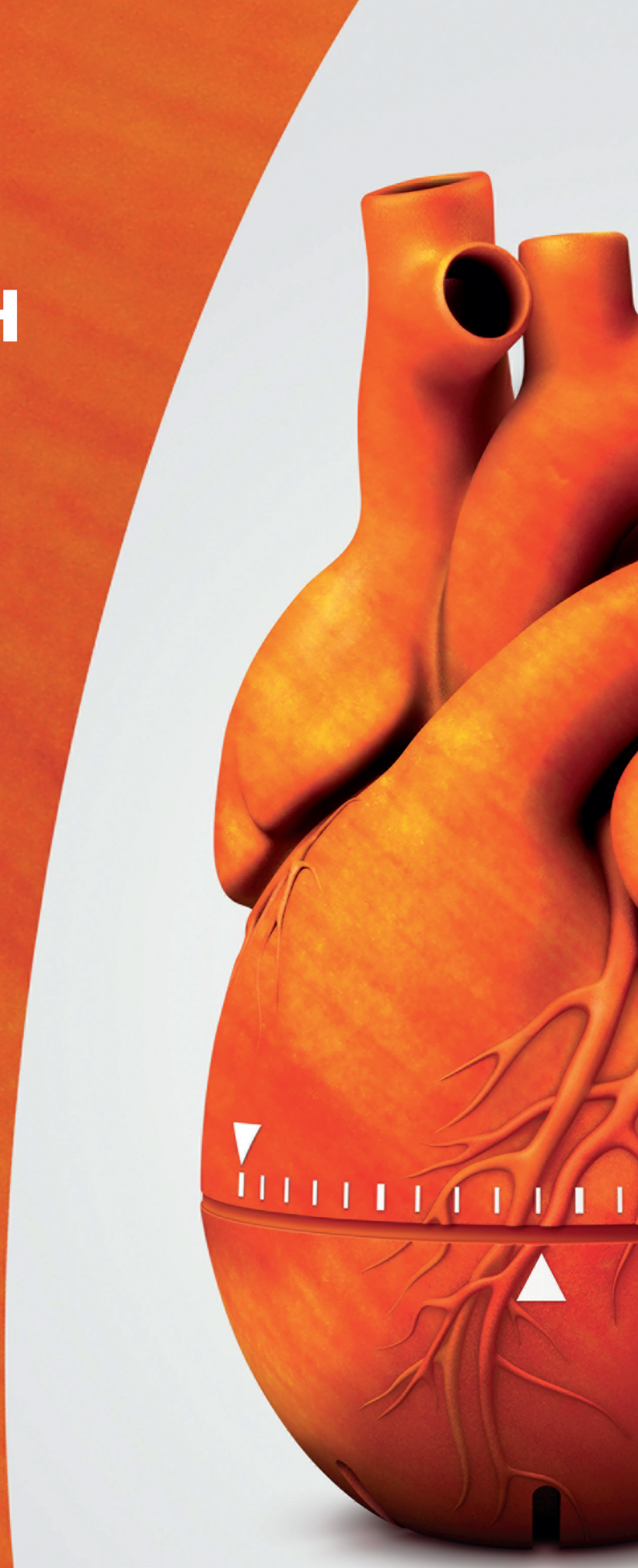
SIMDAX® PRODUCT MONOGRAPH

ORION PHARMA 2018



SIMDAX®
levosimendan

EASE THE CHALLENGE OF
TREATING THE FAILING HEART

Product Monograph
SIMDAX®

ORION PHARMA
Building well-being

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ABBREVIATIONS

ADHF	Acute(ly) decompensated heart failure
AdHF	Advanced chronic heart failure
AHF	Acute heart failure
AMI	Acute myocardial infarction
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
cAMP	Cyclic adenosine monophosphate
CCB	Calcium channel blocker
cGFR	Calculated glomerular filtration rate
CHF	Congestive heart failure
CI	Confidence interval / Cardiac index
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CYP	Cytochrome P450 enzymes
ECMO	Extracorporeal membrane oxygenation
EDV	Left ventricular end-diastolic volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESV	Left ventricular end-systolic volume
GMP	Gastric mucosal perfusion
HR	Heart rate
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
K_{ATP} channel	ATP-dependent potassium channel
LCOS	Low cardiac output syndrome
LS	Levosimendan
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LYS	Life years saved
MAP	Mean arterial pressure
MPAP	Mean pulmonary artery pressure
MR	Mitral regurgitation

NSVT	Nonsustained ventricular tachycardia
NT-proANP	N-terminal prohormone atrial natriuretic peptide
NYHA	New York Heart Association
PAOP	Pulmonary artery occlusion pressure
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PDE	Phosphodiesterase
PET	Positron emission tomography
PICU	Paediatric intensive care unit
PTCA	Percutaneous transluminal coronary angioplasty
PVR	Pulmonary vascular resistance
PVB	Premature ventricular beats
RBF	Renal blood flow
RD	Risk difference
RVP	Renal venous pressure
RVSP	Right ventricular systolic pressure
SOFA	Sequential Organ Failure Assessment
SPC	Summary of Product Characteristics
STEMI	ST-elevation myocardial infarction
SVB	Supraventricular beats
VAD	Ventricular assist device

TRIAL ACRONYMS

ALARM-HF	Acute Heart Failure Global Survey of Standard Treatment
CHEETAH	Levosimendan in High Risk Patients Undergoing Cardiac Surgery
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
LAICA	Long-Term Intermittent Administration of Levosimendan in Patients With Advanced Heart Failure
LEODOR	Repetitive Levosimendan Infusion for Patients with Advanced Chronic Heart Failure
LEOPARDS	Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis
LEVO-CTS	Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery on Cardiopulmonary Bypass
LEVOREP	Efficacy and Safety of Pulsed Infusions of Levosimendan in Outpatients with Advanced Heart Failure
LICORN	Preoperative Levosimendan in CABG Patients With Poor LV Function
LIDO	Levosimendan Infusion versus Dobutamine
LION-HEART	Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients
REVIVE I and II	Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy trials I and II
RUSSLAN	Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct
SURVIVE	Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support

LEVOSIMENDAN - KEY POINTS

SUMMARY

Levosimendan (SIMDAX®) is a calcium sensitiser developed for intravenous use in hospitalised patients with acute heart failure (AHF). SIMDAX® is proven effective and well tolerated in large-scale clinical trials of hospitalised patients with heart failure. By December 2017, more than 1.5 million patients worldwide have been treated with SIMDAX®.

Clinical data from heart failure patients showed that SIMDAX® offers:

- Improved haemodynamics[1-3] without a significant increase in oxygen consumption.[4, 5]
- Reduced symptoms of acute heart failure.[1, 2, 6, 7]
- Beneficial effect on neurohormone levels.[6-8]
- Sustained efficacy due to formation of an active metabolite.[8, 9]
- Additional benefit in patients under beta-blockade.[1, 10]

SIMDAX® is well tolerated and no major interactions with concomitant medications commonly used in heart failure have been reported.

SIMDAX® offers:

- A good and predictable safety profile.[1-3, 7]
- No impairment of diastolic function.[11, 12]
- No development of tolerance.[9]
- No adverse effect on survival.[1, 7, 13-16]

The effects of SIMDAX® are mediated through:

- Increased cardiac contractility by calcium sensitisation of troponin C.[17-20]
- Vasodilation through the opening of potassium channels.[21-24]
- Cardioprotection through the opening of mitochondrial potassium channels.[25-27]

Health economic analyses of the clinical data have shown that SIMDAX® is cost-effective in AHF patients.[28-30]

IN ACUTE HEART FAILURE

SIMDAX® (levosimendan) is indicated for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate. For product details, see the current Summary of Product Characteristics (SPC).

IN OTHER THERAPEUTIC AREAS

Cardiac surgery

Levosimendan has been studied in more than 30 clinical trials in connection with cardiac surgery. The results of these studies have shown uncompromised safety and beneficial haemodynamic and cardioprotective effects.

Repetitive administration in advanced chronic heart failure

Several investigator-initiated studies and case reports with repetitive levosimendan dosing have shown beneficial effects on haemodynamics, neurohormone levels and symptoms in patients suffering from advanced chronic heart failure.

Others

Levosimendan has also shown preliminary positive effects - mainly in small-scale investigator-initiated studies - in right ventricular failure, cardiogenic shock, and in other states requiring inotropic support.

INTRODUCTION

This monograph focuses on the regulatory studies performed with intravenous levosimendan (SIMDAX®). Most of the studies have been performed in patients with acute worsening of chronic heart failure and, to a lesser extent, in patients with left ventricular failure due to an acute myocardial infarction, cardiac surgery, and other therapeutic use. The regulatory clinical program has included nearly 3,500 patients.

In addition, levosimendan has been assessed in numerous clinical studies by independent investigators throughout the world. The focus of these investigator-initiated studies has lately been on the use of levosimendan in an operative setting and on repetitive dosing of levosimendan in advanced chronic heart failure. Further, smaller scale studies in several other clinical settings have been published. The results of these studies are also presented in this monograph.

Marketing authorisation was first granted for SIMDAX® in 2000 in Sweden. Currently, SIMDAX® has marketing authorisation in over 60 countries worldwide and it is estimated that by December 2017, more than 1.5 million patients had been exposed to SIMDAX® infusion in everyday clinical practice.

ACUTE HEART FAILURE

Acute heart failure (AHF) is a severe and life-threatening condition. In-hospital mortality varies between categories of heart failure and is up to 40-60% in patients with cardiogenic shock, but less than 10% in other categories.[31] No single or simple treatment protocol can be recommended for acute heart failure because of the wide range of problems underlying the decompensation episode.

Multiple agents are being used to treat acute heart failure, but there is a paucity of clinical studies data and their use is largely empiric.[32] I.v. diuretics and vasodilators constitute the corner stones of the treatment of AHF and rapid relief of symptoms can usually be obtained with these agents.[33] The current European Society of Cardiology (ESC) guideline[34] for the treatment of AHF recommends to reserve the use of inotropic agents and vasopressors for patients with such severe reduction in cardiac output that vital organ perfusion is compromised. Owing to their suspected detrimental effect on survival, their use is recommended only for the most severe cases and they should be withdrawn as soon as adequate organ perfusion is restored and/or congestion is reduced. Accordingly, the US heart failure guideline[35] recommends (Class I recommendation) the use of positive inotropic agents as a temporary treatment only to patients with cardiogenic shock until definitive therapy/resolution of the acute precipitating problem, and finds their use reasonable (Class IIb recommendation) in those hospitalised patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end organ performance.

The following table presents the currently used medications for AHF and the risks/adverse effects related to their use.

Table 1. Traditional medications for AHF: Indications/adverse effects.

Medication	Indication	Risks / adverse effects
Loop-diuretics: - i.v furosemide	Fluid overload	Hypotension, hypokalemia, renal impairment
Vasodilators: - nitrates - nitroprusside	Venous and arterial dilatation → relieve dyspnoea	Hypotension Development of tolerance (nitrates) Toxic metabolite (nitroprusside)
Positive inotropes: - dobutamine - PDE-inhibitors (milrinone)	Cardiogenic shock or pulmonary oedema not responding to first-line therapy	Myocardial ischaemia, arrhythmias, possibly increased mortality
Vasoconstrictors: - dopamine - noradrenaline	Cardiogenic shock unresponsive to inotropic drugs and fluid resuscitation	Similar to positive inotropes

CHEMISTRY

Levosimendan,(-)-(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono] propanedinitrile, belongs to a new class of drugs, the calcium sensitisers. The structural formula of levosimendan is presented in Figure 1. Levosimendan is a moderately lipophilic drug with molecular weight 280.3. It is a weak acid with pKa 6.3. Solubility of levosimendan in distilled water and phosphate buffer (pH 8) is poor (0.04 mg/ml and 0.9 mg/ml, respectively). Solubility in ethanol is 7.8 mg/ml and therefore levosimendan in its pharmaceutical composition (levosimendan 2.5 mg/ml infusion concentrate) is diluted in ethanol.[36]

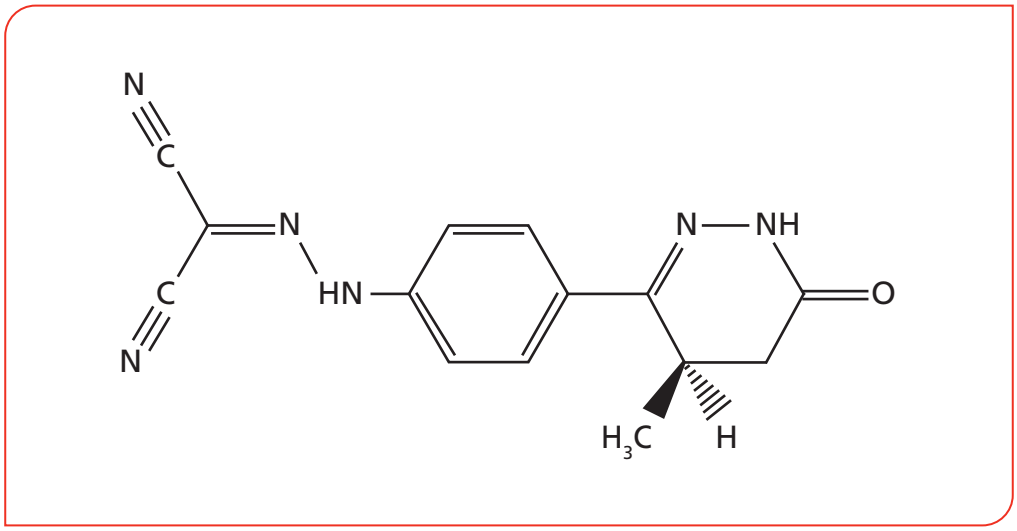


Figure 1. Structural formula of levosimendan.

PHARMACOLOGY

TRIPLE MECHANISM OF ACTION

Levosimendan has three key mechanisms of action:[37, 38] calcium sensitisation[17, 18, 38-40] and opening of adenosine triphosphate dependent-potassium (K_{ATP}) channels both on the sarcolemma of the smooth muscle cells of the vasculature,[21-24] and in the mitochondria of cardiomyocytes.[26, 27, 41]

1. Calcium sensitisation by selective binding to calcium-saturated cardiac troponin C[19, 20, 42-45] increases the contractile force of the cardiac myocytes[39,46-48] without affecting relaxation.[18, 49]
2. Opening of K_{ATP} channels in vascular smooth muscle cells[21, 22] elicits both arterial[50] and venous vasodilation[22] as well as improvement in coronary artery circulation.[23, 51]
3. Opening of K_{ATP} channels in the mitochondria of cardiomyocytes[41] achieves a cardioprotective effect in situations when the heart is subjected to ischaemic events.[26, 27, 52-55]

Through calcium sensitisation, levosimendan improves cardiac contractility in the failing heart without affecting muscle electrophysiology.[17] Through the opening of K_{ATP} channels in vascular smooth muscle cells, levosimendan improves oxygen supply to the myocardium.[54, 56, 57]

Because levosimendan augments myofibril contractions by increasing calcium sensitivity rather than by increasing intracellular calcium,[58, 59] it is not associated with increased myocardial oxygen demand,[4, 57, 60, 61] ischaemia,[54, 55, 62, 63] or tolerance,[9] conditions sometimes incurred with agents traditionally used to treat decompensated heart failure.

In brief, the mechanism of action for levosimendan involves three clinically relevant features that are specific to the cardiovascular system; levosimendan acts on the contractile apparatus of the myocardial cells, on the vascular smooth muscle cells and on the mitochondria of the cardiomyocytes via independent, but complementary, mechanisms.

Calcium sensitisation

The heart muscle consists of cardiac myocytes that show a striated subcellular structure: each cell contains myofibrils with actin and myosin filaments, which form the contractile apparatus. The actin filaments are associated with the regulatory proteins tropomyosin and troponin, which is complex of three smaller proteins (TnC, TnI, and TnT) (Figure 2).

When intracellular Ca^{2+} concentration increases, troponin C becomes Ca^{2+} saturated, which triggers the contraction. When calcium is removed from the cytosol, troponin C, now Ca^{2+} free, allows the sarcomere relaxation.

Levosimendan selectively binds to calcium-saturated cardiac troponin C (Figure 3).[19, 20, 42-45, 64]

By binding to troponin C and stabilising the troponin C - Ca^{2+} complex, levosimendan enhances the sensitivity of the myofilament and facilitates the actin-myosin crossbridge formation.[18, 19, 38] The

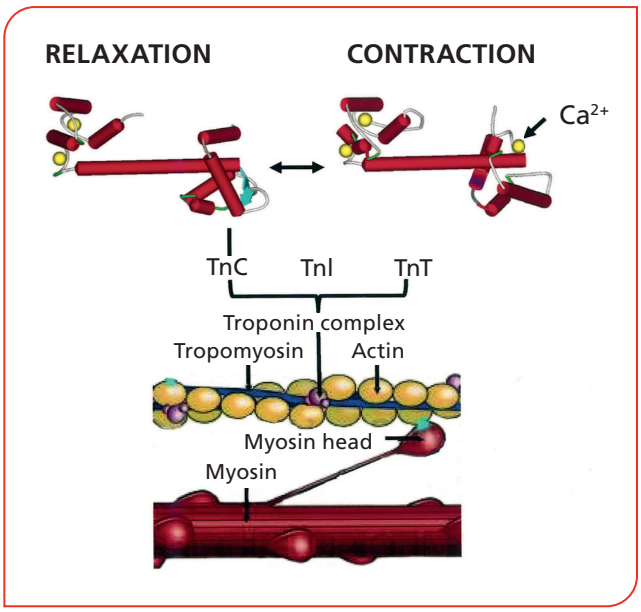


Figure 2. Role of troponin C in the mechanism of contraction.

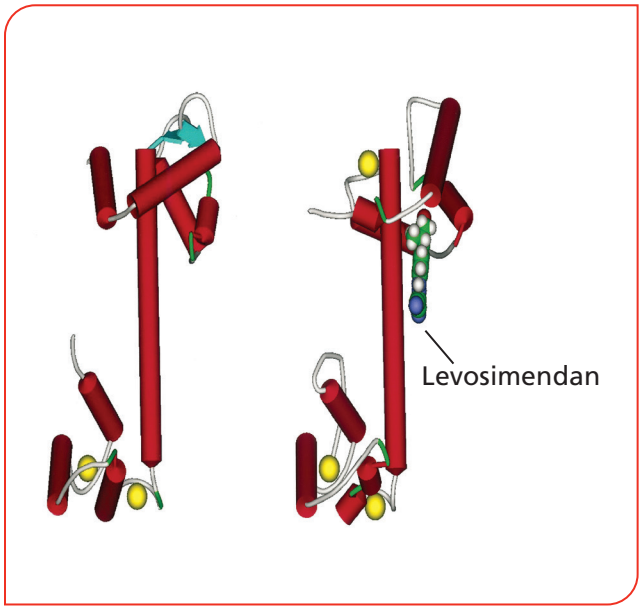


Figure 3. Levosimendan selectively binds to calcium saturated cardiac troponin C.

calcium sensitisation effect of levosimendan has been shown in many in vitro models from skinned fibres to isolated hearts.[17, 23, 39, 46, 48, 58-60, 64-67] Levosimendan has positive inotropic effects in normal[68, 69] and heart failure models.[70, 71]

The formation of the troponin C - Ca^{2+}-levosimendan complex is calcium-dependent[17, 18, 64] and calcium sensitivity is enhanced only when intracellular calcium concentration is elevated. As a result of this unique property, levosimendan increases contractile force during systole when intracellular calcium concentration is increased. Importantly, levosimendan does not impair relaxation during diastole when intracellular calcium concentration is decreased[18, 65] or even improves relaxation.[49] Levosimendan has been shown to increase contractility considerably with only a modest increase in intracellular calcium, even in ventricular muscle strips from end-stage failing human hearts.[38, 59] This finding is significant in relation to clinical effect in that levosimendan does not increase energy consumption[5, 57, 60, 72, 73] and the risk of proarrhythmic events is low.[52, 62, 74] Other agents shown to improve cardiac output, such as milrinone, have different mechanisms of action from levosimendan.[18] In fact, milrinone increases cardiac contractility, but it does so by increasing intracellular calcium concentrations, thereby increasing energy consumption and the potential for arrhythmia.[75, 76]

Calcium sensitisation with levosimendan offers increased cardiac contractility

- without increasing intracellular calcium.[58, 59]
- without increasing oxygen consumption.[5, 57, 60, 72, 73]
- without affecting cardiac rhythm[52, 62, 74] and relaxation.[18, 65, 77]

Opening of K_{ATP} channels in the vascular smooth muscle cells

The heart muscle consists of cardiac myocytes that show a striated subcellular structure: each cell contains myofibrils with actin and myosin filaments, which form the contractile apparatus. The actin filaments are associated with the regulatory proteins tropomyosin and troponin, which is complex of three smaller proteins (TnC, TnI, and TnT) (Figure 2).

When intracellular Ca^{2+} concentration increases, troponin C becomes Ca^{2+} saturated, which triggers the contraction. When calcium is removed from the cytosol, troponin C, now Ca^{2+} free, allows the sarcomere relaxation.

Vasodilation with levosimendan results from the opening of K_{ATP} channels; it reduces preload and afterload, and improves oxygen supply to the myocardium. Vasodilation with levosimendan has been demonstrated in both arterial[21] and venous[22] vascular beds, and in the coronary arteries.[23] Opening of K_{ATP} channels has also been observed in ventricular myocytes - an effect that may help to protect ischaemic myocardium.[78]

The opening of K_{ATP} channels by levosimendan has been both electrophysiologically[21] and pharmacologically[23] demonstrated in arterial and venous preparations and in coronary arteries.[79] It has also been shown that the venodilatory effect of levosimendan on the noradrenaline-constricted human portal vein[22] or serotonin-constricted human saphenous vein[80] is also mediated by the opening of K_{ATP} channels. In addition, some pharmacological findings indicate that levosimendan may open the calcium-dependent potassium channels in arteries and veins[80] as well as voltage-dependent potassium channels in coronary arteries.[81]

In light of the above-mentioned studies, it seems that levosimendan may preferentially stimulate K_{ATP} channels in small resistance vessels.[24] In large conductance vessels the vasodilatation appears to be mediated mainly through opening of voltage- as well as calcium-dependent potassium channels.

Opening of K_{ATP} channels in the cardiomyocyte mitochondria

By opening mitochondrial adenosine triphosphate-dependent potassium (mitoK_{ATP}) channels,[41] levosimendan protects the heart against ischaemia-reperfusion damage.[26, 27, 52-54, 74] The fact that levosimendan can prevent or limit myocyte apoptosis via the activation of mitoK_{ATP} channels provides a potential mechanism whereby this agent might protect cardiac myocytes during episodes of acute heart failure[26, 82-87] as well as in chronic heart failure situation.[88, 89]

Additional in vitro results

In vitro studies indicate that levosimendan is a highly selective phosphodiesterase (PDE) III inhibitor compared to other PDE isoenzymes.[39] The PDE III inhibition alone is not sufficient to increase the cyclic adenosine monophosphate (cAMP) intracellular level.[59] Hence, this mechanism of action does not contribute significantly to the contractility-enhancing and vasodilatory effects of levosimendan in isolated guinea-pig heart[38, 48, 90] and, therefore, probably not in clinical practice either. It has been shown that the inotropic effect of levosimendan cannot be blocked by a protein kinase inhibitor[48] that is known to prevent the activity of PDE-inhibiting drugs. Simultaneous inhibition of both PDE III and PDE IV is needed to increase cAMP and intracellular calcium, which is seen with non-selective PDE inhibitors[90] (such as enoximone and milrinone).

PHARMACOKINETICS

General pharmacokinetics

Levosimendan is extensively metabolised before excretion into urine and faeces. The main pathway is conjugation with glutathione to form inactive metabolites. The minor pathway (approximately 6% of the total levosimendan dose) is reduction in the intestine to an intermediate metabolite (OR-1855), which is further acetylated to the active metabolite, OR-1896.[91] Levosimendan is excreted as conjugates via the urine and faeces and only traces of unchanged levosimendan are found in experimental animals and in man.[92, 93] Levosimendan metabolism is illustrated in Figure 4.

The metabolite OR-1896 has been shown to have haemodynamic and pharmacologic properties similar to those of the parent drug in preclinical models.[24, 39, 69, 94, 95]

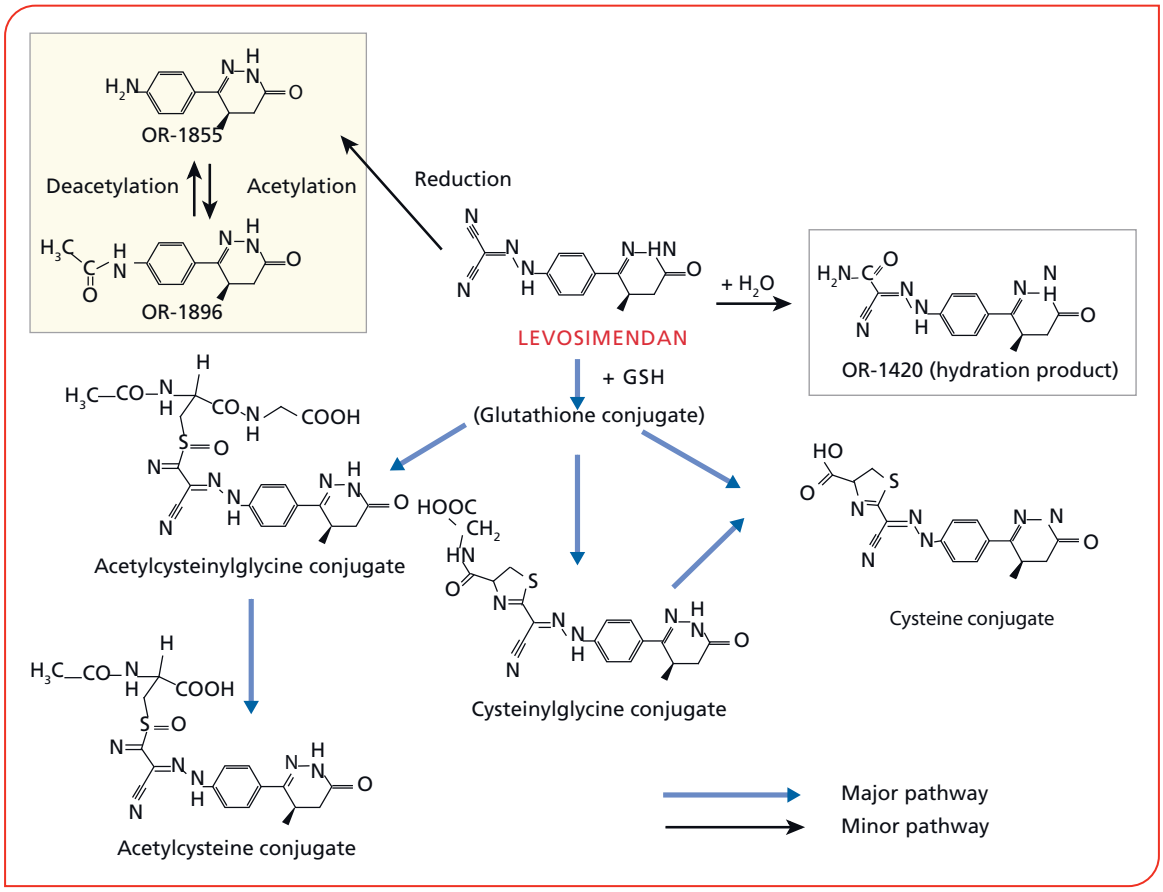


Figure 4. Metabolism of levosimendan.

The terminal elimination half-life ($t_{1/2el}$) of levosimendan is about 1 hour both in healthy volunteers and in patients with heart failure (Table 2) and it rapidly disappears from the circulation after the infusion is stopped. Levosimendan is highly bound to plasma proteins (97-98%).[93, 96] The plasma concentrations of levosimendan increase dose-proportionally.[97, 98]

The mean elimination half-life values for the levosimendan metabolites OR-1855 and OR-1896 are approximately 80 hours and their plasma protein binding is about 40% (Table 2).[98, 99] The time curves of the concentrations of levosimendan and the metabolite OR-1896 are shown in Figure 5.

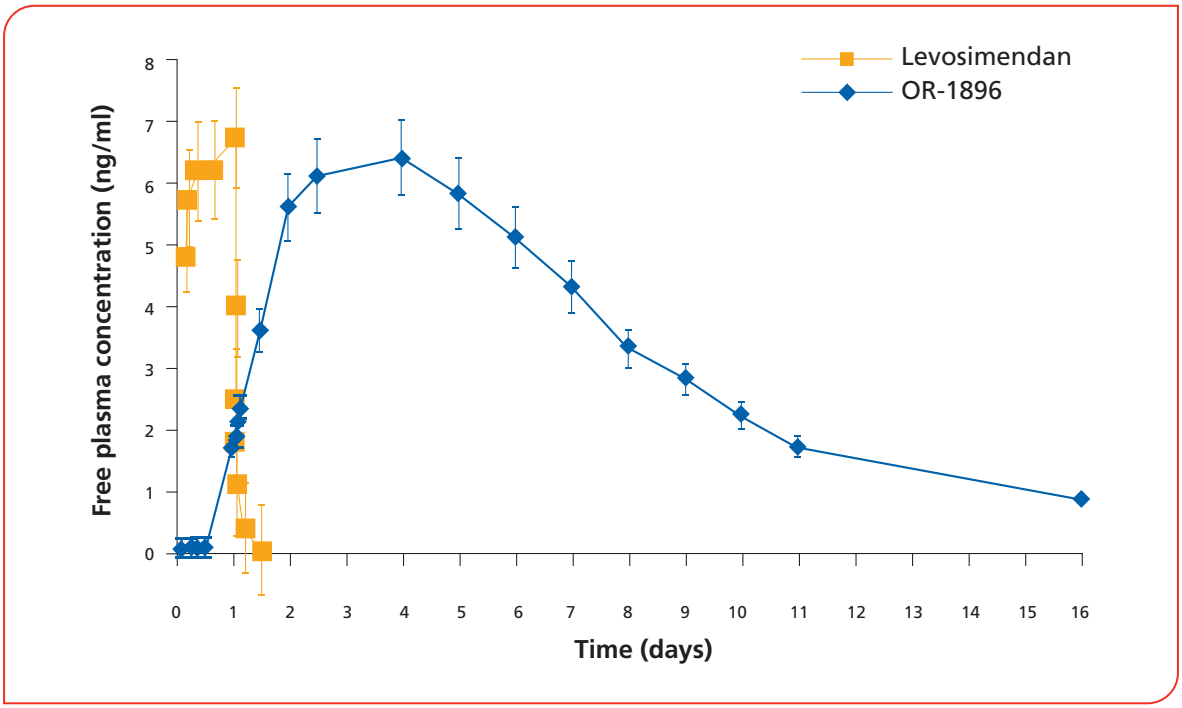


Figure 5. Free plasma concentrations of levosimendan and OR-1896 during and after a 24-h infusion (mean values ± SD).[99]

Table 2. Pharmacokinetic variables of levosimendan and its active metabolite OR-1896 in patients with NYHA III-IV heart failure.[98-100]

Variable	Levosimendan	Metabolite OR-1896
$t_{1/2el}$ (h)	1.1 - 1.4	77.4 - 81.3
CL_{tot} (l/h/kg)	0.18 - 0.22	na
V_c (l/kg)	0.33 - 0.39	na
Protein binding (%)	97	42

$t_{1/2el}$ = terminal elimination half-life, CL_{tot} = total clearance, V_C = volume of distribution based on area under the curve (AUC), na = not assessed

The activity of the enzyme responsible for the acetylation, the N-acetyltransferase, is known to differ considerably in man. Most Caucasian populations in Europe and North America have 40% to 70% slow acetylators, whereas most Asian populations have only 10% to 30% slow acetylators.[101] The acetylator status of a patient affects the pharmacokinetics of levosimendan metabolites, but not that of the parent drug. In rapid acetylators, the OR-1896 levels were significantly higher and OR-1855 significantly lower; in slow acetylators the opposite was seen. However, the effects on heart rate, blood pressure, pulmonary capillary wedge pressure and cardiac output were similar in the two acetylator types. These findings could be explained either by assuming that both metabolites are active in man or by the fact that the differences in OR-1896 levels seen in the study were too small to produce different haemodynamic responses.[102]

Pharmacokinetics in special populations

Population pharmacokinetic analysis has shown no effects of age, ethnic origin (Caucasians vs. African Americans) or gender on the pharmacokinetics of levosimendan.[103] However, the same analysis revealed that volume of distribution and total clearance are dependent on weight.

The pharmacokinetic profile of levosimendan in paediatric patients with congenital heart disease was similar to that of adult patients after a single intravenous bolus dose of levosimendan (12 µg/kg).[104] The study of Pellicer et al. with a longer levosimendan infusion showed that the same metabolites (OR-1855 and OR-1896) as in adults are also formed in neonates.[105]

The pharmacokinetics of levosimendan in patients with severe renal impairment or undergoing chronic haemodialysis revealed that the elimination of the metabolite OR-1896 was prolonged 1.5-fold compared with healthy subjects and the exposure to the metabolites (area under the curve AUC) was up to 170% higher.[106] However, no clinically relevant differences in the pharmacokinetics of the parent drug were observed. The metabolites were dialysable, but the parent drug seemed not to transfer to dialysate. The probable explanation is the lower plasma protein binding of the metabolites compared to the parent drug.

In patients with moderate hepatic impairment, the elimination of the metabolite OR-1896 was also prolonged 1.5-fold, but exposure to the metabolites was not significantly altered.[107] Similarly to renal impairment, the pharmacokinetics of levosimendan itself was not altered in hepatic impairment.

In patients undergoing cardiac surgery, the formation of the metabolites OR-1855 and OR-1896 was delayed compared to patients with chronic heart failure. In chronic heart failure, the peak concentrations of the metabolites were seen 2-4 days after starting the infusion,[99] compared to 6 days[108] in patients undergoing cardiac surgery. The reason is not fully known, but may be related to initiation of therapy following a fasting state and the use of broad-spectrum antibiotics. These conditions reduce populations of intestinal bacteria involved in the acetylation of levosimendan, leading to reduced/delayed formation of metabolites OR-1855 and OR-1896. The steady state plasma concentrations of the parent drug were somewhat lower in cardiac surgery patients than in chronic heart failure with the AUC 14% lower with similar dosing (approximately 1200 vs. 1400 h × ng/ml, respectively).[108]

Interactions

Preclinical findings suggest that cytochrome P450 (CYP) enzymes do not play any role in the metabolism of levosimendan or its metabolites OR-1855 and OR-1896 (see SPC).

Several clinical interaction studies with levosimendan have been performed. In pharmacokinetic interaction studies between intravenous or oral levosimendan and itraconazole,[96] warfarin,[109] captopril,[110] isosorbide mononitrate[111] or alcohol,[112] no clinically significant effects of concomitant administration on levosimendan pharmacokinetics were found. Furthermore, studies with felodipine[113] and carvedilol[114] have revealed no relevant haemodynamic or pharmacokinetic interactions.

PHARMACODYNAMICS

Haemodynamics

The haemodynamic effects of levosimendan are thoroughly presented in Haemodynamics section starting on page 22 . Briefly, levosimendan produces dose-dependent increases in cardiac output, stroke volume and heart rate, and decreases in pulmonary capillary wedge pressure, mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral resistance.[3] The effects are seen in minutes if a loading dose is used.[115] There is no sign of development of tolerance even with a prolonged infusion up to 48 hours.[9] Due to the formation of an active metabolite, the haemodynamic effects are maintained several days after stopping levosimendan infusion.[8]

Myocardial energy and oxygen consumption

The beneficial effects of levosimendan on haemodynamics are not associated with any significant increase in myocardial energy consumption, as evidenced using dynamic positron emission tomography (PET) in hospitalised patients with heart failure (NYHA III-IV) (Figure 6).[5] The patients were given levosimendan (18 µg/kg as a loading dose followed by a continuous infusion of 0.3 µg/kg/min for about 5 hours) and placebo in a crossover fashion. Despite increases in both cardiac output and stroke volume, myocardial oxygen consumption was unaltered by levosimendan.

Similarly, bolus doses of 8 µg/kg or 24 µg/kg did not increase myocardial oxygen consumption in postoperative patients, although cardiac function markedly improved.[4]

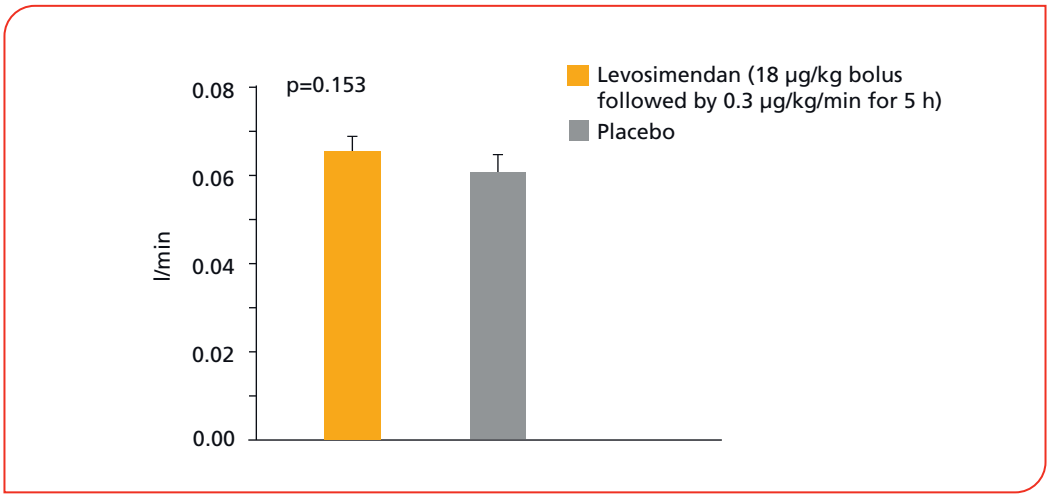


Figure 6. Myocardial oxygen consumption in heart failure patients.[5]

Anti-stunning

Levosimendan also possesses anti-stunning effects. This was shown in a randomised, double-blind study in patients with an acute myocardial infarction who had undergone percutaneous transluminal coronary angioplasty (PTCA).[11] The patients received levosimendan 24 µg/kg as a bolus dose (n=16) or corresponding placebo (n=8) 10 minutes after completion of the successful PTCA. The study showed that levosimendan clearly improved the function of stunned myocardium, as shown by a substantial reduction in the number of hypokinetic segments in the left ventricular wall (-2.4) compared with placebo (which showed an increase of 0.8, p = 0.016).

Diastolic function

The same study also showed that diastolic function was not worsened by levosimendan; end diastolic pressure-volume ratio and chamber compliance during late diastole changed similarly with levosimendan and placebo. In addition, the index of isovolumic relaxation (Tau) was improved in the levosimendan group and impaired in the placebo group, which suggests improved diastolic function. A similar finding was observed in a study using intracoronary infusions.[12] Ten patients with heart failure received two intracoronary doses of levosimendan without systemic effects (3.75 and 12.5 µg/min and dextrose [control] as bolus doses). In this study Tau was improved with the higher dose, but was unaffected with the lower dose of levosimendan. Levosimendan also increased left ventricular +dP/dt dose-dependently at various paced heart rates, indicating a direct contractility enhancing effect with levosimendan.

TRIALS IN ACUTE HEART FAILURE

CLINICAL PROGRAM

The regulatory clinical program of levosimendan included nearly 3,500 patients. The design of the most important studies is described in the following sections and summarised in Table 3.

Table 3. The pivotal trials with levosimendan.

Study	N (total/ LS)	Dose (µg/kg/min), duration of LS infusion (h)[a]	Comparator	Diagnosis/ NYHA class	Primary endpoint
Dose ranging	151/95	0.05-0.6, 24	Placebo/ dobutamine	CHF/III	Invasive haemodynamics
Dose escalation and withdrawal	146/98	0.1-0.4, 24 or 48	Placebo	CHF/III-IV	Invasive haemodynamics
LIDO	203/103	0.1-0.2, 24	Dobutamine	CHF /(III)-IV	Invasive haemodynamics
RUSSLAN	504/402	0.1-0.4, 6	Placebo	Post AMI/IV	Safety
REVIVE I	100/51	0.1-0.2, 24	Placebo	CHF/IV	Clinical composite
REVIVE II	600/299	0.1-0.2, 24	Placebo	CHF/IV	Clinical composite
SURVIVE	1327/664	0.1-0.2, 24	Dobutamine	CHF/IV	Mortality

[a] In all studies, a loading dose (3-36 µg/kg) preceded the continuous infusion.

LS = levosimendan, AMI = acute myocardial infarction, CHF = congestive heart failure

Dose-finding study: The therapeutic dose range of levosimendan administered over a 24-hour period was studied in a placebo-controlled, double-blind, parallel-group, randomised study including 151 patients with stable (mainly NYHA class III) heart failure of ischaemic origin. Patients were treated with a 24-hour intravenous infusion of levosimendan at doses ranging from 0.05 to 0.6 µg/kg/min.[3]

Dose escalation study: Forced up-titration, maintenance and withdrawal of levosimendan was studied in a placebo-controlled, double-blind, parallel-group, randomised study in 146 patients hospitalised for decompensated heart failure (NYHA class III or IV) due to coronary artery disease or dilated cardiomyopathy. Patients were treated with an intravenous infusion of levosimendan at doses ranging from 0.1 to 0.4 µg/kg/min. The study was divided into three phases. During the

first 6 hours, escalated doses of levosimendan (n=98) were compared with placebo (n=48). From 6 to 24 hours, the patients in the levosimendan group continued to receive the study medication as an open-label infusion. At 24 hours, the remaining patients were randomised to continue on levosimendan (levosimendan continuation group) or placebo (levosimendan withdrawal group), administered double-blind up to 48 hours.[2, 9]

LIDO study: Levosimendan was compared with dobutamine in a double-blind, parallel-group, randomised study in 203 patients with low-output heart failure, with either an ischaemic or non-ischaemic aetiology of heart failure, who required right heart catheterisation and treatment with an intravenous inotropic drug. Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1 to 0.2 µg/kg/min.[1]

RUSSLAN study: The safety of levosimendan in patients with left ventricular failure complicating an acute myocardial infarction was studied in a placebo-controlled, double-blind, parallel-group, randomised study in 504 patients within 5 days of acute myocardial infarction.[13] Patients randomised to levosimendan were treated with a 6-hour i.v. infusion of levosimendan at doses ranging from 0.1 to 0.4 µg/kg/min. Invasive haemodynamics were not assessed in this study.

The REVIVE studies: The REVIVE I and REVIVE II studies evaluated the efficacy of levosimendan on symptoms of heart failure with a new composite endpoint. These were randomised, double-blind, placebo-controlled, parallel-group studies in patients with AHF. REVIVE I (n=100) was a pilot study designed to evaluate the suitability of the endpoint;[6] REVIVE II (n=600) was the phase III study.[6] Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1 to 0.2 µg/kg/min. Both studies were conducted mainly in the U.S. The study design for REVIVE II is shown in Figure 7.

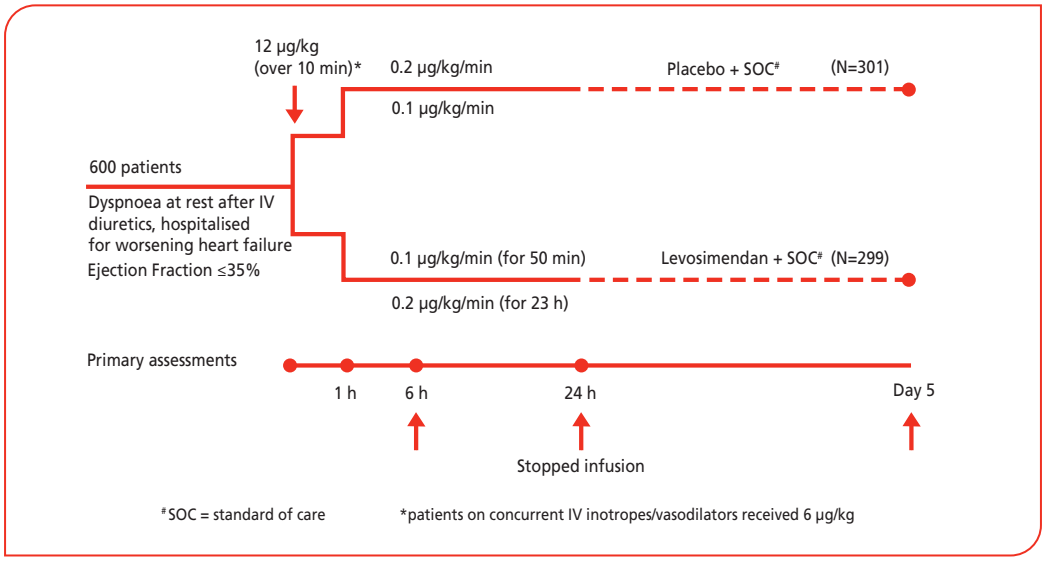


Figure 7. REVIVE II trial design.

The SURVIVE study: The SURVIVE study was a double-blind, parallel-group, randomised study in 1327 patients with severe systolic heart failure comparing the effects of levosimendan with dobutamine on mortality. Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1 to 0.2 µg/kg/min.[7] The study design is shown in Figure 8.

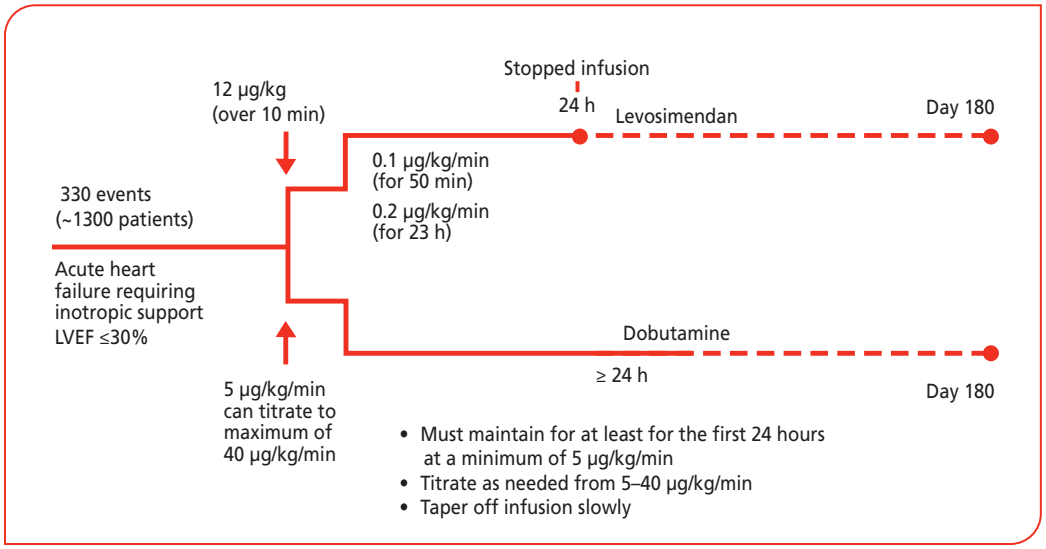


Figure 8. SURVIVE trial design.

HAEMODYNAMICS

Levosimendan produces significant, dose-dependent increases in cardiac output (Figure 9), stroke volume and heart rate, and decreases in pulmonary capillary wedge pressure (Figure 9), mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral resistance.[3]

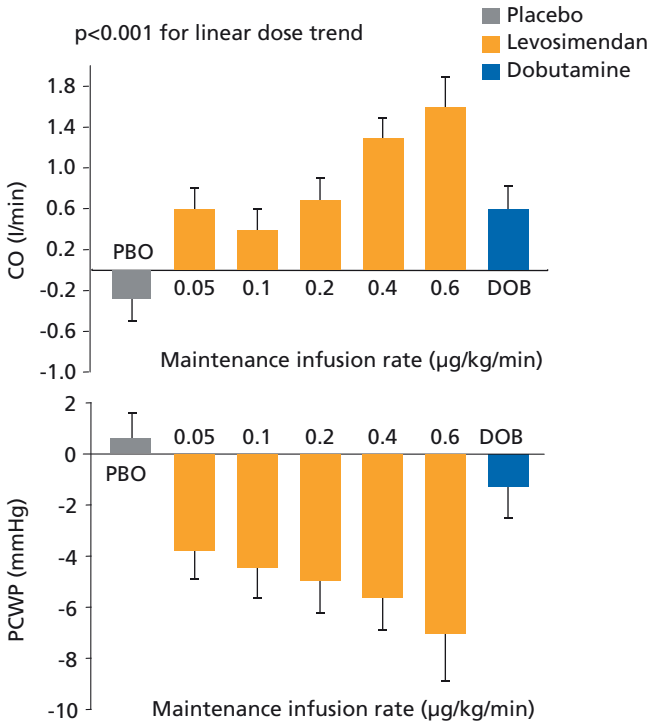
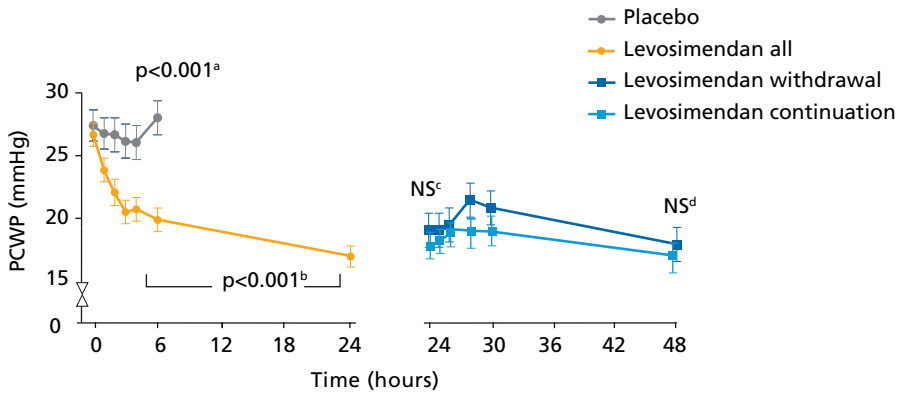


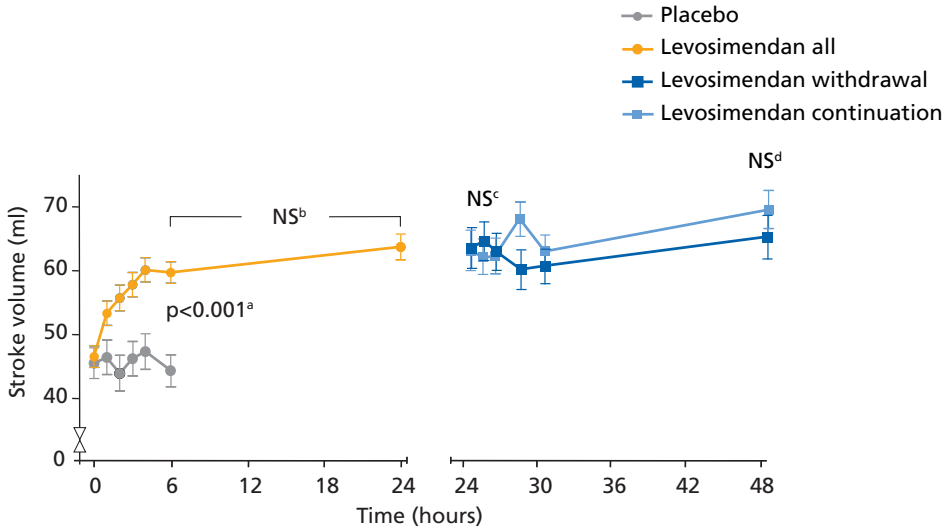
Figure 9. Change in cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) 24 hours post-baseline after a 24-hour infusion of levosimendan, placebo or dobutamine in patients with stable heart failure.[3]

The effect of levosimendan on haemodynamic variables (cardiac output, stroke volume, heart rate and pulmonary capillary wedge pressure) was clearly evident already at the end of a 5-minute bolus infusion.[115] There is no sign of development of tolerance even with a prolonged infusion up to 48 hours (Figure 10 and Figure 11).[9]



a) Levosimendan vs. placebo at 6 hours
b) Levosimendan at 6 hours vs. levosimendan at 24 hours
c) Levosimendan continuation vs. withdrawal at 24 hours
d) Levosimedan continuation vs. withdrawal at 48 hours

Figure 10. Mean pulmonary capillary wedge pressure (PCWP) in the dose escalation trial.[9]



a) Levosimendan vs. placebo at 6 hours
b) Levosimendan at 6 hours vs. levosimendan at 24 hours
c) Levosimendan continuation vs. withdrawal at 24 hours
d) Levosimedan continuation vs. withdrawal at 48 hours

Figure 11. Mean stroke volume in the dose escalation trial.[9]

Due to the formation of the active metabolites, the haemodynamic effects are maintained several days after stopping levosimendan infusion (Figure 12).[8]

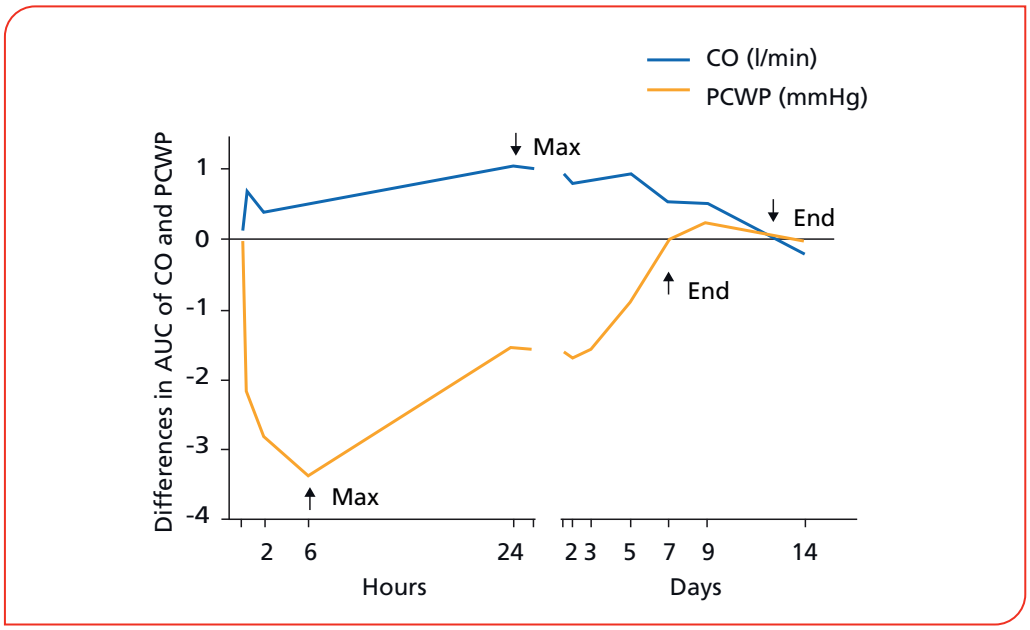


Figure 12. Differences in the AUC for changes in Doppler echocardiography derived pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) with levosimendan for 24 hours (n=11) vs. placebo (n=11).[8]

Compared with dobutamine, levosimendan produces a slightly greater increase in cardiac output and a profoundly greater decrease in pulmonary capillary wedge pressure.[1, 116] In contrast to dobutamine, the haemodynamic effects are not attenuated with concomitant ß-blocker use (Figure 13).[1]

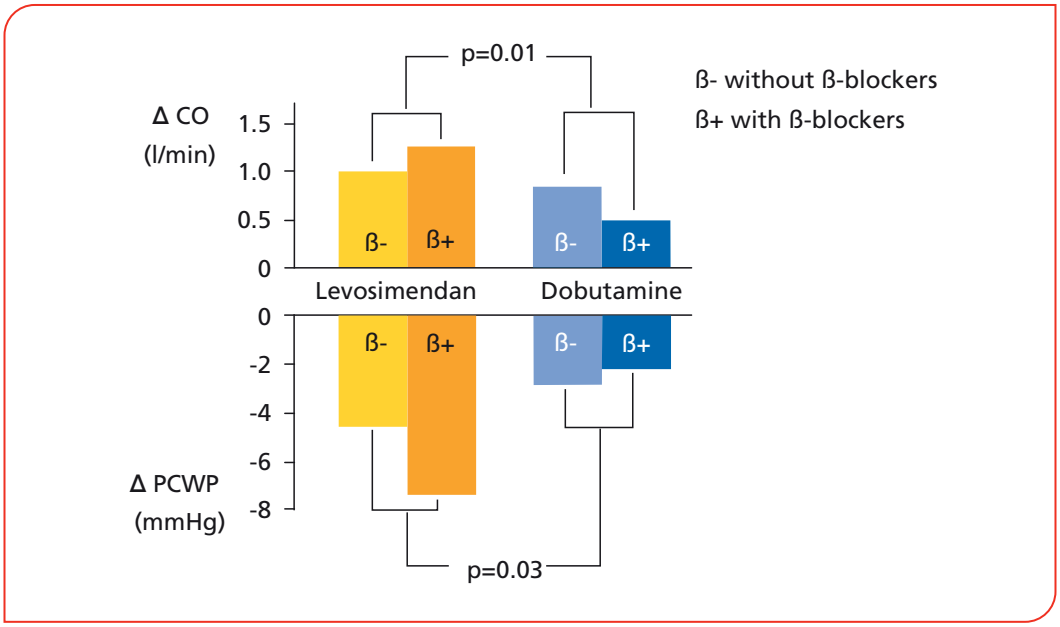


Figure 13. Effect of previous ß-blocker use on cardiac output and pulmonary capillary wedge pressure (PCWP) after a 24-hour infusion of levosimendan or dobutamine at 24 hours post-baseline (LIDO).[1]

It has also been shown that at 48 hours after the start of infusion, a 24-hour infusion of levosimendan achieves superior haemodynamic effects over a 48-hour dobutamine infusion in patients with severe AHF on ß-blockers (Figure 14).[116]

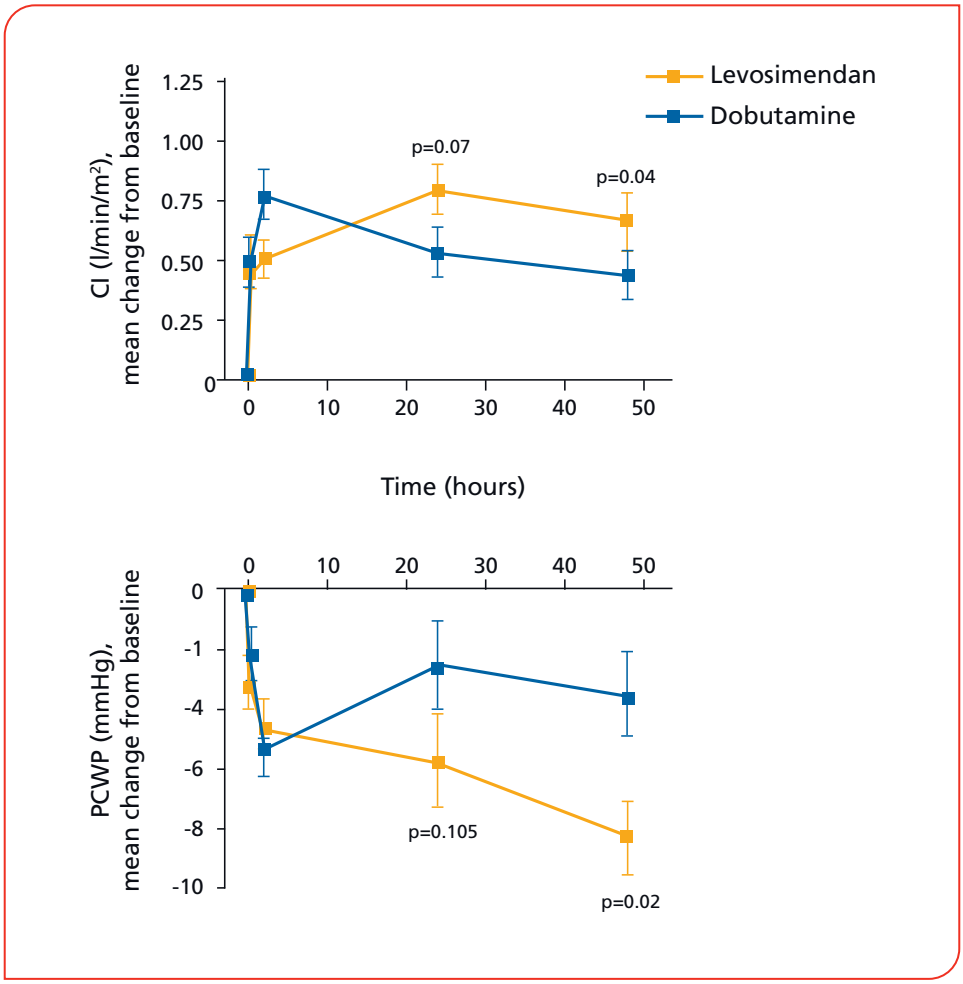


Figure 14. Mean change from baseline in cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) following a 24-hour levosimendan or 48-hour dobutamine infusion in patients with ongoing ß-blocker treatment.[116]

SYMPTOMS

In the dose escalation and withdrawal study, dyspnoea improved in significantly more patients treated with levosimendan compared with placebo at 6 hours after starting the treatment (Figure 15).[2]

In the LIDO study, symptoms improved equally well in the levosimendan and dobutamine treated patients at 24 hours after start of infusion. Dyspnoea improved in 68% and 59% (p = 0.865) of the patients with baseline symptoms in the levosimendan and dobutamine groups, respectively, while fatigue improved in 63% and 47% (p = 0.155), respectively.[1]

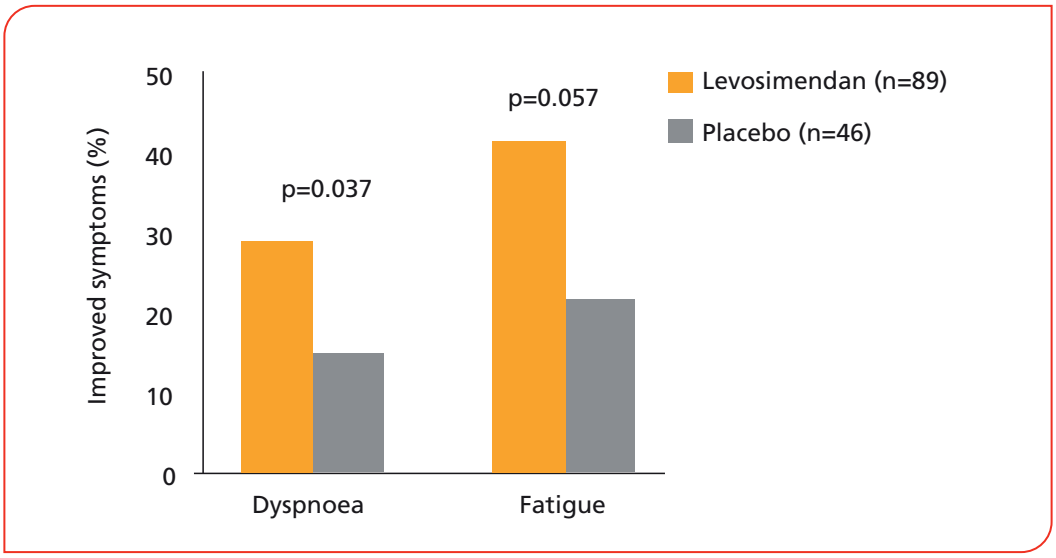


Figure 15. Patients reporting improved symptoms of heart failure 6 hours after starting levosimendan or placebo infusion.[2]

In the REVIVE II study, symptoms over the 5-day assessment period improved significantly more with levosimendan than with placebo (Figure 16).[6] It should be noted that levosimendan (or placebo) was administered on top of the standard of care and that in the placebo group, the majority of the patients also improved.

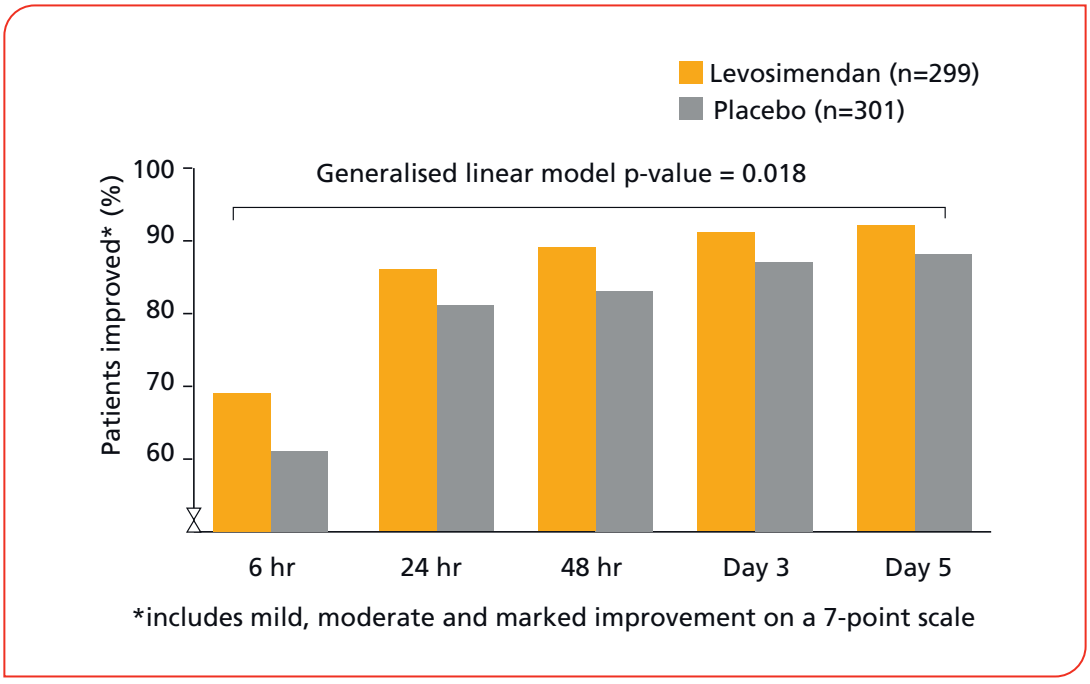


Figure 16. Improvement of dyspnoea over time in REVIVE II.[6]

COMPOSITE ENDPOINT

In the REVIVE II study, the primary endpoint was a composite consisting of patients' subjective symptom assessments (at 6 hours, 24 hours, and 5 days) and signs of worsening symptoms (including death) during the 5 days after starting a 24-hour study drug infusion.

Improvement was observed more frequently (19 vs. 15%) and worsening less frequently (19 vs. 27%) in levosimendan treated patients compared with placebo (p = 0.015) (Figure 17).[6]

The improvement in the composite endpoint was accompanied by a lower need for rescue medication in the levosimendan group (Figure 18 and Table 4).[6]

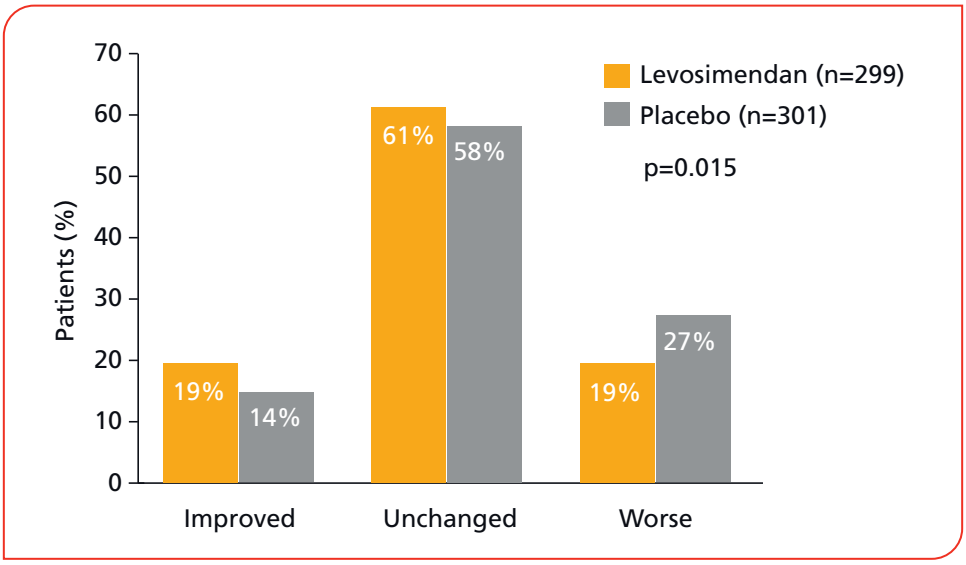


Figure 17. The primary endpoint result in REVIVE II.[6]

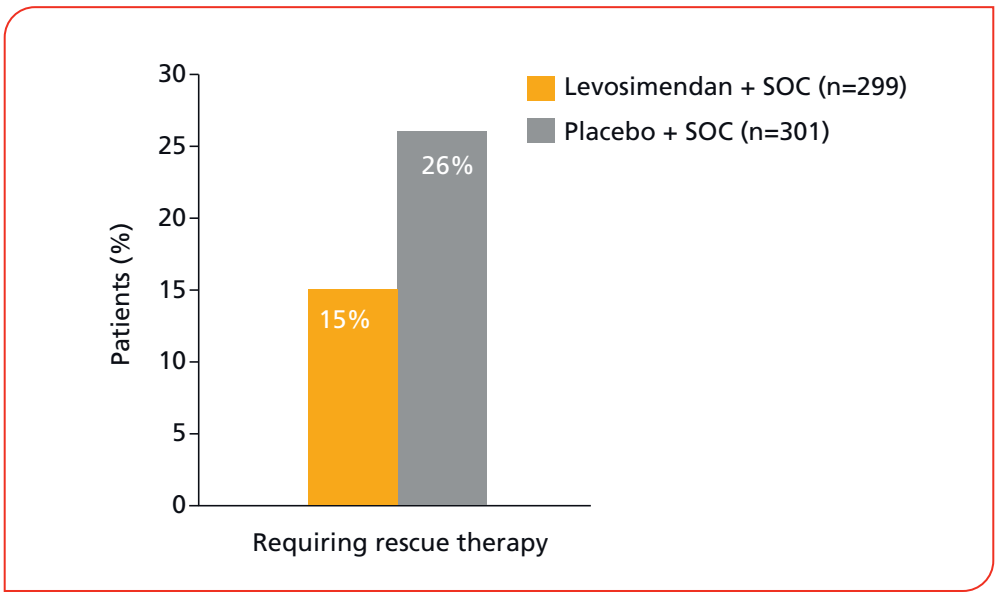


Figure 18. Use of rescue medication in REVIVE II.[6] (SOC = Standard of care)

Table 4. Drugs used as rescue medication in REVIVE II.[6]

Rescue medication	Levosimendan (n=45)	Placebo (n=79)
Furosemide	23	47
Nesiritide	17	24
Dobutamine	12	19
Milrinone	12	18

NEUROHORMONES

Plasma concentrations of natriuretic peptides are useful biomarkers in the diagnosis of heart failure and in the management of patients with chronic heart failure.[117] Discharge BNP values have been shown to be strong predictors of subsequent outcomes in patients admitted for AHF.[118, 119]

Numerous studies indicate that levosimendan produces a rapid and sustained decrease in natriuretic peptides. Lilleberg et al. found that a 24-hour levosimendan infusion induced a 40% decrease in plasma N-terminal prohormone atrial natriuretic peptide (NT-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels and the treatment effect was estimated to last up to 16 and 12 days, respectively (Figure 19).[8]

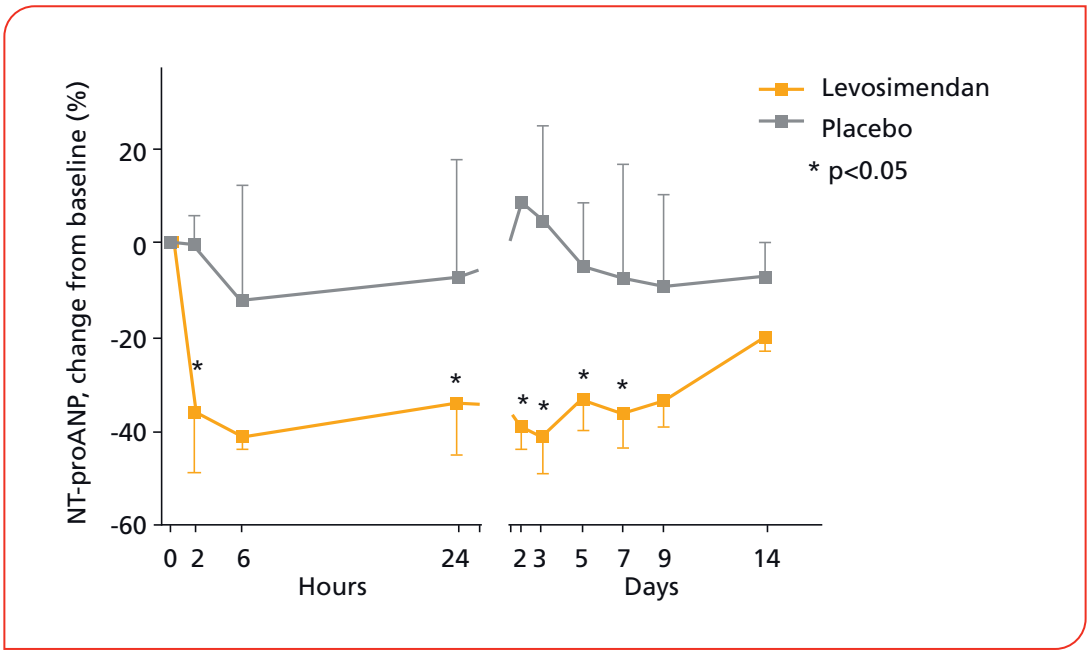


Figure 19. Median change in N-terminal prohormone atrial natriuretic peptide (NT-proANP) levels over 14 days (n=11 in both groups) in patients with heart failure receiving levosimendan or placebo for 24 hours.[8]

In the SURVIVE study, a similar decrease in BNP was seen (Figure 20).[7] The duration of the effect could not be determined as the last time-point for measuring BNP was 5 days. In the REVIVE II study the effect was also evident until day 5.[6]

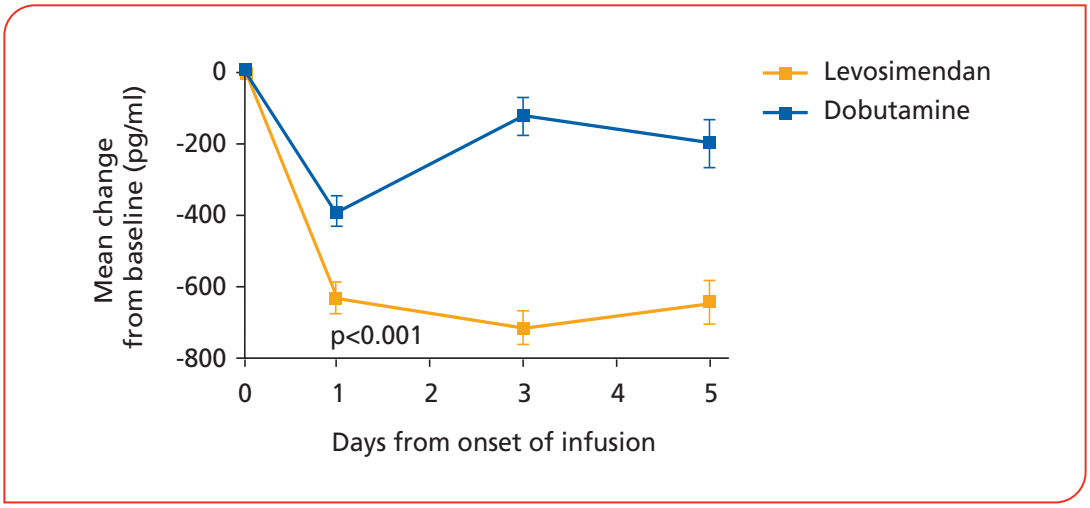


Figure 20. Changes in BNP levels up to 5 days after the start of infusion in SURVIVE.[7]

MORTALITY

In the LIDO study, mortality was followed as a secondary endpoint for 31 days. During that time, 8% of patients assigned to levosimendan died, compared with 17% assigned to dobutamine (hazard ratio 0.43, p = 0.049). The follow-up was retrospectively extended to 180 days, at which point the respective figures were 26% for levosimendan and 38% for dobutamine (hazard ratio 0.57, p = 0.029) (Figure 21).[1]

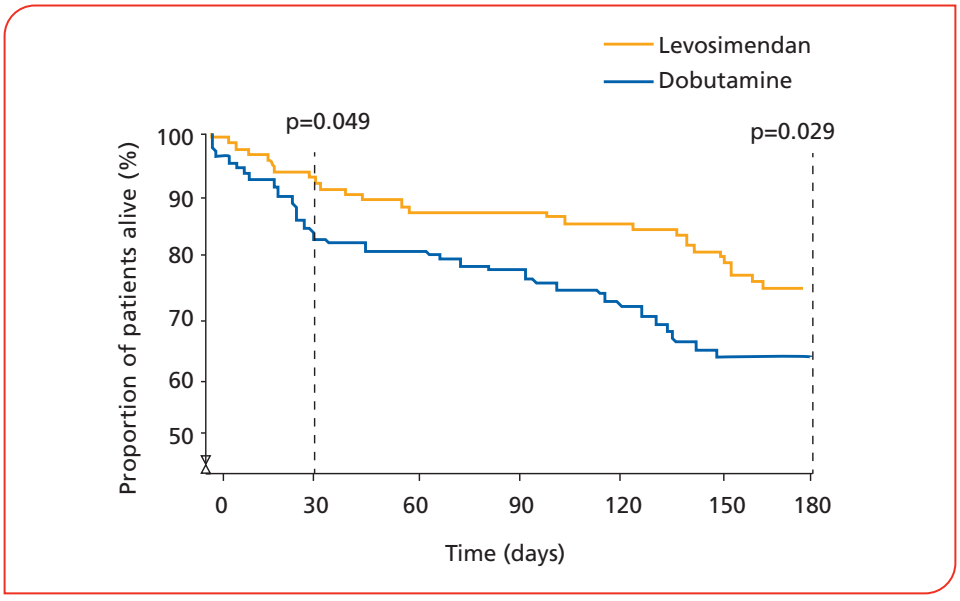


Figure 21. All-cause mortality up to 180 days after starting a 24-hour infusion of levosimendan or dobutamine in patients hospitalised for AHF (LIDO).[1]

In the RUSSLAN study, mortality was prospectively followed for 14 days after starting the treatment. The mortality rate was 12% in levosimendan- and 20% in placebo-treated patients (p = 0.031). There was a trend for maintaining this positive effect up to 180 days in a retrospective analysis (23 vs. 31%, respectively, p = 0.053) (Figure 22).[13]

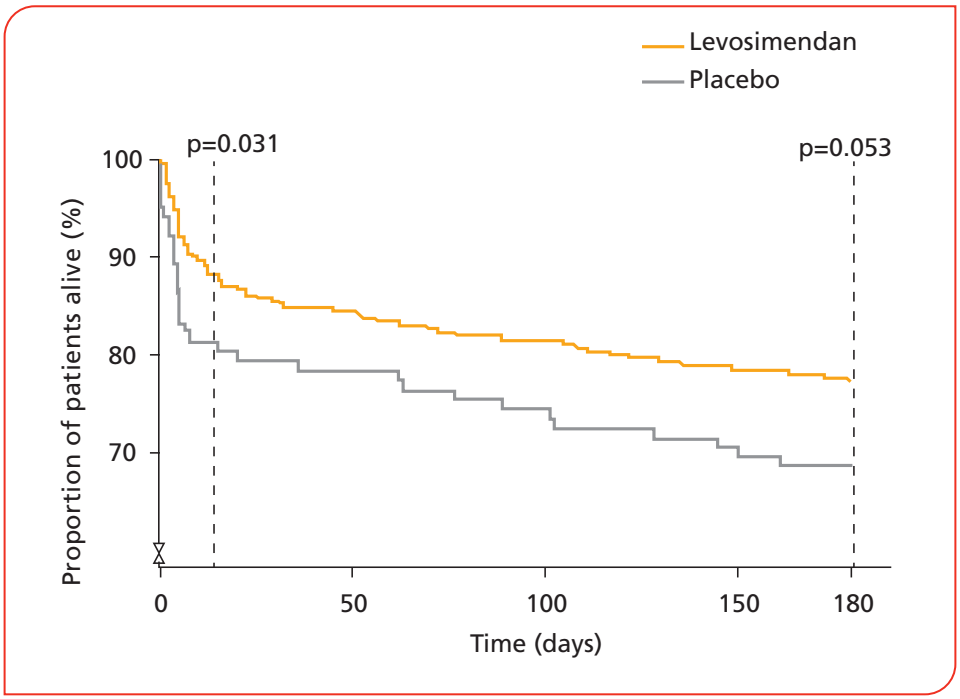


Figure 22. All-cause mortality up to 180 days after a 6-hour infusion of levosimendan or placebo in patients with heart failure complicating an acute myocardial infarction (RUSSLAN).[13]

In the REVIVE II study, survival was numerically, but not statistically significantly, lower in the levosimendan group, with 45 (15%) deaths in the levosimendan group and 35 (12%) in the placebo group during the 90-day study period (hazard ratio 1.33, p = 0.21).[6]

In the SURVIVE study, there was no significant difference in survival between levosimendan and dobutamine. The all-cause mortality at 180 days was 26% in the levosimendan group and 28% in the dobutamine group (hazard ratio 0.91, 95% CI 0.74-1.13, p = 0.40), a net benefit of 12 fewer deaths with levosimendan.[7]

The pooled mortality data of the sponsored studies is presented in Figure 23. Both in the placebo- and dobutamine-controlled studies, the hazard ratio is favouring levosimendan, but the result is statistically non-significant.[120]

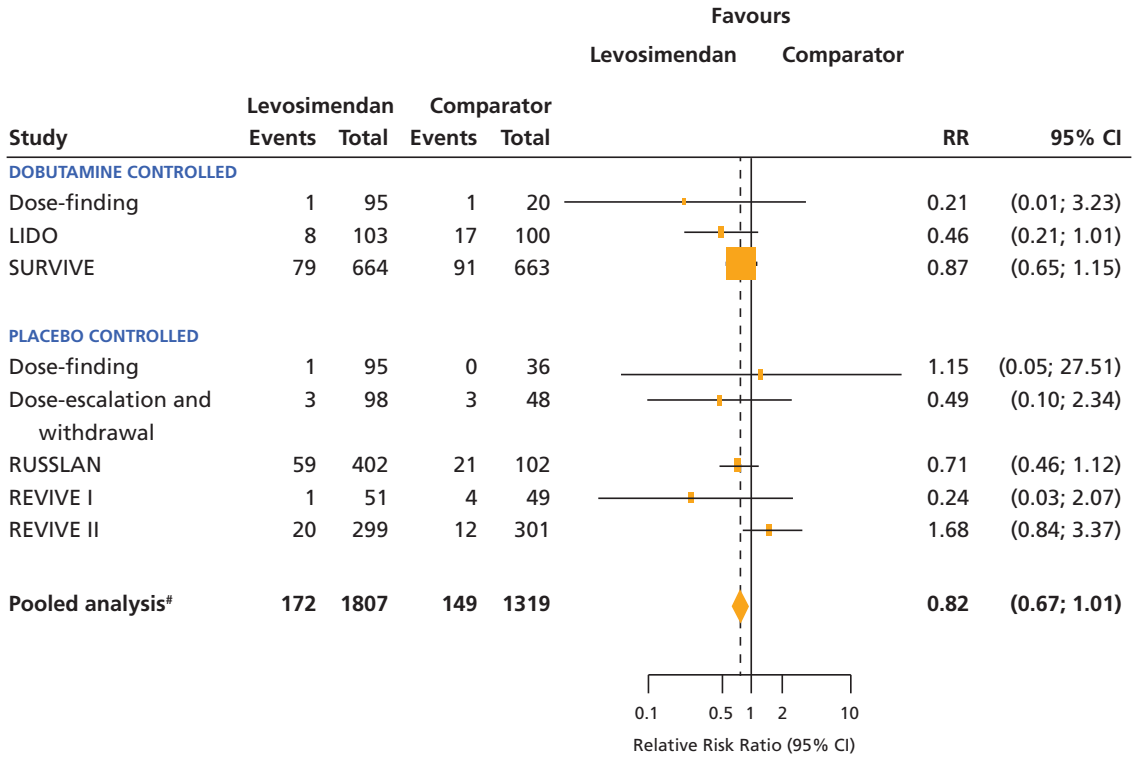


Figure 23. Pooled 31-day mortality analysis from the main levosimendan studies.[120]

Independent investigators have published their own analyses, which have included – in addition to the studies above – outcome data from randomised investigator-initiated studies.

The meta-analysis by Landoni et al. included 45 clinical trials with intravenous levosimendan with a total of 5480 patients (of which 2915 received levosimendan).[16] The studies had to be randomised and controlled, and studies which lacked mortality data were excluded. Twenty-three studies used levosimendan in a cardiological setting, while 17 studies used it in cardiac surgery patients. The 23 studies in the cardiology setting included 4100 patients (of which 2207 received levosimendan). Levosimendan significantly reduced mortality in this population compared with the control arm (20.0 vs. 25.6%, respectively; risk ratio 0.67, 95% CI 0.51-0.86).

The demonstrated survival benefit of levosimendan is in contrast to previous results with conventional inotropes, where rather a detrimental effect has been observed.[121] Levosimendan is thus the first inotropic agent which seems to improve survival in patients with acute heart failure.

A registry study, **ALARM-HF**, reviewed in-hospital treatments in eight countries.[122] Unadjusted analysis showed a significantly higher in hospital mortality rate in patients receiving intravenous inotropes (25.9%) compared to those who did not (5.2%) ($p < 0.0001$). Propensity-based matching (n=954 pairs) confirmed that intravenous catecholamine use was associated with 1.5-fold increase for dopamine or dobutamine use and a > 2.5-fold increase for noradrenaline or adrenaline use. A propensity-based analysis was performed to compare in-hospital mortality of patients treated only with intravenous levosimendan versus those treated only with catecholamine within 24 h of therapy initiation. Propensity score matching produced 104 matched pairs and showed that the use of levosimendan resulted in a significant reduction in the risk of in-hospital mortality (hazard ratio 0.25, 95% CI 0.07-0.85) (Figure 24).

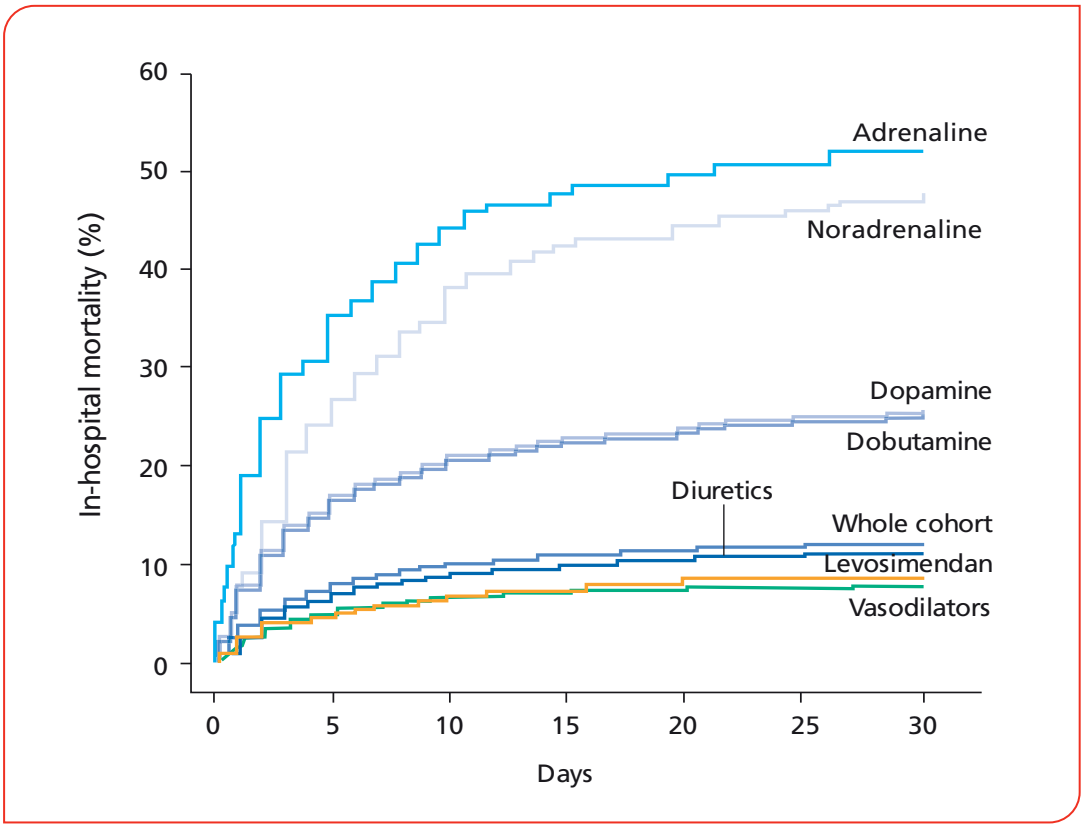


Figure 24. Effect of the vasoactive intravenous (i.v.) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality in the ALARM-HF study.[122, 123]

Subgroup analyses from REVIVE II and SURVIVE data

Baseline blood pressure in REVIVE II

The REVIVE II data showed that levosimendan significantly decreased blood pressure compared to placebo. Accordingly, the current SPC-labelling suggests levosimendan to be used with caution in patients with low baseline systolic or diastolic blood pressure or those at risk for a hypotensive episode.

Post-hoc analyses identified systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg at baseline as a factor increasing mortality risk.[6] In patients with low blood pressure at baseline, mortality was 27% for levosimendan vs. 16% for placebo. Conversely, in patients with higher blood pressure at baseline (systolic ≥ 100 mmHg and diastolic ≥ 60 mmHg), mortality was 8% for levosimendan and 9% with placebo. Figure 25 illustrates the relationship of baseline systolic blood pressure and mortality.

Of importance is the finding that the primary endpoint was still positive in the subgroup with higher baseline blood pressure (Table 5).

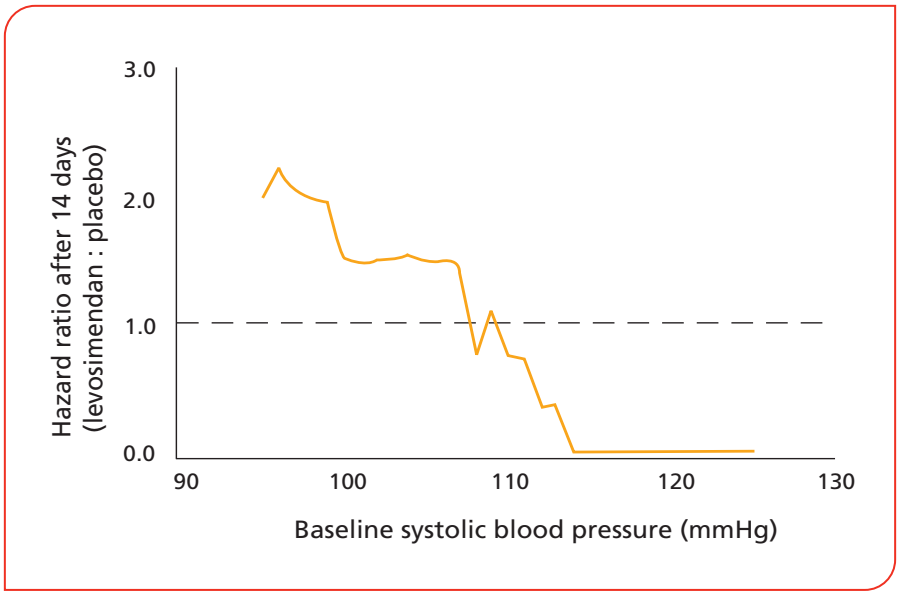


Figure 25. Hazard ratio for all-cause mortality (levosimendan/placebo) at 14 days as a function of the systolic blood pressure at randomisation.[6]

Table 5. Primary and secondary outcomes in REVIVE II divided by baseline blood pressure.[28]

Study outcome	All REVIVE II patients		Patients according to current labelling (BP > 100/60 mmHg)	
	Levosimendan (n=299)	Placebo (n=301)	Levosimendan (n=190)	Placebo (n=197)
Primary (N, %)	**p=0.015**		**p=0.036**	
Improved	58 (19.4%)	44 (14.6%)	39 (20.5%)	29 (14.7%)
Unchanged	183 (61.2%)	175 (58.1%)	118 (62.1%)	119 (60.4%)
Worsened	58 (19.4%)	82 (27.2%)	33 (17.4%)	49 (24.9%)
Secondary (N, %)				
Death during index admission	15 (5.0%)	6 (2.0%)	3 (1.6%)	5 (2.5%)
Death during follow-up	29 (9.7%)	29 (9.6%)	12 (6.3%)	13 (6.6%)
Total deaths	44 (14.7%)	35 (11.6%)	15 (7.9%)	18 (9.1%)

Mortality subgroup analyses in SURVIVE

The primary endpoint of the study was 180-day mortality and no significant difference between levosimendan and placebo was observed.[7] However, there was a non-significant net benefit in favour of levosimendan seen early at the course of the study (Figure 26).[10]

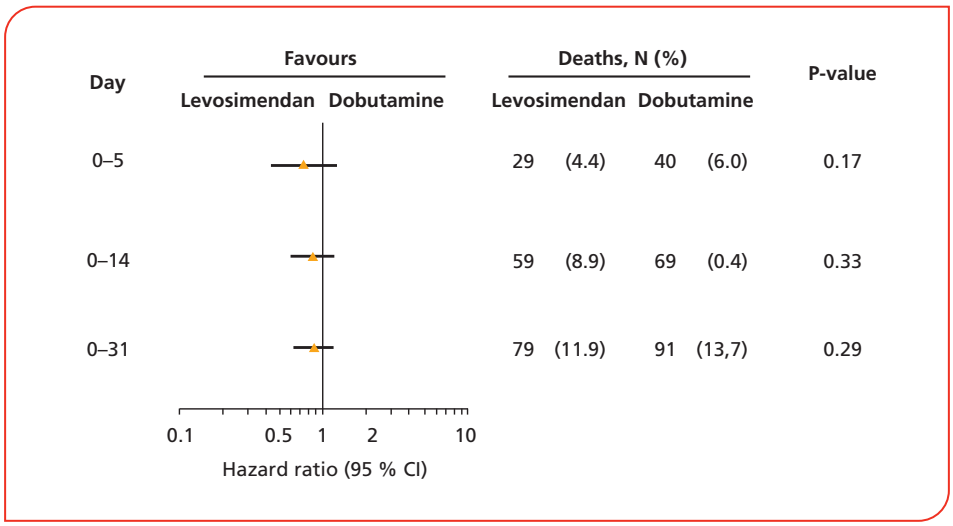


Figure 26. Hazard ratios for all-cause mortality rates up to 31 days after levosimendan and dobutamine therapy (SURVIVE).[10]

A majority (88%) of the patients had a history of AHF. In those patients, levosimendan outperformed dobutamine. In the subgroup of patients with a history of heart failure, mortality was significantly ($p = 0.046$) lower with levosimendan, with a net benefit of 19 fewer deaths up to 31 days.[10]

In the subgroup of patients with concomitant ß-blocker, mortality was significantly lower with levosimendan during the first 5 days (Figure 27).[10]

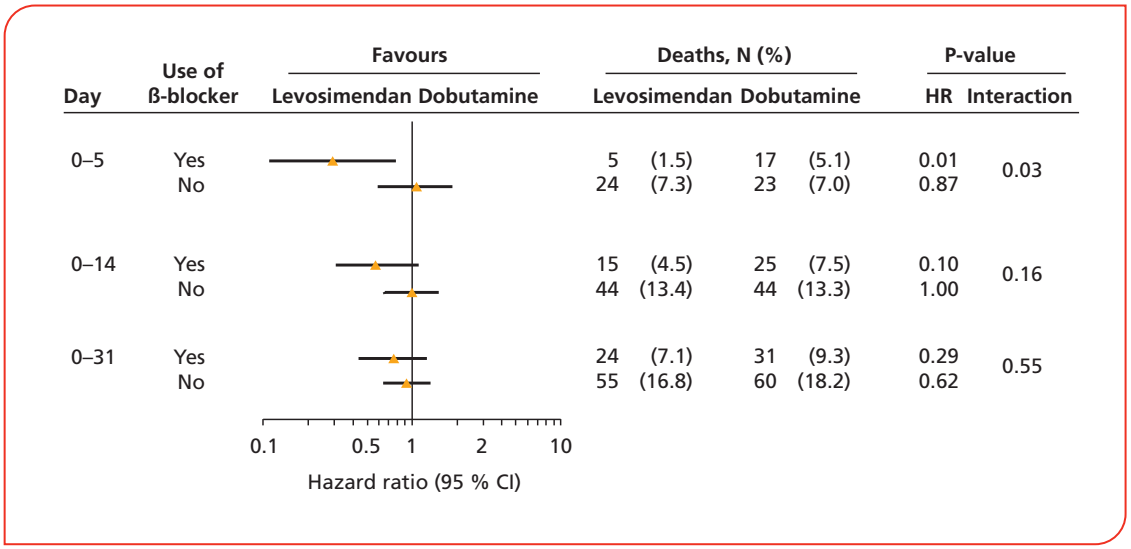


Figure 27. Hazard ratios for all-cause mortality rates up to 31 days after levosimendan and dobutamine therapy (SURVIVE) stratified for ß-blocker use at the start of the study.[10]

There were country-specific differences in the patient outcome in SURVIVE. The treatment by country interaction for mortality in Finland vs. other countries was significant, p = 0.029. Levosimendan treated patients had a lower 180-day mortality compared to dobutamine treated (17% vs. 40%, p = 0.023) in the Finnish sub-population (Figure 28). Baseline variables predicting survival in the whole SURVIVE trial population included age, systolic blood pressure, heart rate, myocardial infarction during admission, levels of NT-pro-BNP, glucose, creatinine, and alanine transferase, use of ACE inhibitors and ß-blockers, oliguria, time from hospital admission to randomisation, history of cardiac arrest, and left ventricular ejection fraction. Finnish patients were more frequently treated with ß-blockers (88% vs. 52%, p < 0.0001), their study treatment was started earlier (mean ± SD 41 h ± 40 h vs. 81 h ± 154 h; p < 0.0001), and they had more often acute myocardial infarction at admission (39% vs. 16%, p < 0.0001).[124] The results of this post hoc analysis suggest that levosimendan may be superior to dobutamine in these patients and conditions.

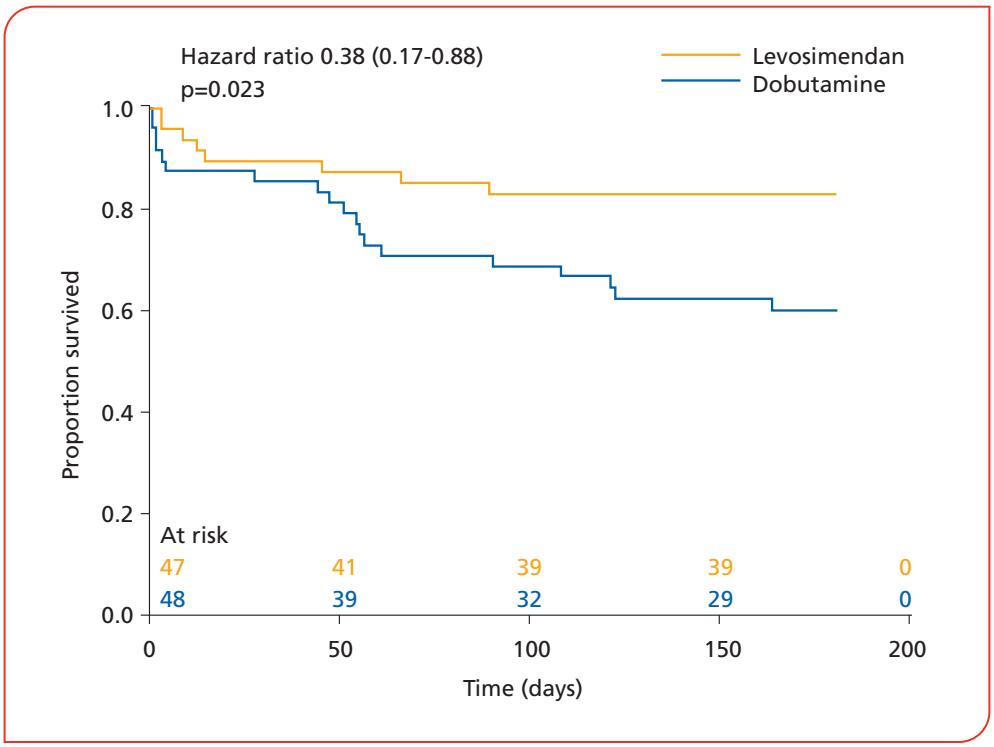


Figure 28. 180-day mortality in SURVIVE in Finnish patients.[124]

HOSPITALISATION

One way to consider the effect of a medication on both mortality and morbidity is to assess the number of days a patient is both alive and out of hospital during the follow-up period. In the LIDO study, patients in the levosimendan group spent significantly more days alive and out of hospital than dobutamine-treated patients in a retrospective 180-day follow-up analysis (median 157 vs. 133 days for levosimendan and dobutamine, respectively; p = 0.027).[1] In the RUSSLAN study, the combined risk of death and worsening heart failure was significantly lower in patients treated with levosimendan than in patients treated with placebo, both during the infusion period (2 vs. 6%, respectively; p = 0.033) and at 24 hours (4 vs. 9%, respectively; p = 0.044).[13]

In the REVIVE II study, the mean duration of the initial hospitalisation was almost 2 days shorter in the levosimendan group (7.0 days) than in the placebo group (9.0 days) (Figure 29). Significantly more patients treated with levosimendan were released within 5 days and fewer had extended hospitalisations (p = 0.008).[28] In line with these results, in the earlier mentioned meta-analysis by Landoni et al., the mean length of stay in hospital was 1.59 (95% CI 0.85-2.33) days shorter in levosimendan treated patients in the cardiology setting (p < 0.0001).[16]

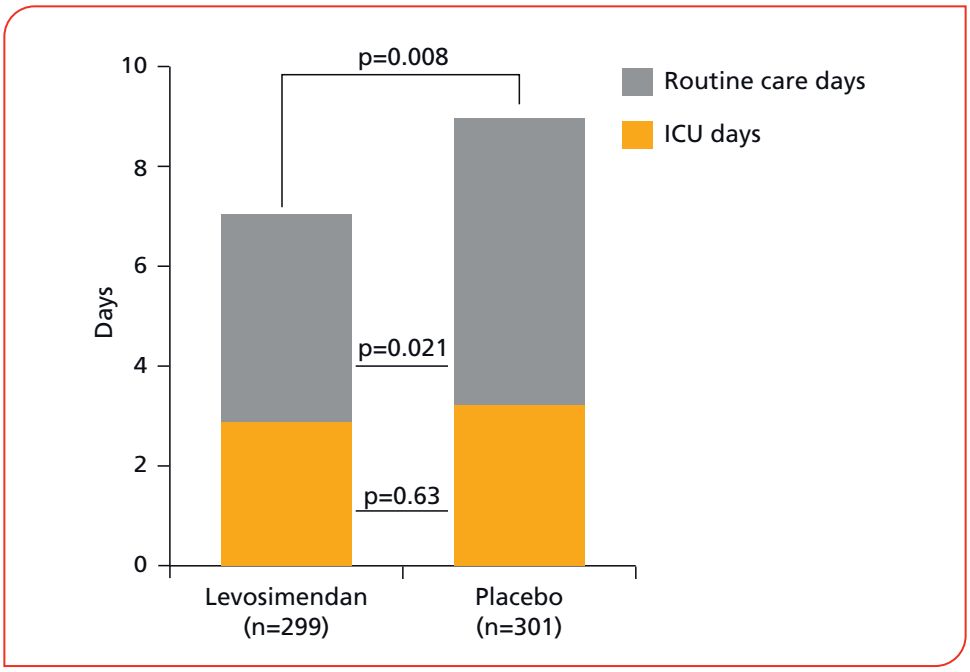


Figure 29. Mean duration of initial hospitalisation divided by time spent in intensive care unit (ICU) and in general ward in REVIVE II.[28]

EFFECTS ON RENAL FUNCTION

Worsening renal function often develops in patients with acute heart failure and is associated with adverse outcomes. Several investigator initiated studies have evaluated the effect of levosimendan on renal function. Levosimendan was compared to dobutamine in patients with heart failure who required inotropic therapy. Calculated glomerular filtration rate (cGFR) improved in levosimendan but was unchanged in dobutamine treated patients (Figure 30).[125]

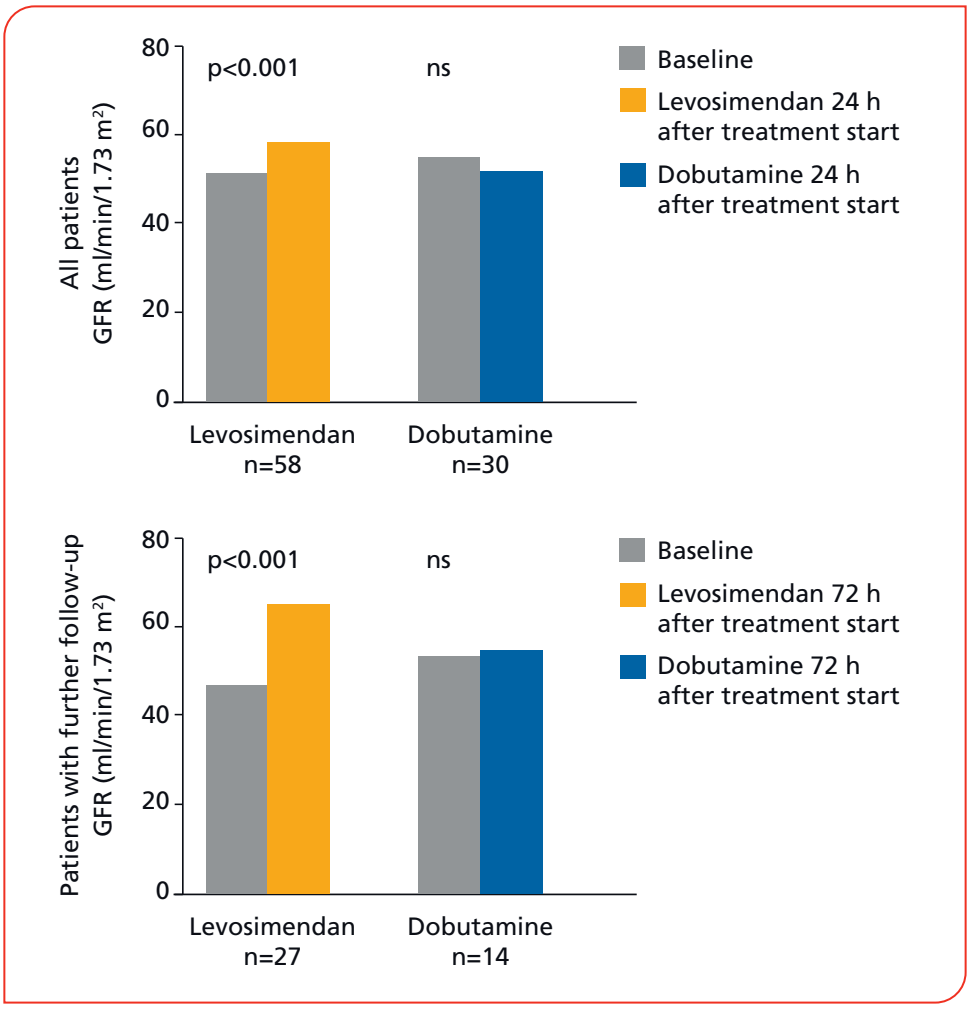


Figure 30. Change in calculated glomerular filtration rate from baseline (treatment start) to 24 h and 72 h in patients with severe chronic heart failure treated with levosimendan or dobutamine.[125]

A placebo-controlled study in 66 patients hospitalised for decompensated heart failure and renal dysfunction, showed a statistically significant improvement of estimated glomerular filtration rate (eGFR) in levosimendan treated patients (Figure 31). The peak effect was seen at three days after a 24-hour infusion and the effects persisted up to 14 days.[126] The result suggests that the metabolites of levosimendan prolong the beneficial effects on renal function.

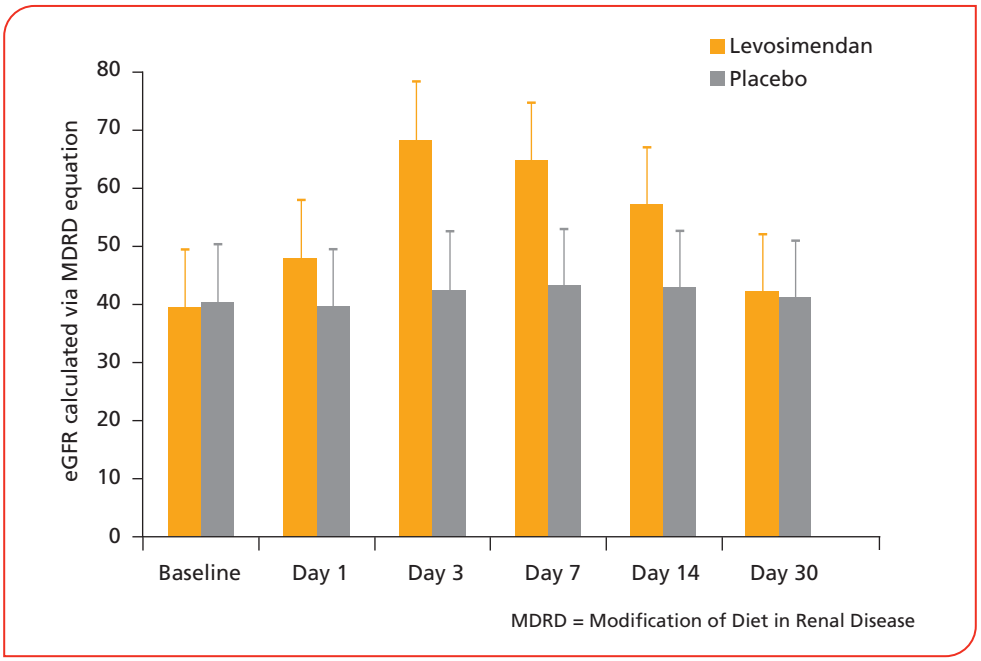


Figure 31. Estimated glomerular filtration (eGFR) rate in patients hospitalised for decompensated heart failure and renal dysfunction treated with levosimendan or placebo. [126]

The mechanisms behind the improved renal function by levosimendan are multifactorial. In addition to beneficial effects on central haemodynamics - increased cardiac output, decreased left- and right sided filling pressures and afterload – levosimendan has direct effects on renal circulation. Bragadottir et al. showed that levosimendan induces preglomerular vasodilation, leading to improved renal blood flow and glomerular filtration rate (Figure 32).[127]

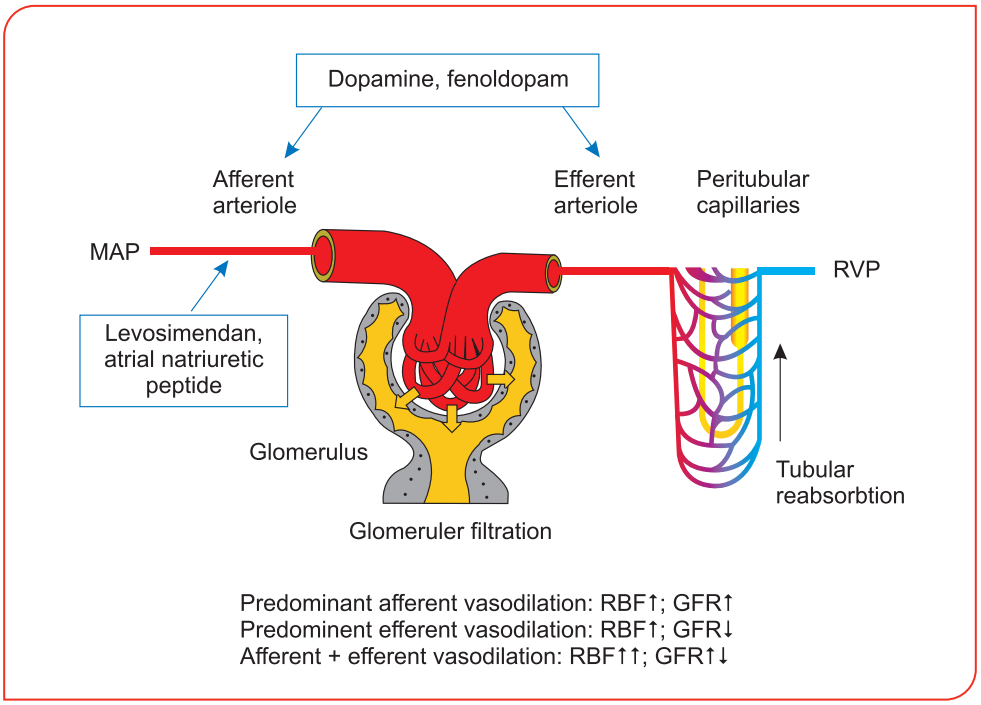


Figure 32. Direct effects of levosimendan on renal circulation and glomerular filtration.[127] MAP, mean arterial pressure; RVP, renal venous pressure; RBF, renal blood flow; GFR, glomerular filtration rate.

EFFECTS ON LIVER FUNCTION

Liver transferases were followed repeatedly in the SURVIVE study. The values were elevated in about half of the patients and were associated with higher mortality.[128] Both levosimendan and dobutamine induced a rapid decrease in transferases, but the effect was greater in levosimendan treated patients (Figure 33). More recently, some liver protective effects by levosimendan have been observed in non-clinical models[129] and Memis et al. found a superior effect over dobutamine in liver function of septic patients.[130]

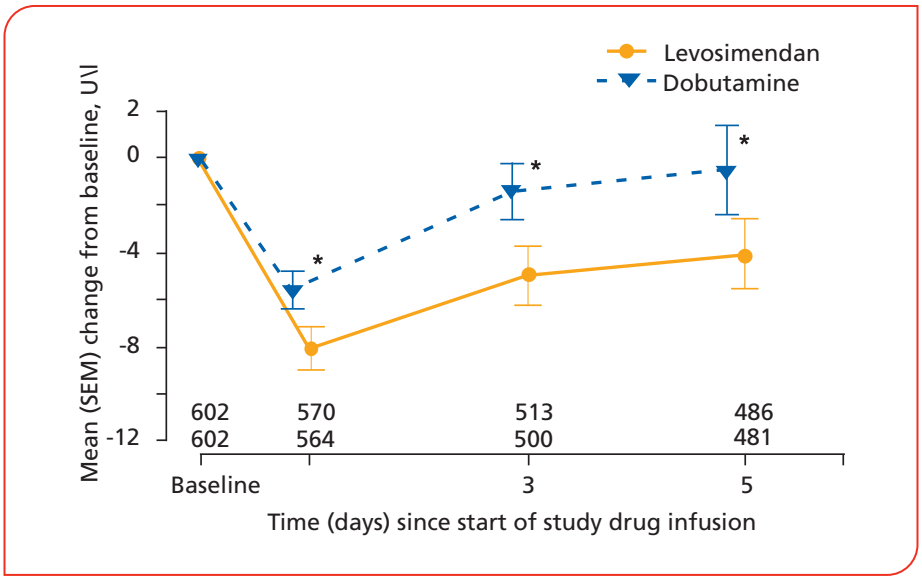


Figure 33. Change in alkaline phosphatase values in levosimendan and dobutamine treated patients in the SURVIVE study (*p < 0.012).[128]

SAFETY

Adverse events

Levosimendan infusion has generally been rather well tolerated in this very ill patient population. Based on the data from the two largest studies conducted so far, the REVIVE II and SURVIVE studies, hypotension was more frequently seen with levosimendan compared with placebo, but not when compared with dobutamine (Table 6 and Table 7).

Levosimendan was also associated with a higher incidence of atrial fibrillation compared both with placebo and with dobutamine. However, conflicting results have been presented with regard to ventricular arrhythmias. In REVIVE II, a higher incidence of ventricular tachycardia was observed with levosimendan compared with placebo. In SURVIVE, ventricular tachycardia was observed with similar frequency in the levosimendan and dobutamine groups.[7] In both studies, cardiac failure as an adverse event was less frequent in levosimendan arm, although the result was statistically significant only in SURVIVE (Table 6 and Table 7).

Table 6. Incidence (%) of selected adverse events in REVIVE II.[6]

Adverse events	Levosimendan (n=292)	Placebo[a] (n=294)	p-value
Hypotension	50	36	< 0.001
Ventricular tachycardia	25	17	0.031
Cardiac failure	34	37	NS
Atrial fibrillation	8.5	2.0	< 0.001
Ventricular extrasystoles	7.5	2.0	0.002
Sudden death	0.3	0.0	NS
Torsade de Pointes	0	0.3	NS

[a] Patients received standard of care. NS = not significant

Table 7. Incidence (%) of selected adverse events in SURVIVE.[7]

Adverse events	Levosimendan (n=660)	Placebo[a] (n=660)	p-value
Hypotension	15.5	13.9	NS
Ventricular tachycardia	7.9	7.3	NS
Cardiac failure	12.3	17.0	0.019
Atrial fibrillation	9.1	6.1	0.048
Ventricular extrasystoles	6.1	3.6	NS
Sudden death	1.5	0.9	NS
Torsade de Pointes	0.6	0.8	NS

NS = not significant

Safety laboratory values

The changes in safety laboratory variables have been modest in levosimendan studies. Clinically non-significant decreases in haemoglobin, erythrocyte and red blood cell counts have been observed. Also, a decrease in potassium levels have been seen with levosimendan more often than with comparators.

TRIALS IN OTHER THERAPY AREAS

CARDIAC SURGERY

Introduction

Acute cardiovascular dysfunction occurs perioperatively in more than 20% of patients undergoing cardiac surgery; yet current acute heart failure classification is not applicable to this period. Indicators of major perioperative risk include unstable coronary syndromes, decompensated heart failure, significant arrhythmias and valvular disease. Clinical risk factors include history of heart disease, compensated heart failure, cerebrovascular disease, presence of diabetes mellitus, renal insufficiency and high-risk surgery.[131]

Preserving heart function during cardiac surgery, with aggressive measures as needed, is a major goal. The aim of monitoring is to detect and assess the mechanisms underlying perioperative cardiovascular dysfunction early. Volume status should be assessed by dynamic measurement of haemodynamic parameters including Doppler echocardiography and pulmonary artery catheter (especially in right heart dysfunction) and i.v. fluids should be administered to achieve euvolemia. In vasoplegia-induced hypotension, noradrenaline is the drug of choice in maintaining adequate perfusion pressure. Inotropic agents are used to treat myocardial dysfunction. The traditional choices are, either alone or in combination, low-to-moderate doses of dobutamine and adrenaline and milrinone. In heart dysfunction with suspected coronary hypoperfusion, an intra-aortic balloon pump (IABP) is recommended. A ventricular assist device should be considered before end-organ dysfunction becomes evident. Extracorporeal membrane oxygenation is a rationale solution as a bridge to recovery and/or decision making.[131]

Optimal perioperative use of inotropes and vasopressors in cardiac surgery remains controversial Further, the use of an IABP is associated with substantial morbidity, including artery injury, aortic perforation, femoral artery thrombosis, peripheral embolisation, femoral vein cannulation, limb ischaemia, and visceral ischaemia.[132]

Levosimendan in cardiac surgery

Levosimendan has been studied in numerous small scale or single centre studies in cardiac surgery setting. The studies and their main results are presented in Table 8.

The data from these studies suggest that levosimendan is superior to traditional inotropes (dobutamine, PDE-inhibitors) as it achieves: 1) sustained haemodynamic improvement 2) diminished myocardial injury 3) better outcome and less hospital days. The studies also suggest that the optimal dosing is 0.1 µg/kg/min for 24 hours and that levosimendan infusion should be started preoperatively.[133]

Table 8. Use of levosimendan in cardiac surgery studies.[134]

First author - year of publication	Setting	Trial design	Levosimendan dose	Start of treatment	Comparator	Patients in LS arm vs comparator	Primary end-points/evaluations	Secondary end-points/evaluations
Lilleberg J et al. 1998 [4]	Low-risk CABG surgery	Randomised double-blind	8 µg/kg bolus or 24 µg/kg bolus	Post-surgery	Placebo	15 vs. 8	Improved haemodynamics	No increase in myocardial oxygen consumption or substrate extractions
Alvarez J et al. 2005 [135]	Postoperative cardiac index < 2.5 l/min/m^2 in patients to whom CABG was performed	Randomised open-label	12 µg/kg bolus followed by 0.2 µg/kg/min for 24 h	Post-surgery	Dobutamine 7.5 µg/kg/min for 24 h	15 vs. 15	Cardiac index and heart rate increased, and mean arterial pressure, systemic and pulmonary vascular index decreased significantly in LS group	
Al-Shawaf E et al. 2006 [136]	Postoperative LCOS (within 12 h) in patients with type 2 DM and preoperative LVEF < 35%, to whom CABG was performed	Randomised open-label	12 µg/kg bolus followed by 0.1-0.2 µg/kg/min for 24 h	Within 12-h post-surgery	Milrinone 50 µg/kg bolus followed by 0.3-0.5 µg/kg/min for 24 h	14 vs. 16	Superior hemodynamic effects (cardiac index, mixed venous saturation) with LS	No difference in insulin requirements Time in ventilator & ICU shorter with LS
Alvarez J et al. 2006 [137]	Postoperative cardiac index < 2.5 l/min/m^2 in patients to whom CABG was performed	Randomised open-label	12 µg/kg bolus followed by 0.2 µg/kg/min for 24 h	Within 4 h post-surgery	Dobutamine 7.5 µg/kg/min for 24 h	25 vs. 25	More pronounced heart rate and cardiac index increase, and more pronounced decrease in systemic vascular resistance in LS group	The hemodynamic effects lasted beyond study drug infusion period only in LS group
Tritapepe L et al. 2006 [138]	Patients undergoing elective CABG	Randomised double-blind	24 µg/kg as a bolus in 10 min	Just before placing patient on CPB	Placebo	12 vs. 12	Lower troponin I release ($p < 0.05$)and a higher cardiac index ($p < 0.05$) postoperatively in LS group	
De Hert SG et al. 2007 [139]	Patients with preoperative LVEF ≤ 30% and to whom CABG and or valvular surgery was performed	Randomised open-label; assessment of outcomes by blinded observers	0.1 µg/kg/min for 19 h	Immediately after release of aortic crossclamp	Milrinone 0.5 µg/kg/min for 83 h	15 vs. 15	Stroke volume increased initially similarly, but the effect lasted longer in LS group	Secondary inotrope and vasoconstrictor need lower in LS group Tracheal intubation time shorter in LS group

To be continued...

First author - year of publication	Setting	Trial design	Levosimendan dose	Start of treatment	Comparator	Patients in LS arm vs comparator	Primary end-points/ evaluations	Secondary end-points/evaluations
Järvelä K et al. 2008 [140]	Patients undergoing aortic valve surgery with or without CABG	Randomised double-blind	0.2 µg/kg/min for 24 h	Immediately after induction of anaesthesia	Placebo	12 vs. 12	LVEF maintained in LS group, but decreased in control group after operation	LS prevented postoperative decreases in mixed venous saturation and central venous oxygen saturation
Levin RL et al. 2008 [141]	Postoperative LCOS (within 6-h) in pts to whom CABG was performed	Randomised open-label	10 µg/kg bolus followed by 0.1 µg/kg/min for 24 h	Within 6-h post-surgery	Dobutamine 5-12.5 µg/kg/ min for 24 h	69 vs. 68	Postoperative mortality lower in LS group (8.7% vs. 25%); $p < 0.05$)	Lower need for secondary inotropes (8.7% vs. 36.8%), vasopressors (11.6% vs. 30.9%) and intra-aortic balloon pump (2.9% vs. 14.7%) in LS group; $p < 0.05$ for all
Eriksson HI et al. 2009 [108]	Patients with 3-vessel coronary disease and LVEF < 50% to whom CABG was performed	Randomised double-blind	12 µg/kg bolus followed by 0.2 µg/kg/min for 24 h	Immediately after induction of anaesthesia	Placebo	30 vs. 30	Primary weaning from cardiopulmonary bypass successful in 73% vs. 33% in LS and placebo groups, respectively; p=0.002	Need for additional inotropic or mechanical therapy lower in LS group
Tritapepe L et al. 2009 [85]	Patients undergoing elective CABG	Randomised double-blind	24 µg/kg as a bolus in 10 min	Just before placing patient on CPB	Placebo	52 vs. 50	Length of ICU stay shorter in LS group: 25 (7) vs. 32 (13) hours; p=0.002	Length of hospital stay and tracheal intubation time shorter in LS group. Troponin I release lower in LS group
Lahtinen P et al. 2011 [142]	Patients undergoing CABG or valve operation or both	Randomised double-blind	24 µg/kg bolus followed by 0.2 µg/kg/min for 24 h	Immediately after induction of anaesthesia	Placebo	99 vs. 101	Heart failure defined as cardiac index < 2.0 l/min/m^2 or failure to wean from CPB 15% vs. 58% in LS and placebo groups, respectively; $p < 0.001$	Rescue inotrope and intra-aortic balloon pump needed less, but vasopressor more in LS group

To be continued...

First author -year of publication	Setting	Trial design	Levosimendan dose	Start of treatment	Comparator	Patients in LS arm vs comparator	Primary end-points/evaluations	Secondary end-points/evaluations
Leppikangas H et al. 2011 [143]	Patients undergoing aortic valve surgery and CABG; additionally preoperative LVEF < 50% or LV thickness > 12 mm	Randomised double-blind	12 µg/kg bolus followed by 0.2 µg/kg/min for 24 h	24 h before surgery	Placebo	12 vs. 12	Cardiac index and stroke volume index higher in LS group for the 4 day postoperative period	
Levin RL et al. 2012 [144]	Patients with preoperative LVEF < 25% undergoing CABG	Randomised open-label	10 µg/kg bolus followed by 0.1 µg/kg/min for 24 h	24 h before surgery	Placebo	127 vs. 125	Postoperative LCOS (7.1% vs. 20.8%; $p < 0.05$) and mortality (3.9% vs. 12.8%; $p < 0.05$) lower in LS group	Difficult weaning from cardiopulmonary bypass, need for secondary inotropes, vasopressors and intra-aortic balloon pump less frequent in LS group
Lomivorotov VV et al. 2012 [145]	90 consecutive patients with LVEF < 35%, who underwent CABG, were included	Randomised open-label	12 µg/kg bolus followed by 0.1 µg/kg/min for 24 h with or without IABP	Immediately after induction of anaesthesia	Intra-aortic balloon pump one day before operation	30 LS+IABP vs. 30 LS vs. 30 IABP	Cardiac index significantly higher in LS treated subjects	Toponin I lower in LS treated subjects
Gandham R et al. 2013 [146]	Patients undergoing mitral valve surgery on cardiopulmonary bypass (LVEF ≈ 60%)	Randomised double-blind	0.1 µg/kg/min for 24 h	Started at weaning off from CPB	Dobutamine 5 µg/kg/min for 24 h	30 vs. 30	Higher need for additional inotropic and vasoconstrictor support in the LS group	Prolonged effect in LS group; higher cardiac index 12-h post-infusion
Dogan OF et al. 2013 [147]	Patients undergoing isolated CABG surgery (LVEF ≈ 25%)	Randomised double-blind	"slow drip"; exact dose not explained	Started 6 h before surgery and stopped before the initiation of CPB	Placebo	100 vs. 100	Postoperative atrial fibrillation lower in LS group (12% vs. 36%; p=0.005)	TnI and CK-MB release significantly lower and hospital stay shorter in LS group

To be continued...

First author -year of publication	Setting	Trial design	Levosimendan dose	Start of treatment	Comparator	Patients in LS arm vs comparator	Primary end-points/evaluations	Secondary end-points/evaluations
Baysal A et al. 2014 [148]	Patients undergoing mitral valve surgery on cardiopulmonary bypass (LVEF ≤ 45%)	Randomised double-blind (observers blinded)	6 µg/kg bolus followed by 0.1 µg/kg/min for 24 h	Started after removal of the aortic cross-clamp	Standard inotropic therapy	64 vs. 64	Postoperative eGFR significantly higher in LS group	Numerically lower need for renal replacement therapy in LS group (6.3% vs. 15.6%; p=0.089)
Anastasiadis K et al. 2016 [149]	Patients undergoing CABG (LVEF ≤ 40%)	Randomised open-label	0.1 µg/kg/min for 24 h	Started 24 h prior surgery	Placebo	16 vs. 16	LVEF increased significantly at day 7 post-surgery only in LS group (35.8 ± 5% preoperatively to 42.8 ± 7.8%, p=0.001)	
Atalay H et al. 2016 [150]	Patients with end-stage renal disease undergoing CABG	Randomised double-blind	3 µg/kg loading in 6-h followed by 0.03-0.06 µg/kg/min up to 24 h	Started 6 h prior to surgery	Placebo	25 vs. 33	Postoperative hemodynamics significantly improved in LS group (cardiac index increased, PCWP and systemic vascular resistance decreased)	Lactate and troponin levels and need for secondary inotropes and IABP lower in LS group
Mishra A et al. 2016 [151]	Patients with valvular heart disease and pulmonary artery hypertension undergoing valve surgery	Randomised double-blind (observers blinded)	10 µg/kg bolus followed by 0.1 µg/kg/min for 24 h	Started at weaning off from CPB	Milrinone 50 µg/kg bolus followed by 0.5 µg/kg/min for 24 h	20 vs. 20	Both drugs induced similar decrease in pulmonary artery pressure and pulmonary vascular resistance postoperatively	LS use was associated with higher heart rate, increased cardiac index, decreased systemic vascular resistance index, and increased requirement of noradrenaline use
Sahu MK et al. 2016 [152]	Patients undergoing CABG (LVEF > 50%)	Randomised open-label	10 µg/kg bolus followed by 0.1 µg/kg/min for 24 h	Just before surgery	Nitroglycerine 0.5 µg/kg/min	15 vs. 15	Length of ICU stay and duration of ventilation significantly shorter in LS group	Higher cardiac index, lower systemic vascular resistance and heart rate in LS group

Randomised multicentre double-blind studies in cardiac surgery

Three larger clinical studies - CHEETAH, LEVO-CTS, and LICORN - evaluated the role of levosimendan in patients with cardiac surgery. CHEETAH and LICORN were investigator initiated studies and LEVO-CTS was a phase III study.

CHEETAH[153]: In the CHEETAH trial, levosimendan or placebo was administered to cardiac surgery patients, who – according to predefined criteria – developed postoperative Low Cardiac Output Syndrome (LCOS). In total, 1000 patients were to be included and the primary endpoint was 30-day mortality. The study was performed in 14 centres in Italy, Russia and Brazil. The study was stopped for futility after 506 patients were enrolled. A total of 248 patients received levosimendan and 258 placebo. The mean infusion rate and duration of levosimendan was 0.07 µg/kg/min for 33 h. There was no difference in 30-day mortality between the levosimendan and placebo groups (32 patients [12.9%] vs. 33 patients [12.8%], p = 0.97). There were no statistically significant differences in other efficacy endpoints either - some positive trends in renal function were noted and ICU stay just fell short of being significantly shorter with levosimendan (72 h vs. 84 h, p = 0.08). No significant difference in the adverse events of hypotension (25 vs. 21%, p = 0.31) or supraventricular arrhythmias (14 vs.17%, p = 0.41) were noted.

LEVO-CTS[154]: The study was a Phase III clinical trial sponsored by TENAX Therapeutics Inc. and run by DUKE University. The aim was to obtain a marketing authorisation in US and Canada for levosimendan. The study was discussed and agreed with the US Food and Drug Administration (FDA) beforehand. The study population consisted of patients undergoing cardiac surgery and a reduced left ventricular ejection fraction before the operation. The study was run at 70 US and Canadian sites, on 882 patients on scheduled or urgent cardiac surgery, CABG and/or mitral valve surgery with or without other valves. All patients were at risk of developing postoperative LCOS. Levosimendan (0.2 µg/kg/min for 60 min, followed by 0.1 µg/kg/min for 23 h) or placebo was started at the induction of anaesthesia to assess whether the drug could decrease the development of LCOS and its detrimental consequences. The study had two composite primary endpoints, consisting of deaths, perioperative myocardial infarction, need for renal replacement therapy or mechanical ventricular assist device. There was no significant difference between levosimendan and placebo in the primary endpoints. However, levosimendan group had statistically significantly less LCOS events (18% vs. 26%, p = 0.007) and needed less inotropic support (55% vs. 63%, p = 0.02), and cardiac index improved more (2.86±0.61 vs. 2.68±0.65 l/min/m^2; p < 0.001) in levosimendan treated patients (Figure 34). There were also fewer deaths in levosimendan group (7.1% vs. 4.7%, p = 0.12) (Figure 35). Hypotension (36% vs. 33%, p = 0.29) and atrial fibrillation (38% vs. 33%, p = 0.12) were seen with similar frequency in levosimendan and placebo groups.

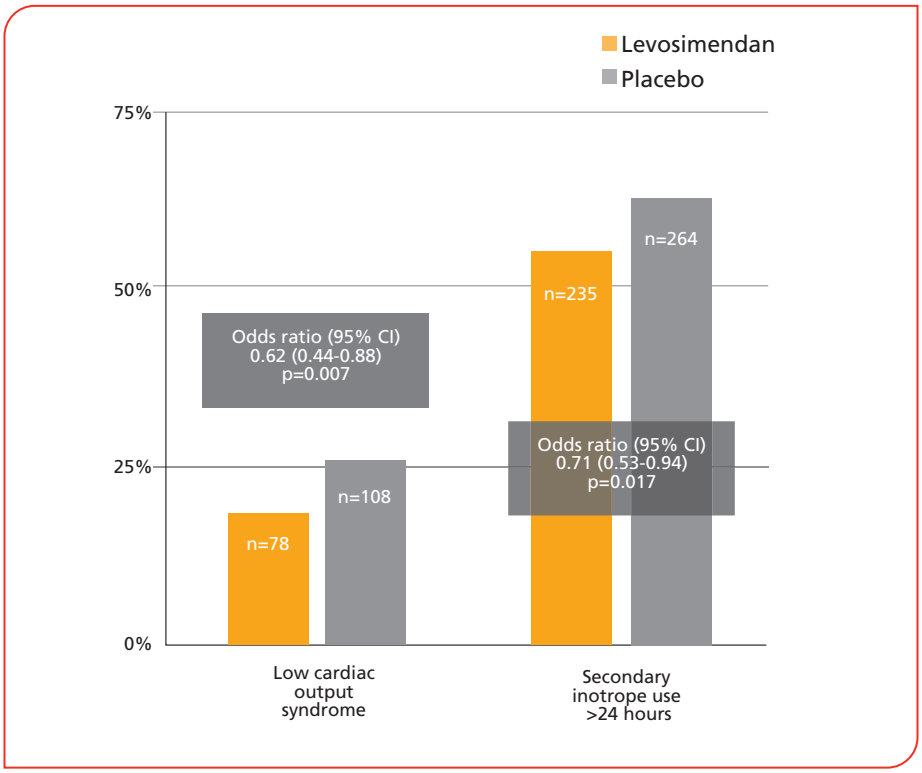


Figure 34. LCOS events and the need for secondary inotropic support in levosimendan and placebo treated patients in the LEVO-CTS study.[154]

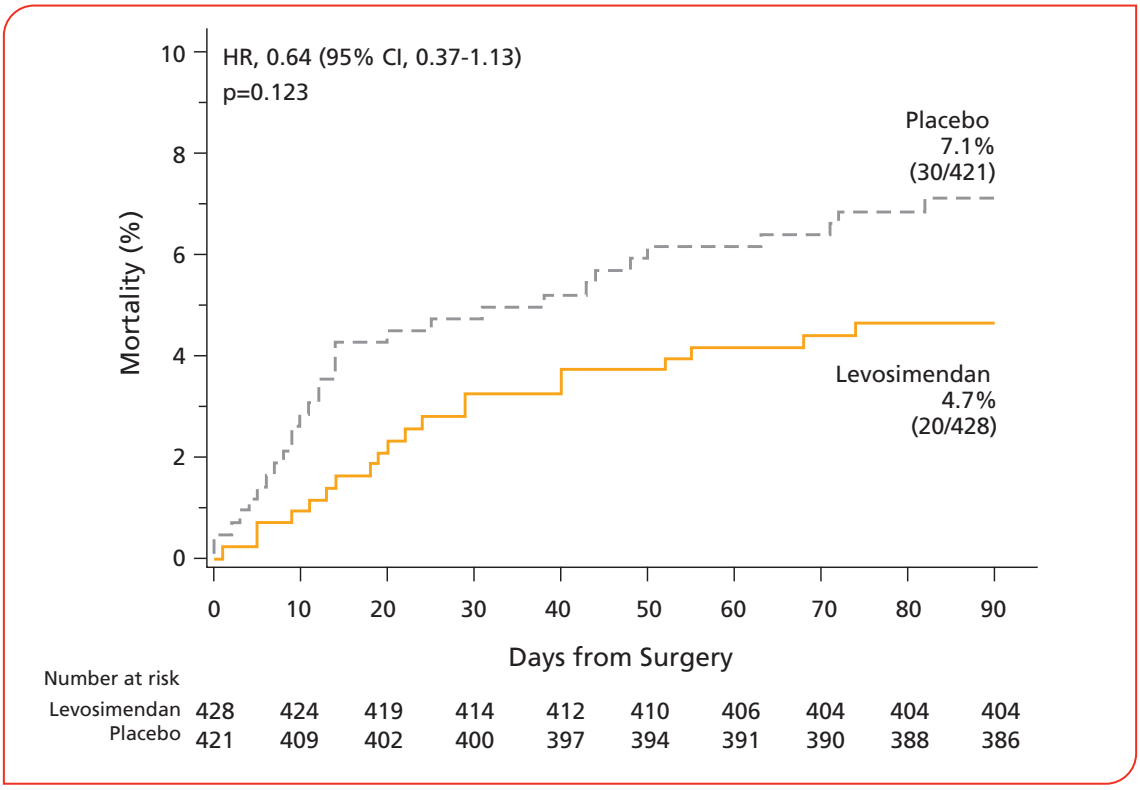


Figure 35. Mortality in placebo and levosimendan treated patients in the LEVO-CTS study.[154]

A post hoc analysis on patients to whom isolated CABG was performed (66% of the patients) revealed that levosimendan improved 90-day survival significantly (Figure 36). This was accompanied with a significant improvement in postoperative cardiac index, in the frequency of LCOS and in the need for further inotropic support (Figure 37).[155]

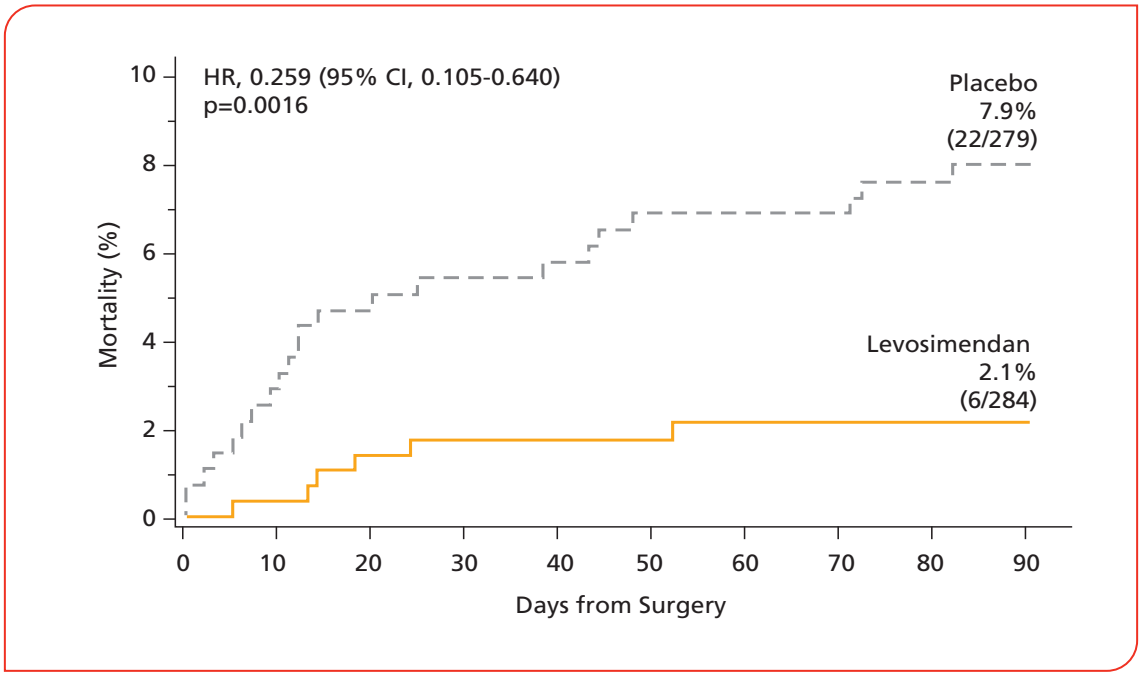


Figure 36. Mortality in patients to whom isolated CABG was performed in the LEVO-CTS study.[155]

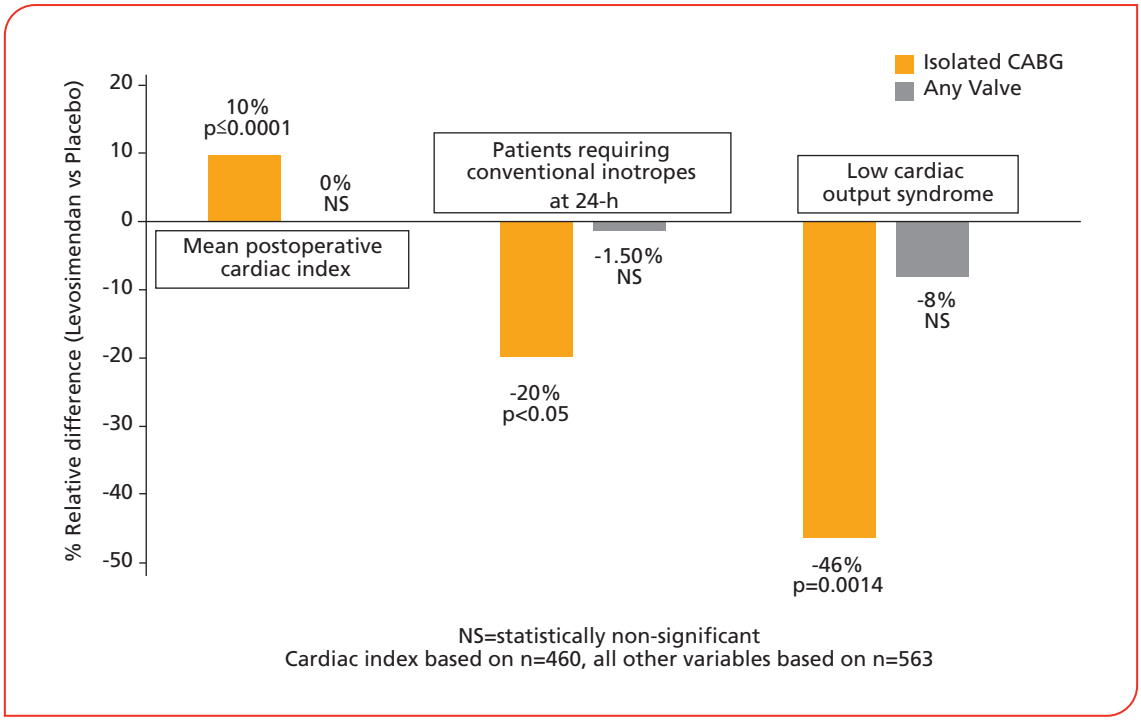


Figure 37. Relative difference in cardiac index, in LCOS events and in the need for further inotropic support in the levosimendan and placebo groups in patients to whom either isolated CABG or any valve operation was performed in LEVO-CTS study.[155]

LICORN[156]: The LICORN trial assessed the efficacy of a preoperative infusion of levosimendan in reducing postoperative LCOS in patients with poor LVEF undergoing CABG. 336 patients with LVEF ≤ 40% undergoing CABG were recruited from 13 French hospitals. The study drug was started after anaesthesia induction and infused over 24 h (0.1 µg/kg/min). Postoperative LCOS was evaluated by using a composite criterion consisted of: 1) need for catecholamine infusions beyond 48 h following discontinuation of the study drug; 2) need for postoperative mechanical assist devices or failure to wean from these techniques when inserted preoperatively; 3) need for renal replacement therapy. It was expected that levosimendan would decrease the occurrence of the primary endpoint by 15% compared to placebo group (50% vs. 65%). However, the primary endpoint occurred in 87 patients (52%) in the levosimendan group and 101 patients (61%) in the placebo group (p = 0.15). Thus, only a trend in favour of levosimendan was observed. Of the primary endpoint components, the need for catecholamine infusions was the most frequent. Levosimendan decreased this need in numerically – but not statistically significantly - more patients (p = 0.09). There was no difference in mortality or length of ICU stay or any other secondary endpoints. Numerically, but not statistically significantly more patients in the levosimendan group experienced hypotension (57% vs. 48%, p = 0.11) and atrial fibrillation (50% vs. 40%, p = 0.09).

Interpretation of the results

Dosing

In the CHEETAH study, the study drug preparation was described as follows: "Levosimendan was diluted as 12.5 mg in 100 ml of 5% glucose". This is against the SPC guidance according to which one vial of Simdax (12.5 mg) should be diluted in at least 250 ml of 5% glucose solution (1:50). There is a risk of precipitation if higher concentrations are used and this exposes the patient to unpredictable dosing (lower than intended dose). In the CHEETAH, the infusion rate was 0.07 µg/kg/min, which is lower than in earlier cardiac surgery. Thus, underdosing might have been an issue in CHEETAH for these two reasons.

In LEVO-CTS and LICORN, the maintenance dose was 0.1 µg/kg/min, which is currently considered the optimal infusion rate in regards to balance in efficacy and safety. However, in both studies, levosimendan was initiated at the induction of anaesthesia giving levosimendan relatively short time to exert its preconditioning effect before surgery. In some of the previous studies[144] and in clinical practice levosimendan is started up to 24 h before the operation.

Efficacy

None of the studies showed a statistically significant improvement in the chosen primary endpoint. It has to be noted that the primary endpoints in LEVO-CTS and LICORN were experimental. Similar endpoints have not been used in earlier studies. The LEVO-CTS primary endpoints were agreed with FDA, who required clinical events to be included in the endpoint.

There is, however, clear evidence of efficacy in LEVO-CTS. The lower incidence of LCOS and in the need of inotropic support (Figure 34) and the improvement in cardiac index prove that levosimendan did have efficacy. These effects were pronounced in the subgroup of patients with isolated CABG (Figure 37). In LICORN and CHEETAH, only suggestive signs of improvement were noted.

Safety

Safety was not a concern in the studies – there was no significant excess of arrhythmias or hypotension or other major adverse events (Table 9). Further, there was no increase in mortality in levosimendan treated patients. In fact, mortality was numerically lower in LEVO-CTS and this result was significant in the subgroup of isolated CABG (Figure 35 and Figure 36).

Table 9. Selected adverse events in LEVO-CTS, LICORN and CHEETAH studies.

ADVERSE EVENTS	LEVO-CTS		LICORN		CHEETAH	
	LS	PL	LS	PL	LS	PL
Any serious AE* (%)	56	55	89	86	44	52
Hypotension (%)	36	33	57	48	25	21
Atrial fibrillation (%)	38	33	50	40	14	17
Ventricular tachycardia(%)	11	10	12	11	1.6	2.8
Ventricular fibrillation (%)			14	16		
Stroke (%)	3.5	2.9	0.1	1.0	4.5	3.5
Cardiogenic shock (%)	2.3	2.6	2.7	5.2	?	?

*Any AEs in LEVO-CTS
Arrhythmias reported as supraventricular and ventricular arrhythmias in CHEETAH, VF & VT combined in LEVO-CTS
Strokes/TIAs/hypoxic encephalopathy in CHEETAH

Meta-analyses in cardiac surgery

Several meta-analyses on the outcome effects of levosimendan and other inodilators in cardiac surgery have been published.

The meta-analysis by Harrison et al.[157] was performed before the completion of the CHEETAH, LEVO-CTS and LICORN studies. The authors divided the patients by their preoperative ejection fraction. In total, 1155 patients were included. Those with a mean EF < 40% were designated as low-EF. The authors concluded that the use of levosimendan was associated with reduced mortality and other adverse outcomes in patients undergoing cardiac surgery, and these benefits were greatest in patients with reduced EF (< 40%).

A Bayesian network meta-analysis evaluated the role of different inodilators in cardiac surgery.[158] Also this meta-analysis was performed before the completion CHEETAH, LEVO-CTS and LICORN studies and it included data on 2647 patients. The analysis found that only the use of levosimendan was associated with a decrease in mortality when compared with placebo (posterior mean of odds ratio 0.48, 95% CI 0.28-0.80).

The most recent meta-analysis on milrinone in cardiac surgery was published by Ushio et al.[159] The analysis included 12 randomised controlled studies and 537 patients. No statistically significant difference in mortality in milrinone vs. comparator treated subjects was observed (odds ratio 1.25, 95% CI 0.45-3.51, p = 0.67).

Two meta-analyses on levosimendan in cardiac surgery including the data from CHEETAH, LEVO-CTS and LICORN studies have been published.

Chen et al. included 17 studies involving a total of 2756 patients.[160] Overall, levosimendan therapy was associated with a significant reduction in 30-day mortality, but this reduction was not significant in multicentre and in high-quality subgroup-analysis trials. However, in high-quality trials, levosimendan was associated with reduced mortality in patients in a preoperative low-EF subgroup (risk ratio 0.58, 95% CI 0.38-0.88, p=0.01).

Putzu et al. included data up to September 2017 and employed Cochrane methodology.[161] They had data from 40 randomised controlled trials in 4246 patients. Again, analysis including all trials found that levosimendan was associated with lower postoperative mortality (odds ratio 0.56, 95% CI 0.44-0.71, p < 0.00001). However, pooled analysis of 5 low risk of bias trials (1910 patients) showed no association between levosimendan and mortality (odds ratio 0.86, 95% CI 0.62-1.18, p = 0.34). The authors concluded that there is not enough high-quality evidence to neither support nor discourage the systematic use of levosimendan in cardiac surgery.

ADVANCED CHRONIC HEART FAILURE

Introduction

Most patients with heart failure due to reduced LVEF respond favourably to pharmacological and non-pharmacological treatments and enjoy a good quality of life and enhanced survival. However, some patients do not improve or experience rapid recurrence of symptoms despite optimal medical therapy. Such patients characteristically have symptoms at rest or on minimal exertion (NYHA III-IV), including profound fatigue; cannot perform most activities of daily living; frequently have evidence of cardiac cachexia; and typically require repeated and/or prolonged hospitalisations for intensive management. These patients represent the most advanced stage of heart failure and should be considered for specialised treatment strategies, such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation or hospice care. Before a patient is considered to have refractory heart failure, physicians should confirm the accuracy of the diagnosis, identify any contributing conditions, and ensure that all conventional medical strategies have been optimally employed.[162]

Patients with refractory heart failure are hospitalised frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs in an effort to improve cardiac performance, facilitate diuresis and promote clinical stability.[162]

Despite favourable haemodynamic and symptomatic improvement in small clinical studies, concerns on the safety of intermittent or continuous inotropic therapy have been raised. Both dobutamine and milrinone increase the myocardial oxygen demand and intracellular calcium concentration, thus increasing the susceptibility for arrhythmic events and possibly excessive mortality.[163, 164] The theoretical advantages of levosimendan over these agents include:

- No increase in intracellular calcium concentration or myocardial oxygen demand.
- Prolonged effect via the formation of an active metabolite.
- Beneficial haemodynamic (pulmonary capillary wedge pressure and cardiac output), neurohormonal (natriuretic peptides) and symptomatic effects.
- No attenuation of the effects in beta-blocked patients.
- Beneficial effect in renal function and peripheral organ perfusion.
- Meta-analyses in decompensated heart failure have shown superior mortality effect in comparison with placebo and dobutamine.

Levosimendan in advanced chronic heart failure

Several small-scale studies with repeated levosimendan infusions have been published (Table 10). Most of these studies were open-label, single-centre studies which hampers the interpretations. They suggest that levosimendan improves haemodynamics, reduces neurohormone levels and may improve outcome.

Later, three randomised, multicentre, double blind, placebo-controlled studies in advanced chronic heart failure (AdHF) have been conducted with repeated levosimendan infusions. The largest study was the LEVO-REP study.[165] Levosimendan or corresponding placebo was administered as 6-hour infusions with infusion rate 0.2 µg/kg/min every 2 weeks (4 infusions per patient) in 120 patients with advanced chronic heart failure. The primary outcome was the proportion of patients with a ≥ 20% improvement in the 6-minute walk test and a ≥ 15% score increase on the Kansas City Cardiomyopathy Questionnaire. There was no significant difference between the groups; 19% of patients receiving levosimendan and 15.8% of patients receiving placebo met the endpoint (odds ratio 1.25, 95% CI 0.44-3.59, p = 0.810). Compared to placebo, levosimendan was associated with a 50% lower risk of cardiac death (4 vs. 1), heart transplants (2 vs. 1), or acute heart failure (14 vs. 9) (Figure 38).

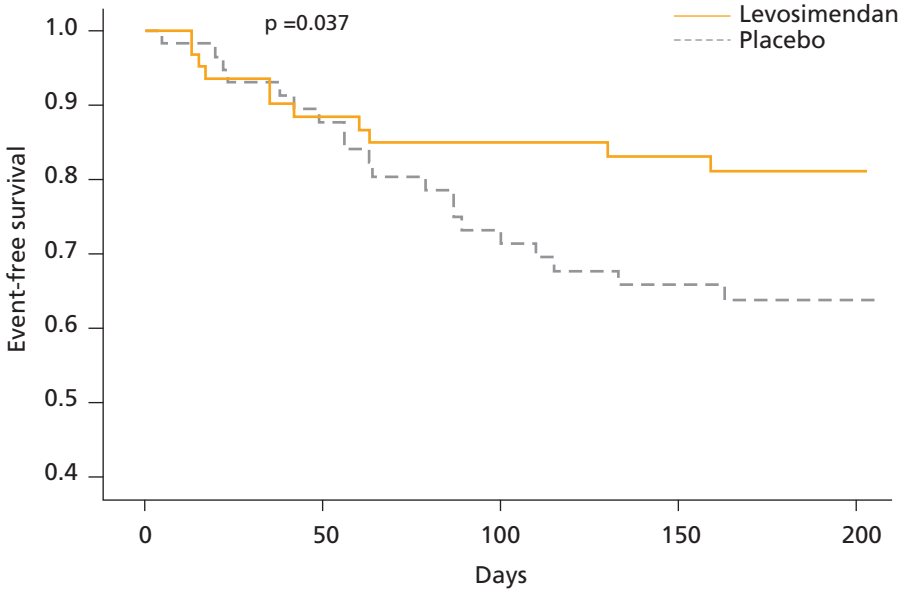


Figure 38. Event-free survival (deaths, heart transplantation, and acute heart failure events) in the LEVO-REP study.[165]

Table 10. Repetitive use of levosimendan in chronic advanced heart failure

First author -year of publication	Setting	Trial design	Levosimendan group	Comparator	Duration of follow-up	Patients in LS arm vs comparator	Main findings	Additional findings
Nanas JN et al. 2005 [166]	NYHA IV refractory to dobutamine infusion -all patients received dobutamine for 24 h at initiation -mean LVEF ≈ 23%	Non-randomised open-label	6 µg/kg bolus followed by a 24-h infusion 0.2 µg/kg/min, followed by 24-h infusions 0.2 µg/kg/min every 2 weeks	Dobutamine 10 µg/kg/min for 48 h, followed by 8-h daily infusion for the next 3 days, and weekly infusions thereafter	3 months	18 vs. 18	45-day survival rates 6% vs. 61% (p=0.0002) favouring levosimendan	
Parissis J et al. 2006 [167]	Advanced heart failure (NYHA III or IV) -mean LVEF ≈ 23%	Randomised open-label	6 µg/kg bolus followed by 0.1 µg/kg/min for 24 h every 3 weeks	Placebo	4 months	17 vs. 8	Left ventricle size, NT-proBNP, hs-CRP, IL-6 all decreased significantly in LS group	
Mavrogeni S et al. 2007 [168]	Advanced heart failure (NYHA III or IV) -mean LVEF ≈ 22%	Randomised open-label	Monthly 24-h infusions bolus of 6 µg/kg followed by 0.1-0.2 µg/kg/min for 24 h	Standard of care	6 months	25 vs. 25	Improvement in symptoms (dyspnoea and fatigue); 65% vs. 20%, (p<0.01) and LVEF 28±7 vs. 21±4%, (p=0.003), in LS group	No increase in supraventricular or ventricular beats or supraventricular tachycardia and VT episodes in LS group
Kleber FX et al. 2009 [169]	Pulmonary hypertension of various aetiologies (including secondary to left-sided heart failure)	Randomised double-blind	Initial 24-h infusion with 0.2 µg/kg/min followed by four 6-h infusions with 0.2 µg/kg/min every 2 weeks	Placebo	2 months	18 vs. 10	Pulmonary vascular resistance and pulmonary artery pressure decreased significantly in LS group during the first 24-h infusion. With the last 6-h infusion, similar decrease was noted, but the difference to placebo was non-significant	
Bonios MJ et al. 2012 [170]	NYHA IV, refractory to optimal medical therapy, recently hospitalised for AHF and stabilised by an intravenous inotrope	Randomised open-label	Weekly 6-h infusions of 1. Dobutamine (DB) 10 µg/kg/min 2. Levosimendan(LS) 0.3 µg/kg/min 3. LS 0.2 + DB 10 µg/kg/min		6 months	21 vs. 21 vs. 21	Survival free from death or urgent LVAD implantation at 6 months 80% in the LS alone, 48% in the DB alone (p=0.037), 43% in the LS+DB (p=0.009)	Cardiac index increased and PCWP decreased (at 3 months) significantly only in LS alone group

LION-HEART[171] randomised 69 patients with AdHF in 2:1 ratio to levosimendan or placebo. Levosimendan was administered in an ambulatory setting during a 6-h period with 0.2 µg/kg/min every two weeks. In total, six cycles of levosimendan or placebo were given to each patient. The primary endpoint was the change in NT-proBNP throughout the treatment period. The reduction in NT-proBNP was significantly in favour of levosimendan (Figure 39). Further, the patients on levosimendan experienced a reduction in the rate of heart failure hospitalisation (hazard ratio 0.25, 95% CI 0.11-0.56, p = 0.001). Levosimendan treated patients were also less likely to experience a clinically significant decline in health related quality of life measure (EQ-5D VAS) (p = 0.022). Adverse event rates were similar in the two treatment groups.

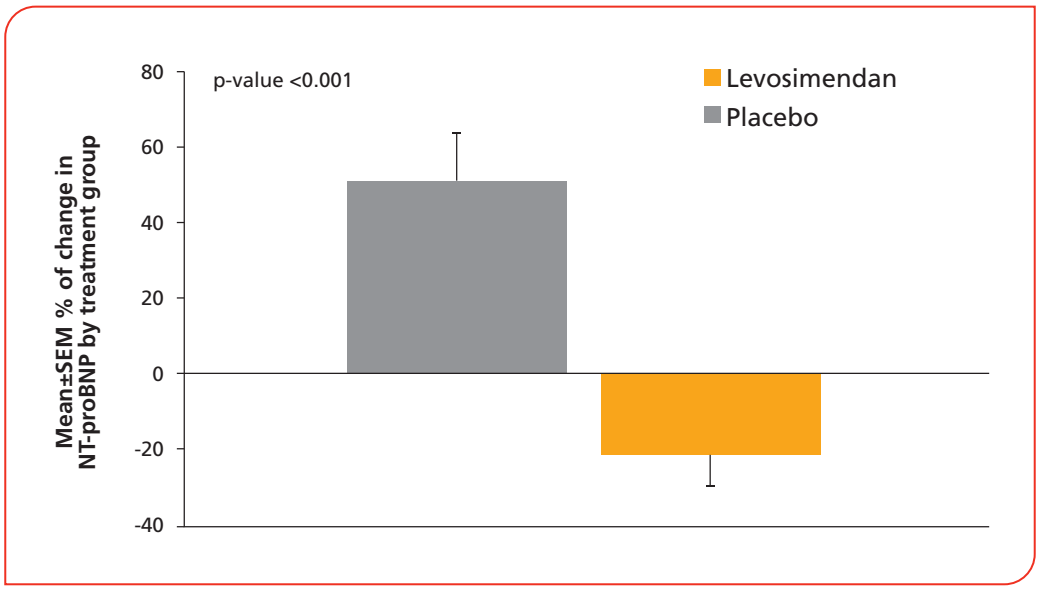


Figure 39. A change in NT-proBNP in levosimendan and placebo treated patients in the LION-HEART study.[171]

In **LAICA** study, 97 patients with AdHF were randomised in 2:1 ratio to levosimendan or placebo. The study design has been published[172], but the results have, so far, only been presented in 2016 ESC Heart Failure meeting in Florence, 2016.[173] Monthly infusions of 24-hour levosimendan with infusion rate 0.1 µg/kg/min were administered up to 12 months (median 6 months). The primary endpoint was the incidence of hospitalisation for acute decompensated HF during the follow-up. Only numerically favourable result in the primary endpoint was seen with levosimendan. However, a significant reduction in mortality was reported in levosimendan treated patients.[173]

Meta-analyses in advanced chronic heart failure

Silvetti and her colleagues have published meta-analyses on mortality[174] and re-hospitalisations[175] of the studies in which levosimendan has been administered repeatedly. The use of levosimendan was associated with significantly lower mortality (Figure 40) and also the re-hospitalisations were significantly less frequent with levosimendan (Figure 41).

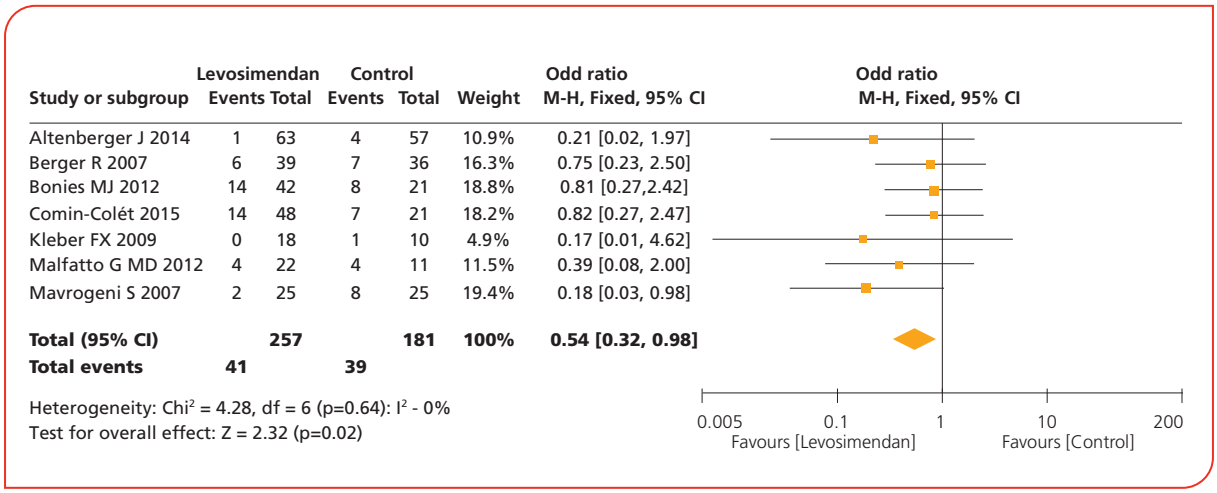


Figure 40. Mortality in studies with repeated administration of levosimendan in advanced chronic heart failure (AdHF) (meta-analysis).[174]

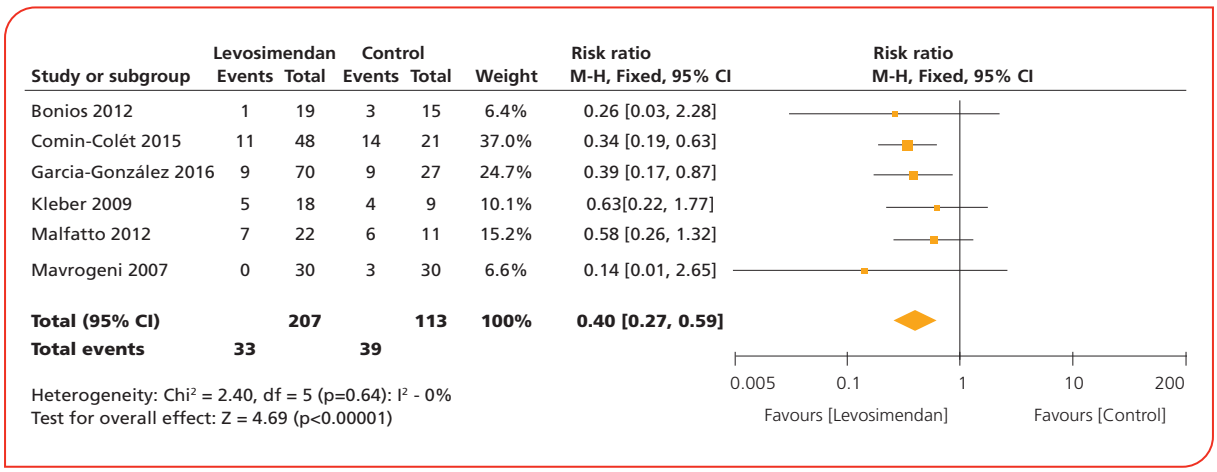


Figure 41. Re-hospitalisations with repeated administration of levosimendan in advanced chronic heart failure (AdHF) (meta-analysis).[175]

Ongoing study with repetitive administrations

An investigator-initiated study with repetitive levosimendan infusions is ongoing. The study, LEODOR, is a multicentre, randomised, double-blind, placebo-controlled, three-arm trial designed to evaluate the efficacy and safety of intermittent levosimendan therapy.

Levosimendan is administered in addition to standard therapy for a period of 12 weeks either as a 6-h continuous infusion at a rate of 0.2 µg/kg/min every 2 weeks or as a 24-h continuous infusion at a rate of 0.1 µg/kg/min every 3 weeks. The primary endpoint will be evaluated after 14 weeks. Another follow-up visit to obtain information on events is scheduled after 6 months. The study intends to include 264 patients in 28 centres in nine European countries.

The primary efficacy assessment will be made using a global rank endpoint in which all participants are ranked across three hierarchical groups (in ascending order): (i) time to death or urgent heart transplantation or implantation of a ventricular assist device (VAD); (ii) time to non-fatal HF requiring i.v. vasoactive therapy; and (iii) time-averaged proportional change in N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to week 14. Secondary efficacy endpoints include individual components of the primary endpoint at short- (14 weeks) and intermediate-term (26 weeks) follow-up, as well as changes in functional status. The trial progress can be followed on its homepage (http://leodortrial.com/).

HEART FAILURE RELATED TO ACUTE CORONARY SYNDROMES

Acute heart failure and/or cardiogenic shock are frequently triggered by ischemic coronary events. However, there are no specific consensus or international guidelines on the pharmacological and non-pharmacological treatments of ACS patients with heart failure available. This is probably related to the fact that patients with acute coronary syndromes are typically excluded from heart failure trials and therefore limited data on the effects of vasoactive agents in these patients exist.

A subgroup analysis on OPTIME-HF trial with milrinone suggested that milrinone is deleterious in patients with ischemic origin for heart failure.[176] Levosimendan, on the other hand, showed significantly lower mortality in the placebo-controlled RUSSLAN study in patients with left ventricular failure complicating an acute myocardial infarction (Figure 22)[13]. This favourable result was later supported by the findings of Jia et al.[177] In 160 patients with acute myocardial infarction accompanied with LVEF < 40% and signs of heart failure, a 24-hour infusion of levosimendan (24 µg/kg bolus in 10 min followed by continuous infusion of 0.1 µg/kg/min) significantly decreased the incidence of death or worsening heart failure during a 6-month follow-up when compared to placebo (43.7 vs. 62.5%, p = 0.041) (Figure 42). In a smaller placebo-controlled study in 61 patients with signs of heart failure in connection with ST-elevation myocardial infarction, a 25-hour levosimendan infusion (0.2 µg/kg/min for 60 min followed by 0.1 µg/kg/min for 24 h) significantly improved left ventricular function (primary endpoint) (Figure 43) and showed non-significant improvement in death or rehospitalisation rates.[178]

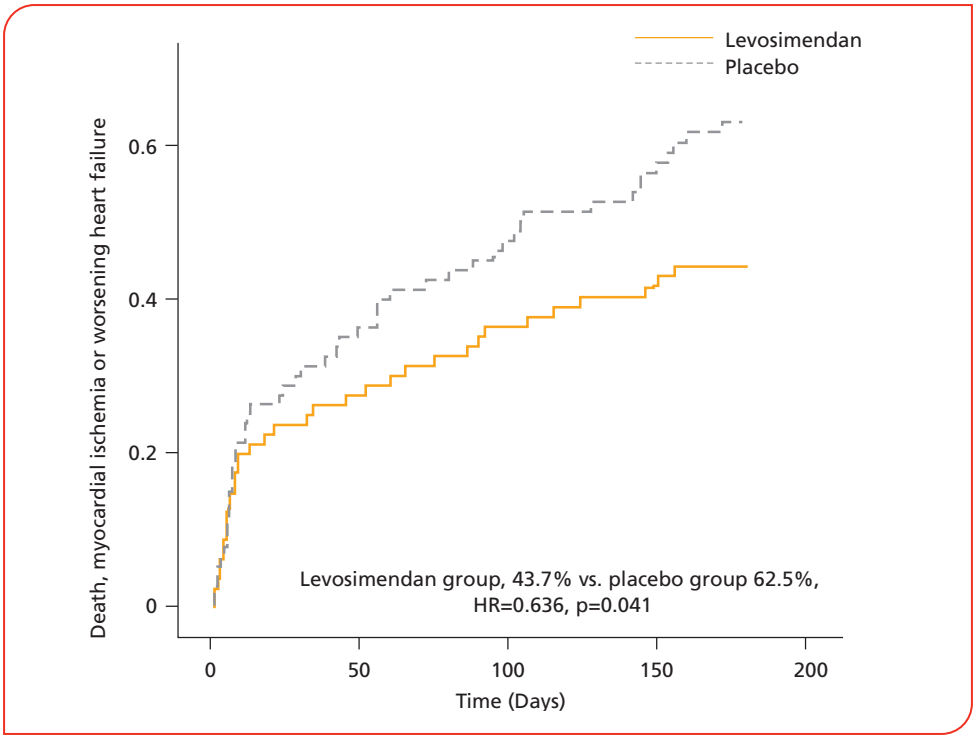


Figure 42. The incidence of death, myocardial ischemia or worsening heart failure in levosimendan or placebo treated patients .[177]

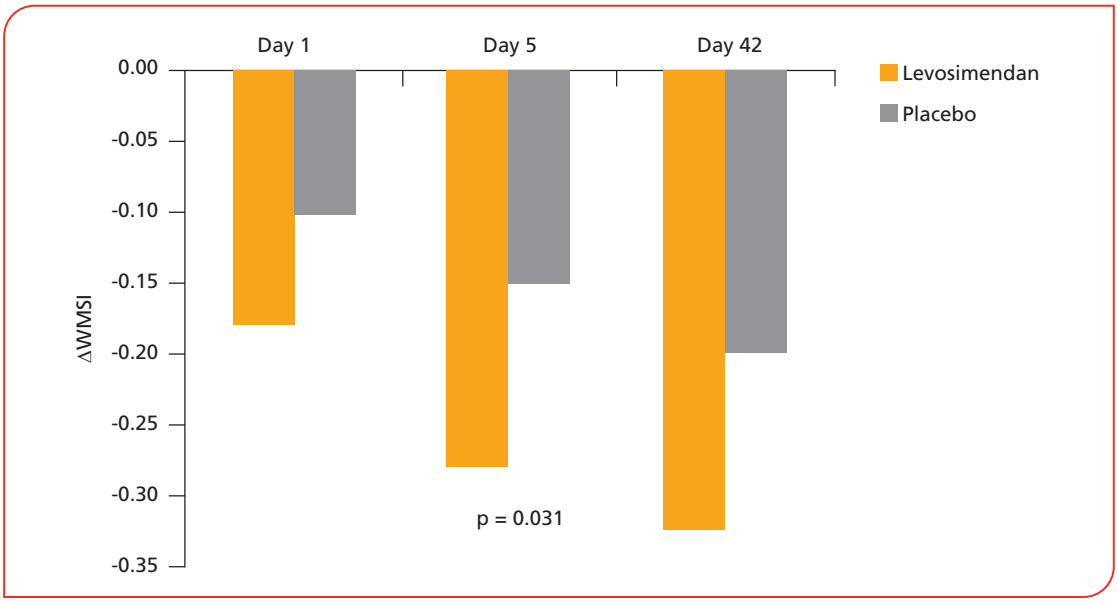


Figure 43. Change in wall motion score index (WMSI) between patients treated with a 25-hour infusion of levosimendan or placebo (mean ± SEM). [178]

Levosimendan has also been tested in patients with cardiogenic shock. The studies have been relatively small, but the results are promising. Fuhrmann et al. performed a prospective, randomised, open-label study comparing levosimendan and enoximone, a PDE III inhibitor, in refractory cardiogenic shock complicating acute myocardial infarction.[179] The standard of care consisted of immediate revascularisation by percutaneous coronary intervention; IABP, fluid resuscitation and conventional inotropes. Thirty-two patients were randomised to receive either levosimendan (loading dose 12 µg/kg followed by 0.1 µg/kg/min infusion for 23 hours) or enoximone (loading dose 0.5 µg/kg followed by 2-10 µg/kg/min infusion). Although no significant differences in invasive haemodynamic parameters were noted, survival rate at 30 days was significantly higher in the levosimendan treated group (69 vs. 37%, p = 0.023) (Figure 44). There was also a lower cumulative dose of catecholamines in the levosimendan treated patients at 72 hours.

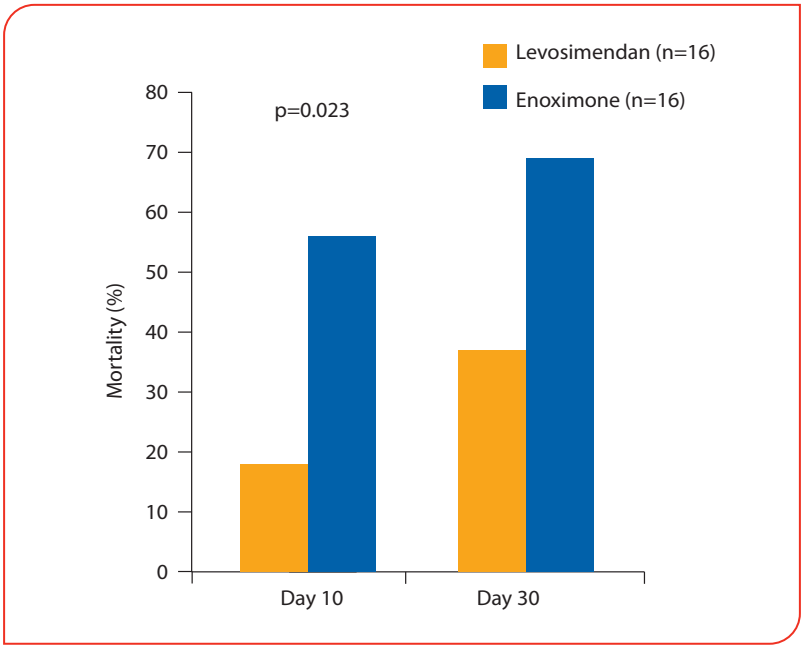


Figure 44. Mortality in cardiogenic shock patients treated with levosimendan or enoximone.[179]

RIGHT VENTRICULAR FAILURE

Right ventricular failure is most commonly related to left ventricular heart failure. Biventricular failure has worse outcome than pure left ventricular failure. In isolated right ventricular failure there is low output syndrome in the absence of pulmonary congestion, with increased jugular venous pressure, with or without hepatic congestion, and a low left ventricular filling pressure.[180] Right ventricular failure can be caused by myocardial ischaemia, volume overload and/or pressure overload.[180]

A few investigator initiated studies have been performed in patients with right ventricular failure. In these studies, levosimendan has been shown to:

- Reduce the increased right ventricular afterload.
- Improve right ventricular contractility.
- Improve diastolic function of the right ventricle.

Parissis et al. showed in a placebo-controlled study in 54 patients with advanced right ventricular heart failure (NYHA III-IV, LVEF < 35%) that levosimendan (0.1-0.2 µg/kg/min for 24 hours) improved Doppler echocardiographic markers of systolic and diastolic right ventricular function.[181]

Poelzl et al. administered open-label levosimendan (6-12 µg/kg followed by 0.075-0.2 µg/kg/min for 24 hours) to 18 patients with acute heart failure (LVEF ≤ 30%, cardiac index ≤ 2.5 l/min/m^2, right atrial pressure ≥ 10 mmHg, pulmonary capillary wedge pressure ≥ 15 mmHg).[182] Levosimendan improved right ventricular contractility but did not affect right ventricular afterload.

Russ et al. evaluated right ventricular function in 25 consecutive acute myocardial infarction patients with cardiogenic shock not responding sufficiently to conventional treatment.[183] A 24-hour levosimendan infusion (12 µg/kg bolus followed by 0.1-0.2 µg/kg/min) decreased PVR and improved cardiac power index (including both right and left ventricles), indicating decreased right ventricular afterload and improved right ventricular contractility.

Morelli et al. studied 35 mechanically ventilated patients with acute respiratory distress syndrome (ARDS) related to septic shock.[184] Patients were treated with a 24-hour infusion of levosimendan (0.2 µg/kg/min, n=18) or placebo (n=17). Levosimendan decreased the elevated pulmonary pressures (PVR and mean pulmonary artery pressure [MPAP]) and improved cardiac index and right ventricular ejection fraction and mixed venous oxygen saturation.

Ebade et al. studied 50 paediatric patients with high systolic pulmonary artery pressure (PAP) undergoing surgical repair of cardiac septal defects. Levosimendan (15 µg/kg bolus followed by 0.1-0.2 µg/kg/min) was superior to dobutamine (4-10 µg/kg/min) in lowering MPAP and increasing cardiac index.[185]

SEPTIC SHOCK

A few investigator-initiated studies with levosimendan in septic shock have been conducted. The results in these trials suggest that levosimendan might have some beneficial effects in this highly vulnerable patient population.

Morelli et al. randomly exposed 28 septic patients with persisting LV dysfunction after 48 hours of conventional treatment to receive a 24 hour infusion of either levosimendan (0.2 µg/kg/min, n=15) or dobutamine (5 µg/kg/min, n=13).[186] In addition to improved haemodynamics, levosimendan increased gastric mucosal flow, creatinine clearance and urinary output and decreased lactate levels, without negatively affecting mean arterial pressure (Table 11).

Table 11. Haemodynamic and laboratory parameters in septic patients with left ventricular dysfunction who received either levosimendan or dobutamine.[186]

Variable	Levosimendan		Dobutamine	
	Baseline	24 h	Baseline	24 h
CI (l min^{-1} m^{-2})	4.1 ± 0.2	4.5 ± 0.2*	4.2 ± 0.3	4.2 ± 0.1
MPAP (mmHg)	26.2 ± 2.4	23.1 ± 2.4*,***	26.7 ± 1.0	26.6 ± 1.1
PCWP (mmHg)	16.8 ± 1.2**	12.0 ± 0.6*,***	13.9 ± 0.6	14.4 ± 0.7*
MAP (mmHg)	76.2 ± 2.8	75.0 ± 3.3	74.7 ± 2.4	73.9 ± 1.7
LVEF (%)	37.1 ± 3.0	45.4 ± 8.4*	37.3 ± 2.6	40.8 ± 11.3
GMP (%)	-	55.3 ± 20.1***	-	2.5 ± 4.7
Arterial lactate (mmol l^{-1})	4.9 ± 1.2	3.7 ± 0.7*,***	5.2 ± 1.1	5.2 ± 1.0
Creatinine clearance (ml min^{-1})	43.9 ± 12.8	72.1 ± 16.2*,***	51.2 ± 17.0	51.3 ± 13.3

*P < 0.05 baseline vs. 24 h, **p < 0.05 levosimendan vs. dobutamine at baseline, ***p < 0.05 levosimendan vs. dobutamine after 24 h

CI = cardiac index, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, MAP = mean arterial pressure, LVEF = left ventricular ejection fraction, GMP = gastric mucosal perfusion

In another study by Morelli et al., 35 mechanically ventilated patients with acute respiratory distress syndrome (ARDS) related to septic shock were treated with a 24-hour infusion of levosimendan (0.2 µg/kg/min, n=18) or placebo (n=17).[184] Levosimendan decreased the elevated pulmonary pressures (PVR and MPAP) and improved cardiac index and right ventricular ejection fraction and mixed venous oxygen saturation.

In a mechanistic study, Morelli et al. showed that levosimendan improved sublingual microcirculation in septic shock patients.[187] The result may explain the beneficial effect of levosimendan on e.g. renal function and gastric mucosal flow[186] as impairment in microvessel function is typically associated with end-organ dysfunction.

Memis et al. demonstrated in 30 patients with septic shock that when compared with dobutamine, levosimendan, in addition to improved haemodynamics, also significantly improved splanchnic perfusion as measured by indocyanine green plasma disappearance rate.[130]

In a retrospective analysis in 420 patients with septic shock, the use of inotropes was associated with increased 90-day mortality without and after adjustment with propensity to receive inotrope. However, although the use of traditional inotropes (dobutamine and adrenaline either alone or in combination) showed significantly increased mortality, the same was not seen with levosimendan.[188]

The favourable results of the smaller studies could not be repeated in a larger 516-patient investigator initiated study **LEOPARDS** in UK.[189] In this study, a 24-hour levosimendan infusion (target dose 0.2 µg/kg/min) or placebo was administered to patients with septic shock. There was no difference between the groups in the primary endpoint of mean daily Sequential Organ Failure Assessment (SOFA) score up to day 28. Moreover, no difference in mortality was seen (34.5% in the levosimendan vs. 30.9% in the placebo group, p = 0.43) and patients in the levosimendan group required more vasopressors and atrial arrhythmias were more frequently seen in levosimendan treated patients. The study was later criticised as there was no requirement to determine the myocardial function before randomisation. This, together with the low need for dobutamine in

the placebo group, suggest that most patients included in the study might not have been in need of inotropic support.[190]

The results of LEOPARDS and the earlier smaller studies indicate that levosimendan or another agent with inotropic properties should not be used in septic shock unless there is a clear evidence of left ventricular failure. In such patients dobutamine or levosimendan may be used.[191]

POTENTIAL OTHER THERAPEUTIC USES

Case reports, uncontrolled small series or small-scale comparative studies with levosimendan have been published e.g. in non-cardiac surgery, Takotsubo cardiomyopathy, in patients difficult to wean from ventilator, in calcium channel blocker intoxications and in paediatric patients. The results have been favourable for levosimendan, but the interpretation is hampered by e.g. the lack of a comparator and the small patient samples.Therefore, larger comparative studies are needed to verify the potential benefits.

Non-cardiac surgery

Congestive heart failure is a relatively common co-morbidity in patients undergoing non-cardiac surgery. It is strongly associated with worse outcome, with a two-fold increase in in-hospital mortality.[192] Levosimendan could have a role in the preoperative optimisation of cardiac function in such patients.[193] Katsaragakis et al.[194] reported on the use of levosimendan in high risk patients undergoing abdominal surgery, while Ponschab et al.[195] described how levosimendan infusion improves haemodynamics in elderly heart failure patients undergoing urgent hip fracture repair. Both groups demonstrated that the administration of levosimendan was safe and observed improvements in ejection fraction, echocardiographic parameters as well as a range of haemodynamic indices both intra- and postoperatively. The drawback in these studies was the lack of a control group.

Takotsubo cardiomyopathy

As the important initiating factor for Takotsubo cardiomyopathy is thought to be supra-physiologic levels of plasma catecholamines and stress-related neuropeptides, traditional inotropes may be an irrational choice for the treatment.

In a non-clinical model of Takotsubo cardiomyopathy, levosimendan was shown to reverse adrenaline-induced apical dysfunction.[196]

The effects of levosimendan in Takotsubo cardiomyopathy related cardiogenic shock or pulmonary oedema have been presented in a number of case reports[197-201] and in one case series[202]. Santoro et al.[202] showed, in 13 consecutive patients with Takotsubo cardiomyopathy, that the use of levosimendan was associated with an improved left ventricular function; mean ejection fraction increased from 28 ± 5% at admission to 36 ± 9% at day 3 ($p < 0.01$) and further to 51 ± 8% at discharge ($p < 0.001$). A common finding in the case reports[198-201] was that as the initial treatment with catecholamines/dobutamine/IABP did not improve clinical status, the introduction of levosimendan rapidly achieved a relief of signs and symptoms of heart failure.

Weaning from ventilator

Acquired diaphragm muscle weakness is a key feature in several chronic conditions, including chronic obstructive pulmonary disease (COPD), congestive heart failure, and difficult weaning from mechanical ventilation in ICU.[203]

In vitro data indicate that levosimendan enhances force generating capacity of diaphragm fibres from patients with and without COPD by increasing calcium sensitivity of force generation.[204] The

same was shown in an experimental model[205] and in a healthy volunteer study.[203] Positive effect was seen both in slow and rapid diaphragm muscle fibres.[204, 205]

About 10-20% of intubated patients in ICU are difficult to wean from mechanical ventilation, resulting in increased morbidity, mortality and health care costs.[206] Mechanical ventilation results in rapid loss of diaphragmatic force production.[207] In addition, shifting from mechanical ventilation to spontaneous ventilation may dramatically increase left ventricular filling pressure and pulmonary artery pressure, especially in patients with pre-existing cardiac and or pulmonary co-morbidities.[208]

Levosimendan was compared to dobutamine in difficult-to-wean COPD patients.[208] Levosimendan resulted in significantly greater inhibition of spontaneous ventilation induced increase in pulmonary artery occlusion pressure. Similarly, mean pulmonary artery pressure increased to a lesser extent with levosimendan than with dobutamine (Figure 45).

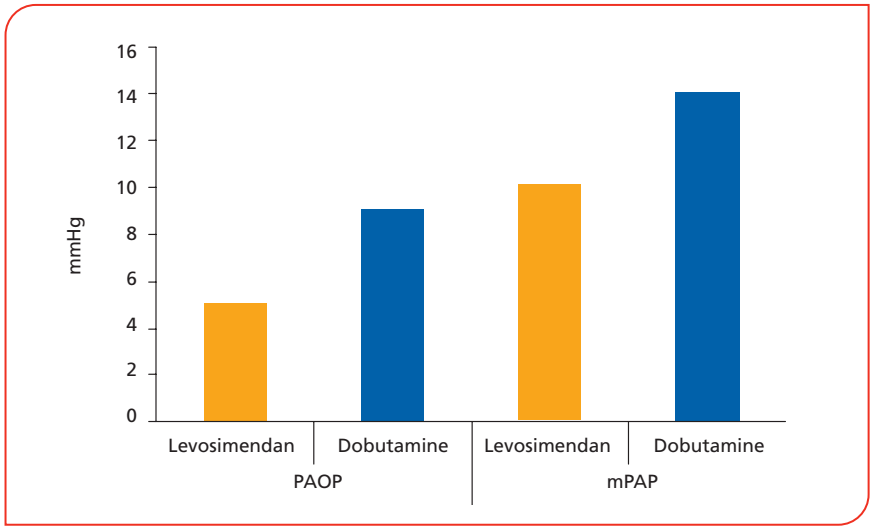


Figure 45. The effect of levosimendan (0.2 µg/kg/min) and dobutamine (7 µg/kg/min) on spontaneous ventilation induced increase in pulmonary artery occlusion pressure (PAOP) and mean pulmonary artery pressure (mPAP) in 10 difficult-to-wean COPD patients.[208]

In a prospective observational study in ventilator-dependent difficult-to-wean ICU-patients with diminished left ventricular function (LVEF < 40%), levosimendan improved cardiac contractility and oxygenation variables (Figure 46) and increased the likelihood of separation from mechanical ventilation.[206]

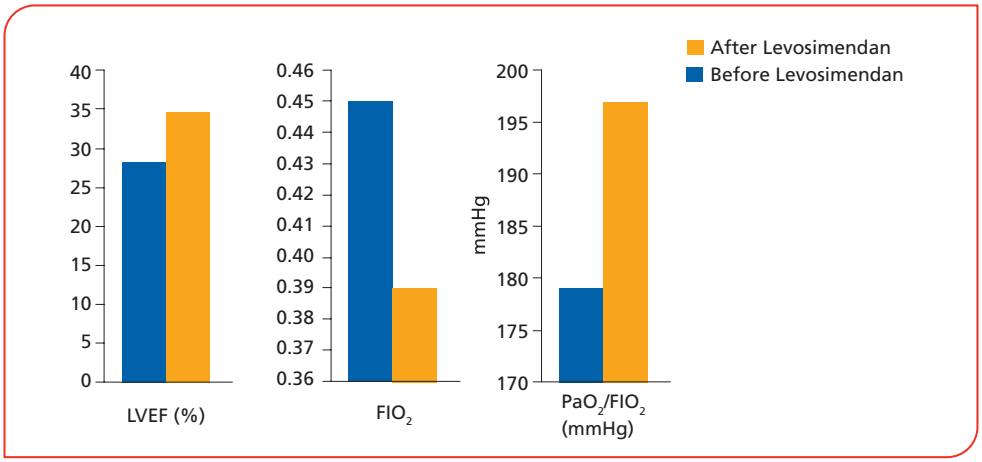


Figure 46. Left ventricular ejection fraction and oxygenation variables before and after a 24-hour levosimendan infusion in 12 difficult-to-wean ICU patients with diminished left ventricular function.[206]

Calcium channel blocker intoxication

Calcium channel blockers (CCB) are the leading substances causing death among cardiovascular drug intoxications. Via negative inotropy and profound vasodilatation, intoxication with CCBs leads to cardiovascular collapse. In case of verapamil and diltiazem overdose, negative chronotropy contributes to the symptoms.[209]

The treatment is supportive and - in addition to measures to prevent further ingestion and absorption of the drug - includes fluid resuscitation, i.v. calcium, catecholamines, glucagon, insulin, ventricular pacing, IABP, extracorporeal membrane oxygenation (ECMO) and mechanical ventilation.[210]

Several preclinical studies have shown that levosimendan increases cardiac output in experimental CCB intoxication. However, the effects on blood pressure have been modest. Mixed results on mortality have been reported.[209, 211-214]

The effects of levosimendan in clinical CCB intoxications have been presented in a few case reports.[210, 215, 216] A common finding in these cases is that when the initial treatment failed, the start of levosimendan quite rapidly improved the clinical status. In line with preclinical findings, hypotension resolved more slowly.

Levosimendan in paediatric use

The use of levosimendan in paediatric patients is contraindicated due to a lack of regulatory studies in this field. A few investigator-initiated studies have, however, been performed and the most important ones are presented below.

The largest published study in paediatrics included retrospectively-gathered data on 484 levosimendan infusions delivered to 293 patients at a single paediatric intensive care unit (PICU).[217] A majority of the patients (65%) were aged 12 months or younger. Most of the physicians surveyed (89%) thought that levosimendan postponed or reduced the need for mechanical cardiac support in children with cardiomyopathy or who were undergoing cardiac surgery.

Levosimendan was shown to be as efficacious as milrinone with comparable haemodynamic data in two randomised and double-blind studies in children and in neonates undergoing cardiac surgery.[218, 219] In another comparison of milrinone and levosimendan in neonates undergoing cardiac surgery, levosimendan group had higher pH, lower blood glucose level and lower inotrope score in the PICU.[105]

Finally, in a randomised double-blind study in children younger than 4 years of age undergoing cardiac surgery, patients receiving levosimendan had significantly higher cardiac index and lower pulmonary artery pressure than children receiving dobutamine.[185]

PHARMACO-ECONOMIC DATA

Heart failure is a major public health problem because of its high prevalence and impact on mortality, morbidity, quality of life and cost of care. Prolonged duration of hospital stay and high re-hospitalisation rate lead to the fact that the management of acute heart failure is one of the most costly diagnosis-related groups in hospital systems. Finding cost-effective therapeutic options that shorten the length of stay in hospital reduce re-hospitalisation and in-hospital mortality is therefore highly desirable.

The effects of levosimendan on hospital resource use and costs, and the cost-effectiveness of levosimendan vs. standard therapies were demonstrated based on several clinical trials using well-established pharmacoeconomic modelling techniques. Findings from these analyses are summarised below.

ECONOMIC ANALYSES

The economic analyses of the LIDO, SURVIVE and REVIVE II trials are based on two major data components:

- Actual use of study medications and actual length of hospital stay during the study period, i.e. the primary "index" or initial hospital stay, when trial treatment was first administered and a 180-day follow-up period
- Actual survival by study group up to the end of follow-up of 180 days.

The second data component consists of overall survival by study group, as projected for patients alive at 180 days, based on long-term survival of similar population in the CONSENSUS and COPERNICUS trials.[220, 221]

CLINICAL ENDPOINTS AND HOSPITAL RESOURCE USE

The **LIDO** trial was a smaller scale study including a total of 203 patients. After discharge from initial hospital period, patient mortality data and hospital days were collected retrospectively up to 180 days. In the LIDO trial, the patients stayed alive for longer, with no increase in hospital days (Figure 47). Effectively, levosimendan offered more days alive and out of hospital.

In the LIDO trial in patients with severe low-output heart failure, 11% more levosimendan patients were alive at the 6 months follow-up and therefore were also at risk of hospitalisation for longer. Despite this, there was no increase in inpatient days on levosimendan.

Based on a long-term projection of overall survival the additional cost of levosimendan per life year saved (3205 €/LYS) is relatively low when compared with other well-established cardiology interventions.

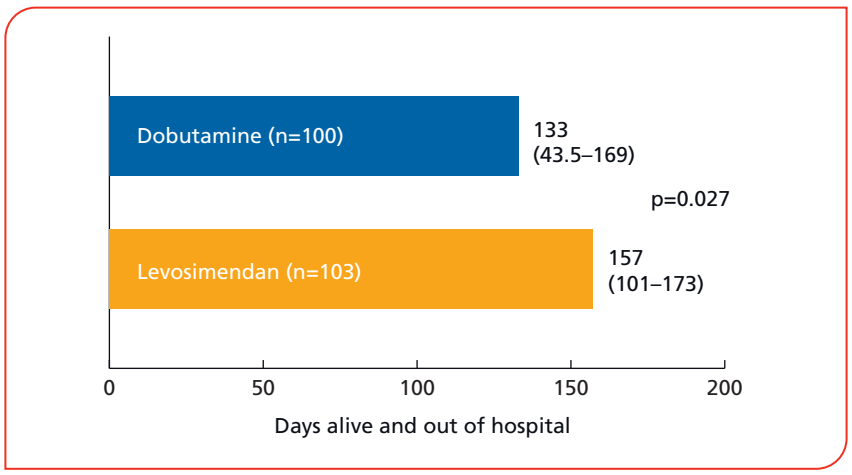


Figure 47. Days alive and out of hospital after initial discharge in the LIDO trial - mean (range).[29]

According to the prescribing information, levosimendan should be used with caution in patients with low baseline systolic or diastolic blood pressure (see SPC). The economic analyses of both the SURVIVE and REVIVE II studies bring this aspect in focus.[28, 30] Duration of hospital stay and the associated costs have been analysed both regarding "All patients treated" and the "Per label subset" (i.e. excluding patients with a baseline systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg).

In the SURVIVE study, there was a numerical survival benefit favouring levosimendan in the overall study population. However, in the REVIVE II study there were a few more deaths in the levosimendan group within 180 days. Neither of the above results was statistically significant. Post-hoc analyses of the clinical data indicated that the slight increase in mortality was specific to patients with low baseline blood pressure. In a subset of patients excluding those with low blood pressure, survival was found to be numerically in favour of levosimendan.

Differences in hospital length of stay during study follow-up

Differences in index (initial) admission stay are relevant directly to the hospital initiating inotropic therapy. Depending on the study and population assessed, the mean initial hospital stay was reduced by 7-46 hours with levosimendan compared to standard of care.

In practice, this represents from one to almost 6-8 hour working shifts of nursing staff. In the REVIVE II study, the ICU stay in the levosimendan group was 8 hours, i.e. one working shift shorter (Figure 48).

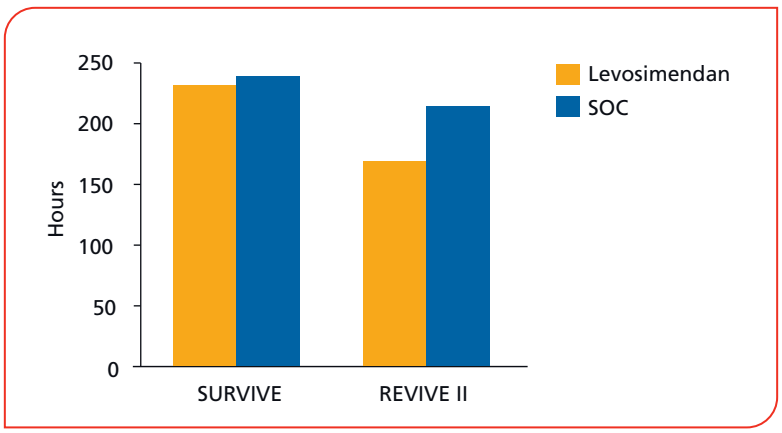


Figure 48. Duration (hours) of the initial hospital stay in SURVIVE and REVIVE II (all patients).[28, 30]
(SOC = standard of care)

Differences in cost of care during study follow-up

To calculate the costs of the ICU/coronary care unit and overall hospital stays per group from each study the following were used:

- Country-specific cost estimates per type of hospital day (LIDO).
- Average of unit costs from UK, France and Germany (SURVIVE).
- US-specific unit costs (REVIVE II).

The cost of 600 - 700 €/vial of levosimendan used as basis for the three analyses closely corresponds with the current, actual cost of levosimendan in most European countries.

When considering all study patients, the costs of total hospital care in the levosimendan group were just slightly higher in LIDO and SURVIVE studies. In the REVIVE II study the costs were significantly lower for the levosimendan group compared with standard of care (Table 12).

Table 12. Costs of total hospital care (all patients).

Trial	Costs during total follow-up period (all patients treated)	
	Levosimendan	Standard care
LIDO, €	12853	12728
SURVIVE, €	5396	5275
REVIVE II, $	23073	26068

Data based on de Lissovoy et al.[28, 30] and Figure 48

COST-EFFECTIVENESS ANALYSIS BASED ON AN OVERALL SURVIVAL MODEL

In the LIDO study,[29] the actual survival benefit of levosimendan at 6 months was 0.0265 life years saved (LYS). The overall projected LYS was approximately 0.35 translating into nearly 4.5 months. Thus, the additional cost of levosimendan was 3205 €/ LYS, which is well within generally acceptable limits.

Two meta-analyses suggested reduction in length of stay in the hospital for patients treated with levosimendan. Maharaj and Metaxa[222] analysed 8 studies where levosimendan was used after coronary revascularisation and showed a significant reduction of length of stay of 26 hours vs. comparator. Landoni et al.[16] showed that length of stay was reduced in the levosimendan group (weighted mean difference = -1.31 days, $p = 0.007$) when all the 17 studies reporting this outcome were included. The reduction in length of stay was confirmed in the cardiology setting (weighted mean difference = -1.59 days, $p < 0.0001$) with 8 studies included.

An Italian research group analysed a study population of acute heart failure patients derived from a single centre Italian observational registry (147 treated with levosimendan and 147 with standard of care).[223] Mean length of hospitalisation was 12.1 and 13.6 days in the levosimendan and control groups, respectively ($p < 0.05$). Re-hospitalisation rates were lower in the levosimendan group at 12 months (7.6 vs. 14.3%; $p < 0.05$), and mortality rate at 1 month was 2.1% vs. 6.9% in the levosimendan and control group, respectively ($p < 0.05$). The per-capita cost of treatment with levosimendan was 79 € higher than that with standard of care during the first hospitalisation, but 280 € lower when the re-hospitalisation rate was also considered.

Levosimendan is widely used for AHF for its beneficial haemodynamic effects. In conclusion, the pharmacoeconomic studies on levosimendan indicate that this treatment is cost-effective and thus a recommendable alternative to standard of care in patients with decompensated heart failure.

CONCLUSIONS AND GUIDANCE FOR CLINICAL USE

ACUTE HEART FAILURE

The clinical program with approximately 3,500 patients and subsequent investigator-initiated studies support the overall conclusion that levosimendan is effective and well tolerated. The trials have been conducted in a variety of hospital settings pertinent to clinical practice, making levosimendan one of the most studied therapies for the treatment of severe AHF. In addition, by the end of December 2017, more than 1.5 million patients have been treated worldwide since its first launch in 2000.

The infusion of levosimendan has very consistently been shown to enhance left ventricular performance and to decrease left ventricular filling pressure and plasma BNP concentrations without an increase in myocardial oxygen consumption. Neither age nor gender has influenced the responses to levosimendan.

Following a 24-hour infusion of levosimendan, the slowly formed and eliminated active metabolites reach pharmacologically active plasma levels, resulting in a prolonged haemodynamic effect. After a 24-hour infusion, the effects persist for at least 7 days. There have been no signs of tolerance development (which is a problem with beta-agonists) to levosimendan, even with prolonged administration.

The haemodynamic and neurohumoral improvement is associated with symptomatic benefit that is sustained and superior to placebo. Unlike with dobutamine, the effects of levosimendan are not attenuated with concomitant ß-blocker use.

In two earlier phase III studies, a significant mortality benefit with levosimendan was observed in comparison with placebo (RUSSLAN) and dobutamine (LIDO). These favourable results were not, however, confirmed in two large-scale studies where levosimendan was compared with placebo (REVIVE II) and dobutamine (SURVIVE). Meta-analyses on the effect of levosimendan on mortality suggest a survival benefit of levosimendan both compared to placebo and dobutamine.

Levosimendan infusion has generally been rather well tolerated in this very ill patient population. Based on the data from the two largest studies conducted so far, the REVIVE II and SURVIVE studies, hypotension was more frequently seen when compared to placebo, but not when compared to dobutamine. Levosimendan was also associated with higher incidence of atrial fibrillation compared both to placebo and dobutamine.

The haemodynamic and other clinical features of levosimendan are summarized in Table 13.

Table 13. Haemodynamic and other clinical features of levosimendan

Haemodynamic and neurohormonal effects	Other clinical effects
Pulmonary capillary wedge pressure ↓↓↓	Relief of symptoms of heart failure
Cardiac output (index) ↑↑	Effects maintained also with ß-blockers
Stroke volume ↑	Sustained effects due to an active metabolite
Systemic vascular resistance ↓↓	No development of tolerance
Pulmonary vascular resistance ↓↓	No increase in myocardial oxygen consumption
Natriuretic peptide levels ↓↓↓	Anti-ischaemic effect
	No impairment of diastolic function

↓ = decrease, ↑ = increase

The pharmacologic and pharmacodynamic properties differentiate levosimendan from other inotropes. Levosimendan is safe also in patients with acute heart failure related to acute coronary syndromes.

It should be borne in mind that, in addition to contractility increasing effects, levosimendan has profound vasodilatory effects. Clinical studies have indicated that levosimendan should be given cautiously to patients with low blood pressure, especially in case of hypovolaemia. In these patients, lower infusion rates without the loading dose should be considered. In Table 14, guidance on the patient selection and dosing for levosimendan are given in acute decompensated heart failure.

Table 14. Optimal patient profile and guidance for treatment in patients with acute heart failure.

Optimal patient profile:
• Existing chronic heart failure with systolic dysfunction (left ventricular ejection fraction below 40%)
• Ongoing ß-blocker therapy
• Signs of hypoperfusion, i.e. cool extremities, oliguria
• Severe pulmonary oedema
• Inadequate response to traditional treatment (however, the start of the levosimendan infusion should not be unnecessarily delayed)
• No severe hypotension or tachycardia

Guidance for the treatment:
• Loading dose (6-12 µg/kg over 10 min) only if immediate effect needed and systolic blood pressure >100 mmHg
• Maintenance infusion rate 0.05-0.2 µg/kg/min with individualised dosing regimen
• Infusion duration up to 24 h • Hypovolaemia to be avoided before and during the treatment (fluid resuscitation as needed; intravenous diuretics with caution) • Vasopressor (noradrenaline) concomitantly if hypotension

In case of unintended overdose, pronounced haemodynamic effects would be expected; mainly hypotension and increased heart rate/arrhythmias. Hypotension should be treated with fluid resuscitation and vasoconstrictors, as needed. Arrhythmias may require e.g. intravenous beta-blockade or amiodarone. Due to the formation of the active metabolite, the follow-up may need to be prolonged, if the amount of the total dose is substantial.

CARDIAC SURGERY AND ADVANCED CHRONIC HEART FAILURE

The current clinical data with levosimendan have focused on AHF and less attention has been paid on other potential uses of the compound. Levosimendan has, however, been relatively profoundly studied in cardiac surgery.

Earlier data in cardiac surgery patients suggested that levosimendan is superior to traditional inotropes (dobutamine, milrinone) as it has sustained haemodynamic effects, causes less myocardial injury, is associated with improved outcome and the length of ICU stay is shorter.

In the more recent placebo-controlled multicentre studies, all these benefits could not be repeated. However, levosimendan use was associated with lower incidence of low cardiac output syndrome and lower need for additional catecholamines. Importantly, safety was not a concern in these larger studies either. No significant difference in adverse event of hypotension, atrial or ventricular arrhythmias were seen in comparison with placebo. In the largest of the studies (LEVO-CTS), mortality was numerically lower in levosimendan group in the whole study population and in the subgroup of patients with isolated coronary artery bypass grafting, the result was significantly favouring levosimendan. Table 15 presents the suggestions of a consensus meeting for the optimal use of levosimendan in cardiac surgery.[133] Although these recommendations were written before the results of the latest trials, the message is still valid.

Table 15. The recommended use of levosimendan in cardiac surgery.[133]

Type of patients	Low preoperative LVEF (e.g. < 35%) High-risk patients (e.g. emergency operation,decompensated heart failure) Weaning failure from CPB Scheduled for mechanical assist device (IABP/LVAD) Postoperative low cardiac output syndrome
Prerequisites for optimal effect and safety	Volume and/or electrolyte optimisation • Crystalloids as needed to reach euvolemia • K+ > 4 mmol/L • Tight blood pressure monitoring especially during the first hours • Administer noradrenaline, if SBP < 90mmHg at euvolemia
Optimisation of diuretics	Reduce dose or stop then repeat
ß-blocker use	Continue whenever possible
Mode of administration	Usually without a bolus Routinely start with continuous infusion: • Start with 0.1 µg/kg/minute • Time for first effects usually 2 hours • Adapt after 2-4 hours (0.05-0.2 µg/kg/minute) Bolus might be considered if: • Immediate effect is necessary (intraoperatively) • Patient has high blood pressure • Patient is volume overloaded

Another field of increasing interest is the use of levosimendan repeatedly in patients with AdHF. The formation of active metabolites prolongs the effects of levosimendan infusions beyond the administration giving rationale for intermittent dosing. Several small-scale studies indicate that levosimendan improves haemodynamics, has beneficial effects on neurohormones and might improve outcome. Optimal dosing scheme is not established but a consensus meeting suggested the patient profiles and dosing instructions presented in Table 16.[224] The ongoing LEODOR study with two different dosing schemes may give further guidance in the future.

Table 16. The patient profile and dosing instructions in patients with AdHF suggested by the consensus meeting.[224]

Patient characteristics
• Severe systolic dysfunction (LVEF < 35%)
• and/or NYHA IIIb-IV and/or INTERMACS levels 4,5,6
• and/or repeated hospitalisation or emergency department visits (≥ 2 in the past year)
• All of the above despite optimal treatment for heart failure

Recommended dosing
• Infusion rate: 0.05 µg/kg/min to 0.2 µg/kg/min; starting with low dose and increasing stepwise during the remaining time when tolerated
• Bolus dose: not recommended
• Duration: 6 to 24 hours
• Interval: every 2 to 4 weeks

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SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Simdax 2.5 mg/ml concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 2.5 mg of levosimendan. One 5 ml vial contains 12.5 mg of levosimendan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The concentrate is a clear yellow or orange solution for dilution prior to administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Simdax is indicated for the short-term treatment of acutely decompensated severe chronic heart failure (ADHF) in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate (see section 5.1.).

4.2 Posology and method of administration

Simdax is for in-hospital use only. It should be administered in a hospital setting where adequate monitoring facilities and expertise with the use of inotropic agents are available.

Method of administration

Simdax is to be diluted prior to administration (see section 6.6).

The infusion is for intravenous use only and can be administered by the peripheral or central route.

Posology

The dose and duration of treatment should be individualised according to the patient's clinical condition and response.

The treatment should be initiated with a loading dose of 6-12 µg/kg infused over 10 minutes followed by a continuous infusion of 0.1 µg/kg/min (see section 5.1). The lower loading dose of 6 µg/kg is recommended for patients on concomitant intravenous vasodilators or inotropes or both at the start of the infusion. Higher loading doses within this range will produce a stronger haemodynamic response but may be associated with a transient increased incidence of adverse reactions.

The response of the patient should be assessed with the loading dose or within 30 to 60 minutes of dose adjustment and as clinically indicated If the response is deemed excessive (hypotension, tachycardia), the rate of the infusion may be decreased to 0.05 µg/kg/min or discontinued (see section 4.4). If the initial dose is tolerated and an increased haemodynamic effect is required, the rate of the infusion can be increased to 0.2 µg/kg/min.

The recommended duration of infusion in patients with acute decompensation of severe chronic heart failure is 24 hours. No signs of development of tolerance or rebound phenomena have been observed followingdiscontinuation of Simdax infusion. Haemodynamic effects persist for at least 24 hours and may be seen up to 9 days after discontinuation of a 24-hour infusion (see section 4.4).

Experience of repeated administration of Simdax is limited. Experience with concomitant use of vasoactive agents, including inotropic agents (except digoxin) is limited In the REVIVE programme, a lower loading dose (6 µg/kg) was administered with baseline concomitant vasoactive agents (see sections 4.4, 4.5 and 5.1).

Monitoring of treatment

Consistent with current medical practice, ECG, blood pressure and heart rate must be monitored during treatment and the urine output measured. Monitoring of these parameters for at least 3 days after the end of infusion or until the patient is clinically stable is recommended (see section 4.4).

In patients with mild to moderate renal or mild to moderate hepatic impairment monitoring is recommended for at least 5 days.

Elderly

No dose adjustment is required for elderly patients.

Renal impairment

Simdax must be used with caution in patients with mild to moderate renal impairment. Simdax should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment

Simdax must be used with caution in patients with mild to moderate hepatic impairment although no dose adjustment appears necessary for these patients. Simdax should not be used in patients with severe hepatic impairment (see section 4.3, 4.4 and 5.2).

Children

Simdax should not be administered to children and adolescents under 18 years of age (see sections 4.4 and 5.2).

The following table provides detailed infusion rates for both the loading and maintenance infusion doses of a 0.05 mg/ml preparation of Simdax infusion:

Patient's weight (kg)	Loading dose is given as an infusion over 10 minutes with the infusion rate (ml/h) below		Continuous infusion rate (ml/h)		
	Loading dose 6 µg/kg	Loading dose 12 µg/kg	0.05 µg/kg/minute	0.1 µg/kg/minute	0.2 µg/kg/minute
40	29	58	2	5	10
50	36	72	3	6	12
60	43	86	4	7	14
70	50	101	4	8	17
80	58	115	5	10	19
90	65	130	5	11	22
100	72	144	6	12	24
110	79	158	7	13	26
120	86	173	7	14	29

The following table provides detailed infusion rates for both the loading and maintenance infusion doses for a 0.025 mg/ml preparation of Simdax infusion:

Patient's weight (kg)	Loading dose is given as an infusion over 10 min with the infusion rate (ml/h) below		Continuous infusion rate (ml/h)		
	Loading dose 6 µg/kg	Loading dose 12 µg/kg	0.05 µg/kg/minute	0.1 µg/kg/minute	0.2 µg/kg/minute
40	58	115	5	10	19
50	72	144	6	12	24
60	86	173	7	14	29
70	101	202	8	17	34
80	115	230	10	19	38
90	130	259	11	22	43
100	144	288	12	24	48
110	158	317	13	26	53
120	173	346	14	29	58

4.3 Contraindications

Hypersensitivity to levosimendan or to any of the excipients.

Severe hypotension and tachycardia (seesections 4.4 and 5.1). Significant mechanical obstructions affecting ventricular filling or outflow or both. Severe renal impairment (creatinine clearance < 30 ml/min) and severe hepatic impairment. History of Torsades de Pointes.

4.4 Special warnings and special precautions for use

An initial haemodynamic effect of levosimendan may be a decrease in systolic and diastolic blood pressure, therefore, levosimendan should be used with caution in patients with low baseline systolic or diastolic blood pressure or those at risk for a hypotensive

episode. More conservative dosing regimens are recommended for these patients. Physicians should tailor the dose and duration of therapy to the condition and response of the patient (see sections 4.2, 4.5 and 5.1).

Severe hypovolaemia should be corrected prior to levosimendan infusion. If excessive changes in blood pressure or heart rate are observed, the rate of infusion should be reduced or the infusion discontinued.

The exact duration of all haemodynamic effects has not been determined, however, the haemodynamic effects, generally last for 7-10 days. This is partly due to the presence of active metabolites, which reach their maximum plasma concentrations about 48 hours after the infusion has been stopped. Non-invasive monitoring for at least 4-5 days after the end of infusion is recommended. Monitoring is recommended to continue until the blood pressure reduction has reached its maximum and the blood pressure starts to increase again, and may need to be longer than 5 days if there are any signs of continuing blood pressure decrease, but can be shorter than 5 days if the patient is clinically stable. In patients with mild to moderate renal or mild to moderate hepatic impairment an extended period of monitoring maybe needed.

Simdax should be used cautiously in patients with mild to moderate renal impairment. Limited data on the elimination of the active metabolites are available in patients with impaired renal function. Impaired renal function may lead to increased concentrations of the active metabolites, which may result in a more pronounced and prolonged haemodynamic effect (see section 5.2).

Simdax should be used cautiously in patients with mild to moderate hepatic impairment. Impaired hepatic function may lead to prolonged exposure to the active metabolites, which may result in a more pronounced and prolonged haemodynamic effect (see section 5.2).

Simdax infusion may cause a decrease in serum potassium concentration. Thus, low serum potassium concentrations should be corrected prior to the administration of Simdax and serum potassium should be monitored during treatment. As with other medicinal products for heart failure, infusions of Simdax may be accompanied by decreases in haemoglobin and haematocrit and caution should be exercised in patients with ischaemic cardiovascular disease and concurrent anaemia.

Simdax infusion should be used cautiously in patients with tachycardia atrial fibrillation with rapid ventricular response or potentially life-threatening arrhythmias.

Experience with repeated administration of Simdax is limited. Experience with concomitant use of vasoactive agents, including inotropic agents (except digoxin), is limited. Benefit and risk should be assessed for the individual patient.

Simdax should be used cautiously and under close ECG monitoring in patients with ongoing coronary ischaemia, long QTc interval regardless of aetiology, or when given concomitantly with medicinal products that prolong the QTc interval (see section 4.9).

The use of levosimendan in cardiogenic shock has not been studied. No information is available on the use of Simdax in the following disorders: restrictive cardiomyopathy, hypertrophic cardiomyopathy, severe mitral valve insufficiency, myocardial rupture, cardiac tamponade, and right ventricular infarction

Simdax should not be administered to children as there is very limited experience of use in children and adolescent under 18 years of age (see section 5.2).

Limited experience is available on the use of Simdax in patients with heart failure after surgery, and in severe heart failure in patients awaiting heart transplantation.

4.5 Interaction with other medicinal products and other forms of interaction

Consistent with current medical practice, levosimendan should be used with caution when used with other intravenous vasoactive medicinal products due to a potentially increased risk of hypotension (see section 4.4).

No pharmacokinetic interactions have been observed in a population analysis of patients receiving digoxin and Simdax infusion. Simdax infusion can be used in patients receiving beta-blocking agents without loss of efficacy. Co-administration of isosorbide mononitrate and levosimendan in healthy volunteers resulted in significant potentiation of the orthostatic hypotensive response.

4.6 Pregnancy and lactation

Pregnancy

There is no experience of using levosimendan in pregnant women. Animal studies have shown toxic effects on reproduction (see section 5.3). Therefore, levosimendan should be used in pregnant women only if the benefits for the mother outweigh the possible risks to the foetus.

Lactation

It is not known whether levosimendan is excreted in human milk. Studies in rats have shown excretion of levosimendan in breast milk, therefore women receiving levosimendan should not breastfeed.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

In placebo-controlled clinical trials for ADHF (REVIVE programme), 53% of patients experienced adverse reactions, the most frequent of which were ventricular tachycardia, hypotension, and headache.

In a dobutamine-controlled clinical trial for ADHF (SURVIVE), 18% of patients experienced adverse reactions, the most frequent of which were ventricular tachycardia, atrial fibrillation, hypotension, ventricular extrasystoles, tachycardia, and headache.

The following table describes the adverse reactions observed in 1% or greater of patients during REVIVE I, REVIVE II, SURVIVE, LIDO, RUSSLAN, 300105, and 3001024 clinical trials. If the incidence of any particular event in an individual trial was greater than that seen across the other trials, then the higher incidence is reported in the table.

The events considered at least possibly related to levosimendan are displayed by system organ class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10).

Table 3. Summary of Adverse Reactions : SURVIVE Clinical Study, REVIVE Programme, and LIDO/RUSSLAN/300105/3001024 Clinical Studies combined

Body System	Frequency	Preferred Term
Metabolism and nutrition disorders	Common	Hypokalaemia
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very Common	Headache
	Common	Dizziness
Cardiac disorders	Very Common	Ventricular Tachycardia
	Common	Atrial Fibrillation
		Tachycardia
		Ventricular Extrasystoles
		Cardiac Failure
		Myocardial Ischaemia
		Extrasystoles
Vascular disorders	Very Common	Hypotension
Gastrointestinal disorders	Common	Nausea
		Constipation
		Diarrhoea
		Vomiting
Investigations	Common	Haemoglobin Decreased

Post-marketing adverse reactions:

In post-marketing experience, ventricular fibrillation has been reported in patients being administered Simdax.

4.9 Overdose

Overdose of Simdax may induce hypotension and tachycardia. In clinical trials with Simdax, hypotension has been successfully treated with vasopressors (e.g. dopamine in patients with congestive heart failure and adrenaline in patients following cardiac surgery). Excessive decreases in cardiac filling pressures may limit the response to Simdax and can be treated with parenteral fluids. High doses (at or above 0.4 µg/kg/min) and infusions over 24 hours increase the heart rate and are sometimes associated with prolongation of the QTc interval. In the event of an overdose of Simdax, continuous ECG monitoring, repeated determinations of serum electrolytes and invasive haemodynamic monitoring should be undertaken. Simdax overdose leads to increased plasma concentrations of the active metabolite, which may lead to a more pronounced and prolonged effect on heart rate requiring a corresponding extension of the observation period.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cardiac stimulants (calcium sensitisers), ATC code: C01CX08

Pharmacodynamic effects

Levosimendan enhances the calcium sensitivity of contractile proteins by binding to cardiac troponin C in a calcium-dependent manner. Levosimendan increases the contraction force but does not impair ventricular relaxation Inaddition, levosimendan opens ATP-sensitive potassium channels in vascular smooth muscle, thus inducing vasodilatation of systemic and coronary arterial resistance vessels and systemic venous capacitance vessels. Levosimendan is a selective phosphodiesterase III inhibitor in vitro. The relevance of this at therapeutic concentrations is unclear. In patients with heart failure, the positive inotropic and vasodilatory actions of levosimendan result in an increased contractile force, and a reduction in both preload and afterload, without adversely affecting diastolic function. Levosimendan activates stunned myocardium in patients after PTCA or thrombolysis.

Haemodynamic studies in healthy volunteers and in patients with stable and unstable heart failure have shown a dose-dependent effect of levosimendan given intravenously as loading dose (3 µgs/kg to 24 µgs/kg) and continuous infusion (0.05 to 0.2 µgs/kg per minute). Compared with placebo, levosimendan increased cardiac output, stroke volume, ejection fraction, and heart rateand reduced systolic blood pressure, diastolic blood pressure, pulmonary capillary wedge pressure, right atrial pressure, and peripheral vascular resistance.

Simdax infusion increases coronary blood flow in patients recovering from coronary surgery and improves myocardial perfusion in patients with heart failure. These benefits are achieved without a significant increase in myocardial oxygen consumption. Treatment with Simdax infusion significantly decreases circulating levels of endothelin-1 in patients with congestive heart failure. It does not increase plasma catecholamine levels at recommended infusion rates.

Clinical Trials

Simdax has been evaluated in clinical trials involving over 2800 heart failure patients. The efficacy and safety of Simdax for the treatment of ADHF were assessed in the following randomised, double-blind, multi-national clinical trials:

REVIVE Programme

REVIVE I

In a double-blind, placebo-controlled pilot study in 100 patients with ADHF who received a 24 hour infusion of Simdax, a beneficial response as measured by the clinical composite endpoint over placebo plus standard of care was observed in the Simdax-treated patients.

REVIVE II

A double-blind, placebo-controlled pivotal study in 600 patients who were administered a 10 minute loading dose of 6-12 µg/kg followed by a protocol-specified stepped titration of levosimendan to 0.05-0.2 µg/kg/minute for up to 24 hours that provided a benefit in clinical status in patients with ADHF who remained dyspnoeic after intravenous diuretic therapy.

The REVIVE clinical programme was designed to compare the effectiveness of levosimendan plus standard-of-care to placebo plus standard-of-care in the treatment of ADHF.

Inclusion criteria included patients hospitalised with ADHF, left ventricular ejection fraction less than or equal to 35% within the previous 12 months, and dyspnoea at rest. All baseline therapies were allowed, with the exception of intravenous milrinone.

Exclusion criteria included severe obstruction of ventricular outflow tracts, cardiogenic shock, a systolic blood pressure of ≤ 90 mmHg or a heart rate ≥ 120 beats per minute (persistent for at least five minutes), or a requirement for mechanical ventilation.

The results of the primary endpoint demonstrated that a greater proportion of patients were categorised as improved with a smaller proportion of patients categorised as worsened (p-value 0.015) as measured by a clinical composite endpoint reflecting sustained benefits to clinical status over three time points: six hours, 24 hours and five days. B-type natriuretic peptide was significantly reduced vs. placebo and standard of care at 24 hours and through five days (p-value=0.001).

The Simdax group had a slightly higher, although not statistically significant, death rate compared with the control group at 90 days (15% vs. 12%). Post hoc analyses identified systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg at baseline as factors increasing the mortality risk.

SURVIVE

A double-blind, double-dummy, parallel group, multicentre study comparing levosimendan vs. dobutamine evaluated 180 day mortality in 1327 patients with ADHF who required additional therapy after an inadequate response to intravenous diuretics or vasodilators. The patient population was generally similar to the patients in the REVIVE II study. However, patients without a previous history of heart failure were included (e.g., acute myocardial infarction), as were patients requiring mechanical ventilation. Approximately 90% of patients entered the trial due to dyspnoea at rest.

The results of SURVIVE did not demonstrate a statistically significant difference between levosimendan and dobutamine in all-cause mortality at 180 days {Hazard Ratio = 0.91 (95% CI [0.74, 1.13] p-value 0.401)}. However, there was a numerical advantage in mortality at Day 5 (4% levosimendan vs. 6% dobutamine) for levosimendan. This advantage persisted through the 31-day period (12% levosimendan vs. 14% dobutamine) and was most prominent in those individuals who received baseline betablocker therapy. In both treatment groups, patients with low baseline blood pressure experienced higher rates of mortality than did those with higher baseline blood pressure.

LIDO

Levosimendan has been shown to lead to dose-dependent increases in cardiac output and stroke volume as well as dose-dependent decrease in pulmonary capillary wedge pressure, mean arterial pressure and total peripheral resistance.

In a double-blind multicentre trial, 203 patients with severe low output heart failure (ejection fraction ≤ 0.35, cardiac index < 2.5 l/min/m^2, pulmonary capillary wedge pressure (PCWP)>15 mmHg) and in need of inotropicsupport received levosimendan (loading dose 24 µg kg over 10 minutes followed by a continuous infusion of 0.1-0.2 µg/kg/min) or dobutamine (5-10 µg/kg/min) for 24 hours. The aetiology of heart failure was ischaemic in 47% of the patients; 45% had idiopathic dilative cardiomyopathy. 76% of the patients had dyspnoea at rest. Major exclusion criteria included systolic blood pressure below 90 mmHg and heart rate above 120 beats per minute. The primary endpoint was an increase in cardiac output by ≥ 30% and a simultaneous decrease of PCWP by ≥ 25% at 24 hours. This was reached in 28% of levosimendan treated patients compared with 15% after dobutamine treatment (p= 0.025). Sixty-eight percent of symptomatic patients had an improvement in their dyspnoea scores after levosimendan treatment, compared with 59% after dobutamine treatment. Improvement in fatigue scores were 63% and 47% after levosimendan and dobutamine treatment, respectively. All-cause 31-day mortality was 7.8% for levosimendan and 17% for dobutamine treated patients.

RUSSLAN

In a further double-blind multicentre trial carried out primarily to evaluate safety, 504 patients with decompensated heart failure after acute myocardial infarction who were assessed to require inotropic support were treated with levosimendan or placebo for 6 hours. There were no significant differences in the incidence of hypotension and ischaemia between the treatment groups.

No adverse effect on survival up to 6 months was observed in a retrospective analysis of the LIDO and RUSSLAN trials.

5.2 Pharmacokinetic properties

General

The pharmacokinetics of levosimendan are linear in the therapeutic dose range 0.05-0.2 µg/kg/min.

Distribution

The volume of distribution of levosimendan (Vss) is approximately 0.2 l/kg. Levosimendan is 97-98% bound to plasma proteins, primarily to albumin. For OR-1855 and OR-1896, the mean protein binding values were 39% and 42%, respectively in patients.

Metabolism

Levosimendan is completely metabolised and negligible amounts of unchanged parent drug are excreted in urine and faeces. Levosimendan is primarily metabolised by conjugation to cyclic or N-acetylated cysteinylglycine and cysteine conjugates. Approximately 5% of the dose is metabolised in the intestine by reduction to aminophenylpyridazinone (OR-1855), which after re absorption is metabolised by N-acetyltransferase to the active metabolite OR-1896. The acetylation level is genetically determined. In rapid acetylators, the concentrations of the metabolite OR-1896 are slightly higher than in slow acetylators. However, this has no implication for the clinical haemodynamic effect at recommended doses.

In systemic circulation the only significant detectable metabolites following levosimendan administration are OR-1855 and OR-1896. These metabolites in vivo reach equilibrium as a result of acetylation and de-acetylation metabolic pathways, which are governed by N-acetyl transferase-2, a polymorphic enzyme. In slow acetylators, the OR-1855 metabolite predominates, while in rapid acetylators the OR-1896 metabolite predominates. The sum of exposures for the two metabolites is similar among slow and rapid acetylators, and there is no difference in the haemodynamic effects between the two groups. The prolonged haemodynamic effects (lasting up to 7-9 days after discontinuation of a 24 hour Simdax infusion) are attributed to these metabolites.

In vitro studies have shown that levosimendan, OR-1855 and OR-1896 do not inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations achieved by the recommended dosing. In addition levosimendan does not inhibit CYP1A1 and neither OR-1855 nor OR-1896 inhibit CYP2C9. The results of drug interaction studies in humans with warfarin, felodipine, and itraconazole confirmed that levosimendan does not inhibit CYP3A4 or CYP2C9, and metabolism of levosimendan is not affected by CYP3A inhibitors.

Elimination and excretion

Clearance is about 3.0 ml/min/kg and the half-life about 1 hour. 54 % of the dose

is excreted in urine and 44 % in faeces. More than 95 % of the dose is excreted within one week. Negligible amounts (< 0.05 % of the dose) are excreted as unchanged levosimendan in the urine. The circulating metabolites OR-1855 and OR-1896 are formed and eliminated slowly. Peak plasma concentration is reached about 2 days after termination of a levosimendan infusion. The half-lives of the metabolites are about 75-80 hours. Active metabolites of levosimendan, OR-1855 and OR-1896, undergo conjugation or renal filtration, and are excreted predominantly in urine.

Special populations
Children:

Levosimendan should not be administered to children (see section 4.4).

Limited data indicate that the pharmacokinetics of levosimendan after a single dose in children (age 3 month to 6 years) are similar to those in adults. The pharmacokinetics of the active metabolite have not been investigated in children.

Renal impairment: The pharmacokinetics of levosimendan have been studied in subjects with varying degrees of renal impairment who did not have heart failure. Exposure to levosimendan was similar in subjects with mild to moderate renal impairment and in subjects undergoing haemodialysis, while the exposure to levosimendan may be slightly lower in subjects with severe renal impairment.

Compared to healthy subjects, the unbound fraction of levosimendan appeared to be slightly increased, and AUCs of the metabolites (OR-1855 and OR-1896) were up to 170% higher in subjects with severe renal impairment and patients undergoing haemodialysis. The effects of mild and moderate renal impairment on the pharmacokinetics of OR-1855 and OR-1896 are expected to be less than those of severe renal impairment.

Levosimendan is not dialysable. While OR-1855 and OR-1896 are dialysable, the dialysis clearances are low (approximately 8-23 ml/min) and the net effect of a 4-hour dialysis session on the overall exposure to these metobolites is small.

Hepatic impairment: No differences in the pharmacokinetics or protein binding of levosimendan were found in subjects with mild or moderate cirrhosis versus healthy subjects. The pharmacokinetics of levosimendan, OR-1855 and OR-1896 are similar between healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Class B), with the exception that elimination half-lives of OR-1855 and OR-1896 are slightly prolonged in subjects with moderate hepatic impairment.

Population analysis has shown no effects of age, ethnic origin or gender on the pharmacokinetics of levosimendan. However, the same analysis revealed that volume of distribution and total clearance are dependent on weight.

5.3 Preclinical safety data

Conventional studies on general toxicity and genotoxicity revealed no special hazard for humans in short term use.

In animal studies, levosimendan was not teratogenic, but it caused a generalised reduction in the degree of ossification in rat and rabbitfoetuses with anomalous development of the supraoccipital bone in the rabbit. When administered before and during early pregnancy, levosimendan reduced fertility (decreased the number of corpora lutea and implantations) and exhibited developmental toxicity (decreased pups per litter and increased the number of early resorptions and post-implantation losses) in the female rat. The effects were seen at clinical exposure levels.

In animal studies, levosimendan was excreted into maternal milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone

Citric Acid, anhydrous

Ethanol, anhydrous

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluents except those stated in section 6.6.

6.3 Shelf life

Vials with chlorobutyl rubber closure: 3 years
Vials with bromobutyl rubber closure: 2 years

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Storage and in-use time after dilution should never exceed 24 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C) Do not freeze.

The colour of the concentrate may turn to orange during storage, but there is no loss of potency and the product may be used until the indicated expiry date if storage instructions have been followed.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and content of container

- 8 ml Type I glass vials
- Chlorobutyl or bromobutyl rubber closure with fluoropolymer coating

Pack sizes

1, 4, 10 vials of 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simdax 2.5 mg/ml concentrate for solution for infusion is intended for single use only.

As for all parenteral medicinal products, inspect the diluted solution visually for particulate matter and discolouration prior to administration.

To prepare the 0.025 mg/ml infusion, mix 5 ml of Simdax 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5 % glucose solution.

To prepare the 0.05 mg/ml infusion, mix 10 ml of Simdax 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5% glucose solution.

The following medicinal products can be given simultaneously with Simdax in connected intravenous lines:

- Furosemide 10 mg/ml
- Digoxin 0.25 mg/ml
- Glyceryl trinitrate 0.1 mg/ml

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2000-09-22 / 2010-09-22

10 DATE OF REVISION OF THE TEXT

3 October, 2016

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