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

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**Conflict-of-interest disclosures** available at [http://www.dcric.duke.edu/research/coi](http://www.dcric.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
- Significant use 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 in CTS

#### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study of Subgroup</th>
<th>Control Events</th>
<th>Event Total</th>
<th>Total Weight</th>
<th>Risk Difference</th>
<th>95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Low EF Studies</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>-0.25</td>
<td>(0.00, 0.50)</td>
<td>0.65</td>
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<td>45</td>
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#### Myocardial Injury

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<td>0.65</td>
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<tr>
<td>Treatment</td>
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#### Dialysis

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#### Mortality

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Objective

To compare the efficacy and safety of levosimendan with placebo in patients with reduced LV function undergoing cardiac surgery with cardiopulmonary bypass support.
Design

Levosimendan

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

CABG, MV, CABG + MV or AoV surgery w/ CPB, LV EF ≤ 35%
Randomization
Pre-op

Placebo

Other therapies standard of care

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

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 4-component* events)
  - Increased to 880 patients due to lower than projected aggregate event rate
- 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 adjusted for covariates of age, sex, LV EF, and type of surgery
- Safety outcomes analyzed as treated

*Quad = death, dialysis, MI or mechanical assist
*Dual = Outcome = 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)

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)

mITT (n=428)

Day 30 (n=428)

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

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)

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=9)
- Renal replacement therapy (n=1)

mITT (n=421)

Day 30 (n=421)

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

Lost to follow-up (n=4)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan n=428</th>
<th>Placebo n=421</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (25(^{th}), 75(^{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(^{th}), 75(^{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>
</tr>
<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>
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</tr>
</thead>
<tbody>
<tr>
<td>Time from study drug to surgery, median (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;), hours</td>
<td>0.33 (0.18, 0.53)</td>
<td>0.32 (0.17, 0.48)</td>
</tr>
<tr>
<td>Dose modification</td>
<td>56 (13.1%)</td>
<td>29 (6.9%)</td>
</tr>
<tr>
<td>Study Drug Duration &lt;23.5 hours</td>
<td>68 (15.7%)</td>
<td>48 (11.4%)</td>
</tr>
</tbody>
</table>
Co-Primary Outcomes

Quad Outcome = death, dialysis, MI or mechanical assist device use
Dual Outcome = death or mechanical assist device use

Odds ratio (99% CI) 1.01 (0.66-1.54) p=0.9775
Odds ratio (96% CI) 1.18 (0.76-1.82) p=0.4501

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

- **Death (30-DAY)**: 15% (Levosimendan) vs. 19% (Placebo)
  - Odds ratio: 0.77 (0.39-1.53), p=0.45

- **Myocardial Infarction (5-DAY)**: 67% (Levosimendan) vs. 63% (Placebo)
  - Odds ratio: 1.06 (0.73-1.53), p=0.78

- **Dialysis (30-DAY)**: 2% (Levosimendan) vs. 3% (Placebo)
  - Odds ratio: 0.54 (0.24-1.24), p=0.15

- **Mechanical Assist (5-DAY)**: 47% (Levosimendan) vs. 38% (Placebo)
  - Odds ratio: 1.24 (0.79-1.95), p=0.34

**Odds ratio (99% CI) values indicate confidence intervals and statistical significance.**
Cardiac Output

<table>
<thead>
<tr>
<th>Cardiac Index</th>
<th>Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan (n=359)</td>
<td>2.86 (0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo (n=340)</td>
<td>2.68 (0.65)</td>
<td></td>
</tr>
</tbody>
</table>
Secondary Outcomes

LOW CARDIAC OUTPUT SYNDROME

Levosimendan: 18.2%
Placebo: 25.7%

SECONDARY INOTROPE USE >24 HOURS

Levosimendan: [VALUE]
Placebo: 264

ICU LENGTH OF STAY

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

Odds ratio (95% CI) 0.62 (0.44-0.88) p=0.007
Odds ratio (95% CI) 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>
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<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 is 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.
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Thank you!
Publication