LEVO CTS
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

LEVO-CTS funded by Tenax Therapeutics

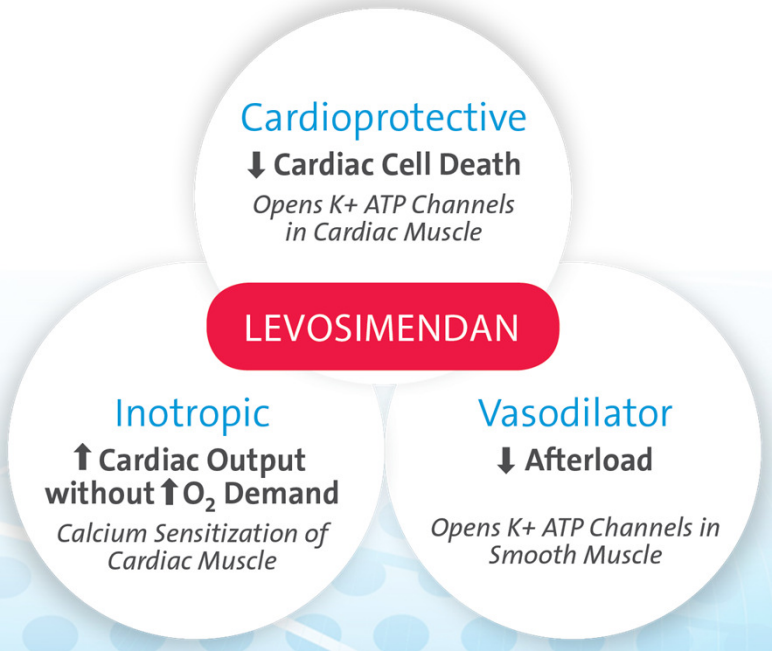
Research support: Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, US FDA, US NIH, Pfizer, Tenax Therapeutics

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



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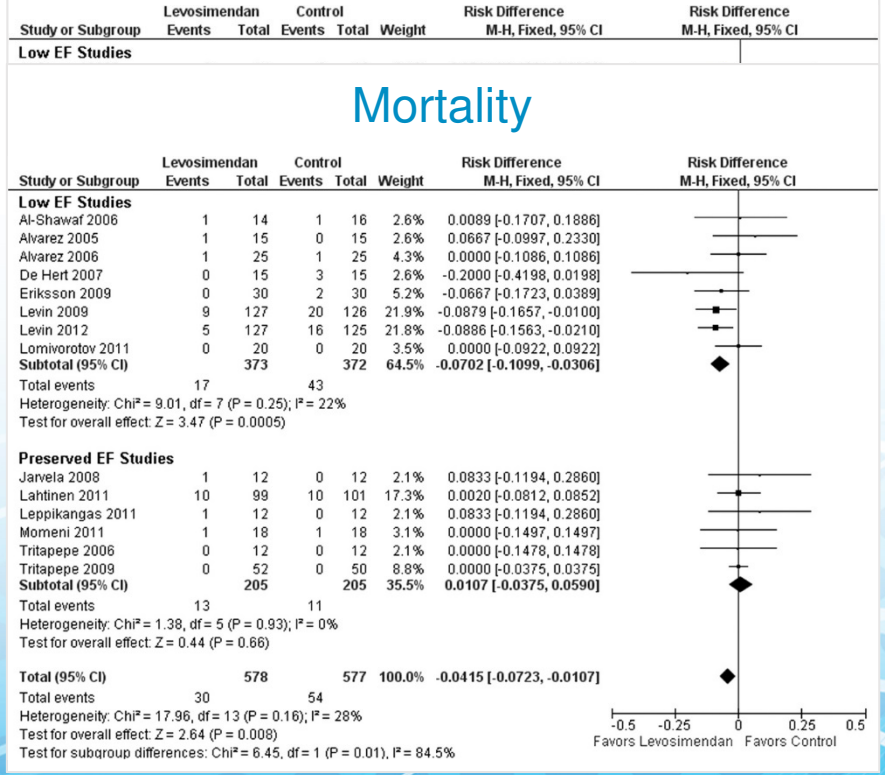
Rognoni A, et al., Curr Pharm Des 2013;19:3974-8
Toller W, et al., Int J Cardiol 2015;84:323-6

Meta-Analysis of Prior Trials in CTS

Atrial Fibrillation

Mortality



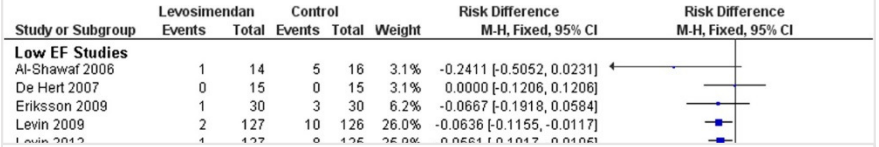
Study or Subgroup	Levosimendan Events	Levosimendan Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Low EF Studies						
Al-Shawaf 2006	1	14	1	16	2.6%	0.0089 [-0.1707, 0.1886]
Alvarez 2005	1	15	0	15	2.6%	0.0667 [-0.0997, 0.2330]
Alvarez 2006	1	25	1	25	4.3%	0.0000 [-0.1086, 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

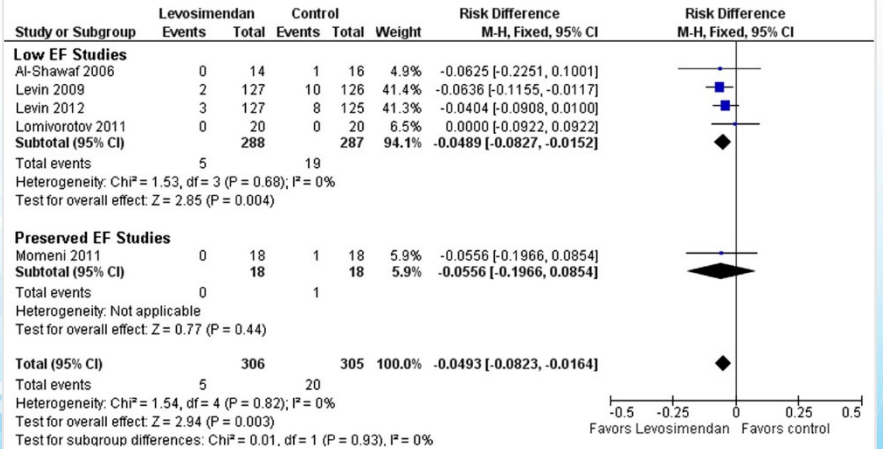
Myocardial Injury



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	5	16	3.1%	-0.2411 [-0.5052, 0.0231]
De Hert 2007	0	15	0	15	3.1%	0.0000 [-0.1206, 0.1206]
Eriksson 2009	1	30	3	30	6.2%	-0.0667 [-0.1918, 0.0584]
Levin 2009	2	127	10	126	26.0%	-0.0636 [-0.1155, -0.0117]

Risk Difference M-H, Fixed, 95% CI

Dialysis



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	0	14	1	16	4.9%	-0.0625 [-0.2251, 0.1001]
Levin 2009	2	127	10	126	41.4%	-0.0636 [-0.1155, -0.0117]
Levin 2012	3	127	8	125	41.3%	-0.0404 [-0.0908, 0.0100]
Lomivorotov 2011	0	20	0	20	6.5%	0.0000 [-0.0922, 0.0922]
Subtotal (95% CI)		**288**		**287**	**94.1%**	**-0.0489 [-0.0827, -0.0152]**
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%	-0.0556 [-0.1966, 0.0854]
Subtotal (95% CI)		**18**		**18**	**5.9%**	**-0.0556 [-0.1966, 0.0854]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**306**		**305**	**100.0%**	**-0.0493 [-0.0823, -0.0164]**
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%						

Risk Difference M-H, Fixed, 95% CI

-0.5 -0.25 0 0.25 0.5

Favors Levosimendan Favors control

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

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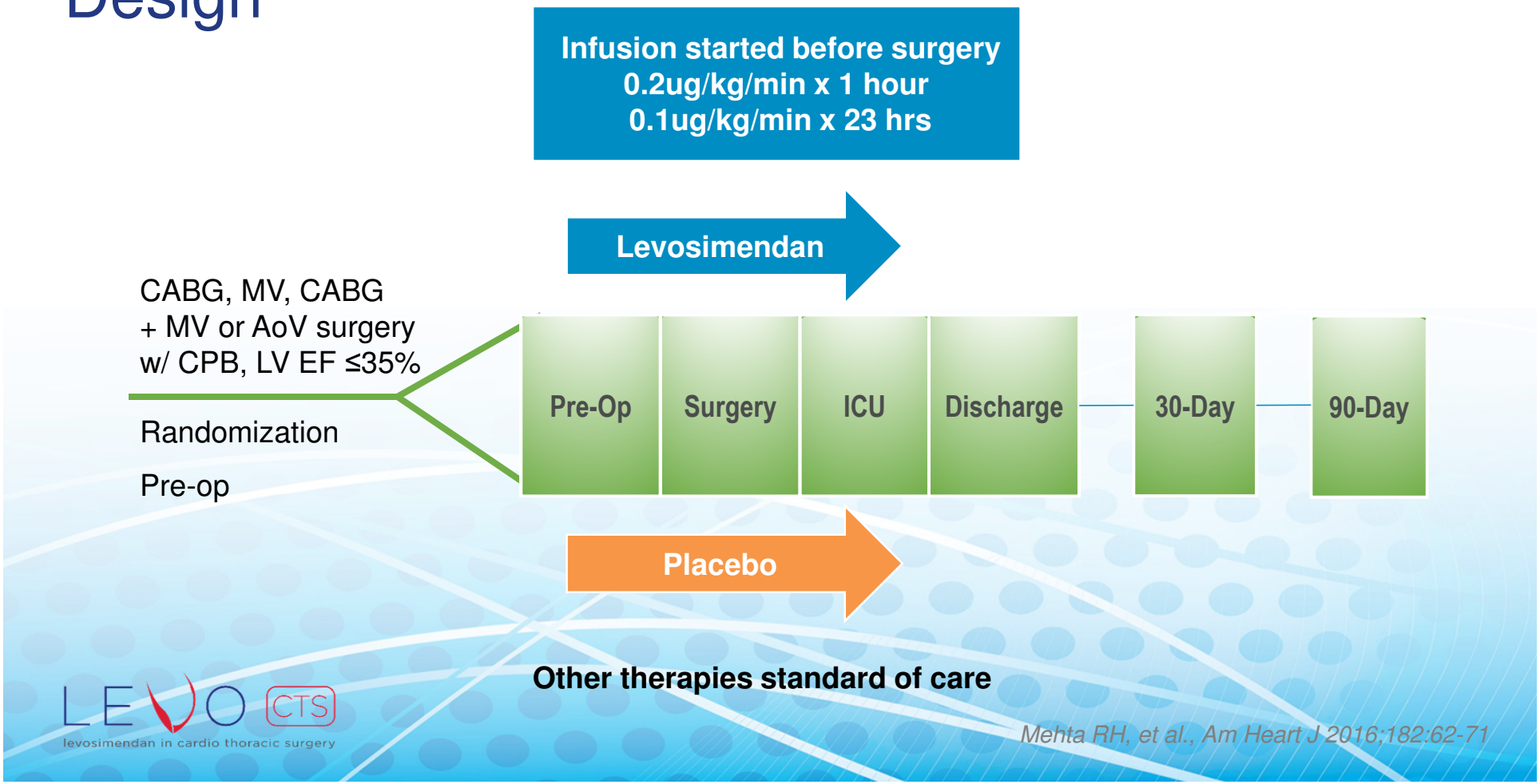
Design


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
30-Day
90-Day
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 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

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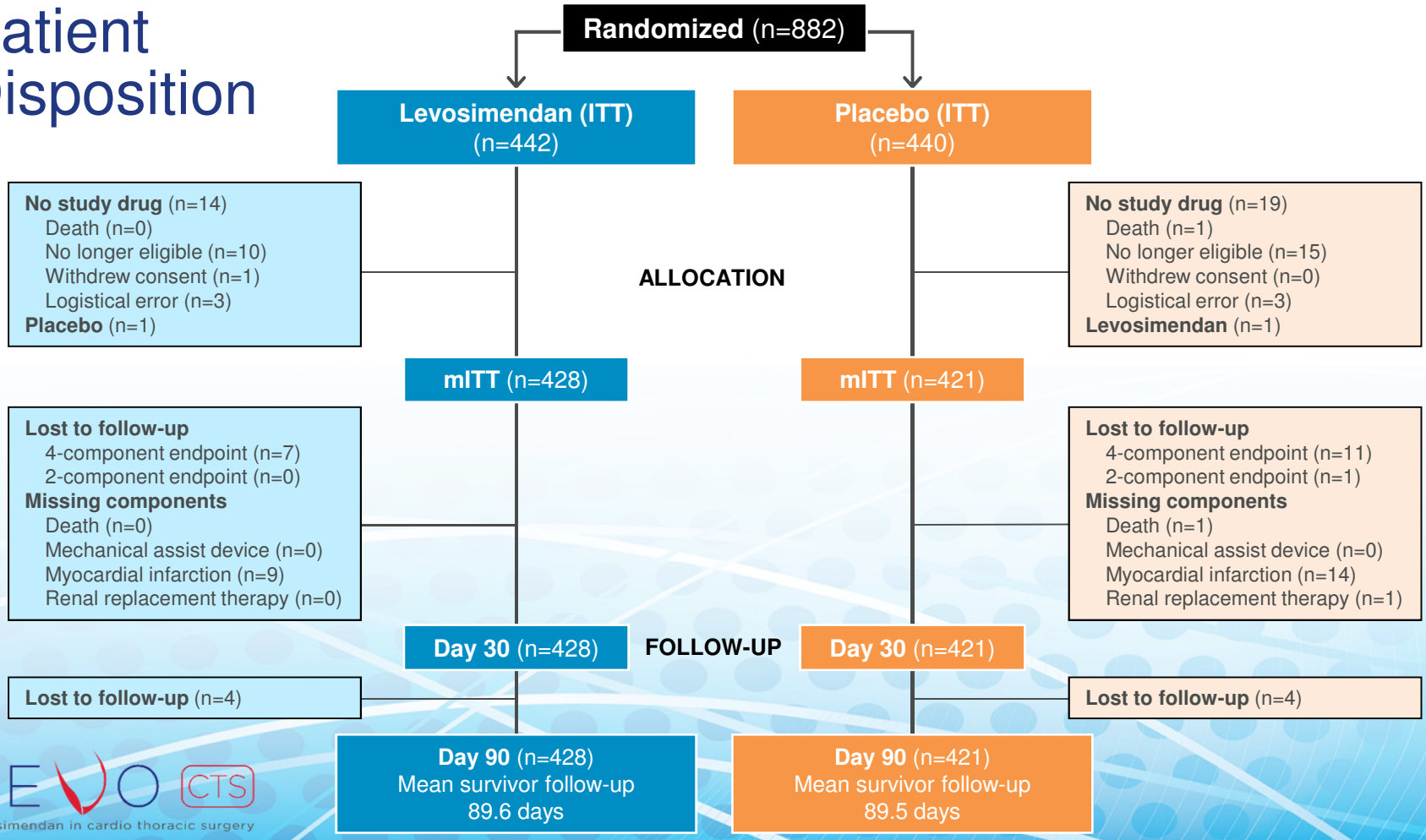
*Quad = death, dialysis, MI or mechanical assist
*Dual = Outcome = death or mechanical assist

Patient Disposition



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)
Dose modification	56 (13.1%)	29 (6.9%)
Study Drug Duration <23.5 hours	68 (15.7%)	48 (11.4%)

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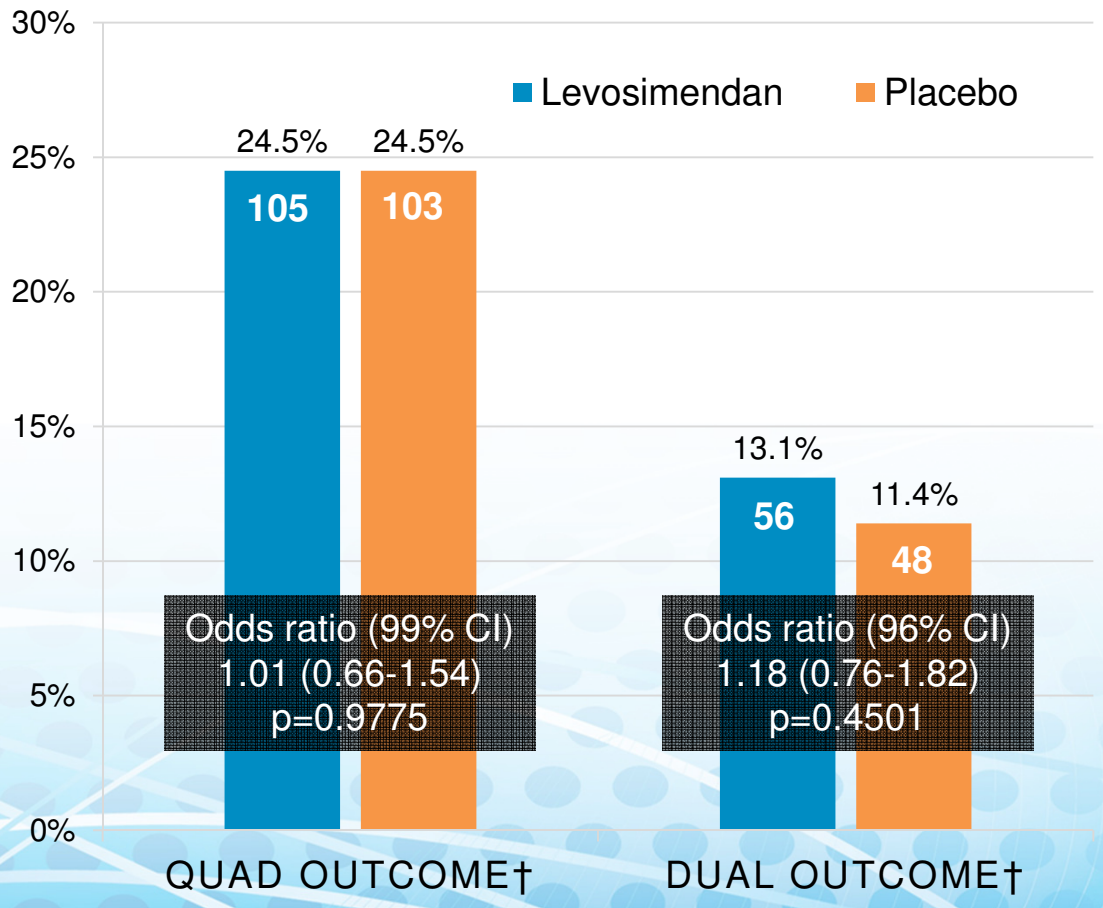
Co-Primary Outcomes



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

Dual Outcome = death or mechanical assist device use

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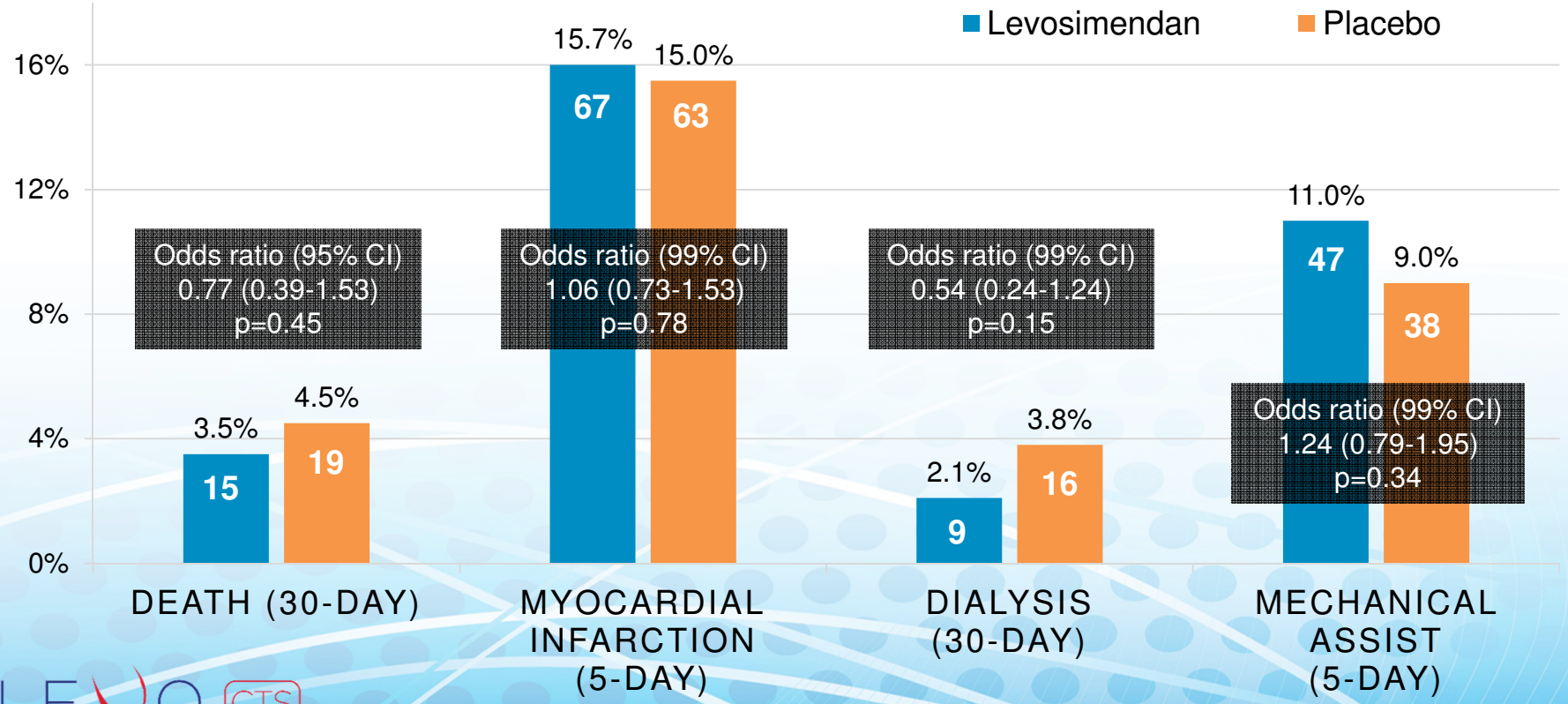
†Adjusted for covariates: type of surgery, LVEF, age, sex

Individual Outcomes Components



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Cardiac Output

Cardiac Index	**Mean (SD)**	
Levosimendan (n=359)	2.86 (0.61)	p<0.0001
Placebo (n=340)	2.68 (0.65)	

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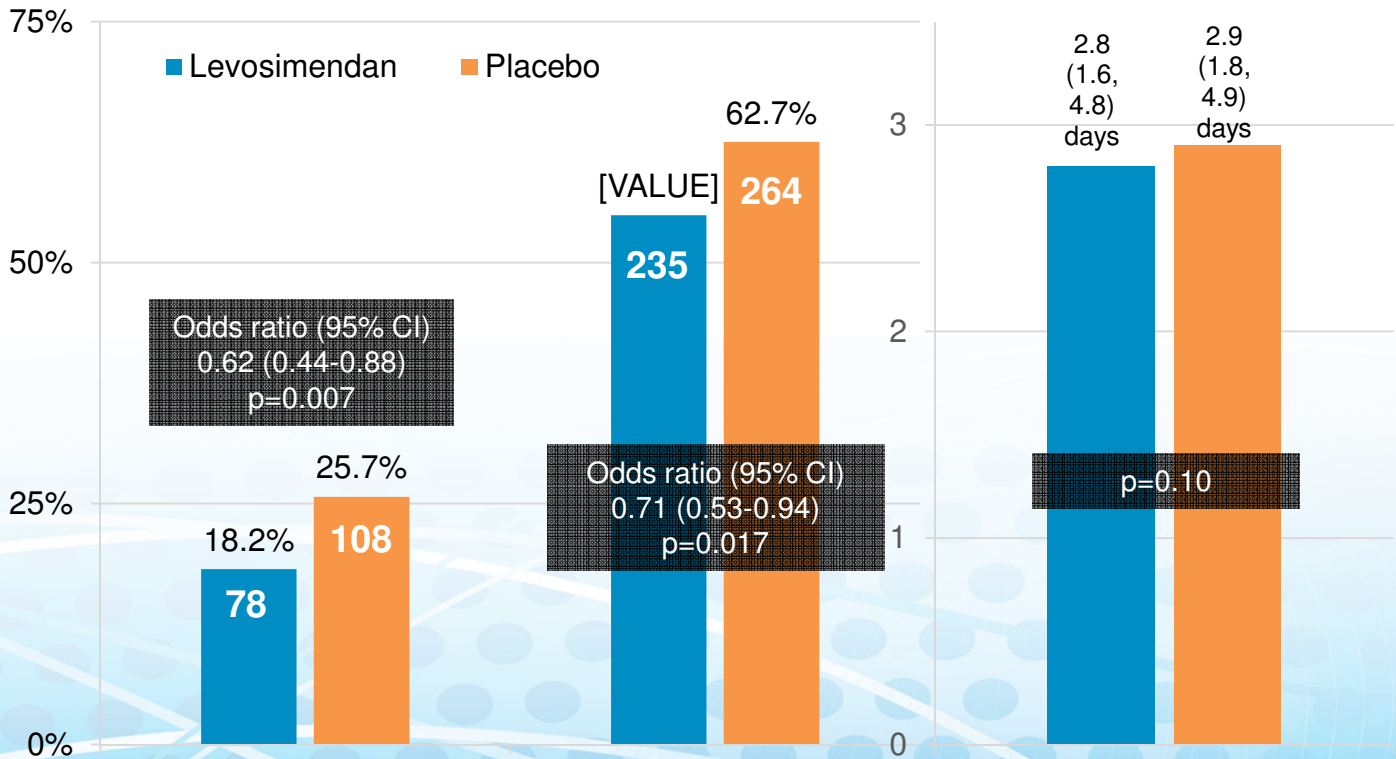
Secondary Outcomes



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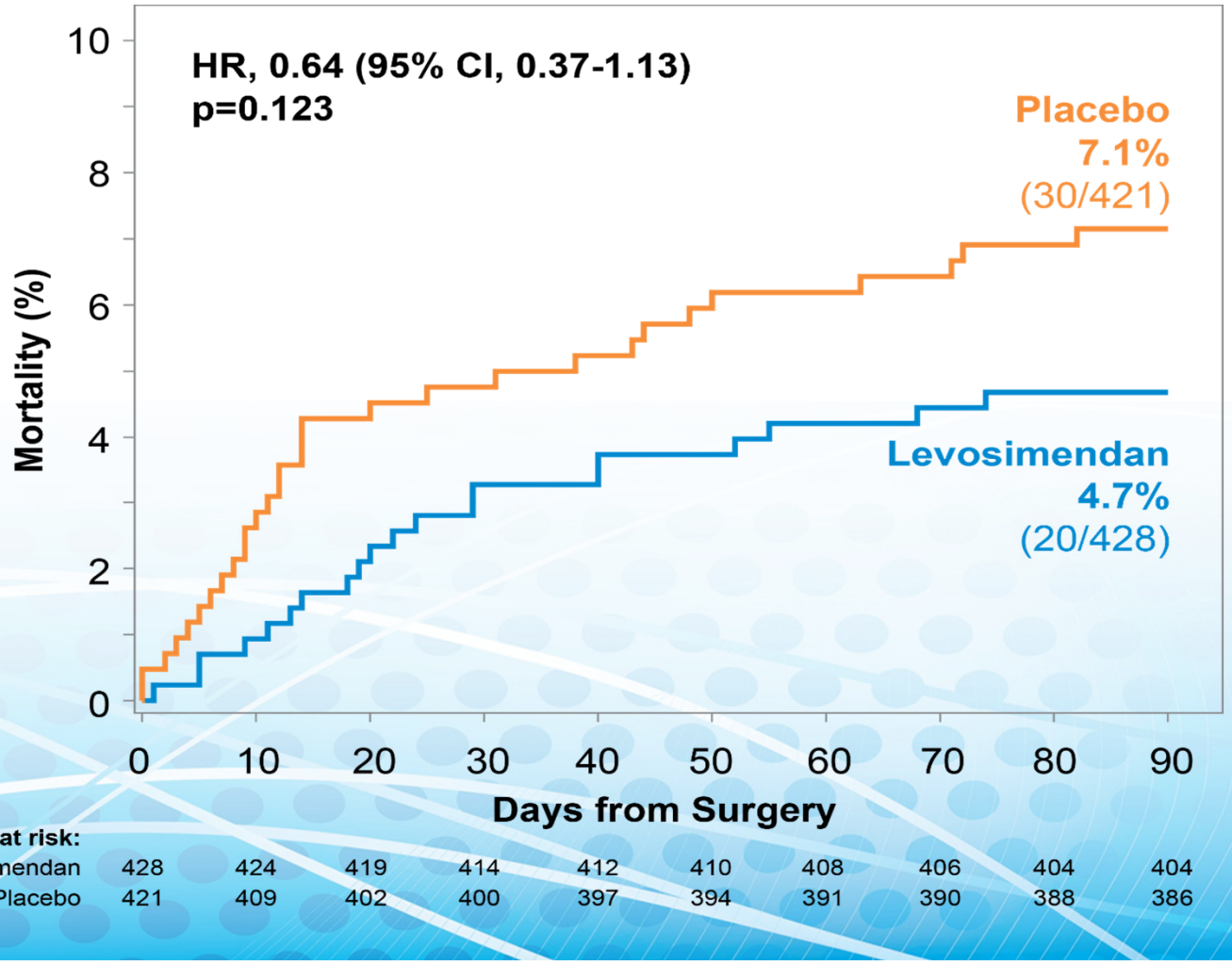
30-Day Safety Outcomes

	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

90-Day Mortality



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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 is 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.

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Thank you!

Publication