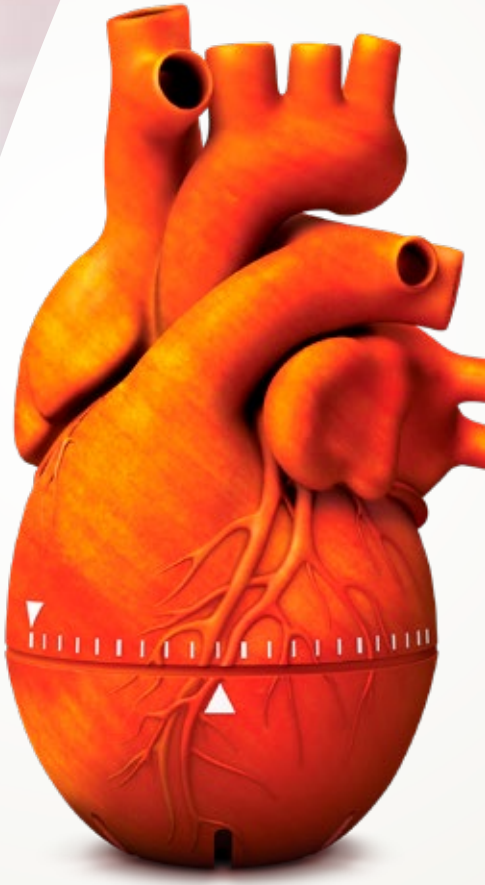
SIMDAX® GIVES YOU TIME IN ACUTE HEART FAILURE



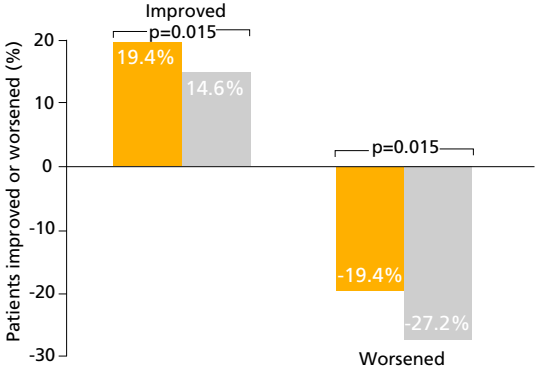
ORION PHARMA
Building well-being

SIMDAX®
levosimendan

SIMDAX® RELIEVES SYMPTOMS IN AHF

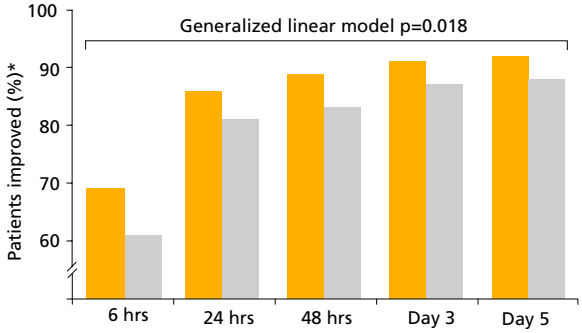
SIMDAX® improves symptoms of dyspnoea and fatigue in acute heart failure. In the Phase III regulatory study REVIVE, symptoms over the 5-day assessment period improved significantly more with SIMDAX® than with placebo when administered on top of the standard of care.[1]

Improvement in clinical status



The primary endpoint result in the REVIVE trial[1], 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 drug infusion.

Improvement in dyspnea



Effects of levosimendan vs placebo on top of standard of care on dyspnea in patients with AHF.[4]

*Includes mild, moderate and marked improvement on a 7-point scale

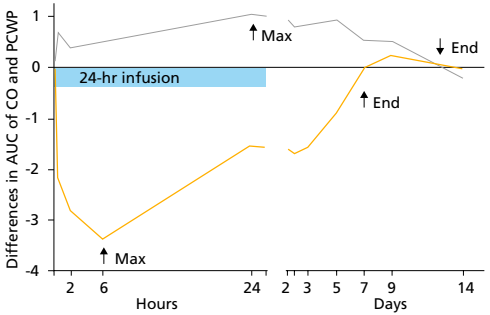
Reference: 1. Packer M. *et al. JCHF.* 2013;1(2): 103-11.

...WITH SUSTAINED HEMODYNAMIC AND NEUROHORMONAL EFFECTS

The hemodynamic effects of SIMDAX® on cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) have been shown in several clinical trials.[1-3]

The effect of SIMDAX is sustained,[1,4] as also seen in a prolonged decrease of brain natriuretic peptide in the SURVIVE clinical trial.[4]

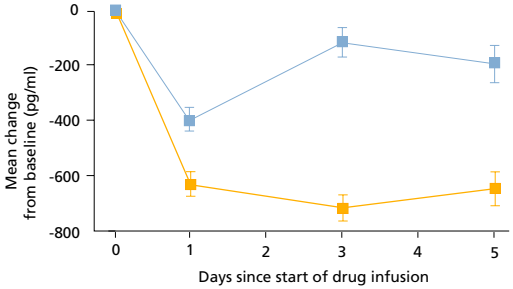
Sustained hemodynamic effects



CO (L/min)
PCWP (mmHg)

Figure 1: Duration of action of 24-hour infusion of levosimendan.[1]
CO = Cardiac Output;
PCWP = pulmonary capillary wedge pressure

Sustained effects on neurohormone levels



Levosimendan
Dobutamine

p<0.001 at all timepoints

Figure 2: Rapid and sustained reduction in B-type natriuretic peptide. In SURVIVE, a double-blind randomized, multicenter study comparing levosimendan and dobutamine in 1327 patients hospitalized for AHF, a more profound reduction in BNP was seen with levosimendan.[4]

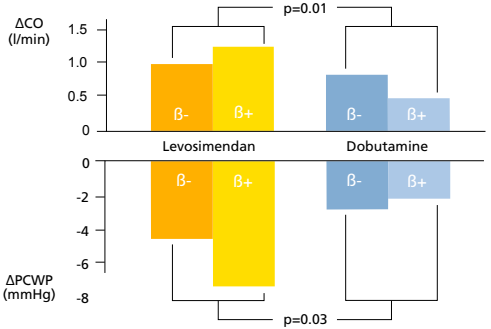
References: 1. Lilleberg J *et al. Eur Heart J.* 1998;19:660–668.
2. Follath F. *et al. Lancet.* 2002;360:9328):196-202. 196-202.
3. Kivikko M *et al. Circulation.* 2003 Jan 7;107(1):81-6.
4. Mebazaa A. *et al. JAMA.* 2007;297(17):1883-91.

...THE BENEFITS ARE PRONOUNCED IN THE PRESENCE OF β-BLOCKERS

In the ESC heart failure guidelines[1] SIMDAX® is recommended for acute heart failure in patients with reduction of cardiac output and in presence of β-blockers.[1]

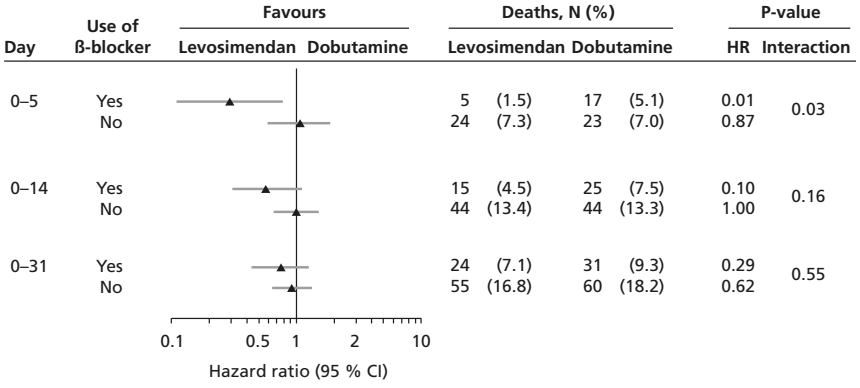
SIMDAX® can be used in patients receiving beta-blocking agents without loss of efficacy.[2]

Indeed a beneficial effect on 31 days survival is also noticeable in presence of β-blockers.[3]



ß– without ß-blockers
ß+ with ß-blockers

Effect of previous beta-blocker use on cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) after a 24-hour infusion of levosimendan or dobutamine at 24 hours post-baseline (LIDO)[2]



Hazard ratios for all-cause mortality rates up to 31 days after levosimendan and dobutamine therapy (SURVIVE) stratified for beta-blocker use at the start of the study.[2]

References: 1. Ponikowski P *et al. Eur Heart* J 2016;37:2129-2200.
2. Follath F. *et al. Lancet.* 2002;360:9328):196-202. 196-202.
3. Mebazaa A *et al Eur J Heart Fail.* 2009;11(3):304-11.

HOW TO USE SIMDAX® IN AHF

Example of use

AHF patients with systolic dysfunction (LVEF < 40%) and with the following characteristics may be considered for SIMDAX® treatment:

- signs of hypoperfusion, i.e. cool extremities, oliguria
- severe pulmonary oedema
- inadequate response to traditional treatment (however, the start of the SIMDAX® infusion should not be unnecessarily delayed.)

Exclusion criteria

- severe hypotension and/or tachycardia
- severe renal impairment
- severe hepatic impairment
- history of Torsades de Pointes

Dosing

Dosing of SIMDAX® will be according to the SPC. However, the bolus dose should only be given if immediate effects are needed and the baseline blood pressure is > 120 mmHg.1 Thus, in most cases:

- SIMDAX®-infusion will be started with an infusion rate of 0.1 mcg/kg/min.
- The rate can be increased to 0.2 mcg/kg/min if further effect is warranted or decreased to 0.05 mcg/kg/min if adverse effects (e.g. hypotension) occurs.
- The maximum duration of the infusion should not exceed 24 hours.

What to expect?

Haemodynamic and neurohormonal effects
Pulmonary capillary wedge pressure ↓↓↓
Cardiac output (index) ↑↑
Stroke volume ↑
Systemic vascular resistance ↓↓
Pulmonary vascular resistance ↓↓
Natriuretic peptide levels ↓↓↓

↓ = decrease, ↑ = increase

Other clinical effects
Relief of symptoms of heart failure
Effects maintained also with beta-blockers
Sustained effects due to an active metabolite
No development of tolerance
No increase in myocardial oxygen consumption
Anti-ischemic effect
No impairment of diastolic function

Reference: 1. Nieminen MS *et al. Heart Lung Vessels.*

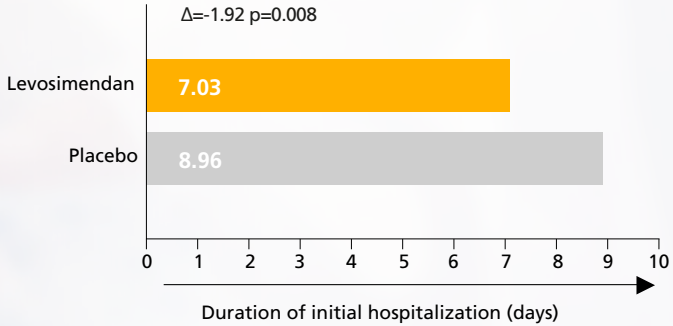
IN AHF THE EFFECTS OF SIMDAX® ALLOW A SHORTER HOSPITAL STAY

SIMDAX®, on top of standard of care, shortens hospital stay in acute heart failure. These data have been shown in a phase III study (vs placebo).[1,2]

Hospital stay is reduced by

1.92 DAYS

Hospitalization length of acute heart failure patients



Data from an economic analysis of the REVIVE II study of 600 patients hospitalized for treatment of acute decompensated heart failure.[1]

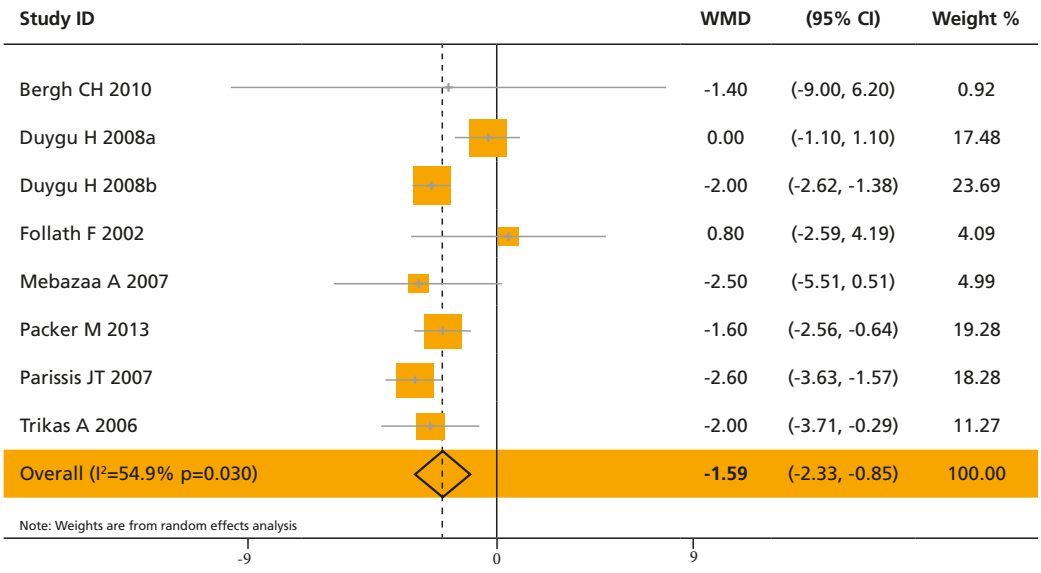
References: 1. De Lissovoy G *et al. Eur J Health Econ.* 2010;11:185–193. **2**. Packer M *et al. JACC Heart Fail.* 2013;1(2):103-11

...WHICH IS CONFIRMED BY META-ANALYSIS OF SEVERAL STUDIES

These results are corroborated by a meta-analysis of 8 studies in which SIMDAX® was used in cardiology settings:

Length of stay in hospital was decreased by 1.59 days in SIMDAX® treated patients in addition to a significant reduction in mortality.[1]

Meta-analysis of the levosimendan effects on length of stay in hospital[1]



Reference: 1. Landoni G *et al. Crit Care Med.* 2012;40:634–646 (electronic supplementary material).

BETTER OUTCOME THAN WITH OTHER VASOACTIVE I.V. AGENTS

ALARM-HF[1] registry

The effect of i.v. vasoactive drugs on in-hospital mortality was studied in 4.953 AHF patients (Figure 1. unadjusted analysis).

A propensity-based analysis was performed to compare in-hospital mortality of patients treated only with SIMDAX® versus those treated with only catecholamines showing a significant reduction in the risk of in-hospital mortality (HR 0.25, 95% CI 0.07–0.85).

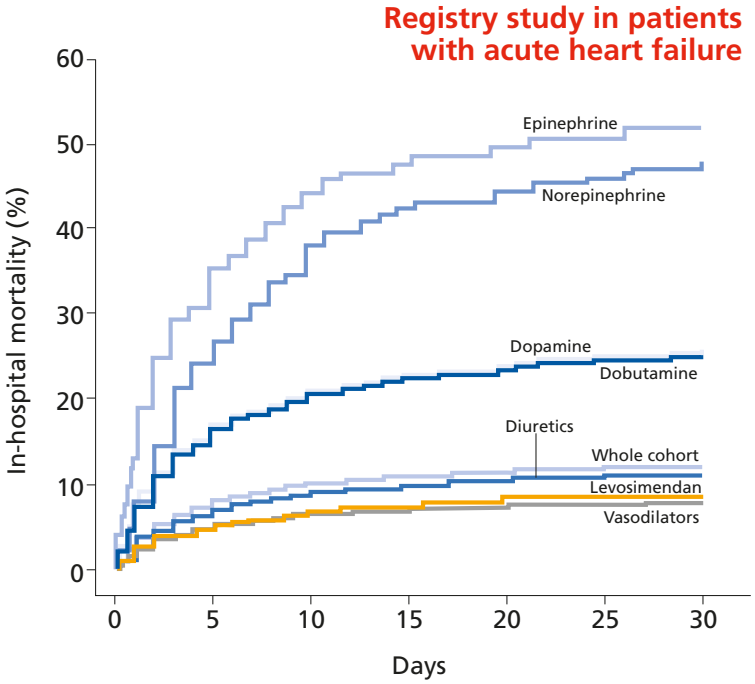


Figure 1: Effect of the main intravenous (IV) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality.

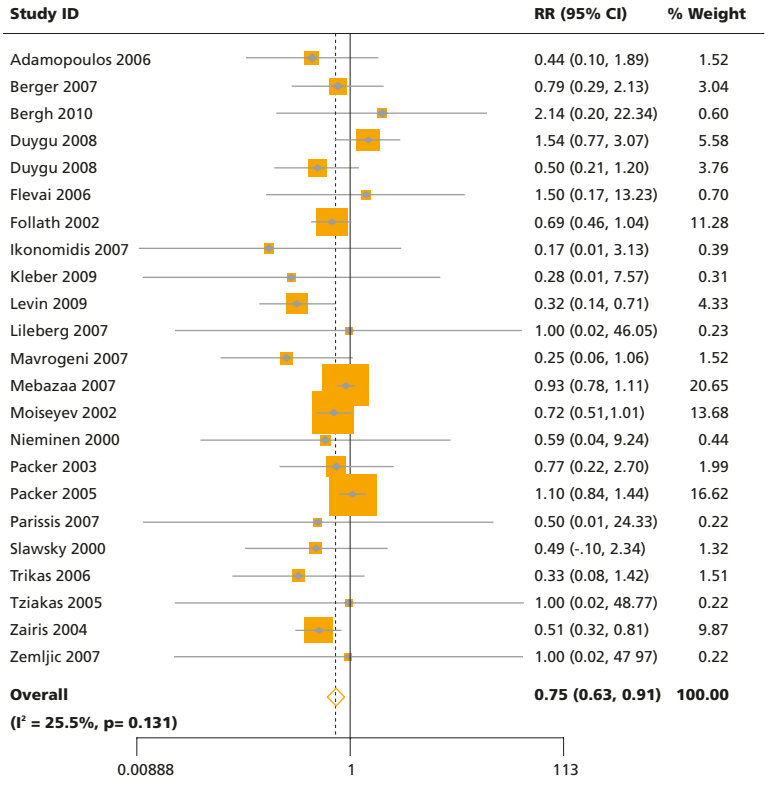
Reference: 1. Mebazaa A *et al. Intensive Care Med.* 2011;37:290-301.

...WITH NO COMPROMISE ON LONG-TERM SURVIVAL

The use of SIMDAX® was associated with improved survival.

A meta-analysis of 23 studies describing the use of SIMDAX® in cardiology settings showed a 25% risk reduction [SIMDAX® 441/2207 (20.0%), control 484/1893 (25.6%), RR=0.75 (95% CI 0.63, 0.91), p for effect: 0.003, p for heterogeneity: 0.131, NNT=18].[1]

Meta-analysis on mortality of levosimendan clinical trials in cardiology settings[1]

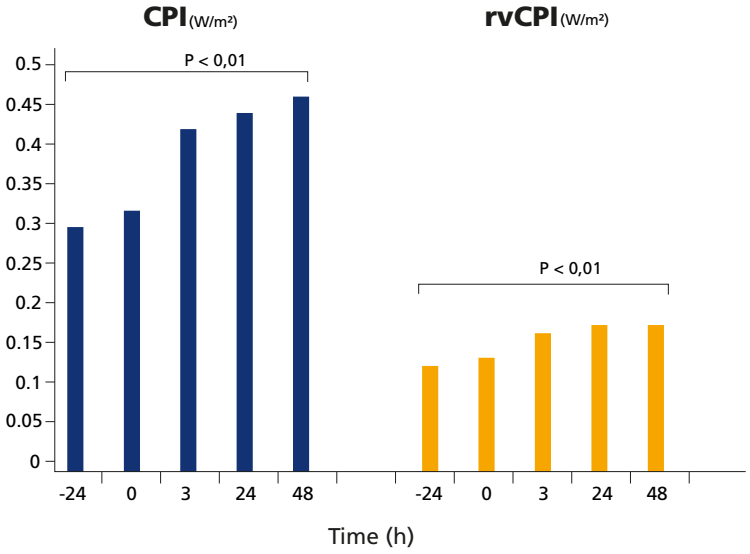


Reference: 1. Landoni G *et al. Crit Care Med.* 2012;40:634–646.

IMPROVEMENT OF HEMODYNAMIC PARAMETERS IN CARDIOGENIC SHOCK

SIMDAX® increases cardiac index in patients who did not improve with conventional therapy (including use of dobutamine and norepinephrine)[1]

Levosimendan has effects on both left and right ventricular performance



-24 = 24 h before levosimendan application;
0 = application of levosimendan after conventional therapy;
3, 24, 48 = time after levosimendan application

Reference: 1. Russ MA *et al. Crit Care Med.* 2009;37:3017-23

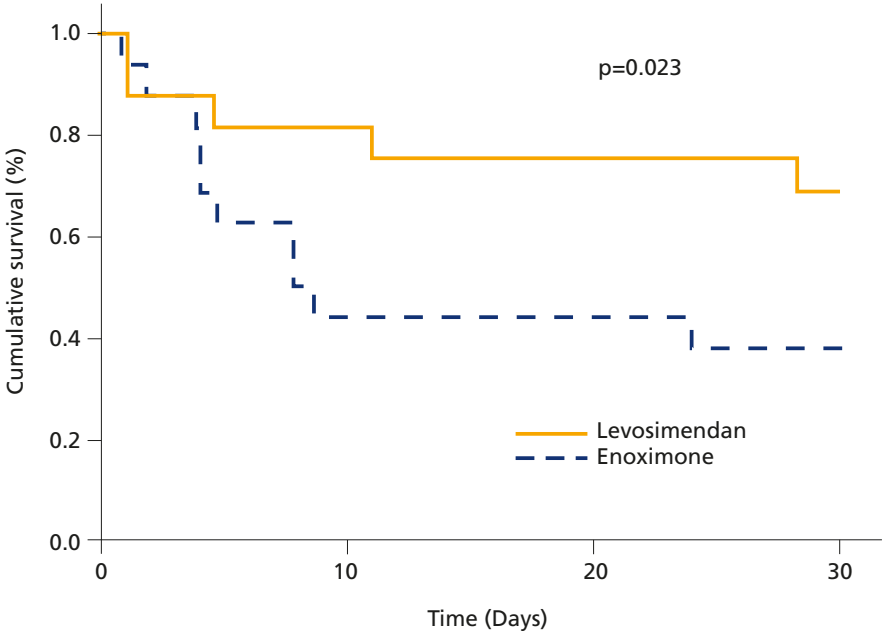
...WITH NO COMPROMISE ON OUTCOME

SIMDAX® was compared with enoximone in 32 patients with refractory cardiogenic shock complicating acute myocardial infarction.[1]

The standard of care consisted of immediate revascularisation by percutaneous coronary intervention, IABP, fluid resuscitation and conventional inotropes.

SIMDAX® use was associated with similar hemodynamic effects, but mortality was significantly lower.

30 day survival in patients with cardiogenic shock



Reference: 1. Fuhrmann JT *et al. Crit Care Med.* 2008 ;36:2257-66.

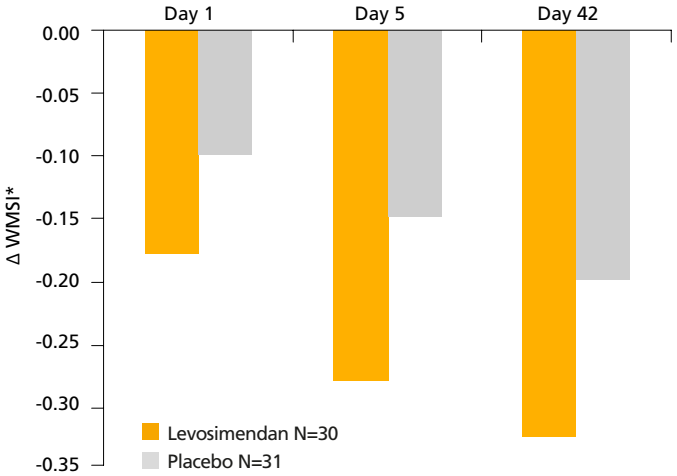
IMPROVEMENT OF LEFT VENTRICULAR FUNCTION IN HEART FAILURE AFTER ACUTE CORONARY SYNDROME

Sixty patients developing clinical signs of heart failure or cardiogenic shock within 48 hours after a primary percutaneous coronary intervention were randomized to a 25 hour infusion of SIMDAX® or placebo.[1]

SIMDAX® significantly improved the change in wall motion score index from baseline to day 5 as measured by echocardiography (see chart).[1]

One and four patients died in the SIMDAX® and placebo groups, respectively.[1]

Levosimendan effect on wall motion score index in acute heart failure following acute coronary syndrome



Change in wall motion score index between patients treated with a 25 hour infusion of levosimendan (n=30) or placebo (n=31), mean values±SEM. *Primary endpoint p=0.031.[1]

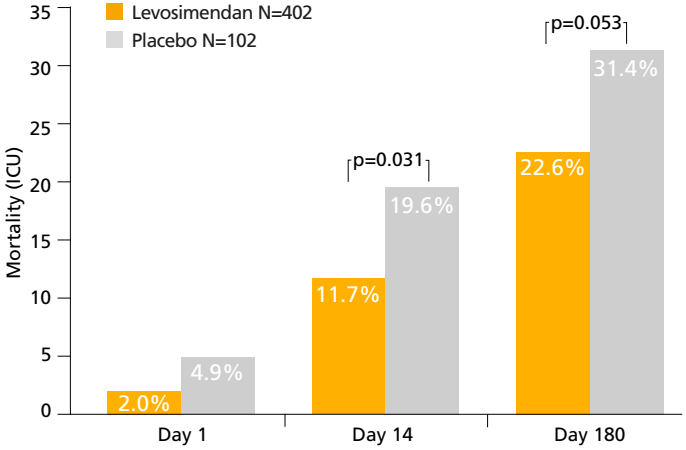
Reference: 1. Husebye T *et al. Eur J Heart Fail.* 2013;15:565–572.

...WITH NO COMPROMISE ON SURVIVAL

In the placebo-controlled RUSSLAN trial, 6-hour infusions of SIMDAX® were shown to be safe in patients who developed heart failure after an acute myocardial infarction, and significantly increased survival at 14 days after administration.[1]

The positive effect of SIMDAX® on survival in these settings was confirmed by a recent meta-analysis of nine studies.[2]

The effect of levosimendan on survival in acute heart failure following acute myocardial infarction



Mortality in 504 patients with left ventricular failure complicating acute myocardial infarction, the RUSSLAN trial.[1]

Reference: 1. Moiseyev V *et al. Eur Heart J.* 2002;23:1422–1432.
2. Shang G *et al. Am J Cardiovasc Drugs* 2017 [ePub Jun 8] DOI 10.1007/s40256-017-0237-0.

RECOMMENDATION ON THE USE IN ACS RELATED AHF

Expert panel consensus on the use of vasoactive drugs in acute heart failure related to acute coronary syndrome[1,a]

Killip class	II, rales, pulmonary congestion		III, acute pulmonary edema	IV, hypotension or CS
AHF/CS, segmentation by SBP	SBP>110 mmHg	85<SBP<110 mmHg, worsening of HF	85<SBP<110 mmHg, decreasing	SBP<85 mmHg, evidence of peripheral vasoconstriction
Loop diuretic (e.g. furosemide i.v.)	+	+	+	+
ß-blocker	maintain	reduce or withdraw according to patient status[b]	withdraw[b]	withdraw
Vasodilator (e.g. nitrate)	+	+ initially	+ initially	–
inotrope I.V. (e.g. dobutamine)	–	+ initially	+ in case of poor response to standard therapy	+ initially
Vasopressor i.v. (e.g. norepinephrine)	–	– not initially	– not initially	+ aiming for SBP>90 mmHg, with inotrope or inodilator
Inodilator i.v. levosimendan	–/+ (when ß-blocker is used and urinary output is insufficient after diuretics)	–/+ (when ß-blocker is used and urinary output is insufficient after diuretics)	+ (When SBP>90 mmHg; if hypotensive response, consider filling or combining vasopressor)	+ with vasopressor
ECMO, LVAD, (IABP[c])	–	–	–	+ (with CI<1.8 l/min and not responding to medical treatment)

ACS = acute coronary syndrome; AHF = acute heart failure; CI = cardiac index; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; SBP = systolic blood pressure.

[a] Monitoring, fluid challenge, arrhythmia care, cardiac catheter including angiography/Percutaneous Coronary Intervention (PCI). [b] Some patients in this class need ß-blockade despite hemodynamic impairment, to manage ventricular arrhythmias, or to rate control AF. [c] IABP is indeed not recommended by the most recent STEMI ESC guidelines but in case of mechanical complication.

Reference: 1. Nieminen MS *et al. Int J Cardiol.* 2016;218:150–157.

DOSING AND MONITORING IN ACS RELATED AHF

SIMDAX® dosing:[1]

- The recommended infusion rates are 0.05–0.1 µg/kg/min for 24 hours
- Bolus dose should be avoided due to the risk of hypotension. If a faster onset of action is needed, an infusion of 0.2 µg/kg/min could be used during the first 60 min

Monitoring of treatment:[1]

- Hypotension, a potential side effect of SIMDAX®, is of particular concern in patients with ACS
- Continuous hemodynamic monitoring is recommended. This includes ECG, blood pressure, SaO2, heart rate, urinary output, potassium levels, and clinical signs. End-organ function (liver, kidney, mental status) should be evaluated

Reference: 1. SIMDAX® SPC.

EASING THE CHALLENGE OF TREATING THE FAILING HEART[1] WITH LONG LASTING HEMODYNAMIC STABILIZATION

SIMDAX® GIVES YOU TIME BY PROVIDING:

- Hemodynamic improvement[2,3]
- Symptomatic improvement[2,3]
- Sustained effects[2]
- Synergies with β-blockers[4]
- Shorter hospital stay[5,6]

References: 1. Pölzl G *et al. Int J Cardiol* 2017 [ePub May 24]. **2.** Nieminen MS *et al. Int J Cardiol.* 2014;174(2):360–367. **3.** Husebye T *et al. Eur J Heart Fail.* 2013;15:565–572. **4.** Follath F *et al. Lancet.* 2002;360:196–202. **5.** De Lissovoy G *et al. Eur J Health Econ.* 2010;11:185–193. **6.** Landoni G *et al. Crit Care Med.* 2012;40:634–646.

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levosimendan