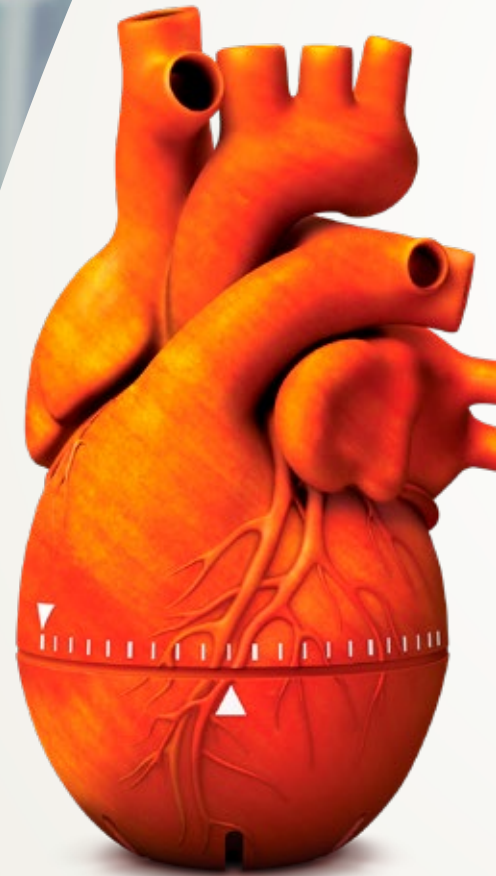


SIMDAX[®] GIVES YOU TIME IN THE OPERATING THEATER

SIMDAX[®]
Levosimendan



COMPARED TO TRADITIONAL INOTROPES...

Current data suggest that SIMDAX® is superior to traditional inotropes when used in operative settings:

- Sustained hemodynamic improvement¹
- Less myocardial injury^{2,3}
- Less renal impairment⁴
- Lower need for IABP⁵
- Safe and efficacious even on patients with preoperative low ejection fraction⁶

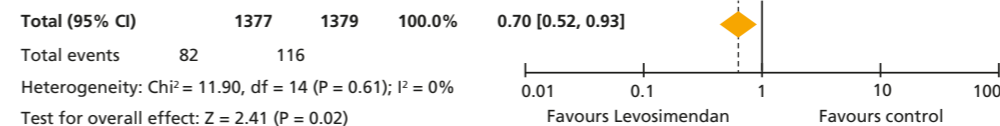
In case of hypotension, vasopressors should be used concomitantly.

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® IS SAFE AND EFFECTIVE IN CARDIAC SURGERY

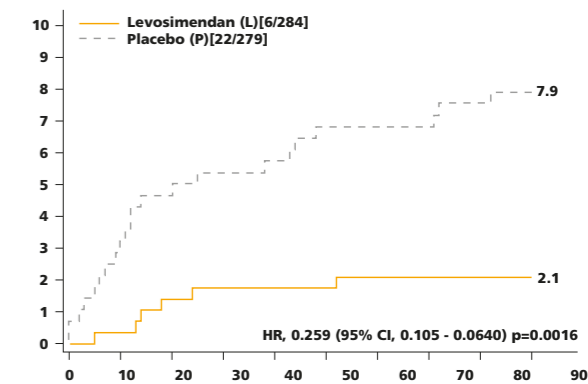
Taking all the available data into consideration, including the experience of three recent larger clinical trials¹⁻³, a panel of experts reached the consensus that **SIMDAX® is a safe and effective agent** for the treatment of patients undergoing cardiac surgery and in need of inotropic support.⁴

In a recent meta-analysis (including the most recent data) the effects of SIMDAX® on mortality were confirmed.⁵ SIMDAX® reduces mortality in patients with preoperative severely reduced ejection fraction (<35%).⁶



References: 1. Mehta RH et al. *N Engl J Med.* 2017;376(21):2032–42; 2. Cholley B et al. *JAMA.* 2017;318(6):548–56; 3. Landoni G et al. *N Engl J Med.* 2017;376(21):2021–31; 4. Guarracino F et al. *J Cardiovasc Pharmacol.* 2018 ;71(1):1-9; 5. Chen Q-H et al. *Critical Care* 2017;21(1):253; 6. Sanfilippo F et al. *Critical Care.* 2017;21:252-62.

Long term mortality in isolated CABG patients treated with levosimendan before operation



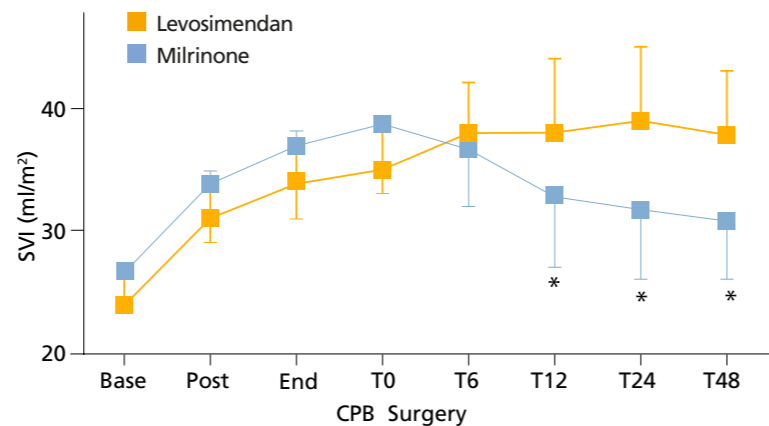
Ninety-day mortality among patients in the LEVO-CTS trial in the subgroup of isolated CABG patients (n=563). Mortality was statistically significantly lower in the levosimendan arm than in the placebo arm.⁴

The effect of levosimendan therapy on postoperative mortality in patients undergoing cardiac surgery.⁵ M-H, Mantel-Haenszel. Meta-analysis of 17 randomized studies, including the latest three multicenter clinical trials LEVO-CTS¹, LICORN², and CHEETAH.³

THE HEMODYNAMIC BENEFITS OF SIMDAX® ARE SUSTAINED

After operation, in a comparative study vs milrinone, the positive hemodynamic effects of 19 hours treatment with SIMDAX® lasted much longer than those from 83 hours treatment with milrinone.¹

Sustained effects of levosimendan when used in cardiac surgery



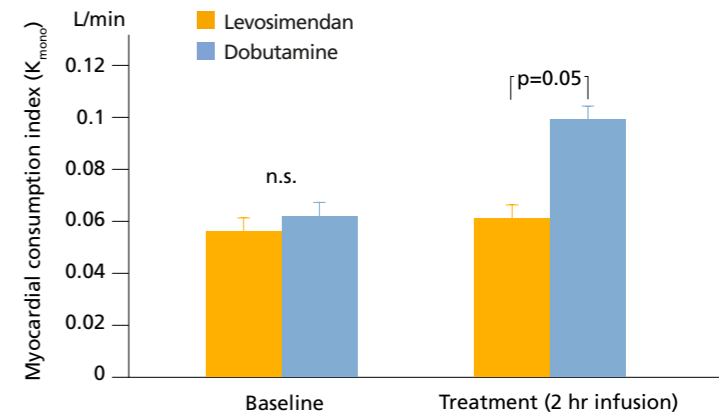
Stroke volume index (SVI) at the start of surgery (base), 15 min after the end of cardiopulmonary bypass (CPB) (post-CPB), at the end of the operation (end surgery), at arrival in the intensive care unit (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) hours later in both groups. Data are mean±sd. Levosimendan (orange) vs Milrinone (blue) *p<0.05.¹

Reference: 1. De Hert SG et al. *Anesth Analg*. 2007;104:766–773.

...WITHOUT AN INCREASE IN OXYGEN CONSUMPTION

The positive inotropic effects of SIMDAX® are achieved without an increase in **oxygen consumption** either in healthy volunteers¹, heart failure patients², or in cardiac surgery settings.³

No significant increase in oxygen consumption



A significant increase in the oxygen consumption is induced by dobutamine while no difference is noticed during treatment with levosimendan.¹

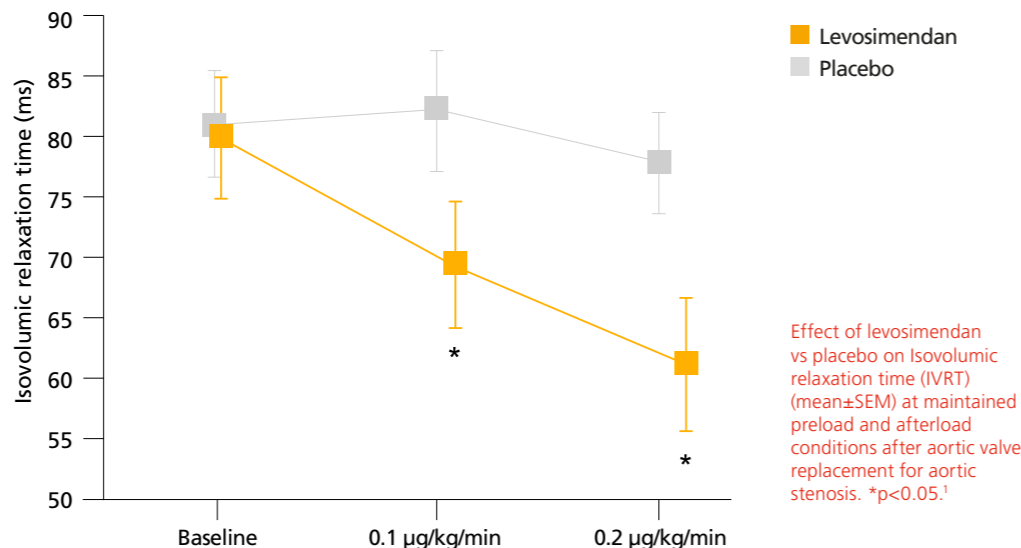
References: 1. Ukkonen H et al. *Clin Pharmacol Ther*. 2000;68(5):522-31.
 2. Ukkonen H et al. *Clin Pharmacol Ther*. 1997;61(5):596-607.
 3. Lilleberg J et al. *Eur Heart J*. 1998;19(4):660-8

SIMDAX® DOES NOT DISTURB RELAXATION

In a study by Jörgensen 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

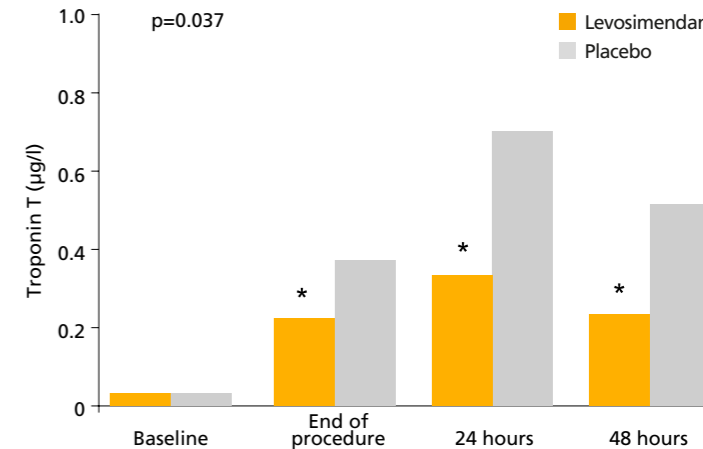


References: 1. Jörgensen K et al. *Circulation*. 2008;117(8):1075–1081.
2. Tavares-Silva M et al *J Cardiovasc Pharmacol Therap* 2017 22(5) 485-95

...AND REDUCES MYOCARDIAL INJURY

Current data suggest that SIMDAX® also **diminished myocardial injury.**^{1,2}

Effects of levosimendan on release of troponin T during cardiac surgery

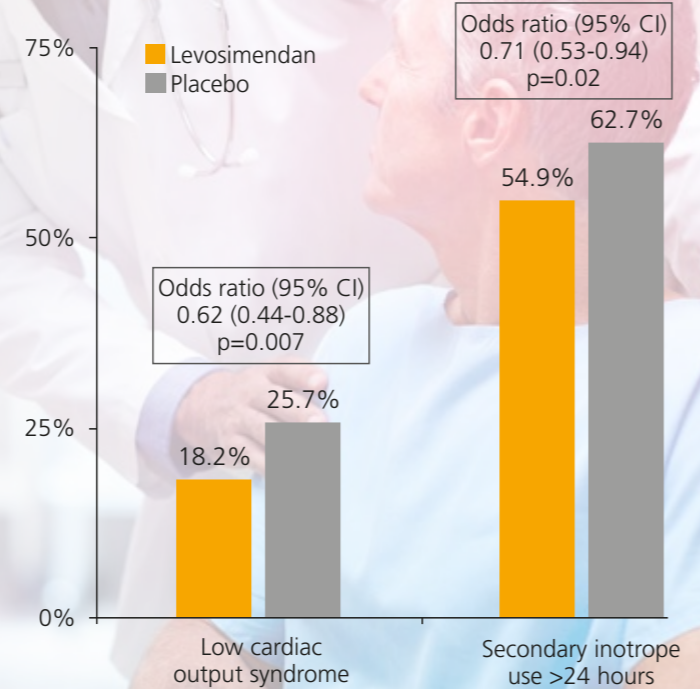


References: 1. Zangrillo A et al. *J Cardiothorac Vasc Anesth*. 2009;23:474–478. 2. Eriksson H et al. *Ann Thor Surg*. 2009;87:448.

SIMDAX[®] REDUCES LCOS

In the recent Phase III trial (LEVO-CTS¹) 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

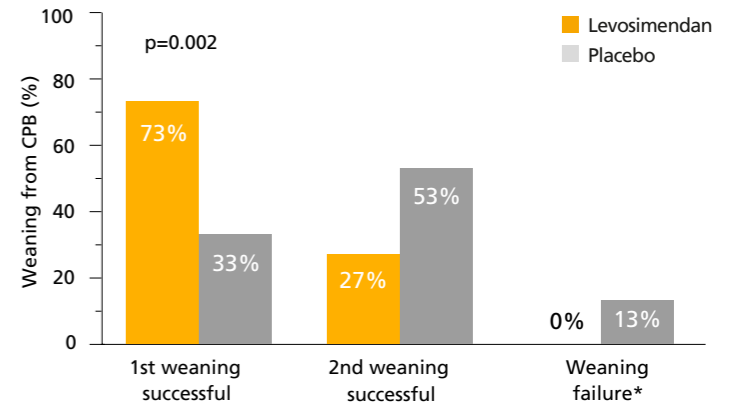


References: 1. Mehta RH et al. *N Engl J Med.* 2017;376(21):2032-2042.

...AND HELPS WEANING FROM CARDIAC PULMONARY BYPASS

SIMDAX[®] helps patients to be successfully weaned from cardiopulmonary bypass.¹

Effects of levosimendan on weaning after cardiac surgery



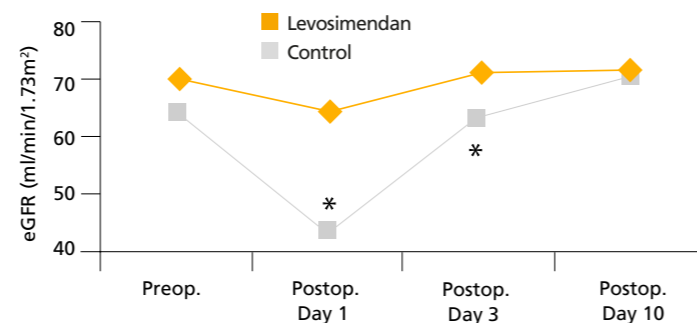
Weaning from cardiopulmonary bypass (CPB). First weaning attempt with levosimendan and placebo. Epinephrine added to second weaning attempt. *Weaning failure leads to use of intra-aortic balloon pump.¹

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

THE BENEFITS OF SIMDAX® FOR RENAL FUNCTION

SIMDAX® preserves GFR during operation¹ and reduces the risk of renal replacement therapy.²

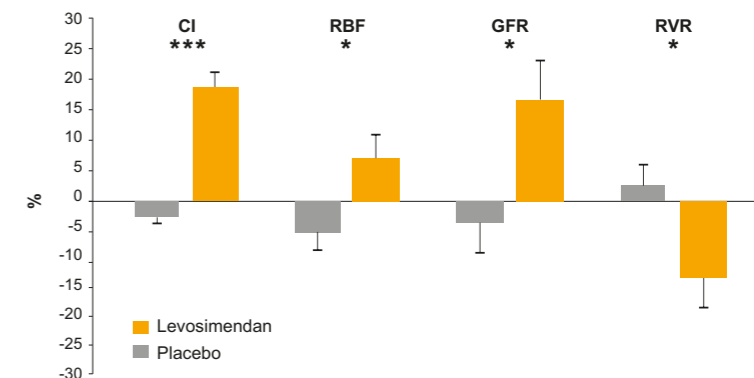
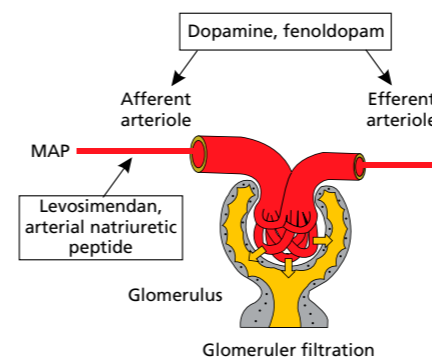
Effects of levosimendan on glomerular filtration rate



The comparison of preoperative (preop) and postoperative (postop) serum estimated glomerular filtration rate (eGFR) in renal disease equation. Levosimendan (orange) vs control (grey).² *p<0.05.

...ARE MEDIATED BY A DIRECT EFFECT ON RENAL CIRCULATION

SIMDAX® selectively vasodilates the afferent renal arterioles¹ thus inducing pre-glomerular vasodilation and leading to **improved renal blood flow and glomerular filtration rate.**² The renal oxygen demand/supply relationship is not affected by SIMDAX®.²



Effects of levosimendan versus placebo on cardiac index (CI), renal blood flow (RBF), glomerular filtration rate (GFR), and renal vascular resistance (RVR). *p < 0.05 ***p < 0.001

References: 1. Baysal A et al. *J Cardiothoracic and Vascular Anesth.* 2014;28(3):586–594. 2. Bove T et al. *Heart Lung Vessels.* 2015;7(1):35–46.

References: 1. Yilmaz MB et al. *Cardiovasc Drugs Ther.* 2013;27(6):581-90; 2. Bragadottir G et al. *Crit Care Med.* 2013;41(10):2328-35

EASING THE CHALLENGE OF TREATING THE FAILING HEART WITH A SUSTAINED HEMODYNAMIC STABILIZATION

SIMDAX[®] GIVES YOU TIME BY PROVIDING:

- Hemodynamic benefits^{1,2}
- Symptomatic benefits^{1,2}
- Sustained effects¹
- Protective effects on heart and other organs^{3,4}
- Stabilizing the patient for operation¹

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.