SIMDAX® GIVES YOU TIME IN THE INTENSIVE CARE UNIT
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 improvement¹
• Less myocardial injury²,³
• Less renal impairment⁴
• Lower need for IABP⁵
• Improved survival on patients with preoperative low ejection fraction⁶

Early initiation of SIMDAX® is preferable.

In case of hypotension, vasopressors should be used concomitantly.


SIMDAX® DOES NOT DISTURB RELAXATION...

In a study by Jørgensen 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


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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 when compared with enoximone in patients with refractory cardiogenic shock complicating acute myocardial infarction, the use of SIMDAX® resulted in a significantly higher survival. 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…”.

When compared with enoximone in patients with refractory cardiogenic shock complicating acute myocardial infarction, the use of SIMDAX® resulted in a significantly higher survival. 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…”.

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.\(^1\)

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.\(^1\)

- **Confounder-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

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

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

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

Low EF Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference MH, Fixed, 95% CI</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>AI-Shawaf 2006</td>
<td>14</td>
<td>16</td>
<td>28</td>
<td>0.007</td>
<td>0.0625 (-0.2253, 0.3503)</td>
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<tr>
<td>Levin 2009</td>
<td>10</td>
<td>12</td>
<td>22</td>
<td>0.0656 (-0.1753, -0.0117)</td>
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<td></td>
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<tr>
<td>Levin 2012</td>
<td>8</td>
<td>12</td>
<td>20</td>
<td>0.0040 (-0.0898, 0.0102)</td>
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<tr>
<td>Summerville et al. 2011</td>
<td>0</td>
<td>20</td>
<td>20</td>
<td>0.0000 (-0.0922, 0.0892)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>288</td>
<td>287</td>
<td>575</td>
<td>94.1%</td>
<td>0.0049 (0.0027, 0.0152)</td>
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</tr>
</tbody>
</table>

Preserved EF Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference MH, Fixed, 95% CI</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momeni 2011</td>
<td>18</td>
<td>18</td>
<td>36</td>
<td>0.2253</td>
<td>0.0656 (-0.1966, 0.0550)</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>18</td>
<td>18</td>
<td>36</td>
<td>0.0556 (-0.1966, 0.0834)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events 2 19 2 2

Heterogeneity: Not applicable

Test for overall effect: Z = 2.85 (P=0.004)

Test for subgroup differences: Chi²=0.01, df=1 (P=0.93), I²=0%

Heterogeneity: Chi² = 1.53, df = 3 (P=0.68); I = 0%

Test for overall effect: Z = 2.85 (P=0.004)

Test for subgroup differences: Chi²=0.01, df=1 (P=0.93), I²=0%


...AND REDUCES THE RATE OF ACUTE RENAL FAILURE


SIMDAX® REDUCES LCOS
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

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.⁴


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: