KURT WEILL'S

AUFSTIEG UND FALL DER STADT

~~MAHAGONNY~~

THE ~~M~~AGONNY

Levosimendan

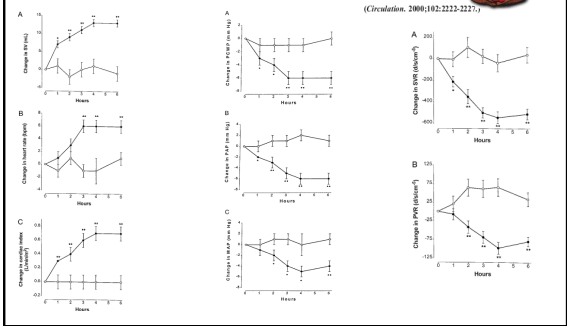
Martin Hülsmann

Libretto by ~~Bertolt Brecht~~

Acute Hemodynamic and Clinical Effects of Levosimendan in Patients With Severe Heart Failure

Mara T. Slawsky, MD, PhD; Wilson S. Colucci, MD; Stephen S. Gottlieb, MD; Barry H. Greenberg, MD; Ernest Haeusslein, MD; Joshua Hare, MD; Steven Hutchins, MD; Carl V. Leier, MD; Thierry H. LeJemtel, MD; Evan Loh, MD; John Nicklas, MD; David Ogilby, MD; Bramah N. Singh, MD, PhD; William Smith, MD; on behalf of the Study Investigators

(*Circulation.* 2000;102:2222-2227.)

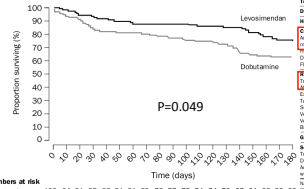


ARTICLES

Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial

F Follath, J G F Cleland, H Just, J G Y Papp, H Scholz, K Peuhkurinen, V P Harjola, V Mitrovic, M Abdalla, E-P Sandell, L Lehtonen, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study*

Lancet 2002; **360:** 196–202



Numbers at risk

Dobutamine	100	94	91	85	82	81	81	80	78	77	75	74	74	72	67	64	63	62	62
Levosimendan	103	101	97	96	94	92	91	90	90	90	90	88	88	87	87	83	80	77	76

Figure 4: **Kaplan-Meier estimates (analysis of time to first event) of risk of death during first 180 days after randomisation (based on the intention-to-treat analysis)**

	Number of patients with adverse events		p*
	Dobutamine (n=100)	Levosimendan (n=103)	
Total adverse events	42	48	0·88
Disorder aggravated	4	2	0·44
Headache or migraine	5	14	0·052
Cardiac and vascular disorders			
Angina pectoris, chest pain or myocardial ischaemia	7	0	0·013
Hypotension	4	2	0·450
Dizziness	1	0	NA
Flushing	3	1	0·207
Rate and rhythm disorders			
Total	13	4	0·023
Atrial fibrillation	3	1	0·304
Extrasystoles	3	1	0·304
Tachycardia	3	0	NA
Supraventricular tachycardia	3	0	NA
Ventricular tachycardia	2	1	0·618
Ventricular fibrillation	1	1	1·0
Bradycardia	1	1	1·0
Gastrointestinal disorders	7	2	0·098
Serious adverse events			
Total	5	1	NA
Deaths	3	0	NA
Adverse events leading to withdrawal	10	6	NA

NA=not analysed. Some patients had more than one adverse event. *Fisher's exact test.

Table 3: **Adverse events during the 24-h treatment period**

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http://dx.doi.org/10.1016/j.jchf.2012.12.004

CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

Milton Packer, MD,* Wilson Colucci, MD,† Lloyd Fisher, PhD,† Barry M. Massie, MD,‡ John R. Teerlink, MD,§ James Young, MD,‖ Robert J. Padley, MD,¶ Roopal Thakkar, MD,¶ Leticia Delgado-Herrera, RPh,¶ Jeffrey Salon, MD,¶ Chris Garratt, MB, ChB,# Bidan Huang, PhD,¶ Toni Sarapohja, MSc,# for the REVIVE Heart Failure Study Group

Dallas, Texas; Boston, Massachusetts; Seattle, Washington; San Francisco, California; Cleveland, Ohio; Abbott Park, Illinois; and Espoo, Finland

Recruitment 2001-2004, publiziert 2013

JACC: Heart Failure
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EDITORIAL COMMENT

Better Late Than Never

A Welcome Publication of Tardy Clinical Trial Results*

Robert M. Califf, MD

Durham, North Carolina

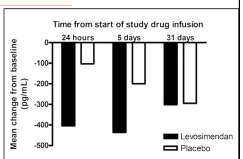

Figure 2 **Change in Plasma B-Type Natriuretic Peptide During and After Infusion of Levosimendan in REVIVE II**

REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy.

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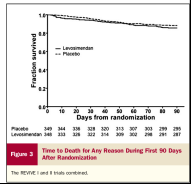

Figure 3 **Time to Death for Any Reason During First 90 Days After Randomization**

The REVIVE I and II trials combined.

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CLINICAL RESEARCH

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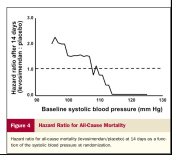


Figure 4 Hazard Ratio for All-Cause Mortality

Hazard ratio for all-cause mortality (levosimendan/placebo) at 14 days as a function of the systolic blood pressure at randomization.

European Journal of Heart Failure (2014) **16**, 898–906
doi:10.1002/ejhf.118

Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial

Johann Altenberger[1], John T. Parissis[2], Angelika Costard-Jaeckle[3], Andreas Winter[4], Christian Ebner[5], Apostolos Karavidas[6], Kurt Sihorsch[7], Ekaterini Avgeropoulou[8], Thomas Weber[9], Lida Dimopoulos[10], Hanno Ulmer[11], and Gerhard Poelzl[12]*

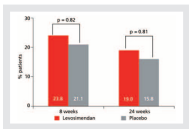


Figure 2 Effects of treatment with levosimendan vs. placebo on the primary endpoint (concomitant improvement in 6 min walk test of ≥20% and Kansas City Cardiomyopathy Questionnaire clinical summary score of ≥15%) after 8 and 24 weeks. The percentages of patients who reached the primary endpoint did not differ between the two groups (Fisher's exact test).

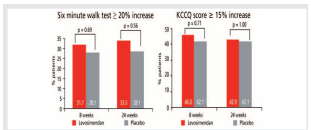


Figure 3 Effects of treatment with levosimendan and placebo on components of the primary endpoint after 8 and 24 weeks (Fisher's exact test). KCCQ, Kansas City Cardiomyopathy Questionnaire.

European Journal of Heart Failure (2014) **16**, 898–906
doi:10.1002/ejhf.118

Efficacy and safety of the pulsed infusions of levosimen heart fail randomiz

Johann Altenber
Christian Ebner
Thomas Weber

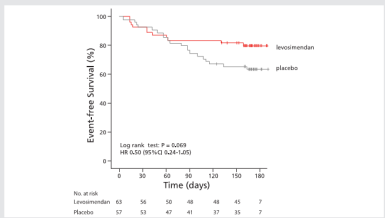


Figure 5 Event-free survival during the 24-week follow-up period. Kaplan–Meier curves are shown for the secondary endpoint comprising freedom from death, heart transplantation, or acute heart failure during the first 180 days after randomization (based on the intention-to-treat analysis). CI, confidence interval; HR, hazard ratio.

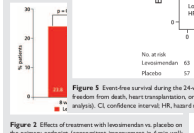
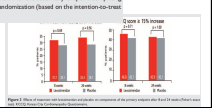


Figure 2 Effects of treatment with levosimendan vs. placebo on the primary endpoint (concomitant improvement in 6 min walk test of ≥20% and Kansas City Cardiomyopathy Questionnaire clinical summary score of ≥15%) after 8 and 24 weeks. The percentages of patients who reached the primary endpoint did not differ between the two groups (Fisher's exact test).



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Vermiero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

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Table 2. Prespecified Clinical Outcomes.*

Outcome	Levosimendan (N = 248)	Placebo (N = 258)	Difference (95% CI)†	P Value
Primary outcome				
30-Day mortality — no. (%)	32 (12.9)	33 (12.8)	0.1 (−5.7 to 5.9)	0.97
Secondary outcomes				
Acute kidney injury, according to RIFLE criteria — no./total no. (%)‡				
Risk	41/247 (16.6)	55/258 (21.3)	−4.7 (−11.5 to 2.1)	0.18
Injury	26/247 (10.5)	27/258 (10.5)	0.1 (−5.3 to 5.4)	0.98
Failure	17/247 (6.9)	22/258 (8.5)	−1.6 (−6.3 to 3.0)	0.49
Renal-replacement therapy — no. (%)	24 (9.7)	33 (12.8)	−3.1 (−8.6 to 2.4)	0.27
Death or renal-replacement therapy — no. (%)	42 (16.9)	49 (19.0)	−2.1 (−8.7 to 4.6)	0.55
Duration of mechanical ventilation — hr				
Median	19	21	−2 (−5 to 1)	0.48
Interquartile range	14 to 40	14 to 41		
Duration of ICU stay — hr				
Median	72	84	−12 (−21 to 2)	0.08
Interquartile range	46 to 114	48 to 139		
Duration of hospital stay — days				
Median	14	14	0 (−1 to 2)	0.39
Interquartile range	8 to 21	9 to 21		
Need for open-label levosimendan — no. (%)	2 (0.8)	8 (3.1)	−2.3 (−4.7 to 0.1)	0.11
Interruption of infusion due to adverse events — no./total no. (%)	9/236 (3.8)	4/246 (1.6)	2.2 (−0.7 to 5.1)	0.17

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Table 3. Additional Clinical and Safety Outcomes.

Outcome	Levosimendan (N = 248)	Placebo (N = 258)	Difference (95% CI)*	P Value
Clinical outcomes				
ECMO — no./total no. (%)	3/245 (1.2)	2/257 (0.8)	0.4 (−1.3 to 2.2)	0.68
Ventricular assist device — no./total no. (%)	1/244 (0.4)	1/257 (0.4)	0.0 (−1.1 to 1.1)	0.99
Myocardial infarction — no./total no. (%)	14/245 (5.8)	15/257 (5.8)	−0.1 (−4.2 to 4.0)	0.99
Neurologic damage — no./total no. (%)†				
Type 1	11/247 (4.5)	9/258 (3.5)	1.0 (−2.4 to 4.4)	0.58
Type 2	30/247 (12.1)	37/258 (14.3)	−2.2 (−8.1 to 3.7)	0.47
Need for tracheostomy — no./total no. (%)	17/247 (6.9)	14/255 (5.5)	1.4 (−2.8 to 5.6)	0.52
Sepsis — no./total no. (%)	16/246 (6.5)	17/255 (6.7)	−0.2 (−4.5 to 4.2)	0.93
Severe sepsis — no./total no. (%)	9/245 (3.7)	13/255 (5.1)	−1.4 (−5.0 to 2.1)	0.43
Septic shock — no./total no. (%)	6/245 (2.4)	10/255 (3.9)	−1.5 (−4.8 to 1.8)	0.35
Mediastinitis — no./total no. (%)	1/242 (0.4)	4/255 (1.6)	−1.2 (−2.9 to 0.6)	0.37
Pneumonia — no./total no. (%)	15/243 (6.2)	13/255 (5.9)	0.2 (−4.0 to 4.4)	0.91
Transfusion in operating room or ICU				
Red-cell transfusion				
No. of patients (%)	125 (50.4)	141 (54.7)	−4.2 (−12.9 to 4.4)	0.34
Units per patient				
Median	2.0	3.0	−1.0 (−1.0 to 1.0)	0.21
Interquartile range	2.0 to 4.0	2.0 to 5.0		
Fresh-frozen plasma transfusion				
No. of patients (%)	72 (29.0)	90 (34.9)	−5.9 (−14.0 to 2.2)	0.16
Units per patient				
Median	3.0	3.0	0.0 (−2.0 to 1.0)	0.40
Interquartile range	2.0 to 4.0	2.0 to 7.0		
Platelet transfusion				
No. of patients (%)	17 (6.9)	26 (10.1)	−3.1 (−8.1 to 1.6)	0.19
Units per patient				
Median	1.0	1.0	0.0 (−1.0 to 1.0)	0.37
Interquartile range	1.0 to 2.0	1.0 to 3.0		
Death — no./total no. (%)				
In the ICU	24/248 (9.7)	19/258 (7.4)	2.3 (−2.6 to 7.2)	0.35
In the hospital	31/248 (12.5)	31/258 (12.0)	0.5 (−5.2 to 6.2)	0.87
At 180 days	38/248 (15.3)	39/254 (15.4)	0.0 (−6.3 to 6.3)	0.99
Safety outcomes				
Hypotension during infusion — no./total no. (%)	62/246 (25.2)	54/253 (21.3)	3.9 (−3.8 to 11.3)	0.31
Managed with vasoconstrictors	43/54 (76.8)	40/53 (75.5)	1.3 (−14.7 to 17.3)	0.87
Managed with dose reduction	26/59 (51.0)	19/45 (42.2)	10.7 (−9.2 to 30.6)	0.29
Arrhythmias during infusion — no./total no. (%)				
Supraventricular	35/246 (14.2)	43/254 (16.9)	−2.7 (−9.1 to 3.7)	0.41
Ventricular	4/246 (1.6)	7/254 (2.8)	−1.1 (−3.7 to 1.4)	0.55
Serious adverse event — no./total no. (%)				
Considered by investigator to be due to trial regimen	0/244	0/254	—	—
Any	107/245 (43.7)	131/254 (51.6)	−7.9 (−16.4 to 0.8)	0.08

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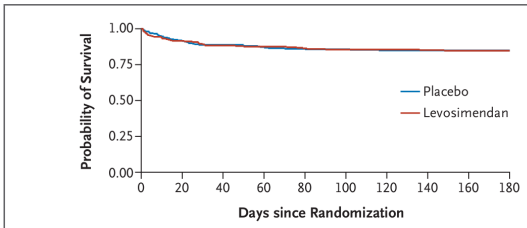

No. at Risk

Placebo	258	237	229	225	222	221	219	219	219	219
Levosimendan	248	227	219	217	214	212	212	211	210	210

Figure 2. Kaplan–Meier Survival Estimates of All-Cause Mortality.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Bobodzhko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

Table 1. (Continued.)

Characteristic	Levosimendan (N=248)	Placebo (N=258)
Inclusion criteria — no. (%)‡		
Preoperative left ventricular ejection fraction <25%	11 (4.4)	11 (4.3)
Intraaortic balloon pump	50 (20.2)	44 (17.1)
High doses of inotropes received for weaning from cardiopulmonary bypass	33 (13.3)	28 (10.9)
High doses of inotropes administered in ICU	154 (62.1)	175 (67.8)

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*

Table 4. End Points.*

End Point	Levosimendan (N = 428)	Placebo (N = 421)	Odds Ratio (95% CI)†	P Value
Primary end points — no. (%)				
Four-component end point‡	105 (24.5)	103 (24.5)	1.00 (0.66–1.54)	0.98
Two-component end point§	56 (13.1)	48 (11.4)	1.18 (0.76–1.82)	0.45
Components of primary end points — no. (%)				
Death at 30 days	15 (3.5)	19 (4.5)	0.77 (0.38–1.53)	0.45
Renal-replacement therapy at 30 days	9 (2.1)	16 (3.8)	0.54 (0.24–1.24)	0.15
Myocardial infarction at 5 days	67 (15.7)	63 (15.0)	1.06 (0.73–1.53)	0.78
Use of mechanical cardiac assist device at 5 days	47 (11.0)	38 (9.0)	1.24 (0.79–1.95)	0.34
Secondary end points¶				
Duration of stay in ICU — days‖				
Median	2.8	2.9	—	0.25
Interquartile range	1.6–4.8	1.8–4.9		
Low cardiac output syndrome — no. (%)‖	78 (18.2)	108 (25.7)	0.62 (0.44–0.88)	0.007
Use of inotrope at or beyond 24 hr after infusion initiation — no. (%)‖	235 (54.9)	264 (62.7)	0.71 (0.53–0.94)	0.02
Other efficacy end points — no. (%)				
Rehospitalization at 30 days‖	54 (12.6)	48 (11.4)	1.14 (0.75–1.7)	0.55
Myocardial infarction at 6–30 days	1 (0.2)	0	—	—
Safety end points — no. (%)				
Death at 90 days	20 (4.7)	30 (7.1)	0.64 (0.37–1.13)	0.12
Any adverse event	238 (55.6)	232 (55.1)	—	0.86
Adverse event considered by site investigator to be related to trial regimen	9 (2.1)	13 (3.1)	—	0.34
Any serious adverse event	77 (18.0)	70 (16.6)	—	0.62
Serious adverse event necessitating permanent discontinuation of trial regimen	6 (1.4)	3 (0.7)	—	0.42
Common prespecified postoperative events — no. (%)‖¶				
Hypotension	155 (36.2)	138 (32.8)	—	0.29
Atrial fibrillation	163 (38.1)	139 (33.0)	—	0.12
Ventricular tachycardia or fibrillation	46 (10.7)	41 (9.7)	—	0.63
Resuscitated cardiac arrest	8 (1.9)	7 (1.7)	—	0.82
Stroke	15 (3.5)	10 (2.4)	—	0.33
Deep-venous thrombosis	3 (0.7)	3 (0.7)	—	0.98
Pulmonary embolism	0	3 (0.7)	—	0.08
Mechanical ventilation for >24 hr	35 (8.2)	37 (8.8)	—	0.75
Pneumonia	9 (2.1)	14 (3.3)	—	0.27
Congestive heart failure	46 (10.7)	57 (13.5)	—	0.21
Wound infection	13 (3.0)	12 (2.9)	—	0.87

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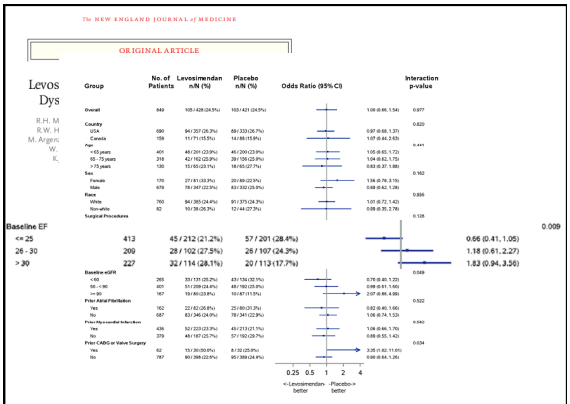
ORIGINAL ARTICLE



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

A.C. Gordon, G.D. Perkins, M. Singer, D.F. McAuley, R.M.L. Orme, S. Santhakumaran, A.J. Mason, M. Cross, F. Al-Beidh, J. Best-Lane, D. Brealey, C.L. Nutt, J.J. McNamee, H. Reschreiter, A. Breen, K.D. Liu, and D. Ashby

ABSTRACT

Table 3. Clinical Outcomes.*

Outcome	Levosimendan (N = 258)	Placebo (N = 257)	Absolute Difference (95% CI)†	P Value
Primary outcome				
Mean daily total SOFA score	6.68±3.96	6.06±3.89	0.61 (−0.07 to 1.29)	0.053
Respiratory	1.30±1.18	1.56±1.15	0.14 (−0.06 to 0.34)	0.23
Coagulation	0.75±1.05	0.75±1.02	0.00 (−0.18 to 0.17)	0.55
Hepatic	0.51±0.84	0.45±0.77	0.06 (−0.08 to 0.19)	0.65
Cardiovascular	2.27±1.20	2.02±1.20	0.25 (0.04 to 0.46)	0.01
Renal	1.40±1.49	1.28±1.38	0.13 (−0.07 to 0.42)	0.32
Mean daily SOFA score excluding cardiovascular score	4.41±3.13	4.05±3.07	0.36 (−0.17 to 0.90)	0.12
Mean daily total SOFA score in the sensitivity analysis‡	7.19±3.72	6.78±3.74	0.41 (−0.24 to 1.06)	—
Secondary outcomes				
Death — no./total no. (%)§				
At 28 days	89/258 (34.5)	79/256 (30.9)	3.6 (−4.5 to 11.7)	0.43
At ICU discharge	83/258 (32.2)	76/257 (29.6)	2.6 (−5.4 to 10.6)	0.59
At hospital discharge	97/258 (37.6)	84/256 (32.8)	4.8 (−3.5 to 13.0)	0.30
Median no. of catecholamine-free days (IQR)	22 (0 to 26)	23 (0 to 26)	−1.0 (−4.5 to 1.0)	0.09
Median no. of ventilation-free days (IQR)	16 (0 to 25)	19 (0 to 25)	−3.0 (−9.5 to 1.0)	0.14
Major acute kidney event over period of 28 days — no./total no. (%)	148/258 (57.4)	139/256 (54.3)	3.1 (−5.5 to 11.6)	0.54
Need for new renal-replacement therapy	62/257 (24.1)	62/257 (24.1)	0.0 (−7.4 to 7.4)	>0.99
Sustained renal failure at day 28 or ICU discharge if before 28 days	118/258 (45.7)	108/257 (42.0)	3.7 (−4.9 to 12.3)	0.45
Median duration of renal-replacement therapy (IQR) — days	3.0 (1.0 to 8.0)	5.0 (2.0 to 9.0)	−2.0 (−3.0 to 0.0)	0.24
Median length of ICU stay (IQR) — days				
All patients	7.3 (3.2 to 14.8)	8.3 (3.9 to 13.5)	−1.0 (−2.6 to 0.8)	0.66
Survivors	9.1 (5.0 to 16.1)	9.0 (4.9 to 14.1)	0.2 (−2.0 to 2.7)	0.31
Nonsurvivors	3.2 (1.4 to 8.9)	5.7 (2.2 to 11.7)	−2.6 (−5.7 to −0.8)	0.09
Median length of hospital stay (IQR) — days				
All patients	19.6 (10.1 to 40.4)	22.7 (11.7 to 42.3)	−3.1 (−7.0 to 2.2)	0.24
Survivors	30.1 (16.8 to 48)	27.7 (18 to 52.3)	2.5 (−5.9 to 8.2)	0.81
Nonsurvivors	8.2 (3.4 to 18.6)	11.3 (5.1 to 25.7)	−3.1 (−6.5 to 0.7)	0.25
Safety outcomes				
Any serious adverse event — no. (%)	32 (12.4)	23 (8.9)	3.5 (−2.3 to 9.2)	0.26
Any life-threatening arrhythmia — no. (%)	15 (5.8)	6 (2.3)	3.5 (−0.3 to 7.3)	0.08
Supraventricular tachyarrhythmia	8 (3.1)	1 (0.4)	2.7 (0.1 to 5.3)	0.04
Bradycardia	0	2 (0.8)	−0.8 (−2.2 to 0.7)	0.48
Ventricular fibrillation or tachycardia	7 (2.7)	3 (1.2)	1.5 (−1.2 to 4.3)	0.34
Myocardial infarction or acute coronary syndrome — no. (%)	3 (1.2)	1 (0.4)	0.8 (−1.1 to 2.7)	0.62
Other — no. (%)¶	18 (7.0)	17 (6.8)	0.4 (−4.3 to 5.1)	>0.99

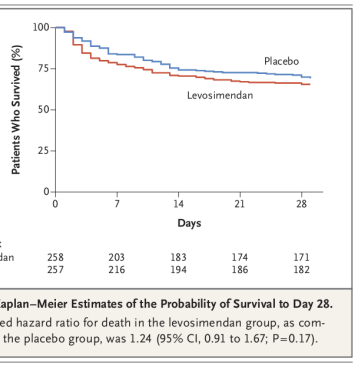
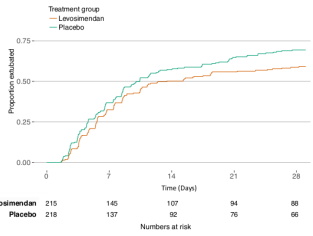


Figure 2. Kaplan–Meier Estimates of the Probability of Survival to Day 28.
The adjusted hazard ratio for death in the levosimendan group, as compared with the placebo group, was 1.24 (95% CI, 0.91 to 1.67; P=0.17).

Figure S13. Time to successful weaning from mechanical ventilation in patients ventilated at baseline / day 1



Red line = levosimendan group, green line = placebo group. The hazard ratio in the levosimendan group compared with placebo was 0.77, (95%CI, 0.60 to 0.97, p=0.03).

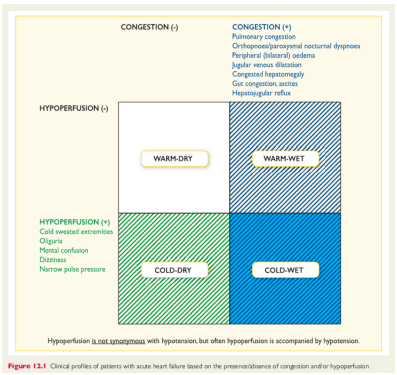
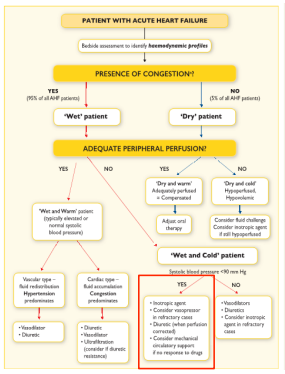


Figure 12.1 Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion



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ESC GUIDELINES

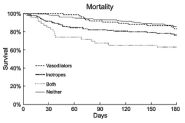
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors			
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/ symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	IIb	C	
An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.	IIb	C	
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	III	A	556,557

Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure

Uri Elkayam, MD,[a] Godaye Tasissa, PhD,[b] Cynthia Binanay, RN, BSN,[b] Lynne W. Stevenson, MD,[c] Mihai Gheorghiade, MD,[d] J. Wayne Warnica, MD,[e] James B. Young, MD,[f] Barry K. Rayburn, MD,[g] Joseph G. Rogers, MD,[h] Teresa DeMarco, MD,[h] and Carl Y. Leier, MD[i] *Los Angeles and San Francisco, CA; Durham, NC; Boston, MA; Chicago, IL; Calgary, Alberta, Canada; Cleveland and Columbus, OH; and Birmingham, AL*

Figure 1



Kaplan-Meier survival curve for all-cause mortality by intravenous vasoactive medication use.

Table IV. Propensity score–adjusted multivariable risk factors for mortality

	HR (95% CI)	P
IV vasoactive therapy		
Vasodilator	1.39 (0.64-3.00)	.403
Inotrope	2.14 (1.10-4.15)	.024
Both	4.81 (2.34-9.90)	<.001
Sodium	0.92 (0.87-0.98)	.006
RAP*	1.03 (1.01-1.05)	.008
BNP (100 U)	1.02 (1.01-1.04)	.006
SUN (10 U)	1.13 (1.02-1.26)	.018
Age (10 y)	1.21 (0.97-1.51)	.087
Ischemic etiology	1.58 (0.91-1.73)	.104
Systolic blood pressure <100 (dichotomous)	1.60 (0.99-2.58)	.055

IV, Intravenous.
*In patients with a pulmonary artery catheter.

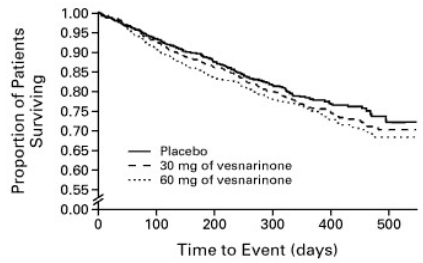
Table V. Propensity score–adjusted multivariable risk factors for mortality or rehospitalization

	HR (95% CI)	P
IV vasoactive therapy		
Vasodilator	1.20 (0.81-1.78)	.370
Inotrope	1.96 (1.37-2.82)	<.001
Both	2.90 (1.88-4.48)	<.001
SUN (10 U)	1.12 (1.05-1.20)	.001
Site	NA	.064
Systolic blood pressure <100 (dichotomous)	1.48 (1.13-1.92)	.004
PCWP*	1.02 (0.99-1.04)	.079
Ischemic etiology	1.14 (0.88-1.49)	.318
Sodium	0.98 (0.95-1.01)	.227

*In patients with a pulmonary artery catheter.

Dobutamine[a]	No	2–20 µg/kg/min (beta+)
Dopamine	No	3–5 µg/kg/min; inotropic (beta+)
		>5 µg/kg/min: (beta+), vasopressor (alpha+)
Milrinone[a,b]	25–75 µg/kg over 10–20 min	0.375–0.75 µg/kg/min
Enoximone[a]	0.5–1.0 mg/kg over 5–10 min	5–20 µg/kg/min

A Dose-Dependent Increase in Mortality with Vesnarinone among Patients with Severe Heart Failure
Survival in the Three Groups.



Cohn JN et al. N Engl J Med 1998;339:1810-1816.

The NEW ENGLAND JOURNAL of MEDICINE

A Dose-Dependent Increase in Mortality with Vesnarinone among Patients with Severe Heart Failure
Causes of Death in the Three Groups.

TABLE 2. CAUSES OF DEATH IN THE THREE GROUPS.*

VARIABLE	PLACEBO (N=1283)			30 mg OF VESNARINONE (N=1275)			60 mg OF VESNARINONE (N=1275)		
	NO.	% OF RANDOMIZED PATIENTS	% OF DEATHS	NO.	% OF RANDOMIZED PATIENTS	% OF DEATHS	NO.	% OF RANDOMIZED PATIENTS	% OF DEATHS
Death from any cause	242	18.9	100	268	21.0	100	292	22.9	100
Death from cardiac causes	231	18.0	95.5	248	19.5	92.5	271	21.3†	92.8
Sudden death‡	117	9.1	48.3	136	10.7	50.7	157	12.3	53.8
Pump failure	109	8.5	45.0	106	8.3	39.6	106	8.3	36.3
Myocardial infarction	5	0.4	2.1	6	0.5	2.2	8	0.6	2.7
Death from noncardiac causes	11	0.9	4.5	20	1.6	7.5	21	1.6	7.2

*Because of rounding, not all percentages total 100.

†$P = 0.02$ for the distribution of cardiac causes of death in the 60-mg vesnarinone group as compared with the placebo group.

‡Hazard ratio for sudden death in the 60-mg vesnarinone group as compared with the placebo group, 1.35 (95 percent confidence interval, 1.08 to 1.69).

Cohn JN et al. N Engl J Med 1998;339:1810-1816.

The NEW ENGLAND JOURNAL of MEDICINE

Intensive Care Med (2016) 42:1322–1335
DOI 10.1007/s00134-016-4449-6

SYSTEMATIC REVIEW

Milrinone for cardiac dysfunction in critically ill adult patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential an

Geert Koster[1*], Hanneke J. Bekema[2], Jann Wetter and Iwan C.C. van der Horst[3]

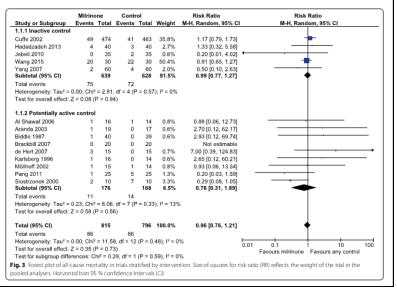
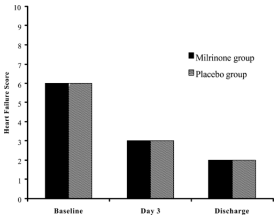


Fig. 3 Forest plot of all-cause mortality in trials stratified by intervention. Size of square for risk ratio (RR) reflects the weight of the trial in the pooled analyses. *Horizontal bars* 95 % confidence intervals (CI)

OPTIME in CHF trial: rethinking the use of inotropes in the management of worsening chronic heart failure resulting in hospitalization



European Journal of Heart Failure
Volume 5, Issue 1, pages 9-12, 27 JAN 2003 DOI: 10.1016/S1388-9842(02)00178-2
http://onlinelibrary.wiley.com/doi/10.1016/S1388-9842(02)00178-2/full#ejhf00178-2-fig-0001

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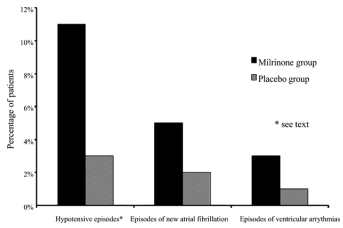

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OPTIME in CHF trial: rethinking the use of inotropes in the management of worsening chronic heart failure resulting in hospitalization

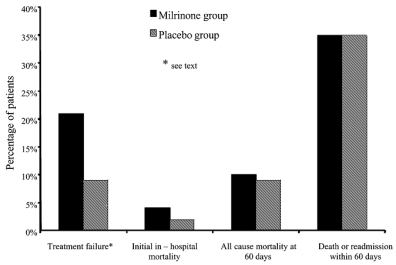

Fig. 3. End points of the OPTIME–CHF trial.

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http://onlinelibrary.wiley.com/doi/10.1016/S1388-9842(02)00178-2/full#ejhf00178-2-fig-0002

CLINICAL RESEARCH
Heart failure

Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials

Marco Metra[1*], Eric Eichhorn[2], William T. Abraham[3], Jennifer Linseman[4], Michael Böhm[5], Ramon Corbalan[6], David DeMets[7], Teresa De Marco[8], Uri Elkayam[9], Michael Gerber[4], Michel Komajda[10], Peter Liu[11], Vyacheslav Maroo[12], Sergio V. Parmon[13], Philip Poole-Wilson[14], Ellen Roecker[7], Jennifer Stewart[4], Kurt Swedberg[15], Michal Tendera[16], Brian White[4], and Michael R. Bristow[17] for the ESSENTIAL Investigators

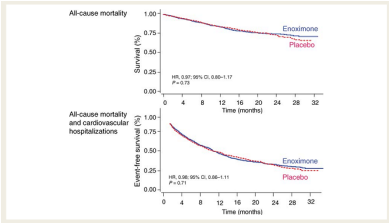


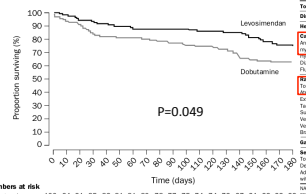
Figure 1 Kaplan–Meier estimates of the time to the safety endpoint of death (up) and to the primary endpoint of death or cardiovascular hospitalization (bottom).

ARTICLES

Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial

F Follath, J G F Cleland, H Just, J G Y Papp, H Scholz, K Peuhkurinen, V P Harjola, V Mitrovic, M Abdalla, E P Sandell, L Lehtonen, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study*

Lancet 2002; **360:** 196–202



Numbers at risk

Dobutamine	100	94	91	85	82	81	81	80	78	77	75	74	74	72	67	64	63	62	62
Levosimendan	103	101	97	96	94	92	91	90	90	90	90	88	88	87	87	83	80	77	76

Figure 4: **Kaplan-Meier estimates (analysis of time to first event) of risk of death during first 180 days after randomisation (based on the intention-to-treat analysis)**

	Number of patients with adverse events		p*
	Dobutamine (n=100)	Levosimendan (n=103)	
Total adverse events	42	48	0·88
Disorder aggravated	4	2	0·44
Headache or migraine	5	14	0·052
Cardiac and vascular disorders			
Angina pectoris, chest pain or myocardial ischaemia	7	0	0·013
Hypotension	4	2	0·692
Dizziness	1	0	NA
Flushing	3	1	0·207
Rate and rhythm disorders			
Total	13	4	0·023
Atrial fibrillation	3	1	0·304
Extrasystoles	3	1	0·304
Tachycardia	3	0	NA
Supraventricular tachycardia	3	0	NA
Ventricular tachycardia	2	1	0·618
Ventricular fibrillation	1	1	1·0
Bradycardia	1	1	1·0
Gastrointestinal disorders	7	2	0·098
Serious adverse events			
Total	5	1	NA
Deaths	3	0	NA
Adverse events leading to withdrawal	10	6	NA

NA=not analysed. Some patients had more than one adverse event. *Fisher's exact test.

Table 3: **Adverse events during the 24-h treatment period**

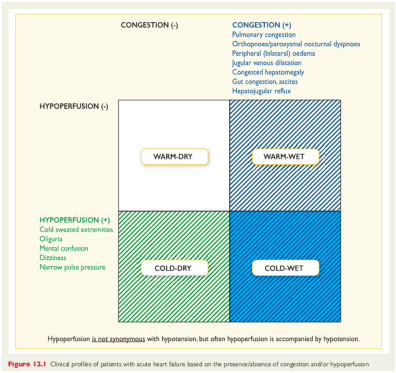
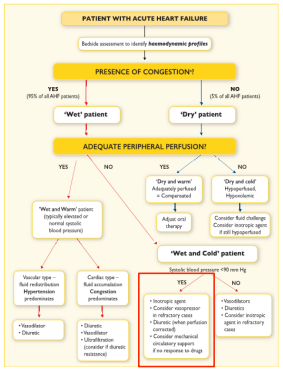


Figure 12.1 Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion



Ich brauche keine Inotropika/ Levosimendan

- Weil ich für Dobutamin keine Evidenz habe
- Weil ich für Milrinon/Enoximon nur negative Studien habe
- Weil ich für Levosimendan nur negative Studien habe
- Weil ich nur für einen kleinen Teil von Patienten mit HI eine intellektuelle Rationale habe

Ich brauche keine Inotropika/ Levosimendan

- Ich brauche eine differenzierte Betrachtungsweise für Patienten mit akuter HI
- Ich brauche Diuretika
- Ich brauche Volumen
- Ich brauche Vasodilatoren