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levosimendan in cardio thoracic surgery

ACC.17
66th Annual Scientific Session & Expo

# 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**


Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

TENAX THERAPEUTICS

# Disclosures

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**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

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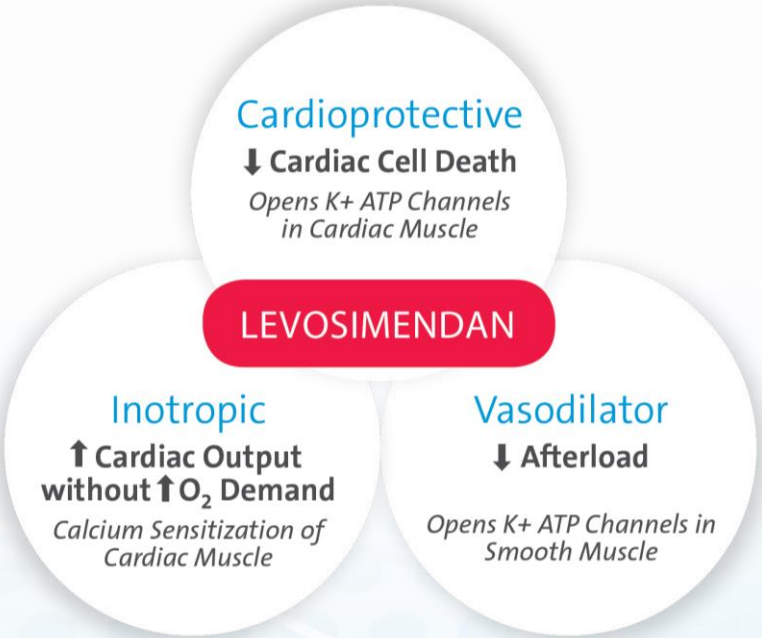
# Levosimendan

- $Ca^{++}$ 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

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*Rognoni A, et al., Curr Pharm Des 2013;19:3974-8*
*Toller W, et al., Int J Cardiol 2015;84:323-6*

# Meta-Analysis of Prior Trials of Levosimendan in CTS

## Dialysis

| Study or Subgroup | Levosimendan Events | Levosimendan Total | Control Events | Control Total | Weight | Risk Difference |
|---|---|---|---|---|---|---|
| **Low EF Studies** | | | | | | |
| Al-Shawaf 2006 | 0 | 14 | 1 | 16 | 4.9% | -0.06 |
| Levin 2009 | 2 | 127 | 10 | 126 | 41.4% | -0.063 |
| Levin 2012 | 3 | 127 | 8 | 125 | 41.3% | -0.04( |
| Lomivorotov 2011 | 0 | 20 | 0 | 20 | 6.5% | 0.00( |
| **Subtotal (95% CI)** | | **288** | | **287** | **94.1%** | **-0.048** |
| Total events | 5 | | 19 | | | |
| Heterogeneity: Chi² = 1.53, df = 3 (P = 0.68); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.85 (P = 0.004) | | | | | | |
| **Preserved EF Studies** | | | | | | |
| Momeni 2011 | 0 | 18 | 1 | 18 | 5.9% | -0.05 |
| **Subtotal (95% CI)** | | **18** | | **18** | **5.9%** | **-0.05** |
| Total events | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.77 (P = 0.44) | | | | | | |
| **Total (95% CI)** | | **306** | | **305** | **100.0%** | **-0.049** |
| Total events | 5 | | 20 | | | |
| Heterogeneity: Chi² = 1.54, df = 4 (P = 0.82); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.94 (P = 0.003) | | | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0% | | | | | | |

## Myocardial Injury

| Study or Subgroup | Levosimendan Events | Levosimendan Total | Control Events | Control Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| | | | | | 1% | -0.2411 [-0.5052, 0.0231] |
| | | | | | 1% | 0.0000 [-0.1206, 0.1206] |
| | | | | | 2% | -0.0667 [-0.1918, 0.0584] |
| | | | | | 0% | -0.0636 [-0.1155, -0.0117] |
| | | | | | 9% | -0.0561 [-0.1017, -0.0105] |
| | | | | | 1% | **-0.0663 [-0.0998, -0.0328]** |
| | | | | | 5% | -0.0164 [-0.1228, 0.0900] |
| | | | | | 5% | 0.0000 [-0.2982, 0.2982] |
| | | | | | 5% | -0.0833 [-0.3459, 0.1792] |
| | | | | | 5% | -0.0200 [-0.0732, 0.0332] |
| | | | | | 9% | **-0.0209 [-0.0894, 0.0476]** |
| | | | | | 0% | **-0.0500 [-0.0827, -0.0174]** |
| | | | | | = 26.6% | |

Risk Difference M-H, Fixed, 95% CI

-0.5 -0.25 0 0.25 0.5

Favors Levosimendan Favors control

## Mortality

| Study or Subgroup | Levosimendan Events | Levosimendan Total | Control Events | Control Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **Low EF Studies** | | | | | | |
| Al-Shawaf 2006 | 1 | 14 | 1 | 16 | 2.6% | 0.0089 [-0.1707, 0.1886] |
| Alvarez 2005 | 1 | 15 | 0 | 15 | 2.6% | 0.0667 [-0.0997, 0.2330] |
| Alvarez 2006 | 1 | 25 | 1 | 25 | 4.3% | 0.0000 [-0.1086, 0.1086] |
| De Hert 2007 | 0 | 15 | 3 | 15 | 2.6% | -0.2000 [-0.4198, 0.0198] |
| Eriksson 2009 | 0 | 30 | 2 | 30 | 5.2% | -0.0667 [-0.1723, 0.0389] |
| Levin 2009 | 9 | 127 | 20 | 126 | 21.9% | -0.0879 [-0.1657, -0.0100] |
| Levin 2012 | 5 | 127 | 16 | 125 | 21.8% | -0.0886 [-0.1563, -0.0210] |
| Lomivorotov 2011 | 0 | 20 | 0 | 20 | 3.5% | 0.0000 [-0.0922, 0.0922] |
| **Subtotal (95% CI)** | | **373** | | **372** | **64.5%** | **-0.0702 [-0.1099, -0.0306]** |
| Total events | 17 | | 43 | | | |
| Heterogeneity: Chi² = 9.01, df = 7 (P = 0.25); I² = 22% | | | | | | |
| Test for overall effect: Z = 3.47 (P = 0.0005) | | | | | | |
| **Preserved EF Studies** | | | | | | |
| Jarvela 2008 | 1 | 12 | 0 | 12 | 2.1% | 0.0833 [-0.1194, 0.2860] |
| Lahtinen 2011 | 10 | 99 | 10 | 101 | 17.3% | 0.0020 [-0.0812, 0.0852] |
| Leppikangas 2011 | 1 | 12 | 0 | 12 | 2.1% | 0.0833 [-0.1194, 0.2860] |
| Momeni 2011 | 1 | 18 | 1 | 18 | 3.1% | 0.0000 [-0.1497, 0.1497] |
| Tritapepe 2006 | 0 | 12 | 0 | 12 | 2.1% | 0.0000 [-0.1478, 0.1478] |
| Tritapepe 2009 | 0 | 52 | 0 | 50 | 8.8% | 0.0000 [-0.0375, 0.0375] |
| **Subtotal (95% CI)** | | **205** | | **205** | **35.5%** | **0.0107 [-0.0375, 0.0590]** |
| Total events | 13 | | 11 | | | |
| Heterogeneity: Chi² = 1.38, df = 5 (P = 0.93); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.44 (P = 0.66) | | | | | | |
| **Total (95% CI)** | | **578** | | **577** | **100.0%** | **-0.0415 [-0.0723, -0.0107]** |
| Total events | 30 | | 54 | | | |
| Heterogeneity: Chi² = 17.96, df = 13 (P = 0.16); I² = 28% | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | |
| Test for subgroup differences: Chi² = 6.45, df = 1 (P = 0.01), I² = 84.5% | | | | | | |

Risk Difference M-H, Fixed, 95% CI

-0.5 -0.25 0 0.25 0.5

Favors Levosimendan Favors Control

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*Harrison RH, et. al., JCTVA 2013;27: 1224–1232*

# 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

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

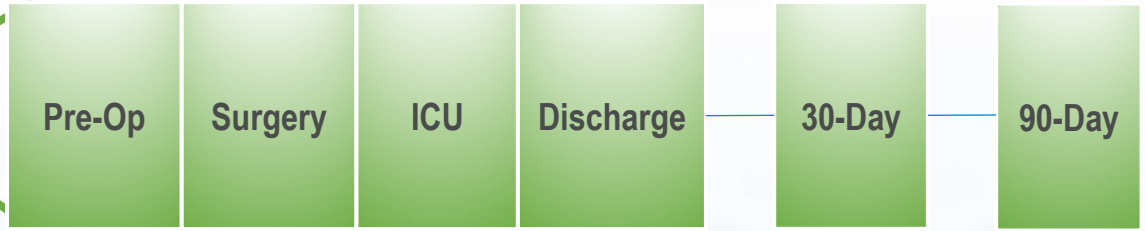
CABG, MV, CABG
+ MV or AoV surgery
w/ CPB, LV EF ≤35%

Randomization

Pre-op

**Levosimendan**

**Placebo**




**Other therapies standard of care**

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*Mehta RH, et al., Am Heart J 2016;182:62-71*

# 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

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*Mehta RH, et al., Am Heart J 2016;182:62-71*

# 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

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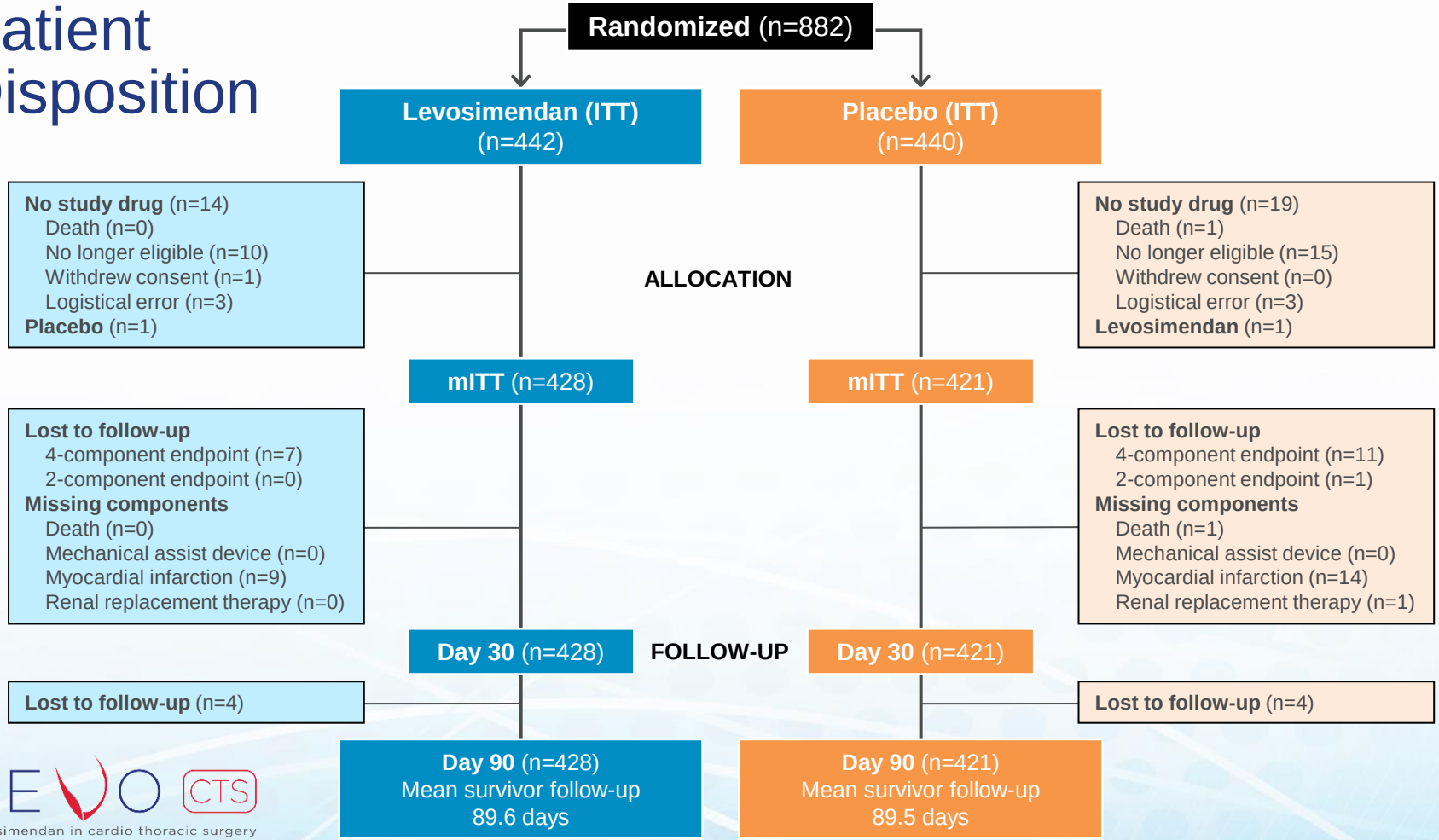
*Quad = death, dialysis, MI or mechanical assist
*Dual = death or mechanical assist

# Patient Disposition

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# Baseline Characteristics

| | Levosimendan n=428 | Placebo n=421 |
|---|---|---|
| **Age, median (25th, 75th), years** | 65 (59, 73) | 65 (58, 72) |
| **Female sex** | 18.9% | 21.1% |
| **White race** | 91.0% | 89.5% |
| **LV EF, median (25th, 75th), %** | 26 (24, 32) | 27 (22, 31) |
| **Surgery type** | | |
| CABG | 66.1% | 66.5% |
| CABG + Aortic valve | 8.4% | 8.1% |
| CABG + Mitral valve | 11.7% | 11.4% |
| CABG + Mitral + Aortic valve | 2.3% | 2.4% |
| Mitral valve | 8.4% | 7.4% |
| Mitral + aortic valve | 2.3% | 3.3% |
| Aortic valve | 0.7% | 0.7% |

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# Study Drug

| | Levosimendan n=428 | Placebo n=421 |
|---|---|---|
| **Time from study drug to surgery, median (25th, 75th), hours** | 0.33 (0.18, 0.53) | 0.32 (0.17, 0.48) |
| **Study Drug Duration <23.5 hours** | 68 (15.7%) | 48 (11.4%) |

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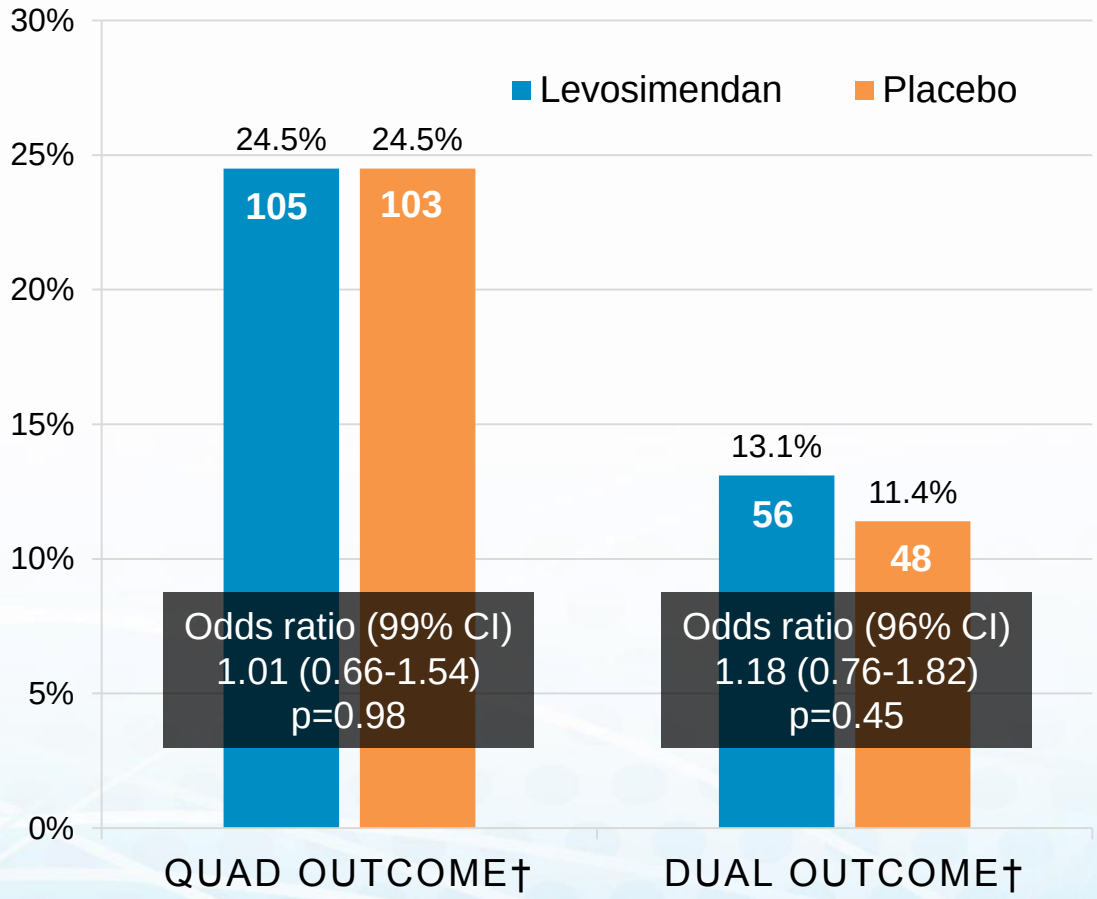
# Co-Primary Outcomes




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

Dual Outcome = death or mechanical assist device use

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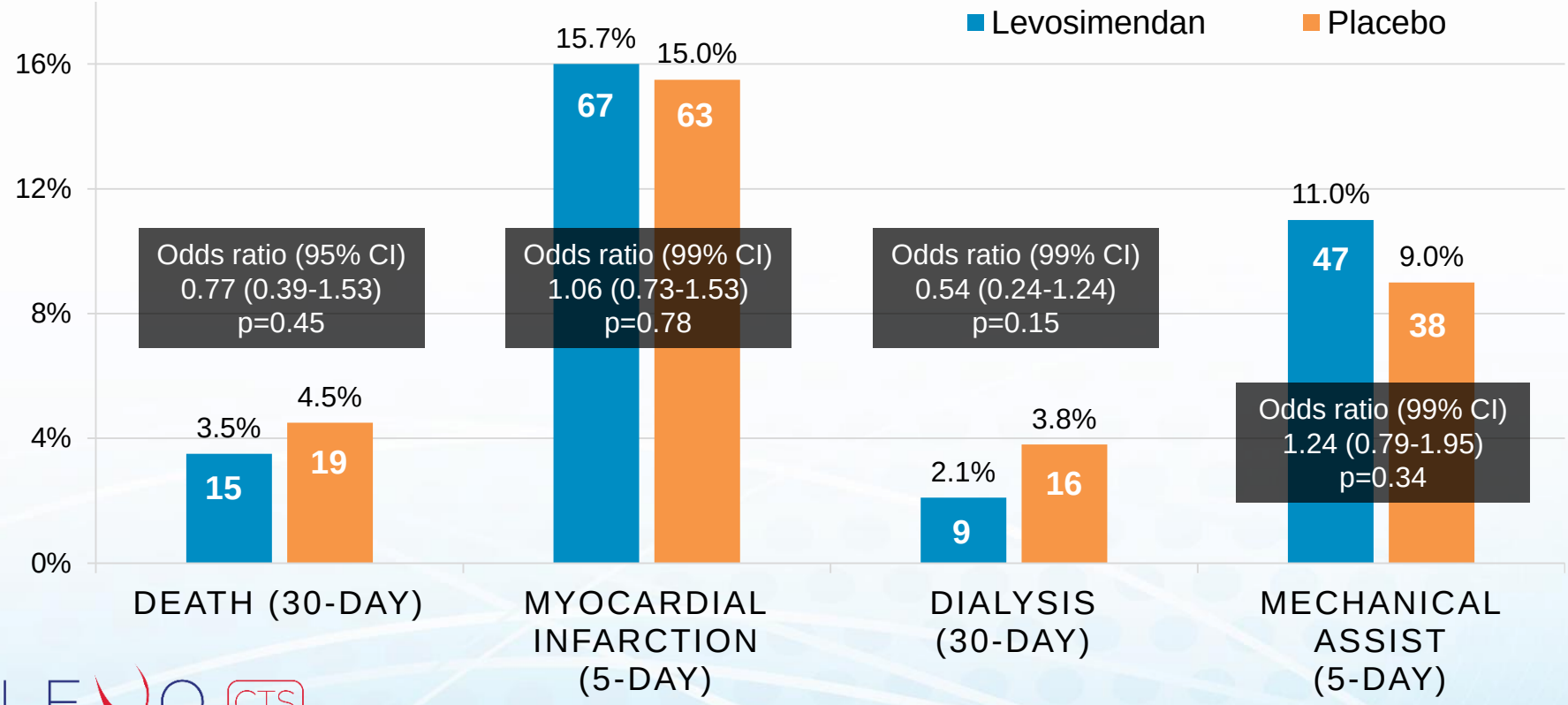
*†Adjusted for covariates: type of surgery, LVEF, age, sex*

# Individual Outcomes Components

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# Cardiac Output

| **Cardiac Index (mls/min/m²)** | **Mean (SD)** | |
|---|---|---|
| Levosimendan (n=359) | 2.86 (0.61) | p<0.0001 |
| Placebo (n=340) | 2.68 (0.65) | |

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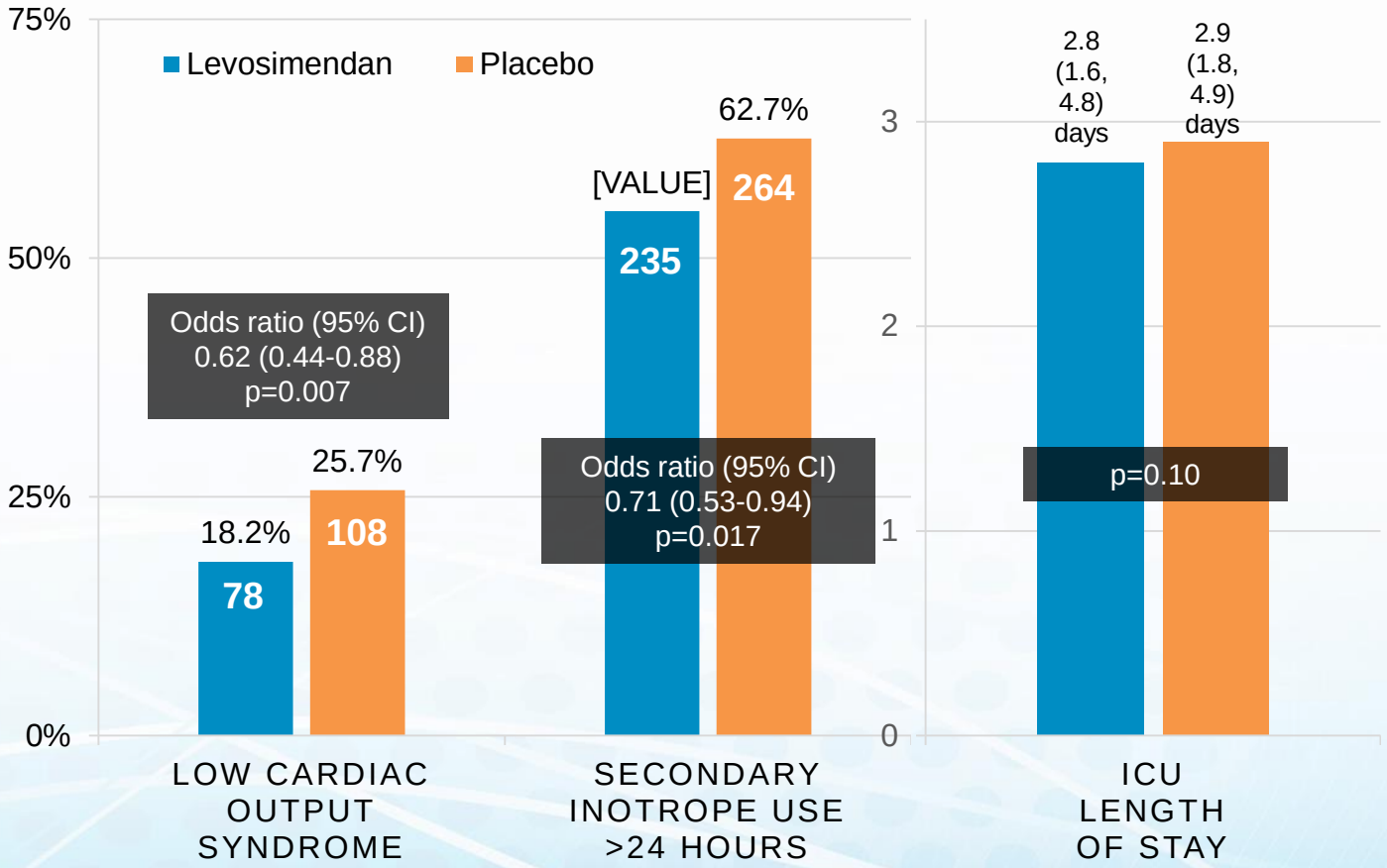
# Secondary Outcomes

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# 30-Day Safety Outcomes

| | Levosimendan n=428 | Placebo n=421 | p-value |
|---|---|---|---|
| **Hypotension** | 155 (36.2%) | 138 (32.8%) | 0.29 |
| **Atrial fibrillation** | 163 (38.1%) | 139 (33.0%) | 0.12 |
| **VT / VF** | 46 (10.7%) | 41 (9.7%) | 0.63 |
| **Stroke** | 15 (3.5%) | 10 (2.4%) | 0.33 |
| **Rehospitalization** | 54 (12.6%) | 48 (11.4%) | 0.55 |

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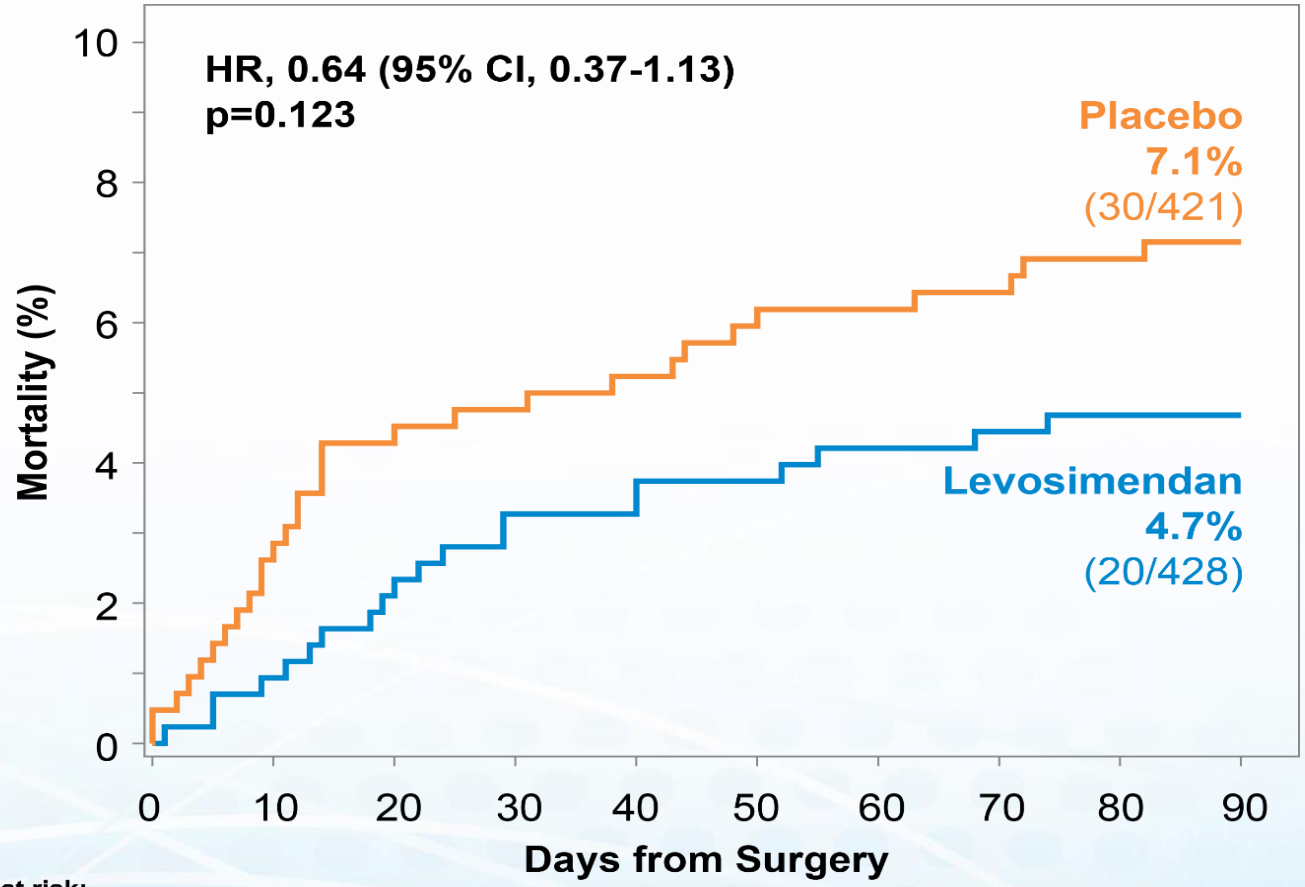
# 90-Day Mortality




**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 |

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# 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

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# 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.

# Publication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

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# Thank you!