Levosimendan In Patients With Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery With Cardiopulmonary Bypass PRIMARY RESULTS OF THE LEVO-CTS TRIAL

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on behalf of the LEVO-CTS Investigators
Disclosures

LEVO-CTS funded by Tenax Therapeutics

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**Consultant:** Bristol-Myers Squibb, Cempra, CryoLife, CSL Behring, Pfizer, Portola, US VA

**Conflict-of-interest disclosures** available at http://www.dcri.duke.edu/research/coi
Levosimendan

- Ca++ sensitizing inotrope — increases sensitivity of troponin C to calcium within myocytes
- Approved in over 60 countries for treatment of acute heart failure
  - used in >1,000,000 patient
- 1000+ PubMed references
- 35+ randomized clinical trials in cardiac surgery
- Used widely peri-cardiac surgery for the prevention & treatment of low cardiac output syndrome (LCOS) in Europe

Toller W, et al., Int J Cardiol 2015;84:323-6
# Meta-Analysis of Prior Trials of Levosimendan in CTS

## Dialysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Difference</th>
<th>Risk Difference</th>
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<tbody>
<tr>
<td><strong>Low EF Studies</strong></td>
<td></td>
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<tr>
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<td>126</td>
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<td>Levin 2012</td>
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<td>Lamivudovor 2011</td>
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<tr>
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<td>366</td>
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</table>

## Myocardial Injury

<table>
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<th>Study or Subgroup</th>
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<td>372</td>
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## Mortality

<table>
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<th>Risk Difference</th>
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<tr>
<td>Al-Shawaf 2006</td>
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<td>0.0286</td>
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<tr>
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<td>0.0000</td>
<td>0.0147</td>
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<td>Talppi 2009</td>
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<td>Subtotal (95% CI)</td>
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<td>205</td>
<td>0.0107</td>
<td>0.0373</td>
<td>0.0590</td>
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Harrison RH, et. al., JCTVA 2013;27: 1224–1232
To compare the efficacy and safety of levosimendan with placebo in patients with reduced LV function undergoing cardiac surgery with cardiopulmonary bypass support
Design

CABG, MV, CABG + MV or AoV surgery w/ CPB, LV EF ≤35%

Randomization

Pre-op

Infusion started before surgery
0.2ug/kg/min x 1 hour
0.1ug/kg/min x 23 hrs

Levosimendan

Pre-Op | Surgery | ICU | Discharge | 30-Day | 90-Day

Placebo

Other therapies standard of care

Outcomes

Co-primary outcomes

• Quad: death (≤30d), dialysis (≤30d), MI (≤5d), or mechanical assist (≤5d)
• Dual: death (≤30d) or mechanical assist (≤5d)

Secondary outcomes

• Low cardiac output syndrome
• Use of secondary inotropes beyond 24 hours
• ICU length of stay

Safety outcomes

• Hypotension
• Atrial fibrillation
• 90-day vital status
Sample Size and Analysis

Sample Size
• 760 patients (201 Quad* events) = 26.4 rate%
  • Increased to 880 patients due to lower than projected aggregate event rate
• 35% risk reduction w/ levosimendan
• 86% power for at least one co-primary outcome

Statistical Analysis
• Efficacy outcomes analyzed as modified intent-to-treat including all randomized patients who received study drug
• Co-primary outcome analysis was adjusted for covariates of age, sex, LV EF, and type of surgery
• Safety outcomes were analyzed as treated

*Quad = death, dialysis, MI or mechanical assist
*Dual = death or mechanical assist
Patient Disposition

Randomized (n=882)

Levosimendan (ITT) (n=442)
- No study drug (n=14)
  - Death (n=0)
  - No longer eligible (n=10)
  - Withdrew consent (n=1)
  - Logistical error (n=3)
  - Placebo (n=1)

Placebo (ITT) (n=440)
- No study drug (n=19)
  - Death (n=1)
  - No longer eligible (n=15)
  - Withdrew consent (n=0)
  - Logistical error (n=3)
  - Levosimendan (n=1)

mITT (n=428)

mITT (n=421)

ALLOCATION

Day 30 (n=428)
- Lost to follow-up (n=4)

Day 30 (n=421)
- Lost to follow-up (n=4)

FOLLOW-UP

Day 90 (n=428)
- Mean survivor follow-up 89.6 days

Day 90 (n=421)
- Mean survivor follow-up 89.5 days

Lost to follow-up
- 4-component endpoint (n=7)
- 2-component endpoint (n=0)

Missing components
- Death (n=0)
- Mechanical assist device (n=0)
- Myocardial infarction (n=9)
- Renal replacement therapy (n=0)

Lost to follow-up
- 4-component endpoint (n=11)
- 2-component endpoint (n=1)

Missing components
- Death (n=1)
- Mechanical assist device (n=0)
- Myocardial infarction (n=14)
- Renal replacement therapy (n=1)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=428)</td>
<td>(n=421)</td>
</tr>
<tr>
<td><strong>Age, median (25\textsuperscript{th}, 75\textsuperscript{th}), years</strong></td>
<td>65 (59, 73)</td>
<td>65 (58, 72)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>18.9%</td>
<td>21.1%</td>
</tr>
<tr>
<td><strong>White race</strong></td>
<td>91.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td><strong>LV EF, median (25\textsuperscript{th}, 75\textsuperscript{th}), %</strong></td>
<td>26 (24, 32)</td>
<td>27 (22, 31)</td>
</tr>
<tr>
<td><strong>Surgery type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>66.1%</td>
<td>66.5%</td>
</tr>
<tr>
<td>CABG + Aortic valve</td>
<td>8.4%</td>
<td>8.1%</td>
</tr>
<tr>
<td>CABG + Mitral valve</td>
<td>11.7%</td>
<td>11.4%</td>
</tr>
<tr>
<td>CABG + Mitral + Aortic valve</td>
<td>2.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>8.4%</td>
<td>7.4%</td>
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<tr>
<td>Mitral + aortic valve</td>
<td>2.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
### Study Drug

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan n=428</th>
<th>Placebo n=421</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time from study drug to surgery, median (25\textsuperscript{th}, 75\textsuperscript{th}), hours</strong></td>
<td>0.33 (0.18, 0.53)</td>
<td>0.32 (0.17, 0.48)</td>
</tr>
<tr>
<td><strong>Study Drug Duration &lt;23.5 hours</strong></td>
<td>68 (15.7%)</td>
<td>48 (11.4%)</td>
</tr>
</tbody>
</table>
Quad Outcome = death, dialysis, MI or mechanical assist device use

Dual Outcome = death or mechanical assist device use

†Adjusted for covariates: type of surgery, LVEF, age, sex
**Individual Outcomes Components**

<table>
<thead>
<tr>
<th>Event</th>
<th>Levosimendan</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEATH (30-DAY)</strong></td>
<td>15</td>
<td>19</td>
<td>0.77 (0.39-1.53)</td>
<td>0.45</td>
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<tr>
<td><strong>MYOCARDIAL INFARCTION (5-DAY)</strong></td>
<td>67</td>
<td>63</td>
<td>1.06 (0.73-1.53)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>DIALYSIS (30-DAY)</strong></td>
<td>9</td>
<td>16</td>
<td>0.54 (0.24-1.24)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>MECHANICAL ASSIST (5-DAY)</strong></td>
<td>47</td>
<td>38</td>
<td>1.24 (0.79-1.95)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levosimendan (n=359)</td>
<td>2.86 (0.61)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=340)</td>
<td>2.68 (0.65)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Secondary Outcomes

LOW CARDIAC OUTPUT SYNDROME

- Levosimendan: 18.2%
- Placebo: 25.7%

SECONDARY INOTROPE USE >24 HOURS

- Levosimendan: 62.7%
- Placebo: 264

ICU LENGTH OF STAY

- Levosimendan: 2.8 days (1.6, 4.8)
- Placebo: 2.9 days (1.8, 4.9)

Odds ratio (95% CI) Levosimendan Placebo

- Low Cardiac Output Syndrome: 0.62 (0.44-0.88) p=0.007
- Secondary Inotrope Use >24 Hours: 0.71 (0.53-0.94) p=0.017

p=0.10
## 30-Day Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan n=428</th>
<th>Placebo n=421</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>155 (36.2%)</td>
<td>138 (32.8%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>163 (38.1%)</td>
<td>139 (33.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>VT / VF</td>
<td>46 (10.7%)</td>
<td>41 (9.7%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (3.5%)</td>
<td>10 (2.4%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>54 (12.6%)</td>
<td>48 (11.4%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
90-Day Mortality

HR, 0.64 (95% CI, 0.37-1.13)  
p=0.123

Placebo  
7.1%  
(30/421)

Levosimendan  
4.7%  
(20/428)

Number at risk:  
Levosimendan: 428 424 419 414 412 410 408 406 404 404  
Placebo: 421 409 402 400 397 394 391 390 388 386
Conclusions

• Levosimendan, given prophylactically prior to cardiac surgery to patients with reduced left ventricular function, had no effect on the co-primary outcomes of...
  • death, dialysis, MI, or mechanical assist device use
  • death or mechanical assist device use

• Levosimendan was effective and safe as an inotrope to increase cardiac output in patients at risk for perioperative low cardiac output syndrome
Clinical Implications

Given its effect on cardiac output, low cardiac output syndrome, and other inotrope use, and the absence of adverse safety signals, levosimendan is a reasonable option to consider in patients undergoing cardiac surgery where increased cardiac output is the desired objective.
Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

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Thank you!

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