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President Argentine Society of Cardiology
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
Background

Levosimendan is not approved by FDA

Hemodynamic effects and mortality rates of levosimendan vs dobutamine

<table>
<thead>
<tr>
<th>Levosimendan</th>
<th>Dobutamine</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28%</td>
<td>15%</td>
<td>1.9 (1.1-3.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>26%</td>
<td>38%</td>
<td>0.57 (0.34-0.95)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Background

Early Mortality

Harrison RW et al. J Cardiothorac Vasc Anesth 2013; 14

Ju Yong Lim et al. J Card Surg 2015; 30
Multicenter, Prospective, Randomized, Double blind, Placebo controlled

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

Levosimendan

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

Randomization

Pre-op

Pre-Op | Surgery | ICU | Discharge

Placebo

Other therapies standard of care

Co-primary outcomes*
- **Quad**: death (≤30d), dialysis (≤30d), MI (≤5d), mechanical assist (≤5d)
- **Dual**: death (≤30d), mechanical assist (≤5d)

Secondary outcomes
- Low cardiac output syndrome
- Use of secondary inotropes beyond 24 hr
- ICU length of stay

Safety outcomes
- Hypotension
- Atrial fibrillation
- 90-day vital status

*Analysis of co-primary outcomes adjusted for covariates of age, sex, LV EF, and type of surgery.

## 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 (25th, 75th), 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 (25th, 75th), %</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>

Mehta RH et al. N Engl J Med 2017; 376
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=0.98

Odds ratio (96% CI)
1.18 (0.76-1.82)  
p=0.45

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

Mehta RH et al. N Engl J Med 2017; 376
Secondary Outcomes

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>

Mehta RH et al. N Engl J Med 2017; 376
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

As an inotrope was effective and safe to increase cardiac output

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