediating both arterial and venous dilation, via the opening of the adenosine triphosphate-sensitive potassium channels¹⁴, levosimendan reduces both cardiac preload and

afterload^{19,20}. The favorable hemodynamic effects and symptomatic improvement are accompanied by the additional benefit of a lower mortality, lasting up to 6 months after the decompensating event, as compared to dobutamine and placebo¹⁹⁻²¹.

The documentation regarding levosimendan is the largest ever on the safety and efficacy of a new acute heart failure agent²²⁻²⁷. The studies include investigations against placebo¹⁹⁻²¹ and the active comparator, which is dobutamine^{20,28}.

The dose-finding trial with increasing doses and a 24-hour infusion²⁰ and RUSSLAN²¹ are studies which enrolled coronary patients and LIDO²⁸ and the dose-escalation study¹⁹ included patients with either dilated cardiomyopathy or systolic dysfunction due to coronary heart disease (Table I)^{19-21,28}. About 80% of the NYHA class III-IV heart failure patients included in levosimendan trials are coronary patients.

There is moreover a very interesting preliminary report regarding patients with myocardial infarction. In 24 patients with AMI, the left ventricular pressure volume loops and the regional myocardial contraction were studied after percutaneous angioplasty of the infarct-related artery during levosimendan and placebo infusions²⁹.

Clinical effects

Hemodynamic effects. In the dose-finding trial including 151 patients with stable heart failure in NYHA class III, all patients had a coronary heart disease background. The 24-hour infusion of levosimendan produced significant, dose-dependent increases in the cardiac output, stroke volume and heart rate, and decreases in the pulmonary capillary wedge pressure (PCWP), mean blood pressure, mean pulmonary artery pressure, mean right arterial pressure, and total peripheral resistance²⁰. All doses of levosimendan (a bolus of 3-36 $\mu\text{g/kg}$ followed by a continuous infusion of 0.05-0.6 $\mu\text{g/kg/min}$) produced significantly larger decreases in PCWP than dobutamine (6 $\mu\text{g/kg/min}$). Levosimendan infusions of 0.4 and 0.6 $\mu\text{g/kg/min}$ produced significantly larger increases in cardiac output than dobutamine. The increase in cardiac output was partly due to an increase in heart rate, especially with higher doses of levosimendan. The hemodynamic effects of levosimendan, especially the

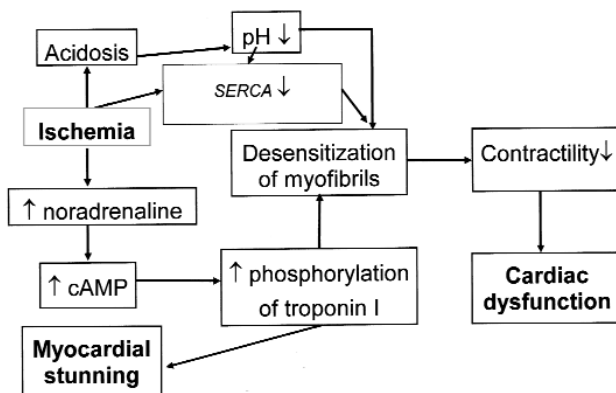


Figure 1. Pathophysiologic effects of ischemia on myocardial function. cAMP = cyclic adenosine monophosphate.

Table I. Patient populations in the phase III studies with levosimendan.

Study	No. patients	No. levosimendan patients (ITT)	Comparator	Diagnosis	NYHA class
Dose-finding ²⁰	151	95	Placebo/dobutamine	CHF	III
LIDO ²⁸	203	103	Dobutamine	CHF	(III)-IV
Dose-escalation ¹⁹	146	98	Placebo	CHF	III-IV
RUSSLAN ²¹	504	402	Placebo	Post-AMI (LV dysfunction)	III-IV
Total	1004	698			

AMI = acute myocardial infarction; CHF = congestive heart failure; ITT = intent-to-treat population; LV = left ventricular.

decrease in PCWP, tended to increase with time, whereas the effect of dobutamine was attenuated over time.

In the dose-escalation trial including 146 patients 62% of the levosimendan-treated patients had coronary heart disease. Levosimendan-treated patients had a 28% increase in the stroke volume ($p < 0.001$) and a 39% increase in the cardiac index ($p < 0.001$) at 6 hours¹⁹. A decrease in PCWP of 22% ($p < 0.001$) and significant decreases in pulmonary artery pressure, pulmonary vascular resistance, mean arterial pressure and systemic vascular resistance and an increase in heart rate of 6 b/min ($p < 0.001$) were also observed. Most of the observed hemodynamic benefits persisted up to 24 hours after the cessation of the levosimendan infusion. Levosimendan-treated patients did not develop tolerance to the drug; indeed, the benefits of levosimendan became more marked in patients receiving levosimendan for 48 hours.

In the LIDO trial of 203 heart failure patients 50% had coronary heart disease. In the LIDO trial significantly more (nearly twice as many) patients had a significant hemodynamic improvement after 24 hours of treatment with levosimendan, compared with dobutamine (28 vs 15%, $p = 0.022$)²⁸. At the end of the 24-hour treatment period, levosimendan produced a significantly greater increase in cardiac output (1.1 vs 0.8 l/min, $p = 0.048$) and significantly greater decreases in PCWP (-6.5 vs -3.0 mmHg, $p = 0.003$) than dobutamine. An important finding from the LIDO study was that the hemodynamic effects of levosimendan were potentiated to a small extent by the concomitant use of a beta-blocker; in contrast, the use of a beta-blocker attenuated the effects of dobutamine²⁸. Accordingly, the hemodynamic advantages of levosimendan over dobutamine were accentuated with beta-blockade ($p = 0.01$ for cardiac output and $p = 0.03$ for PCWP) and indicate that levosimendan can be combined successfully with beta-blockers.

Overall, out of the 997 patients included in these trials 84% had coronary heart disease. Thus, the safety and adverse effects in these trials against placebo or active control reflect the appropriateness of treatment with levosimendan in ischemic heart failure patients.

The role of ischemia as the mechanism of heart failure is interesting. Ischemia at any time and especially during exercise causes local acidosis and energy depletion. These problems cause downregulation of the *SERCA* function resulting in desensitization of myocardial contractility. Ischemia causes desensitization also through the cyclic adenosine monophosphate-related phosphorylation of essential myocyte structures resulting in a decreased cardiac regional contractility and dysfunction with a decreased output (Fig. 1). The ischemic dysfunction manifests both as diastolic and systolic impairment.

In the pressure-volume loop study including patients with AMI, levosimendan improved the systolic and diastolic functions of the left ventricle, while with placebo there was some worsening of both *tau* as a marker of the diastolic and regional functions.

Symptoms of heart failure. In the dose-escalation trial, more levosimendan-treated patients presented with improvements in dyspnea and fatigue than with placebo¹⁹. In the LIDO trial, levosimendan improved symptoms to a greater extent than dobutamine, but the differences were not statistically significant²⁸. Dyspnea improved in 68 and 59% of the patients with baseline symptoms in the levosimendan and dobutamine groups respectively. Fatigue improved in 63% of the levosimendan-treated patients and in 47% of the dobutamine-treated patients respectively. Levosimendan also improved the jugular venous distension and cyanosis to a greater extent compared with placebo.

Mortality and morbidity. In the RUSSLAN and LIDO studies^{21,28}, 118 out of the 504 (23.3%) patients assigned to levosimendan and 70 out of the 203 (35%) patients assigned to the control groups died within 180 days. The risk of death was 35% lower in patients treated with levosimendan compared with the other patients included in these two studies [$p = 0.0057$, hazard ratio 0.65 (0.47-0.88)] (Fig. 2).

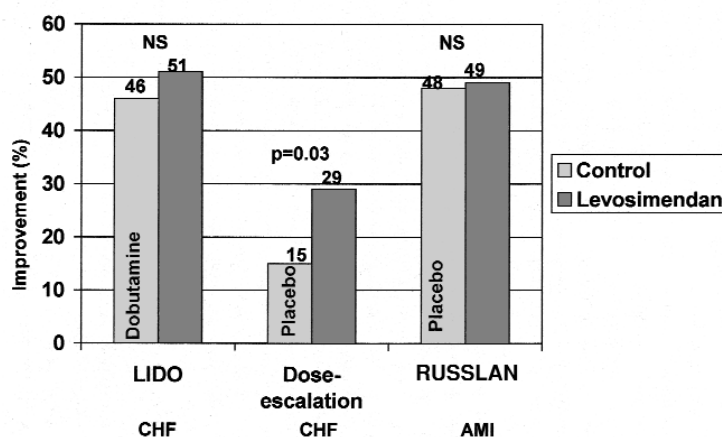


Figure 2. Improvement of dyspnea in phase III trials with levosimendan. AMI = acute myocardial infarction; CHF = congestive heart failure.

In the LIDO study, the number of hospital admissions for any reason per 100 days at risk was 2 times higher in the dobutamine-treated patients than in the levosimendan-treated patients (4.5 vs 2.1, $p = 0.043$)²⁸. A similar difference was also found when the number of hospitalizations for worsening heart failure was analyzed (4.3 vs 1.8, $p = 0.041$).

Safety

The cardiovascular adverse events are presented in table II. In the placebo-controlled studies with patients suffering from congestive heart failure, 35 (18%) of the levosimendan-treated and 4 (5%) of placebo-treated patients discontinued the treatment. The difference was due to the higher number of levosimendan-treated patients meeting the predefined hemodynamic criteria for discontinuation. The reason for discontinuation was an adverse event in 11 (6%) and 3 (4%) for levosimendan and placebo patients, respectively.

In the dobutamine-controlled studies with patients suffering from congestive heart failure, 32 (16%) of the levosimendan-treated patients and 17 (14%) of the dobutamine-treated patients discontinued the treatment. The reason for discontinuation was an adverse event in 8 (4%) levosimendan-treated and in 10 (8%) dobutamine-treated patients.

In the placebo-controlled study including patients with left ventricular failure due to AMI, treatment was permanently withdrawn in 8 (7.8%) placebo patients and in 33 (8.2%) levosimendan patients. The most common adverse event leading to discontinuation in the placebo group was myocardial rupture seen in 4 (3.9%) patients, and hypotension in the levosimendan group observed in 6 patients (1.5%).

In placebo-controlled studies with patients suffering from congestive heart failure (Table II), levosimendan-

treated patients had more adverse events compared to placebo (52 and 29% respectively). The difference was mainly due to the higher incidence of headache (20%) and of hypotension (5.2%) in the levosimendan-treated patients. It is noteworthy that placebo-treated patients had a significantly higher incidence of worsening heart failure (coded as condition aggravated).

In dobutamine-controlled studies with patients suffering from congestive heart failure (Table II), there was no difference in the incidence of the two most common adverse events, headache or hypotension. However, the incidence of tachycardia and condition aggravated were higher in dobutamine-treated than in levosimendan-treated patients.

In the RUSSLAN trial including patients with left ventricular failure due to AMI, the only difference between the treatment groups was the higher incidence of myocardial rupture in the placebo-treated patients²¹.

The proportion of patients who experienced ischemia and/or hypotension in the placebo and combined all four levosimendan groups was similar (10.8 vs 13.4% respectively, $p = 0.456$). Although there was a weak relation between the dose of levosimendan and the risk of hypotension and/or ischemia ($p = 0.054$), this was totally attributable to the higher frequency observed with the highest dose (19% compared with 11-12% in the other levosimendan and placebo groups)²¹.

Discussion

The experience from clinical studies with levosimendan (1321 patients) is of a similar magnitude to that of the clinical trials conducted to date with all the other inotropes together (1583 patients)^{27,30}. Moreover, most patients treated with levosimendan have been ischemic cardiomyopathy patients. Thus, the literature also clearly reflects the safety of levosimendan in these

Table II. Cardiovascular adverse events occurring on the study day or during follow-up in the major studies on levosimendan^{19-21,28}.

Preferred term	Patients with CHF						Patients with LV dysfunction complicating AMI		
	Placebo-controlled studies			Dobutamine-controlled studies					
	Levosimendan (n=193)	Placebo (n=84)	p	Levosimendan (n=198)	Dobutamine (n=120)	p	Levosimendan (n=402)	Placebo (n=102)	p
Tachycardia	11 (5.7%)	1 (1.2%)	0.076	2 (1.0%)	4 (3.3%)	0.024	8 (2.0%)	2 (2.0%)	0.985
Atrial fibrillation	3 (1.6%)	1 (1.2%)	0.821	4 (2.0%)	1 (0.8%)	0.415	19 (4.7%)	3 (2.9%)	0.431
Supraventricular tachycardia	1 (0.5%)	0	0.484	0	3 (2.5%)	0.077	5 (1.2%)	1 (1.0%)	0.827
Ventricular tachycardia	5 (2.6%)	2 (2.4%)	0.873	2 (1.0%)	3 (2.5%)	0.721	5 (1.2%)	1 (1.0%)	0.827
Ventricular fibrillation	—	—	—	2 (1.0%)	3 (2.5%)	0.421	4 (1.0%)	3 (2.9%)	0.134
Angina pectoris	3 (1.6%)	1 (1.2%)	0.821	1 (0.5%)	3 (2.5%)	0.059	14 (3.5%)	3 (2.9%)	0.787
Chest pain	2 (1.0%)	0	0.321	—	—	—	3 (0.7%)	0	0.382
Myocardial infarction	2 (1.0%)	1 (1.2%)	0.932	2 (1.0%)	1 (0.8%)	0.842	2 (0.5%)	1 (1.0%)	0.572
Myocardial rupture	—	—	—	—	—	—	3 (0.7%)	7 (6.9%)	0.001
Myocardial ischemia	—	—	—	—	—	—	17 (4.2%)	2 (2.0%)	0.283

CHF = congestive heart failure; LV = left ventricular.

patients although very few had severe ischemia (400 in the RUSSLAN study²¹ and 12 in the angioplasty-ischemia model²⁹). The levosimendan database is of the same size as that of nesiritide (941 patients), that is the most recently approved drug for the treatment of decompensated heart failure³¹. Furthermore, levosimendan is the only acute decompensated heart failure agent having a potentially positive effect on survival.

Both the dose-finding and dose-escalation trials clearly demonstrate the favorable hemodynamic effects of levosimendan, namely the normalization of preload and PCWP in severely compromised patients and the increase in both the stroke volume and cardiac output^{19,20}. The mean wedge pressure in the hemodynamic study by Slawsky et al.¹⁹ fell from 28 mmHg to the highly satisfactory 18 mmHg, and the stroke volume increased by 40%.

The 8.4% 30-day mortality for severe heart failure patients (LIDO) has to be seen favorably, as the in-hospital mortality in the EuroHeart Failure survey patients (mean age 68 years) was 7.2% and the 3-month mortality was 14.0%^{12,32}. Moreover, the 13% 3-month mortality in the levosimendan-treated patients in the LIDO trial favorably compared with that observed in the EuroHeart Failure survey (14%) and was significantly better than the 23% 3-month mortality observed for dobutamine-treated patients in the LIDO trial²⁸. The EuroHeart Failure survey also included milder heart failure patients, as the mean ejection fraction was 28% while in LIDO the mean ejection fraction was 22%. With regard to mortality, levosimendan may be seen as a feasible therapy although the trials were not powered to analyze this aspect.

However, we must acknowledge that these trials were not originally powered as mortality trials. Secondly, these agents are designed to improve the mortality during hospitalization and immediately afterwards. Most patients in these trials (not only those in the RUSSLAN trial²¹) were patients with congestive heart failure with coronary heart disease as a background condition. According to the EuroHeart Failure survey 68% of heart

failure patients have a coronary heart disease background¹². Thus, the mortality in heart failure populations is not only due to heart failure itself but also to the underlying coronary disease. Besides, for the other inotropic agents no relevant mortality data have been published, except for milrinone in the OPTIME-CHF trial in which a higher mortality was found in milrinone-treated patients^{27,30}. Levosimendan has to be seen as a vasodilator inotropic agent characterized by a new mechanism of action which improves contractility, the calcium-sensitizing effect. Besides, it does not interact with the "arrhythmogenic" ionic channels. The vasodilator effects were well tolerated as at the suggested dosage (a levosimendan bolus of 6-24 µg/kg followed by infusion at 0.05-0.2 µg/kg/min) the frequency of hypotension as an adverse effect was similar to that observed in the placebo group²¹ (Fig. 3, Table II).

The outcome in the coronary heart disease patients in these studies is good and can be thought to be the result of the beneficial effects of levosimendan on the coronary circulation³³ and of the anti-stunning³³ and unloading effects^{19,20}. Neither was there any excess morbidity or an increased frequency of hospitalization after levosimendan infusion in these patients.

Conclusions

No excess mortality, readmissions to hospital or adverse effects (hypotension, arrhythmias) have been observed during or after the short- (6 hours) or long-term (24 hours) use of levosimendan. Besides, the hemodynamic efficacy of the agent in decompensated heart failure in patients with worsening heart failure mainly due to stable coronary heart disease or to AMI is highly satisfactory.

The incidence of hypotension during infusion was generally low except when very high doses of levosimendan were administered.

Therefore, levosimendan should be considered as a useful therapeutic agent for the treatment of episodes of decompensation in patients with heart failure.

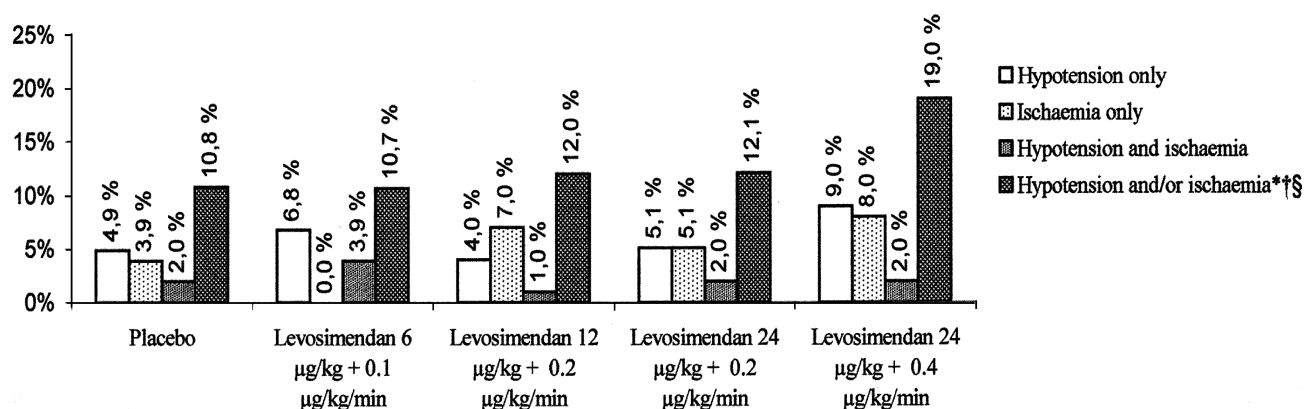


Figure 3. Incidence of clinically significant hypotension or ischemia in the RUSSLAN study. * $p = 0.319$ for comparison between all treatment groups; † $p = 0.456$ for comparison between combined levosimendan groups and placebo; § $p = 0.054$ for dose-response relation.

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