Levosimendan: mechanism of action, pharmacology, clinical data

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Critical Care Proprietary Products (Orion Pharma, Finland)
• an inodilator, with a unique triple mechanism of action
• discovered in the beginning of the 90ties, in Finland
• in clinical use from 2000, authorized in 61 countries in the worlds (whole EU excluded U.K. and Nederland)
• discussion with FDA ongoing
Old school inotropic drugs

- **β-receptor**
- **AC**
- **Ca^{2+}**
- **L-type Ca^{2+} Channel**
- **Sodium pump**
- **RyR**
- **Ca^{2+}**
- **SERCA ATPase**
- **Contractile apparatus**
- **PLB**
- **AMP**
- **Na^{+}/Ca^{2+} exchanger**
- **e.g. Dobutamine**
- **e.g. Digoxin**
- **e.g. Milrinone, Enoximone**

With the old school inotropes more contractility is achieved but with higher risks

- increase in the oxygen consumption in the myocardium, risk for the ischemic patients
- reduced effects in patients on beta-blockers
- arrhythmias due to the high level of intracellular calcium
- acceleration of the myocardial remodelling, apoptosis
- worse prognosis in the middle-long term
Levosimendan binds selectively to calcium saturated cardiac troponin C.
Cardioprotection
Mitochondrial
$K_{\text{ATP}}$ channel opening

levosimendan

Inotropy
Cardiac
Troponin C
sensitization

Vasodilation
Smooth muscle
$K_{\text{ATP}}$ channel
activation

Papp Z et al. Int J Cardiol 2012;159:82-7
No increase in calcium transient

Lancaster and Cook *Eur J Pharmacol* 1997;339:97-100
Levosimendan: no increase of oxygen consumption

CHANGE IN THE VO$_2$ TO $\int (P) dt$ RATIO
(OXYGEN CONSUMPTION VS. WORK)

No effect on myocardial oxygen consumption in HF patients

Levosimendan opens the ATP-dependent K⁺ channels in smooth muscle of vessels.

Levosimendan increases blood perfusion

Blood Flow (Solid Columns) and Calculated Vascular Resistance (Hatched Columns) in the Small Intestine. Data are represented as % change from control. (a) significant (p<0.05) difference from baseline, (abc) significant difference from both low and middle doses, (d) significant difference from the corresponding value in the levosimendan group.

Levosimendan opens the ATP-dependent potassium channels in cardiac mitochondria

Maximal rate of potassium-specific $\Delta \Psi$ decrease (%/s)

Log $[\text{Levosimendan}]$ ($\mu$M)

$EC_{50} = 0.83 \, \mu$M
Levosimendan has a preconditioning effect

- **Control**
  - LVDP or dP/dT

- **Ischemic Preconditioning**

- **Levosimendan Preconditioning**

- **Ischemia**

- **Reperfusion**
  - Stunning

- **Infarct Size**
Levosimendan has a preconditioning effect
Levosimendan has an anti-stunning effect

- In a 24 patient group with ACS the total number of hypokinetic segments decreased in the levosimendan group vs placebo

Sonntag et al. JACC 2004;43:2177
Levosimendan protects against inflammation

SURVIVE study -- Cohen-Solal et al. JACC 2009;53:2349
Levosimendan and its active metabolite
Levosimendan and its active metabolite non-protein bound plasma concentrations

Levosimendan and its active metabolite have similar inotropic effects.
Levosimendan and its active metabolite have similar vasodilatory effects.
Levosimendan sustained effects are due to the presence of its active metabolite.
### Levosimendan Clinical Programme

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Total [Levo])</th>
<th>Dose and duration</th>
<th>Comparator</th>
<th>Diagnosis (NYHA class)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-ranging</td>
<td>151 [95]</td>
<td>0.05–0.6 mcg/kg/min; 24 h</td>
<td>Placebo or dobutamine</td>
<td>CHF [III]</td>
<td>Haemodynamics</td>
</tr>
<tr>
<td>Escalation &amp; withdrawal</td>
<td>146 [98]</td>
<td>0.1–0.4 mcg/kg/min; 24 or 48 h</td>
<td>Placebo</td>
<td>CHF [III]</td>
<td>Haemodynamics</td>
</tr>
<tr>
<td>LIDO</td>
<td>203 [103]</td>
<td>0.1–0.2 mcg/kg/min; 24 h</td>
<td>Dobutamine</td>
<td>CHF [III–IV]</td>
<td>Haemodynamics</td>
</tr>
<tr>
<td>RUSSLAN</td>
<td>504 [402]</td>
<td>0.1–0.2 mcg/kg/min; 6 h</td>
<td>Placebo</td>
<td>Post-AMI [IV]</td>
<td>Safety</td>
</tr>
<tr>
<td>REVIVE I</td>
<td>100 [51]</td>
<td>0.1–0.2 mcg/kg/min; 24 h</td>
<td>Placebo</td>
<td>CHF [IV]</td>
<td>Clinical composite</td>
</tr>
<tr>
<td>REVIVE II</td>
<td>600 [299]</td>
<td>0.1–0.2 mcg/kg/min; 24 h</td>
<td>Placebo</td>
<td>CHF [IV]</td>
<td>Clinical composite</td>
</tr>
<tr>
<td>SURVIVE</td>
<td>1327 [664]</td>
<td>0.1–0.2 mcg/kg/min; 24 h</td>
<td>Placebo</td>
<td>CHF [IV]</td>
<td>Mortality</td>
</tr>
</tbody>
</table>

*AMI = acute myocardial infarction; CHF = chronic heart failure; Levo = levosimendan; NYHA = New York Heart Association*
Increase cardiac output, decrease PCWP

Healthy volunteers

Heart failure patients


no increase in oxygen consumption
Concomitant beta-blocker treatment

mortality in the LIDO and RUSSLAN studies

LIDO (n=203)

RUSSLAN (n=504)

Indications of survival benefit vs. placebo and active control


Moiseyev VS et al. *Eur Heart J* 2002;23:1422–32
mortality in REVIVE and SURVIVE studies

REVIVE (n=700) vs. placebo and active control

Neutral effects on survival vs. placebo and active control


Mebazaa A et al. *JAMA* 2007;297:1883–9
SURVIVE: mortality in β-blocker treated patients

mortality data from real-life clinical practice

Data from ALARM-HF registry, N=4953

from Mebazaa A et al. *Intensive Care Med* 2011;37:290-301
Meta-analysis on adverse events in 45 studies

- **Myocardial infarction**
  - RR= 0.79 (95% CI 0.52, 1.18); p=NS

- **Ventricular arrhythmias**
  - RR=0.89 (95% CI 0.61, 1.28); p=NS

- **Supraventricular arrhythmias**
  - RR=1.00 (95% CI 0.78, 1.29); p=NS

- **Hypotension**
  - RR=1.39 (95% CI 0.99, 1.94); p=NS
Latest clinical trials in acute heart failure

Around 30 large/medium-large sized double-blind trials on new chemical entities (phases IIb and III) were run in the latest 16 years on Acute Heart Failure. The acronyms of the trials are marked as follows: trials on (a) tezosentan, (b) levosimendan, (c) nesiritide, (d) tolvaptan, (e) milrinone, (f) enoximone, (g) rolofylline, (h) istaroxime, (i) clevidipine, (j) SLV320, (k) cinaciguat, (l) serelaxine, (m) omecamtiv mecarbil, (n) dopamine, (o) ularitide, (p) high dose spironolactone, (q) liraglutide. Levosimendan is the only the drugs which is currently authorized for sales as treatment of AHF and still under active research program.

updated from Pollesello P. Int J Cardiol 2014;172:11-13
levosimendan is increasingly used and studied in connection with cardiac surgery

- Pre-operatively before cardiopulmonary bypass (CPB)
- Peri-operatively
- Post-operatively in patients with low cardiac output syndrome
Sustained Effects vs. milrinone

- 30 pts with pre-operative ejection fraction <30% scheduled for elective cardiac surgery with CPB
  - n=15 **milrinone** (0.5 mcg/kg/min) for 83 h (mean)
  - n=15 **levosimendan** (0.1 mcg/kg/min) for 19 h (mean)
  - started immediately after release of aortic cross-clamp

- All patients received dobutamine 5 mcg/kg/min

Stroke volume index


CPB = cardiopulmonary bypass; SVI = stroke volume index
Levosimendan facilitates weaning from CPB

Levosimendan given as 12 mcg/kg bolus followed by 0.2 mcg/kg/min 24-h infusion

- 73% successful 1st weaning
- 53% successful 2nd weaning
- 13% weaning failure

$\text{p} = 0.002$

§) 2 levosimendan patients were weaned in primary attempt although failed to meet primary endpoint hemodynamic criteria.

*) Weaning failure leads to use of Intra-aortic balloon pump.

Levosimendan has a preconditioning effect in coronary artery bypass grafting.
Recent and ongoing SIMDAX investigator initiated studies*

<table>
<thead>
<tr>
<th>study</th>
<th>n.</th>
<th>principal investigator</th>
<th>Publication due/status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheetah (post-operative)</td>
<td>506</td>
<td>G. Landoni (I)</td>
<td>Published on May 21</td>
</tr>
<tr>
<td>Levo-CTS (pre-operative)</td>
<td>881</td>
<td>J. Alexander (USA)</td>
<td>Published on May 19</td>
</tr>
<tr>
<td>Licorn (peri-operative)</td>
<td>375</td>
<td>B. Cholley (F)</td>
<td>Publication expected Q2/2017</td>
</tr>
<tr>
<td>Diaphragm function</td>
<td>40</td>
<td>L. Heunks (NL)</td>
<td>Data expected Q3 2017</td>
</tr>
<tr>
<td>Relevant register (AdHF)</td>
<td>135</td>
<td>F. Oliva (I)</td>
<td>Publication expected Q3/2017</td>
</tr>
<tr>
<td>Levoaki (renal)</td>
<td>40</td>
<td>S.-E. Ricksten (S)</td>
<td>Data expected Q2 2018</td>
</tr>
<tr>
<td>Eldor (renal)</td>
<td>40</td>
<td>S.-E. Ricksten (S)</td>
<td>Data expected Q3 2017</td>
</tr>
<tr>
<td>Lion-Heart (AdHF)</td>
<td>69</td>
<td>J. Comin-Colet</td>
<td>Publication expected Q2/2017</td>
</tr>
<tr>
<td>Laica (AdHF)</td>
<td>97</td>
<td>M.J. Garcia-Gonzalez</td>
<td>Publication expected Q4/2017</td>
</tr>
<tr>
<td>LeoDOR (AdHF)</td>
<td>260</td>
<td>G. Pölzl (A)</td>
<td>Starting Q2/2017</td>
</tr>
</tbody>
</table>

*over 40 patients / double blind
Levosimendan in patients requiring hemodynamic support after cardiac surgery

The recent CHEETAH clinical trial: Kaplan–Meier Survival Estimates of All-Cause Mortality

In CHEETAH trial a low dose of levosimendan (average $0.07 \, \mu g/kg/min$ administered in a 1:20 dilution i.v. form) did not show effect nor adverse events.

Landoni G et al NEJM 2017 [ePub March 21]
LEVO-CTS Study Flow Diagram
Mehta RH et al NEJM 2017 [ePub March 19]

Pre-Op
Randomization
CABG and/or mitral valve, with/without aortic valve;
LVEF ≤35%; planned CPB

Pre-Op | Surgery | ICU | Discharge

Initiate infusion before surgery;
0.2ug/kg/min hour 1
0.1ug/kg/min for 23 hrs

Levosimendan

Placebo

F/U 30 Days
(mortality 90 days)

All patients receive current standard of care
Protocol History; Key Revisions

- FDA Meetings: May 2011, Sept 2011, June 2012
- Version 2.0; November 2014
  - Initial SPA Agreed protocol (subsequent amendments, all SPA agreed)
- Version 2.2; April 2013 *first subjects randomized*
  - Enrichment of study population; LVEF ≤25%
  - Reduced study scope; target 760 pts for 201 events
- Subsequent Amendments through Version 4; July 2015
  - Revised LVEF to ≤35%
  - Primary analysis from ITT to mITT (patients receiving any study drug), as per agreed SAP
Key Inclusion/Exclusion Criteria

- **Inclusion Criteria**
  - Scheduled or urgent cardiac surgery; CABG and/or mitral valve surgery with or without other valves
  - At 70 US and Canadian Sites
  - Surgery will employ CPB pump
  - Documented LVEF ≤35% within 60 days before surgery
  - Men and women, ≥18 years
Key Inclusion/Exclusion Criteria

- **Exclusion Criteria**
  - Dialysis at randomization
  - Estimated glomerular filtration rate (eGRF) < 30 mL/min/1.73m².
  - Patients whose systolic blood pressure (SBP) cannot be managed to ensure SBP > 90mmHg
  - Heart rate ≥ 120 bpm, persistent for ≥ 10 min and unresponsive to treatment
  - Hemoglobin < 80 g/L.
  - Serum potassium < 3.5 mmol/L or > 5.5 mmol/L at baseline
  - Mechanical assist (IABP, LVAD, ECMO) planned at start of surgery or pre-planned before coming off CPB.
  - Aortal femoral occlusive disease that would prohibit use of IABP, unless VAD or ECMO available.
  - Liver dysfunction with Childs Pugh Class B or C
Outcome Measures

- **Co-Primary Endpoints**
  - “Dual” Endpoint
    - All Cause Death (≤30 days)
    - Mechanical Assist; IABP, VAD, ECMO (≤5 days)
  - “Quad” Endpoint
    - All Cause Death (≤30 days)
    - Mechanical Assist; IABP, VAD, ECMO (≤5 days)
    - Perioperative MI (≤5 days)
    - Renal Dialysis (≤30 days)
Outcome Measures

- **Secondary Endpoints**
  - Duration of ICU/CCU length of stay for index hospitalization
  - Incidence of LCOS
  - Postoperative use of secondary inotrope; dobutamine, milrinone, epinephrine or dopamine
Additional Endpoints

- **Safety Endpoints**
  - 90-day all-cause mortality
  - Postoperative atrial fibrillation

- **Other Efficacy Endpoints**
  - Rehospitalization for any cause through 30 days
Projected Event Rates

- **Quad Endpoint**
  - Projected placebo rate = 32%
  - Assumed 35% RRR w/ levosimendan

- **Dual Endpoint**
  - Projected placebo rate = 18%
  - Assumed 35% RRR w/ levosimendan

- **Sample size**
  - Targeted 760 patients; 70 sites (60 US, 10 Canada)
  - Targeted 201 quad events (estimated 113 dual events)
  - 86% power for quad (p≤0.01) and/or dual (p≤0.04) primary endpoints
Steering Committee

- John H. Alexander, MD, Duke University (Chair)
- Robert A. Harrington, MD, Stanford University
- Jerrold Levy, MD, Duke University
- John Luber, MD, Franciscan Health Systems
- Matthias Heringlake, MD, Lübeck University
- Wolfgang Toller, MD, Graz University
- Kevin Anstrom, PhD, Duke University
- Stephen Fremes, MD, Sunnybrook Health Science Center
- John P. Kelley, CEO, Tenax Therapeutics
Patient Disposition

Enrolled (n=956)

Randomized (n=882)

Levosimendan (ITT) (n=442)
- No study drug (n=14)
  - 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)

Lost to follow up
- Quad endpoint (n=11)
  - Dual endpoint (n=0)

Day 30 (n=428)

Day 30 (n=421)

Lost to follow up
(n=TBD)

Lost to follow up
(n=TBD)

Day 90 (n=428)
Median survivor follow-up = TBD

Day 90 (n=421)
Median survivor follow-up = TBD

Not randomized (n=74)
- Not scheduled for surgery with CPB (n=20)
- Not scheduled for protocol-required surgery (n=12)
- Femoral occlusive disease (n=9)
- Other reasons (n=33)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;) yrs</strong></td>
<td>65 (59, 73)</td>
<td>65 (58, 72)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>81 (18.9%)</td>
<td>89 (21.2%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>385 (91.0%)</td>
<td>375 (89.5%)</td>
</tr>
<tr>
<td>Blacks</td>
<td>21 (5.0%)</td>
<td>23 (5.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (4.0%)</td>
<td>21 (5.0%)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>283 (66.1%)</td>
<td>280 (66.5%)</td>
</tr>
<tr>
<td>CABG + Aortic Valve</td>
<td>36 (8.4%)</td>
<td>34 (8.1%)</td>
</tr>
<tr>
<td>CABG + Mitral Valve</td>
<td>50 (11.7%)</td>
<td>48 (11.4%)</td>
</tr>
<tr>
<td>CABG + Mitral + Aortic Valve</td>
<td>10 (2.3%)</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>Mitral Valve</td>
<td>36 (8.4%)</td>
<td>31 (7.4%)</td>
</tr>
<tr>
<td>Mitral + Aortic Valve</td>
<td>10 (2.3%)</td>
<td>14 (3.3%)</td>
</tr>
<tr>
<td>Aortic Valve</td>
<td>3 (0.7%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td><strong>LVEF Value (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>26 (24, 32)</td>
<td>27 (22, 31)</td>
</tr>
</tbody>
</table>
90-Day All-Cause Mortality

N at risk

(L) 428 424 419 412 378 372 368 362 359 333
(P) 419 409 402 399 372 366 363 358 351 333

Kaplan-Meier percentage

Days from reference date

Levosimendan (L) *18/428+
Placebo (P) *30/421+

p-value 0.067
# Co-Primary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dual Endpoint†</strong></td>
<td>56 (13.1%)</td>
<td>48 (11.4%)</td>
<td>1.18 (0.76, 1.82)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Quad Endpoint†</strong></td>
<td>105 (24.5%)</td>
<td>103 (24.5%)</td>
<td>1.01 (0.66, 1.54)</td>
<td>0.98</td>
</tr>
<tr>
<td>Death (≤30 days) ††</td>
<td>15 (3.5%)</td>
<td>19 (4.5%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mechanical Assist (≤5 days)</td>
<td>47 (11.0%)</td>
<td>38 (9.0%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Perioperative MI (≤5 days)</td>
<td>67 (16.0%)</td>
<td>63 (15.5%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Renal Dialysis (≤30 days)</td>
<td>9 (2.1%)</td>
<td>16 (3.8%)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

†Adjusted for Covariates: Type of Surgery, LVEF, Age, Sex
†† two patients received the wrong study drug, patient receiving placebo died; such that as treated incidence 14 (3.3%) vs. 20 (4.8%)
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of LCOS</td>
<td>78 (18.2%)</td>
<td>108 (25.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Post-op 2º Inotropes</td>
<td>235 (54.9%)</td>
<td>264 (62.5%)</td>
<td>0.017</td>
</tr>
</tbody>
</table>
**Key Subgroup – CABG + LVEF ≤25%**  
(identical as Levin et al. trial population)

<table>
<thead>
<tr>
<th>Quad Endpoint Subpopulation</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤25</td>
<td>22/155 (14.2%)</td>
<td>38/148 (25.7%)</td>
<td>0.47 (0.22, 1.02)</td>
<td>0.012</td>
</tr>
<tr>
<td>LVEF &gt;25</td>
<td>21/128 (16.4%)</td>
<td>16/132 (12.1%)</td>
<td>1.35 (0.53, 3.46)</td>
<td>0.407</td>
</tr>
</tbody>
</table>

LEVO-CTS clinical trial: appendix data on 90 day mortality in CABG patients

CABG
n=563

HR, 0.259 (95% CI, 0.105 - 0.640) p=0.0016
### Results: Overall Safety Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>710</td>
<td>641</td>
</tr>
<tr>
<td>Subjects with at least 1 AE</td>
<td>238 (55.6%)</td>
<td>95 (55.1%)</td>
</tr>
<tr>
<td>Total SAEs</td>
<td>113</td>
<td>114</td>
</tr>
<tr>
<td>Discontinuation of study drug for SAE</td>
<td>6 (1.4%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Deaths up to 30 days††</td>
<td>15 (3.5%)</td>
<td>19 (4.5%)</td>
</tr>
</tbody>
</table>

†Adjusted for Covariates: Type of Surgery, LVEF, Age, Sex
†† two patients received the wrong study drug, patient receiving placebo died; such that as treated incidence 14 (3.3%) vs. 20 (4.8%)
## Management of Hypotension

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<th>Levosimendan (N=428)</th>
<th>Placebo (N=421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Inotropes use at 24 hours</td>
<td>235 (54.9%)</td>
<td>263 (62.5%)</td>
</tr>
<tr>
<td>IV Vasopressor use &gt;24 hours</td>
<td>253 (59.1%)</td>
<td>263 (62.5%)</td>
</tr>
<tr>
<td>Study drug dose modification</td>
<td>56 (13.1%)</td>
<td>29 (6.9%)</td>
</tr>
<tr>
<td>Study drug discontinuation before 23.5 hours</td>
<td>52 (12.2%)</td>
<td>39 (9.3%)</td>
</tr>
</tbody>
</table>
LEVO-CTS Conclusions: Efficacy

Co-Primary Endpoints

- No effective in composite co-primary endpoints
  - All-cause mortality and dialysis reductions
  - Peri-operative MI incidence comparable
  - Most effective in CABG, LVEF<25%, GFR<60 subgroups

Secondary Endpoints

- Significant effect in reducing LCOS and use of secondary inotropes
LEVO-CTS Conclusions: Safety

- AEs, SAEs, DCs-AE generally comparable
- Events of special safety interest similar across groups
  - atrial fibrillation, ventricular tachycardia or fibrillation, aborted resuscitated death, stroke
- Hypotension incidence similar across groups
  - Managed with limited use of vasopressors and dose reduction; discontinuations few
- Reduced 90-day all-cause mortality with levosimendan