Levosimendan In Patients With Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery With Cardiopulmonary Bypass

PRIMARY RESULTS OF THE LEVO-CTS TRIAL

John H. Alexander, MD, MHS, FACC
Rajendra H. Mehta, Jeffrey D. Leimberger, Stephen Fremes, John Luber, Wolfgang Toller, Matthias Heringlake, Jerrold H. Levy, Robert A. Harrington, Kevin J. Anstrom

on behalf of the LEVO-CTS Investigators
Disclosures

LEVO-CTS funded by Tenax Therapeutics

Research support: Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, US FDA, US NIH, Pfizer, Tenax Therapeutics

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
- 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

### Mortality

<table>
<thead>
<tr>
<th>Study/Outcome Group</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low EF Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Shawal 2006</td>
<td>1</td>
<td>14</td>
<td>-0.218 (0.060, 0.376)</td>
<td></td>
</tr>
<tr>
<td>Alirezaee 2007</td>
<td>1</td>
<td>15</td>
<td>-0.185 (0.037, 0.333)</td>
<td></td>
</tr>
<tr>
<td>De Hert 2007</td>
<td>0</td>
<td>15</td>
<td>0.218 (0.053, 0.383)</td>
<td></td>
</tr>
<tr>
<td>Eriksson 2009</td>
<td>0</td>
<td>10</td>
<td>0.218 (0.053, 0.383)</td>
<td></td>
</tr>
<tr>
<td>Levin 2009</td>
<td>1</td>
<td>127</td>
<td>0.218 (0.053, 0.383)</td>
<td></td>
</tr>
<tr>
<td>Lomovorotov 2011</td>
<td>0</td>
<td>20</td>
<td>-0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95%)</strong></td>
<td>373</td>
<td>372</td>
<td>0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
</tbody>
</table>

### Dialysis

- **Low EF Studies**
  - Al-Shawal 2006: 1, 14, 5, 16, 3.1% (p=0.003)
  - De Hert 2007: 0, 15, 0, 15, 3.1% (p=0.005)
  - Eriksson 2009: 1, 30, 3, 30, 6.2% (p=0.058)
  - Levin 2009: 2, 127, 10, 126, 26.0% (p=0.011)

## Myocardial Injury

### Mortality

<table>
<thead>
<tr>
<th>Study/Outcome Group</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low EF Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Shawal 2006</td>
<td>0</td>
<td>14</td>
<td>0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td>De Hert 2007</td>
<td>0</td>
<td>15</td>
<td>0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td>Eriksson 2009</td>
<td>0</td>
<td>30</td>
<td>-0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td>Levin 2009</td>
<td>1</td>
<td>127</td>
<td>-0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td>Lomovorotov 2011</td>
<td>0</td>
<td>20</td>
<td>0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95%)</strong></td>
<td>298</td>
<td>287</td>
<td>0.0000 (0.0000, 0.0000)</td>
<td></td>
</tr>
</tbody>
</table>

### Dialysis

- **Low EF Studies**
  - Al-Shawal 2006: 0, 14, 1, 16, 4.9% (p=0.295)
  - Levin 2009: 2, 127, 10, 126, 41.4% (p=0.003)
  - Levin 2012: 3, 127, 8, 125, 41.3% (p=0.004)
  - Lomovorotov 2011: 0, 20, 0, 20, 6.5% (p=0.000)

## Summary

Objective

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

Design

Levosimendan

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 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)

**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)

**ALLOCATION**

**mITT (n=428)**
- Day 30 (n=428)
- Follow-up
- Mean survivor follow-up
  - 89.6 days

**mITT (n=421)**
- Day 30 (n=421)
- Follow-up
- Mean survivor follow-up
  - 89.5 days
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Levosimendan n=428</th>
<th>Placebo n=421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25\textsuperscript{th}, 75\textsuperscript{th}), years</td>
<td>65 (59, 73)</td>
<td>65 (58, 72)</td>
</tr>
<tr>
<td>Female sex</td>
<td>18.9%</td>
<td>21.1%</td>
</tr>
<tr>
<td>White race</td>
<td>91.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td>LV EF, median (25\textsuperscript{th}, 75\textsuperscript{th}), %</td>
<td>26 (24, 32)</td>
<td>27 (22, 31)</td>
</tr>
<tr>
<td>Surgery type</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>
<tr>
<td>Study Drug Duration</td>
<td>Levosimendan n=428</td>
<td>Placebo n=421</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------</td>
</tr>
<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
Individual Outcomes Components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Levosimendan</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (30-day)</td>
<td>15</td>
<td>19</td>
<td>0.77 (0.39-1.53)</td>
<td>0.45</td>
</tr>
<tr>
<td>Myocardial infarction (5-day)</td>
<td>67</td>
<td>63</td>
<td>1.06 (0.73-1.53)</td>
<td>0.78</td>
</tr>
<tr>
<td>Dialysis (30-day)</td>
<td>9</td>
<td>16</td>
<td>0.54 (0.24-1.24)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mechanical assist (5-day)</td>
<td>47</td>
<td>38</td>
<td>1.24 (0.79-1.95)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cardiac Index</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>
<td></td>
</tr>
</tbody>
</table>
Secondary Outcomes

- **Low Cardiac Output Syndrome**: 18.2% in Levosimendan vs. 25% in Placebo. Odds ratio (95% CI) 0.62 (0.44-0.88) p=0.007
- **Secondary Inotrope Use >24 Hours**: 54.9% in Levosimendan vs. 264% in Placebo. Odds ratio (95% CI) 0.71 (0.53-0.94) p=0.017
- **ICU Length of Stay**: 2.8 (1.6, 4.8) days in Levosimendan vs. 2.9 (1.8, 4.9) days in Placebo 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 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.
INVESTIGATORS AND COORDINATORS

United States
(60 sites; 718 patients)
Andra Duncan, Cleveland Clinic Foundation (59)
John Luber, Franciscan Health Syst Research Cntr (54)
Soon Park, Univ Hosp Cleveland Medical Center (45)
Michael Argenziano, Columbia Univ Med Center (38)
Randy Marcel, The Heart Hospital Baylor (34)
Edward Murphy, Spectrum Health (34)
Thomas Washburn Jr., Huntsville Hospital (29)
Manesh Parikshak, Franciscan St. Francis Health (26)
Michael England, Tufts Medical Center (21)
Robert Kramer, Maine Medical Center (19)
Allen Morris, Mercy General Hospital (19)
Daniel Gunn, Baylor University Medical Center (18)
Francis Downey, Aurora Saint Luke’s Med Center (16)
Clarence Owen, Moses H. Cone Memorial Hospital (16)
Andrew Pruitt, Saint Joseph's Mercy (16)
Julie Huffmyer, Univ of Virginia Health System (13)
Michael Wait, Univ of TX Southwestern Med Cntr (13)
Chandrashekhkara Ramaiah, Saint Thomas Hospital (12)
James Wudel, Nebraska Heart Institute (12)
Michael Essandoh, Ohio State Univ Medical Center (11)
Mark Groh, Mission Hospital (11)
James Slater, Morristown Medical Center (11)
Robert Hagberg, Hartford Hospital (10)
Robert Pearl, Stanford University SOM (10)
Vincent Scavo, Lutheran Hospital of Indiana (10)
Andrew Shaw, Vanderbilt Univ Medical Center (10)
Mark Slaughter, Univ of Louisville Jewish Hospital (10)

Canada
(10 sites; 164 patients)
Dimitri Kalavrouziotis, Quebec Heart & Lung Institute (31)
Dave Nagpal, London Health Sciences Centre (29)
John Bozinovski, Victoria Heart Institute Found (22)
Kevin Teoh, Southlake Regional Health Centre, (21)
David Mazer, St. Michael’s Hospital (16)
Benoit de Varennes, McGill Univ Health Centre (13)
Richard Whitlock, Hamilton Health Sciences (9)
Steven Meyer, University of Alberta Hospital (9)
Rakesh Arora, Saint Boniface Hospital (8)
Louis Perrault, Montreal Heart Institute (6)

LEVO-CTS PARTICIPANTS (882)

Thank you!