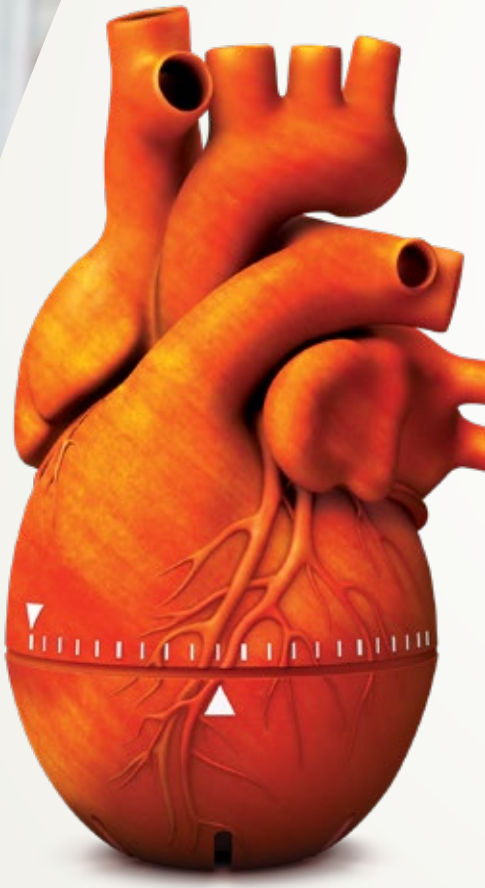
SIMDAX® GIVES YOU TIME IN THE INTENSIVE CARE UNIT

ORION PHARMA
Building well-being



SIMDAX®
levosimendan

SIMDAX® COMPARED TO TRADITIONAL INOTROPES

Current data suggest that SIMDAX® is superior to traditional inotropes (dobutamine, PDE inhibitors) when used in operative settings:

- Sustained hemodynamic improvement[1]
- Less myocardial injury[2,3]
- Less renal impairment[4]
- Lower need for IABP[5]
- Improved survival on patients with preoperative low ejection fraction[6]

Early initiation of SIMDAX® is preferable.

In case of hypotension, vasopressors should be used concomitantly.

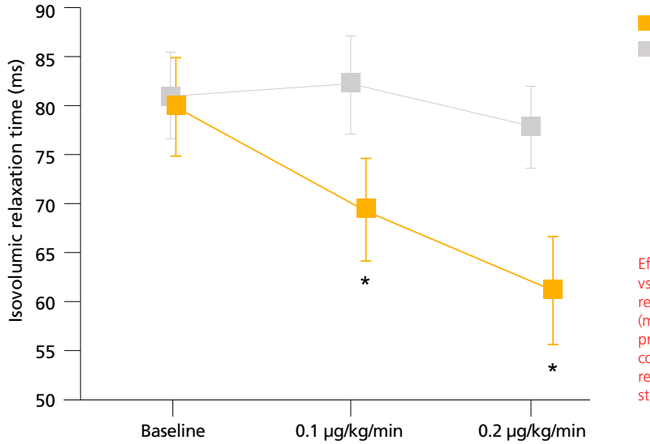
References: 1. De Hert SG *et al. Anesth Analg.* 2007;104:766–773. **2.** Zangrillo A *et al. J Cardiothorac Vasc Anesth.* 2009;23:474–478. **3.** Eriksson H *et al. Ann Thor Surg.* 2009;87:448. **4.** Landoni G *et al. J Cardiothorac Vasc Anesth.* 2010;24:51–57. **5.** Laitinen P *et al. Crit Care Med* 2011;39:1–8. **6.** Sanfilippo F *et al. Critical Care.* 2017;21:252-62.

SIMDAX® DOES NOT DISTURB RELAXATION...

In a study by Jörgenssen et al. SIMDAX® not only improved contractility, but **also decreased isovolumic relaxation time.**[1]

SIMDAX® has beneficial acute systolic and diastolic functional effects in experimental chronic pulmonary hypertension and right ventricle afterload compared to dobutamine and milrinone.[2]

Effects of levosimendan on relaxation time



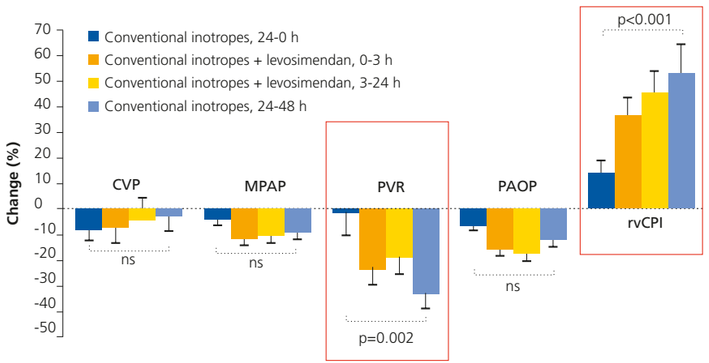
Effect of levosimendan vs placebo on Isovolumic relaxation time (IVRT) (mean±SEM) at maintained preload and afterload conditions after aortic valve replacement for aortic stenosis. *p<0.05.[1]

Reference: 1. Jörgensen K *et al. Circulation.* 2008;117(8):1075–1081.
2. Tavares-Silva M *et al J Cardiovasc Pharmacol Therap* 2017 22(5) 485-95

...IMPROVES RIGHT VENTRICULAR FUNCTION IN CARDIOGENIC SHOCK...

In a study by Russ et al.[1], the investigators included 25 consecutive patients with cardiogenic shock due to myocardial infarction who had not improved sufficiently with conventional therapy (including dobutamine and norepinephrine). All patients received SIMDAX® (as a bolus of 12 mcg/kg/min followed by 0.1 – 0.2 mcg/kg/min) as "bail-out" therapy for 24 hrs while invasive hemodynamic parameters were recorded

Levosimendan decreased pulmonary vascular resistance and improved cardiac power index in both ventricles. These data imply decreased right ventricle afterload and improved right ventricle contractility with levosimendan



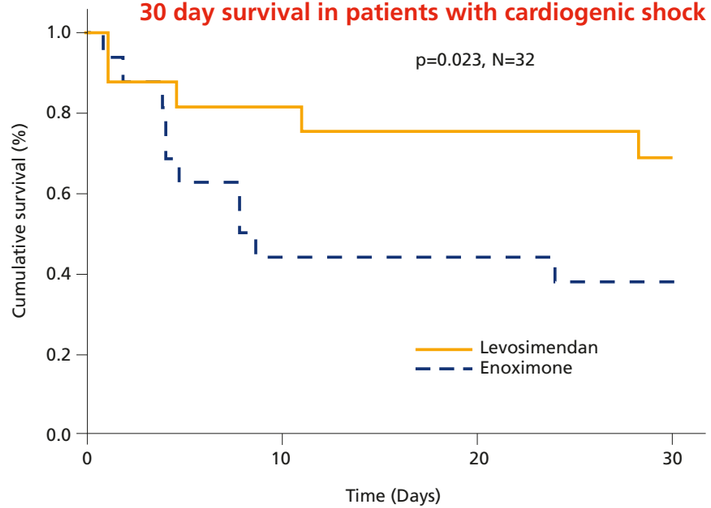
CVP = central venous pressure; MPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; PAOP = pulmonary arterial occlusion pressure; rvCPI = right ventricular cardiac power index

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

...AND IMPROVES SURVIVAL IN CARDIOGENIC SHOCK

When compared with enoximone in patients with refractory cardiogenic shock complicating acute myocardial infarction, the use of SIMDAX® resulted in a significantly higher survival[1]. In the recommendations for the management of shock for cardio-surgical Intensive Care Unit patients, SIMDAX® should be *"…considered in patients with impaired cardiac contractility…"*.[2]

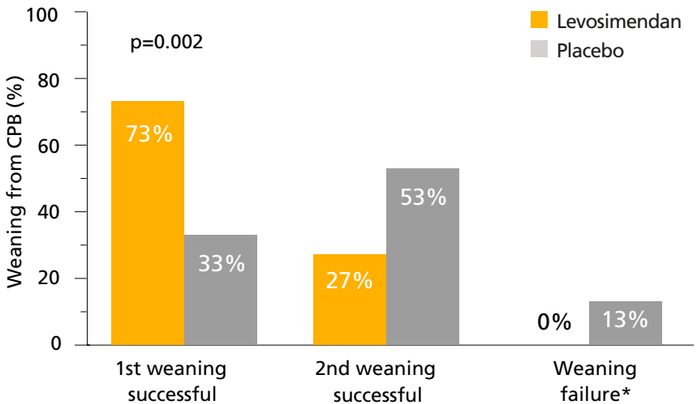
30 day survival in patients with cardiogenic shock



Reference: 1. Fuhrmann JT *et al. Crit Care Med* 2008;36:2257-66;
2. Hauffe T *et al. Card Fail Rev* 2016;2(1):56-62

HELPS WEANING FROM CARDIO-PULMONARY BYPASS

SIMDAX® helps patients to be successfully weaned from cardiopulmonary bypass. In the study by Eriksson et al., SIMDAX® was compared to placebo in 60 patients undergoing coronary artery bypass grafting.[1]



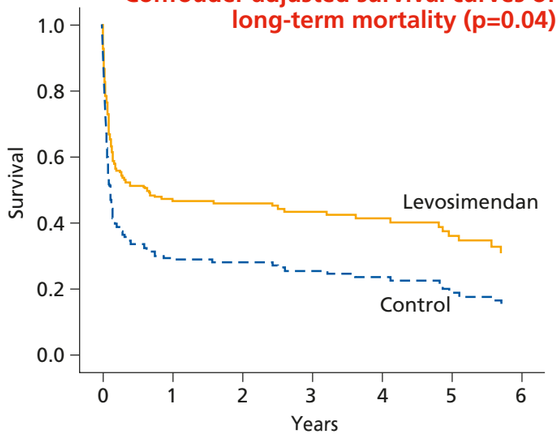
Weaning from cardiopulmonary bypass (CPB). First weaning attempt with levosimendan and placebo. Epinephrine added to second weaning attempt. *Weaning failure leads to use of intra-aortic balloon pump.[1]

References: 1. Eriksson HI *et al. Ann Thorac Surg.* 2009;87:448–454.

...AND HELPS PREVENTING ECMO WEANING FAILURE

In a retrospective analysis (N=240) with ECMO after cardiac surgery, patients with SIMDAX® showed improved ECMO-weaning and reduced short- and long term mortality. The patients received SIMDAX® during the first 24 h after ECMO implantation.[1]

Confouder-adjusted survival curves of long-term mortality (p=0.04)



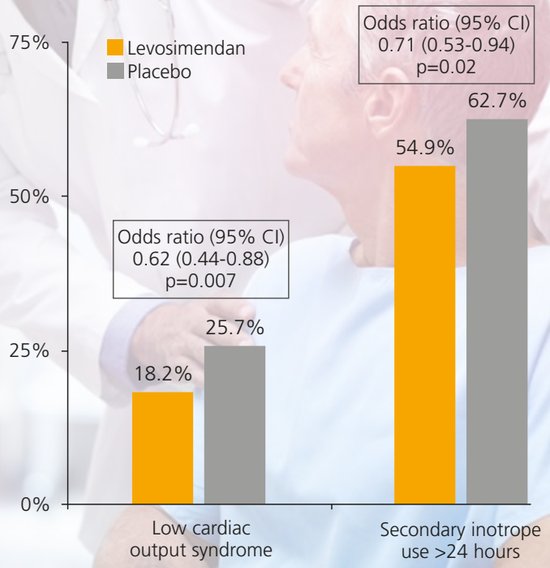
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
ECMO weaning failure	0.54 (0.31–0.93)	0.03	0.41 (0.22–0.80)	0.008
30 day mortality	0.61 (0.39–0.96)	0.03	0.52 (0.30–0.89)	0.016
Long-term mortality	0.77 (0.54–1.09)	0.14	0.64 (0.42–0.98)	0.04

References: 1. Distelmeyer K *et al Br J Anaesth* 2016;117(1):52-8

SIMDAX® REDUCES LCOS

In the recent Phase III trial (LEVO-CTS[1]) SIMDAX®, despite not meeting the primary endpoint, decreased significantly post-surgical low cardiac output syndrome (LCOS). This was accompanied with increased cardiac index and lower need for secondary inotropes.

Incidence of LCOS and secondary inotrope use in the LEVO-CTS trial (N=882)[1]

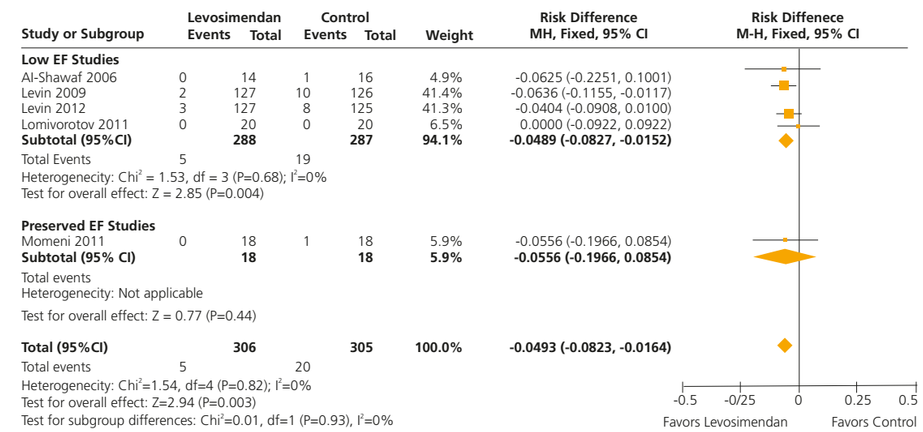


References: 1. Mehta RH *et al. N Engl J Med.* 2017;376(21):2032-2042.

...AND REDUCES THE RATE OF ACUTE RENAL FAILURE

In a meta-analysis of 4 randomized studies on the effect of SIMDAX® in cardiac surgery a **reduction of the rate of acute renal failure** was seen in favor of SIMDAX® treated patients (OR = 0.26 [0.12–0.60], p for effect = 0.002, with 228 patients included).[1]

These data were corroborated by meta-analyses by Harrison et al.[2] and Sanfilippo et al.[3]



References: 1. Landoni G *et al. J Cardiothorac Vasc Anesth.* 2010;24:51–57.
2. Harrison RW *et al. J Cardiothorac Vasc Anesth.* 2013;27(6):1224–1232.
3. Sanfilippo F *et al. Critical Care.* 2017;21:252-62.

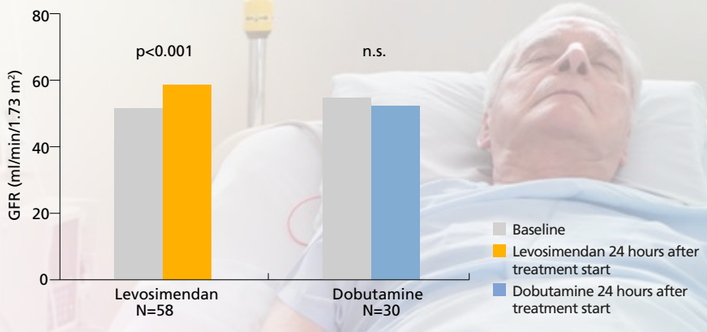
THE BENEFITS OF SIMDAX® FOR RENAL FUNCTION

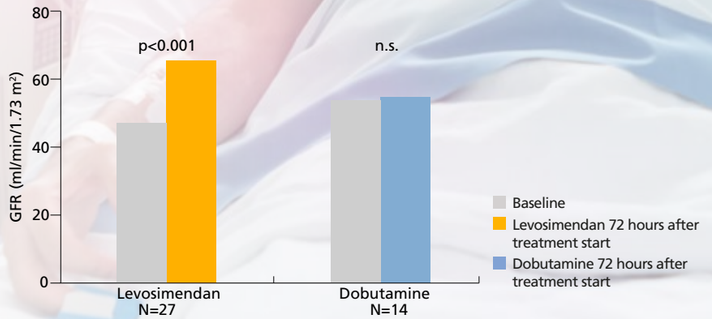
GFR improved in SIMDAX® compared to dobutamine-treated patients with heart failure who required inotropic therapy.[1]

A placebo-controlled study in patients hospitalized for decompensated heart failure and renal dysfunction, showed a statistically significant **improvement of GFR in SIMDAX®**-treated patients.[2]

The peak effect was seen at three days after a 24 hour infusion and the effects persisted up to 14 days.[2]

Effects of levosimendan on glomerular filtration rate





Reference: 1. Yilmaz *et al. Cardiovasc Drugs Ther.* 2007;21:431–435.
2. Hou Z-Q *et al. Cardiovasc Ther.* 2013;31:108–114.

SIMDAX® CONTRAINDICATIONS

Severe renal failure is a contraindication for SIMDAX® use as no formal pharmacokinetic studies in heart failure patients with severe renal failure have been conducted.[1]

However, many heart failure patients in large regulatory studies such as REVIVE and SURVIVE had severe renal failure.[2,3]

The elimination of the SIMDAX® metabolite OR-1896 is prolonged 1.5-fold compared with healthy subjects in non-heart failure patients but with severe renal impairment, or undergoing chronic hemodialysis.[4] The pharmacokinetics of SIMDAX® is not altered.[4]

These results suggest that if SIMDAX® was given to heart failure patients with severe renal impairment, the dose should be reduced.

References: 1. SIMDAX® SPC. **2.** Mebazaa A *et al. JAMA. 2007 May 2;297(17):1883-91.*
3. Packer M *et al. JCHF.* 2013;1:103–111. **4.** Puttonen J *et al. Clin Pharmacokinet.* 2007;46(3):235–246.

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

SIMDAX® GIVES YOU TIME BY PROVIDING:

- Hemodynamic benefits[1,2]
- Symptomatic benefits[1,2]
- Sustained effects[1]
- Helps in weaning the patient[4]

References: 1. De Hert SG *et al. Anesth Analg.* 2007;104:766–773. **2.** Jörgensen K *et al. Circulation.* 2008;117(8):1075–1081. **3.** Zangrillo A *et al. J Cardiothorac Vasc Anesth.* 2009;23:474–478. **4.** Eriksson H *et al. Ann Thor Surg.* 2009;87:448.

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