Novas fronteiras em Cardiologia

Novidades na Insuficiência Cardíaca

Levosimendan: Regresso ao Futuro?

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European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for th… and treatment of acute and chr…

The Task… Chronic … Develope… of the ES…

Authors/Ta… Stamatis A… Auricchio (Switzerlan… Volkmar Fa… fonseca (Portugal), …en), Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

15.6 Acute he…

The treatment of acute hea… with little good evidence to guide …

Intravenous nitrates—efficacy and safety still uncertain.
Levosimendan—efficacy and safety still uncertain.
Omecamtiv mecarbil—is it effective and safe?
Ultrafiltration—efficacy and safety unknown.

Eficacia e segurança duvidosas
"gap in evidence"

Intensive Care Med (2011) 37:619–626
DOI 10.1007/s00134-010-2113-0

ORIGINAL

F. Follath
M. B. Yilmaz
J. F. Delgado
J. T. Parissis
R. Porcher
E. Gayat

Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)

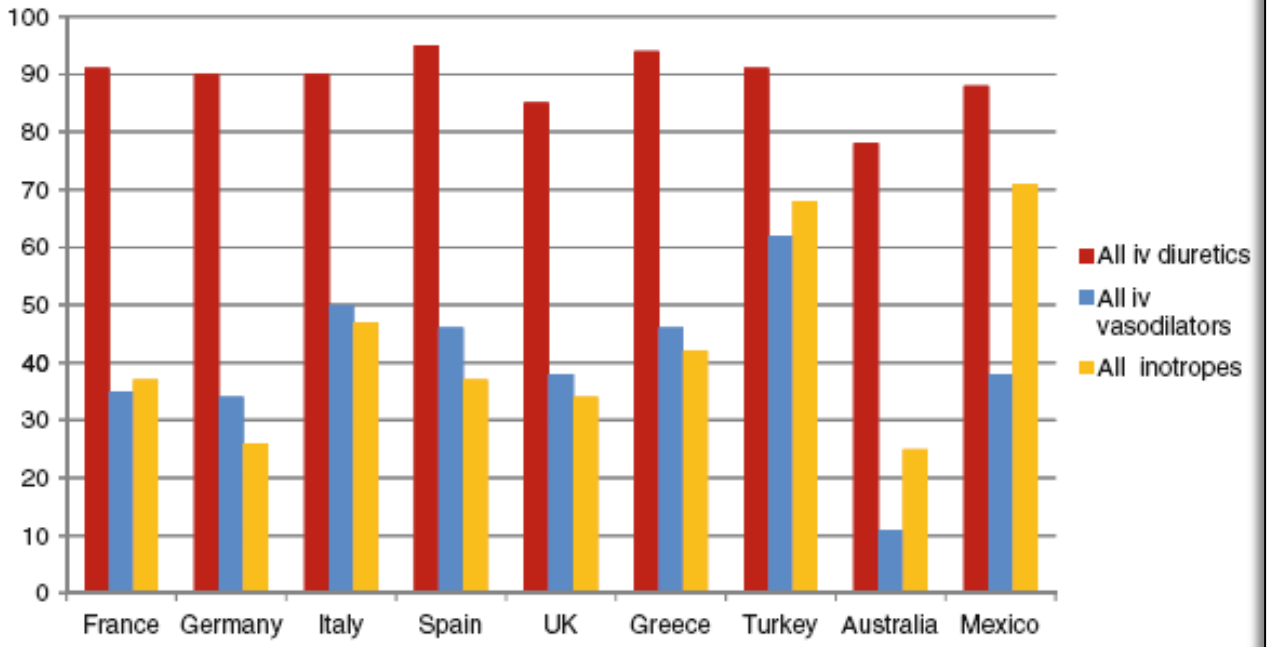


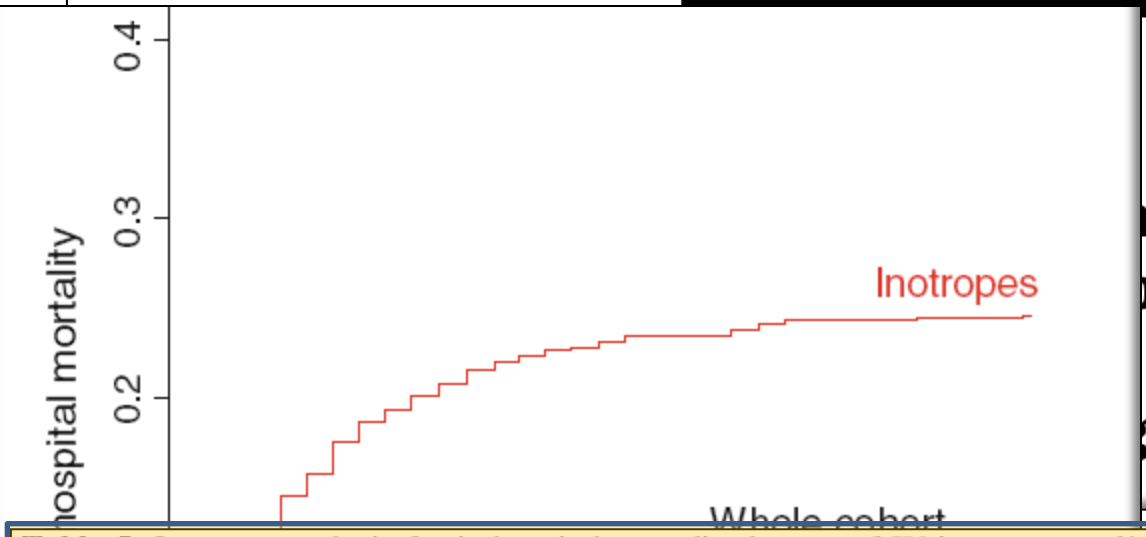
Fig. 2 Bar graph showing treatment strategies, namely intravenous diuretics, intravenous vasodilators and inotropes, among participating countries

Table 4 Outcomes and length of stay in ALARM-HF study

Novidades na IC – Levosimendan: regresso ao Futuro?

Intensive Care Med (2011) 37:290–301
DOI 10.1007/s00134-010-2073-4

ORIGINAL



l by treatment
ospitalized with acute heart
ALARM-HF registry using
g methods

Table 5 Outcome analysis for in-hospital mortality by use of IV inotropes and/or vasopressors during the first 48 h

Outcome analysis	Any inotrope/ vasopressor	Individual effect of inotropic and/or vasopressor agents				
		Dopamine	Dobutamine	Epinephrine	Norepinephrine	Levosimendan
Analysis on the whole cohort						
Unadjusted	5.34 (4.41–6.46)	2.48 (2.03–3.02)	2.78 (2.33–3.32)	4.16 (3.19–5.41)	2.88 (2.23–3.72)	0.71 (0.46–1.09)
Adjusted[a]	3.01 (2.39–3.78)	1.62 (1.30–2.02)	2.15 (1.76–2.61)	2.73 (2.04–3.65)	1.74 (1.31–2.29)	0.79 (0.50–1.24)
Propensity analysis I[b]						
Unadjusted	2.53 (1.98–3.22)	1.48 (1.05–2.07)	1.88 (1.43–2.46)	4.26 (2.61–6.94)	2.84 (1.93–4.16)	0.55 (0.30–1.02)
Adjusted[a]	2.43 (1.87–3.17)	1.30 (0.92–1.85)	1.84 (1.40–2.41)	3.98 (2.55–6.23)	1.77 (1.15–2.73)	0.86 (0.49–1.52)
Propensity analysis II[b]						
Unadjusted	2.62 (1.83–3.74)	1.44 (0.91–2.28)	1.79 (1.25–2.56)	3.39 (1.48–7.74)	3.68 (2.23–6.08)	0.61 (0.28–1.36)
Adjusted[a]	2.48 (1.70–3.60)	1.54 (0.94–2.53)	1.64 (1.09–2.47)	2.84 (1.35–5.98)	2.15 (1.21–3.84)	0.98 (0.43–2.19)

vasodilators (mostly nitrates, $n = 1{,}930$), IV inotropes and/or IV vasopressors ($n = 1{,}617$)

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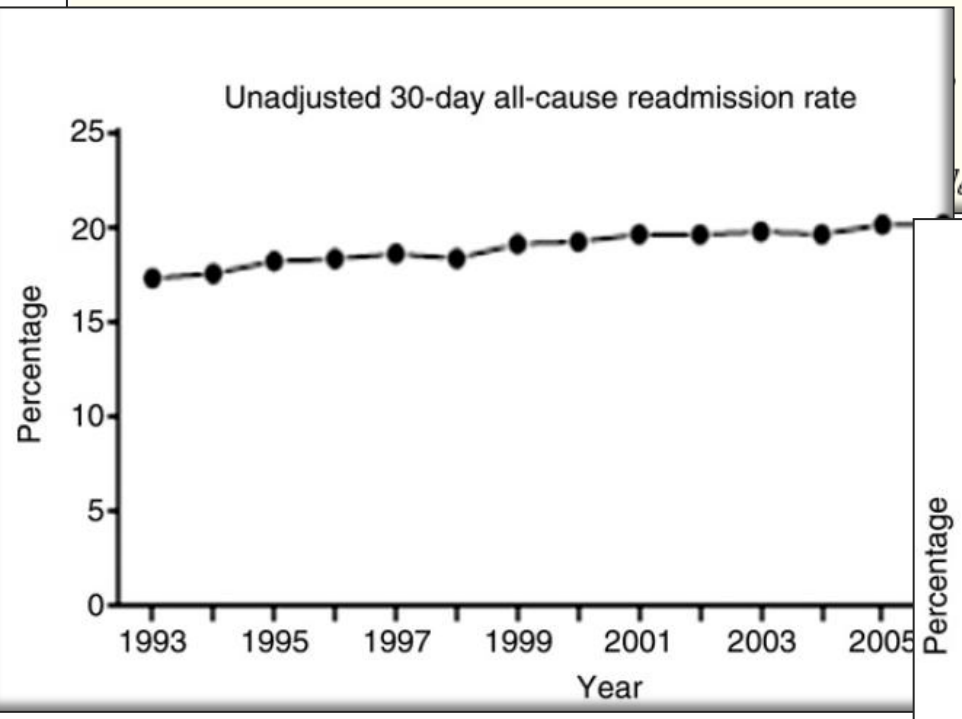
STATE-OF-THE-ART PAPER

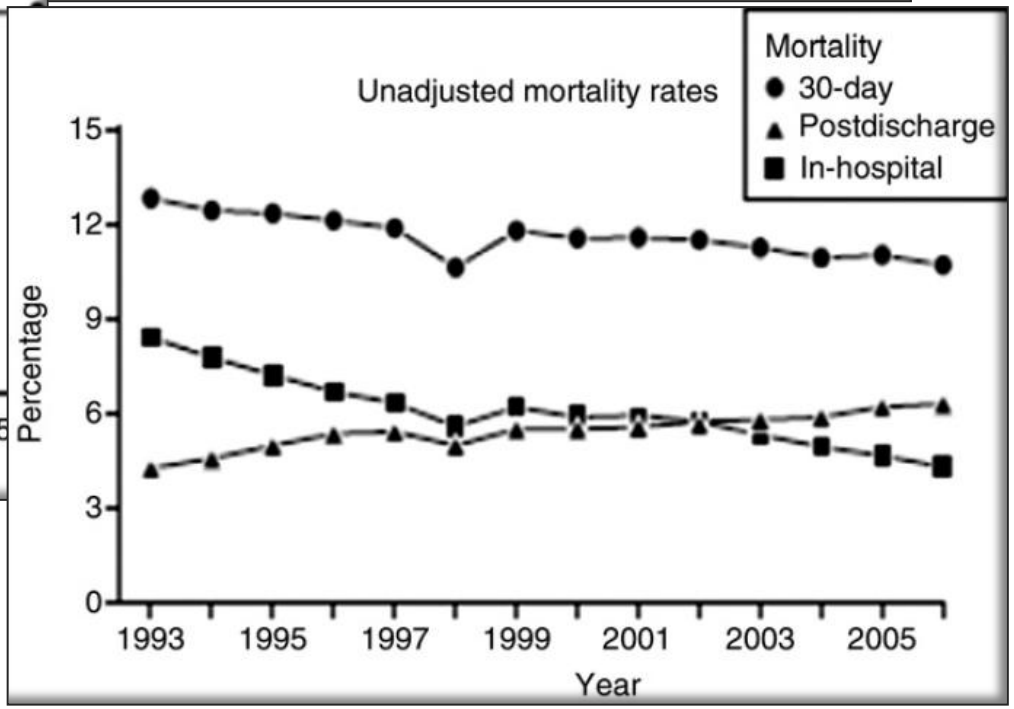
Rehospitalization for Heart Failure

Problems and Perspectives

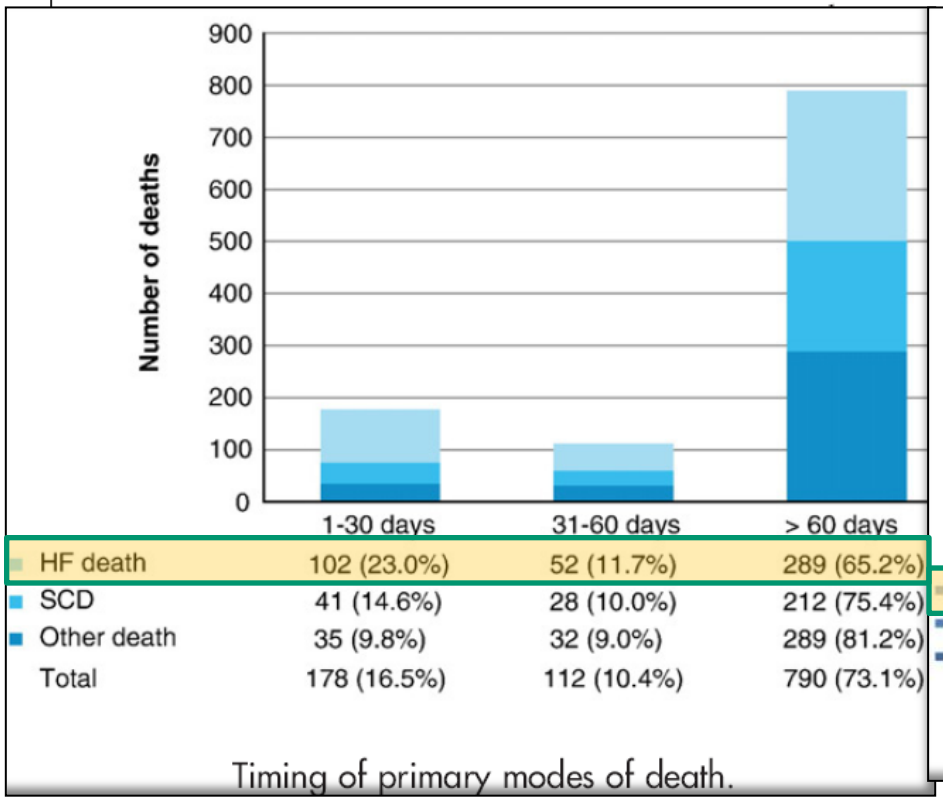
MD, MPH,† Gregg C. Fonarow, MD,‡

les, California



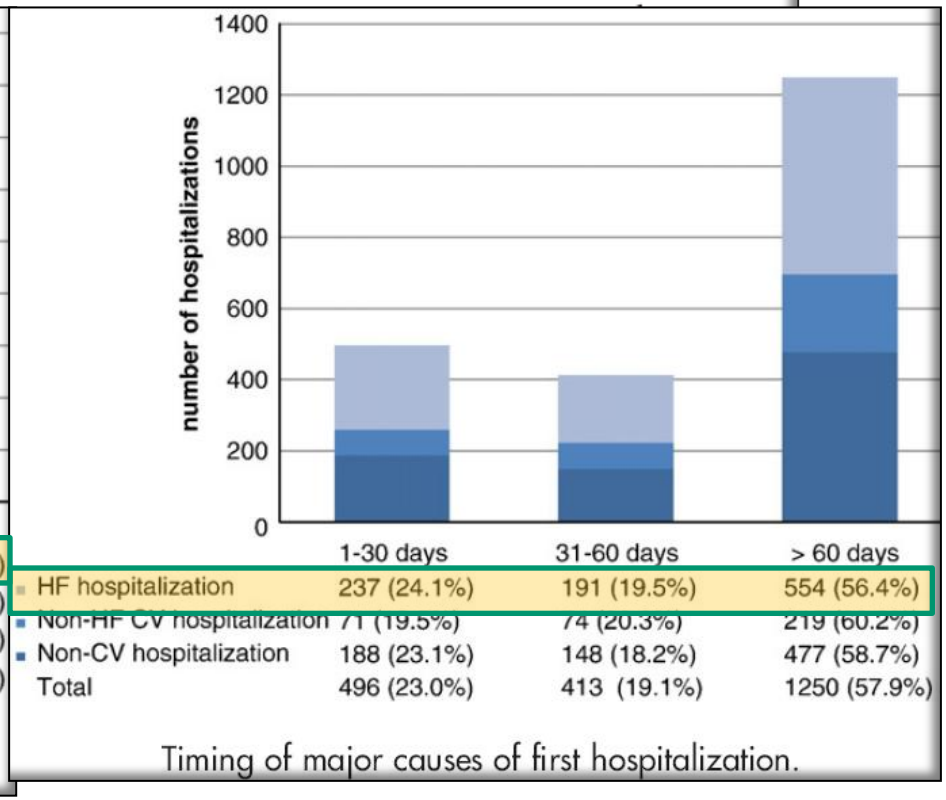


Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: Results from efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) program



	1-30 days	31-60 days	> 60 days
HF death	102 (23.0%)	52 (11.7%)	289 (65.2%)
SCD	41 (14.6%)	28 (10.0%)	212 (75.4%)
Other death	35 (9.8%)	32 (9.0%)	289 (81.2%)
Total	178 (16.5%)	112 (10.4%)	790 (73.1%)

Timing of primary modes of death.



	1-30 days	31-60 days	> 60 days
HF hospitalization	237 (24.1%)	191 (19.5%)	554 (56.4%)
Non-HF CV hospitalization	71 (19.5%)	74 (20.3%)	219 (60.2%)
Non-CV hospitalization	188 (23.1%)	148 (18.2%)	477 (58.7%)
Total	496 (23.0%)	413 (19.1%)	1250 (57.9%)

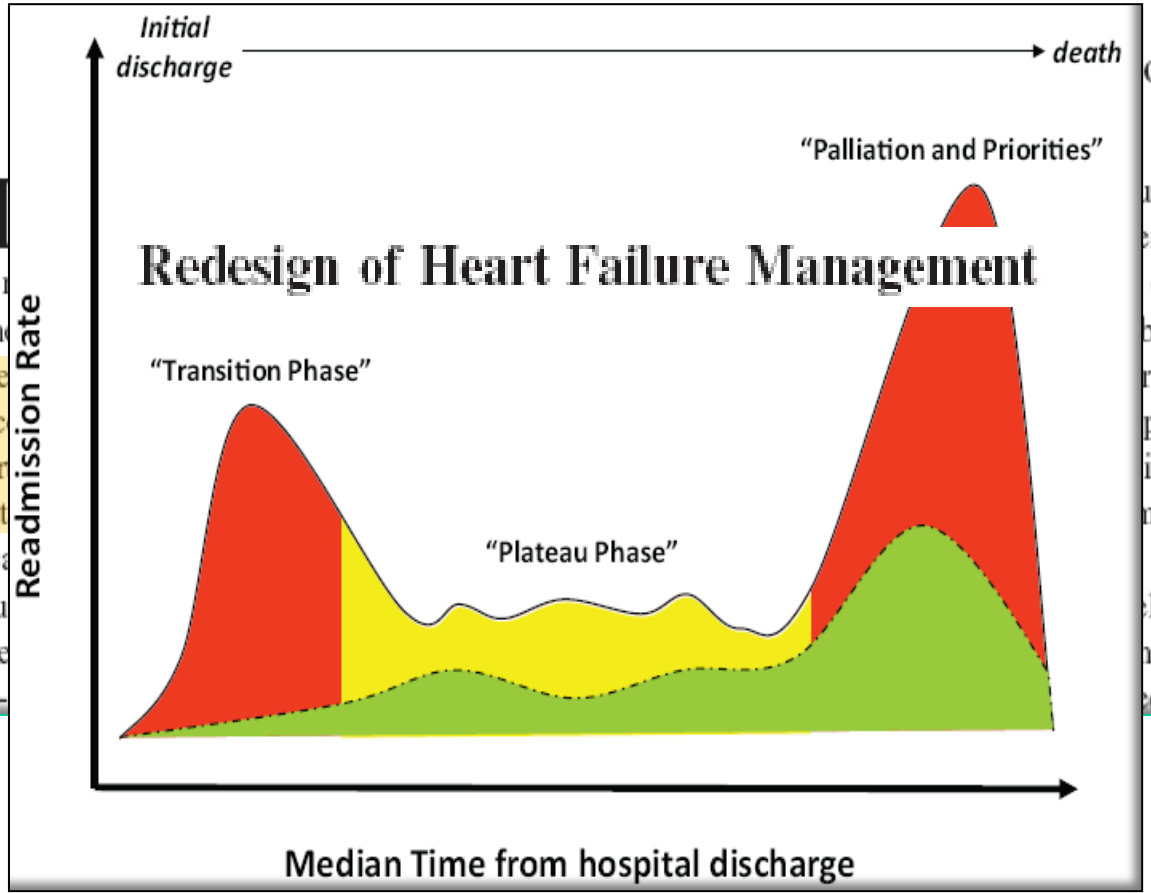
Timing of major causes of first hospitalization.

Special Report

Circulation. 2012;126:501-506

Rehospitalization for Heart Failure

Predict or Prevent?



on, MD

ures at which clinical decompensation
r in the patients with heart failure with
exceeds the median daily levels during
bility.[16] Data from trials of implantable
rs confirm that the risk for heart failure
pled to the degree of chronic filling
ith progressively higher risk once the
monary artery diastolic pressure rises

legantly outlined a 3-phase terrain of
nission based on analysis of a cohort of
d Canadian patients with heart failure

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2012) **14**, 955–956
doi:10.1093/eurjhf/hfs122

EDITORIAL

Why do drugs for acute heart failure fail?

Adriaan A. Voors* and Dirk J. van Veldhuisen

Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

- The wrong drug?
- Maby the wrong population?
- Maby the wrong design/ endpoints?

Why do drugs for acute heart failure fail?

➢Maby the wrong population?

- ✓A collection of syndromes
  - Different phenotypes
  - Different pathophysiology
- ✓Most AHF trials were performed in LVSD
  - Already well treated pts
- ✓Different underlying aetiologies

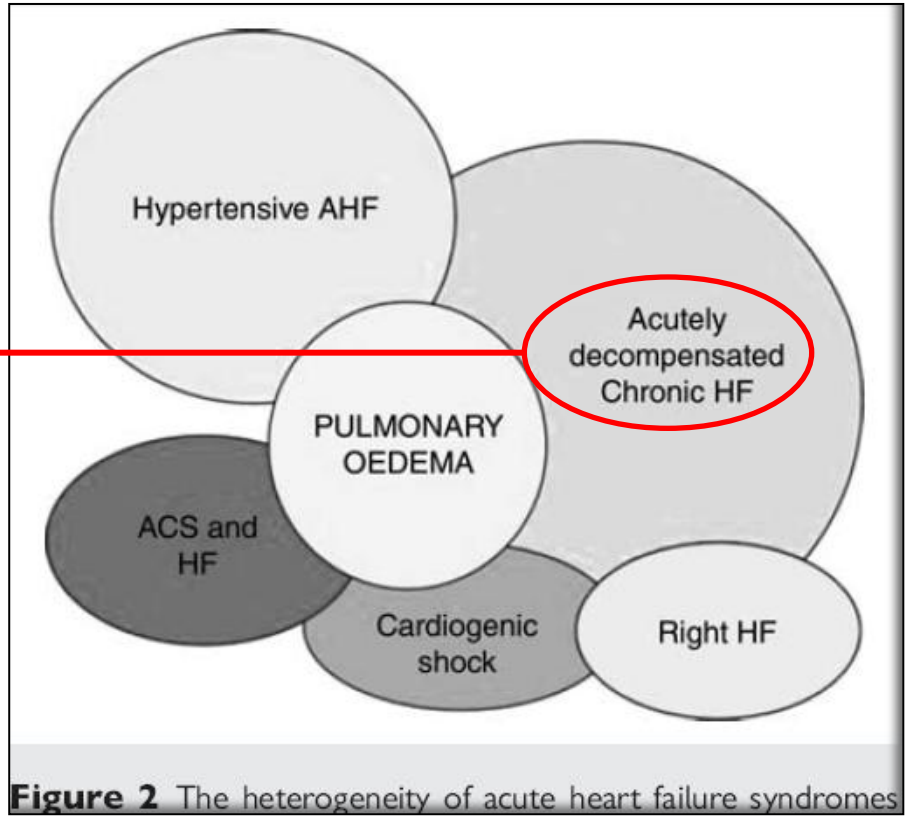


Figure 2 The heterogeneity of acute heart failure syndromes

Why do drugs for acute heart failure fail?

➢Maby the wrong design/endpoints?

- Whether to use a placebo or an active control?
- Size matters?
- Is it possible to improve post-discharge long-term mortality with a drug given iv for only few hours or days in hodpital?
- Endpoints based on symptoms / signs?
- Timming to start the study drug (6h; 12h; 16h; 24H)?
- Standard therapy in many trials is very good at relieving symptoms!

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European Journal of Heart Failure (2011) **13**, 1253–1260
doi:10.1093/eurjhf/hfr126

POSITION STATEMENT

Clinical trials in acute heart failure: simpler solutions to complex problems. Consensus

- Composite endpoints including morbidity and mortality
- Mortality should be all cause
- The timming shou
- Readmissions sho costs).
- Do not recommen symptoms/signs.

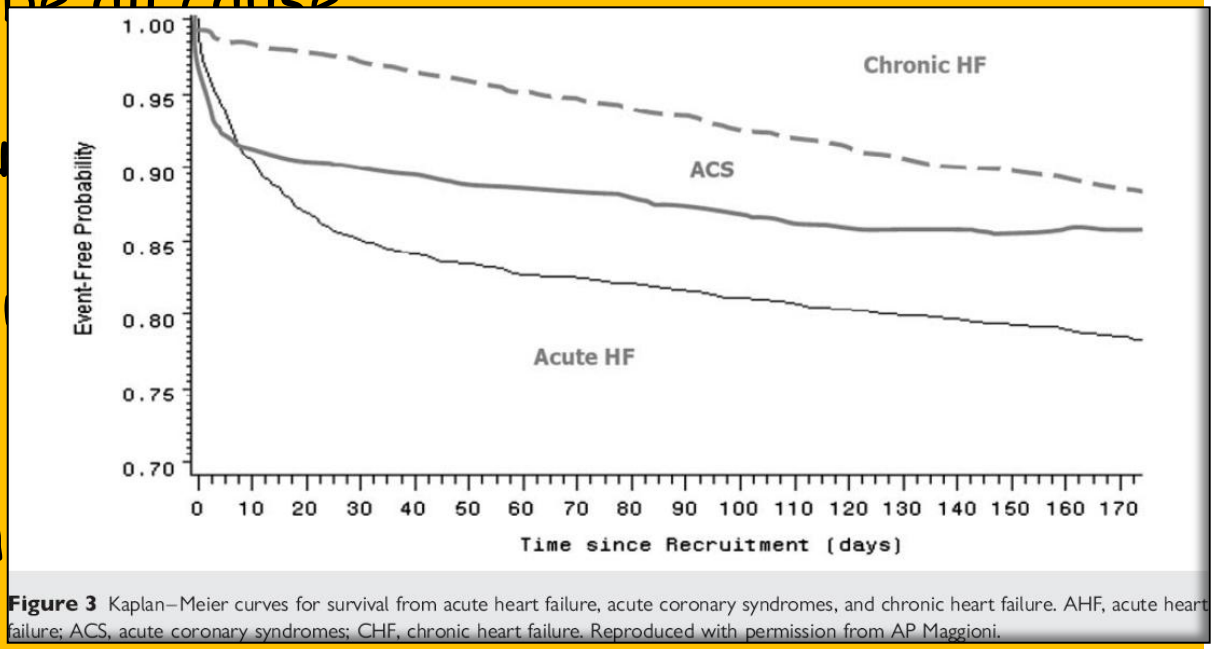

Figure 3 Kaplan–Meier curves for survival from acute heart failure, acute coronary syndromes, and chronic heart failure. AHF, acute heart failure; ACS, acute coronary syndromes; CHF, chronic heart failure. Reproduced with permission from AP Maggioni.

Federal Drug Administration (FDA) Study Group

(1) Symptom relief.
(2) Measures of congestion relief (i.e. improvement in clinical signs).
(3) Index hospitalization data (e.g. length of stay).
(4) Prevention of end-organ damage (heart and kidney).
(5) Post-discharge: death and rehospitalization data.

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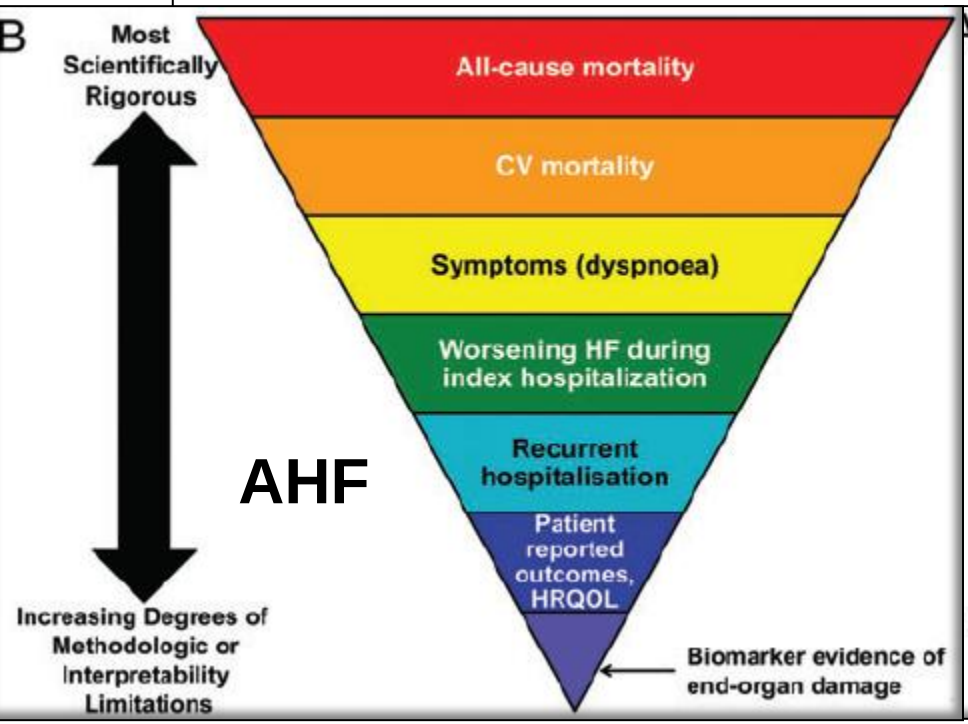
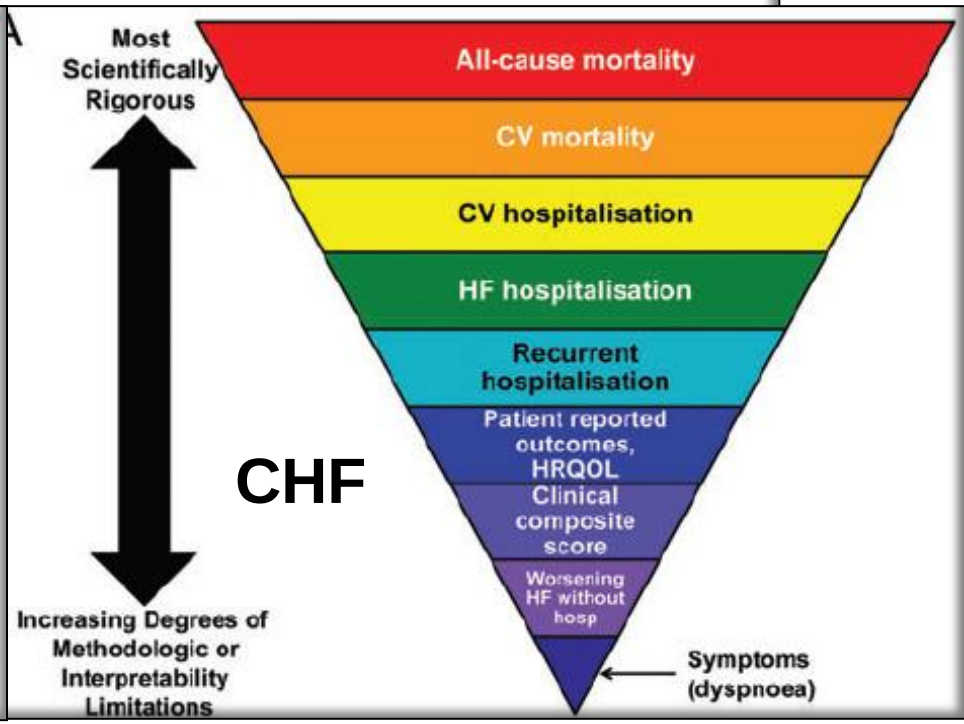
European Journal of Heart Failure (2013) **15**, 1082–1094
doi:10.1093/eurjhf/hft095

REVIEW

Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document





Novidades na IC – Levosimendan: regresso ao Futuro?

Heart Fail Rev (2009) 14:265–275
DOI 10.1007/s10741-008-9128-4

Levosimendan: from basic science to clinical practice

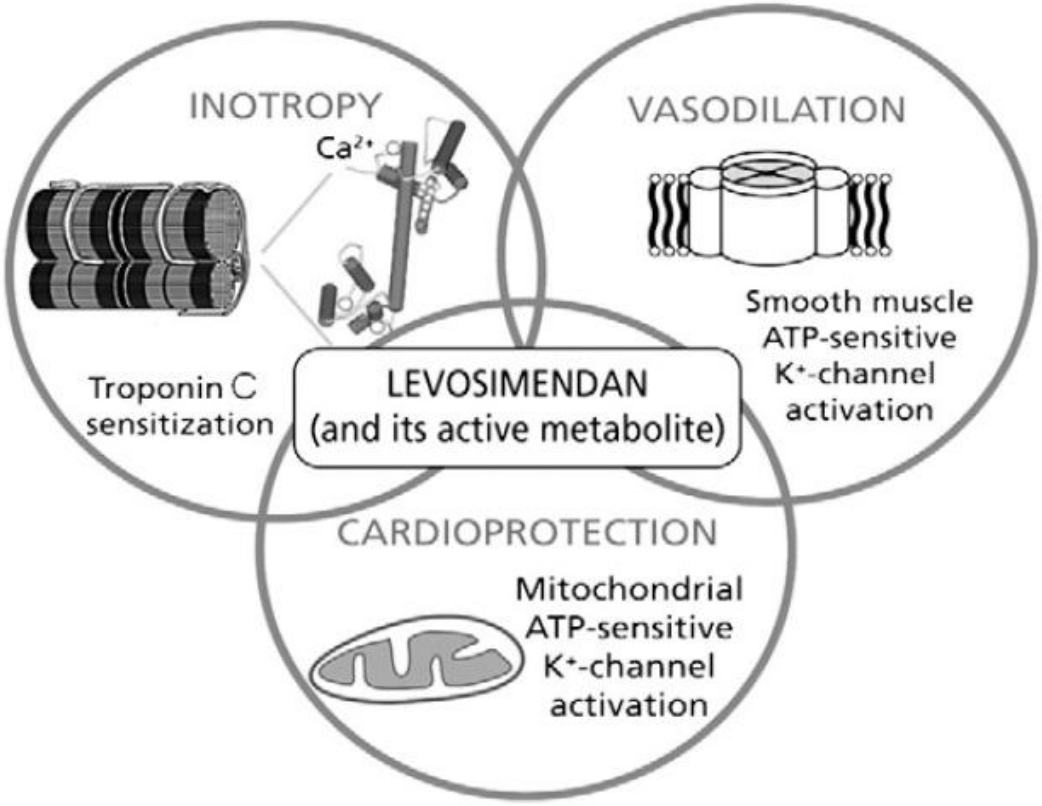


Fig. 1. The cardiovascular effects of levosimendan and of its active metabolite, OR-1896

ed from references [11, 14])

Therapeutic effects
Increased ejection fraction
Decreased left ventricular filling pressures
Lowered pre- and after-load
Anti-ischemic
Better tissue perfusion
Normalization of neurohormones
Cardioprotection
Anti-ischemic

Novidades na IC – Levosimendan: regresso ao Futuro?

Heart Fail Rev (2009) 14:265–275
DOI 10.1007/s10741-008-9128-4

Table 2 Large-scale randomized clinical trials co
acutely decompensated chronic heart failure (modi

Trial acronym	*N*	Treatment arms
RUSSLAN	504	Levosimendan vs. Placebo in Post-MI cardiac failure
LIDO	203	Levosimendan vs. Dobutamine in Decompensated heart failure
REVIVE-1	100	Levosimendan vs. placebo in Decompensated heart failure
REVIVE-2	600	Levosimendan vs. placebo in Decompensated heart failure
SURVIVE	1327	Levosimendan vs. dobutamine in Decompensated heart failure

Potential adverse effects during levosimendan administrations in clinical trials and in meta-analyses.

Adverse effect	Incidence	Study	References
Hypotension	8.7% vs. 4% (dobutamine) NS	LIDO	[3]
	4–7% (at 0.1–0.2 μg/kg/min) 9% (at 0.4 μg/kg/min) vs. 4.9% (placebo) NS	RUSSLAN	[4]
	50% vs. 36% (placebo) NA	REVIVE-II	[95]
	15.5% vs. 13.9% (dobutamine) NS	SURVIVE	[5]
	11.1% vs. 9.7% (control) P = 0.02	Meta-analysis in critically ill patients	[7]
Headache	13.6% vs. 5% (dobutamine) NS	LIDO	[3]
	2–3% (at 0.1–0.2 μg/kg/min) 1% (at 0.4 μg/kg/min) vs. 1% (placebo) NS	RUSSLAN	[4]
	8.3% vs. 4.7% (dobutamine) P = 0.01	SURVIVE	[5]
Atrial fibrillation	1.9% vs. 1% (dobutamine)	LIDO	[3]
	1–4% (at 0.1–0.2 μg/kg/min) 3% (at 0.4 μg/kg/min) vs. 2% (placebo) NS	RUSSLAN	[4]
	8% vs. 2% (placebo) NA	REVIVE-2	[95]
	9.1% vs. 6.1% (dobutamine) P = 0.05	SURVIVE	[5]
	22.9% vs. 31.4% (control) P = 0.003	Meta-analysis in patients undergoing cardiac surgery	[8]
Hypokalaemia	9.4% vs. 5.9% (dobutamine) P = 0.02	SURVIVE	[5]
Tachycardia	0% vs. 2% (dobutamine) NA	LIDO	[3]
	5% vs. 5% (dobutamine) NS	SURVIVE	[5]

Novidades na IC – Levosimendan: regresso ao Futuro?

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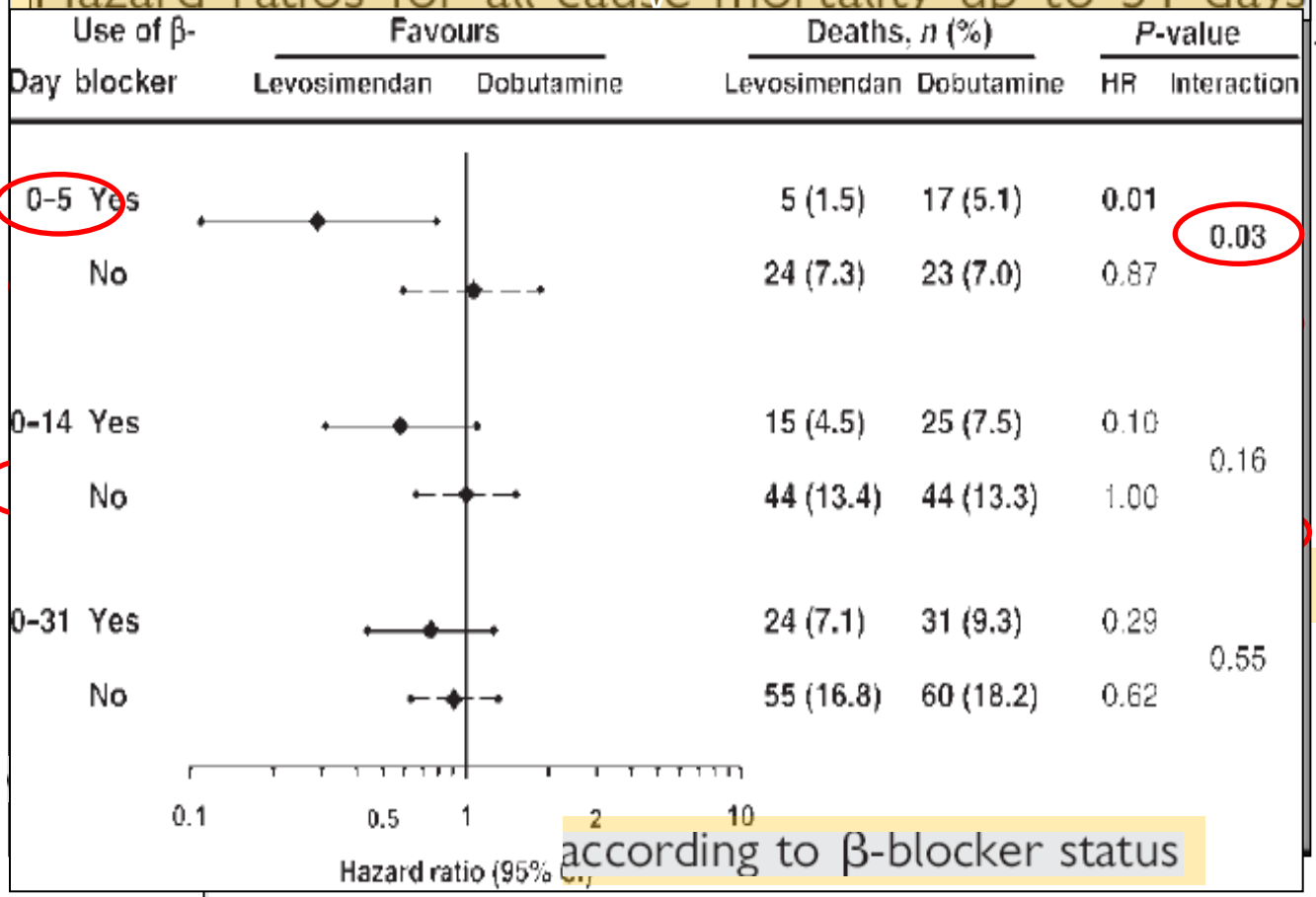
European Journal of Heart Failure (2009) **11**, 304–311
doi:10.1093/eurjhf/hfn045

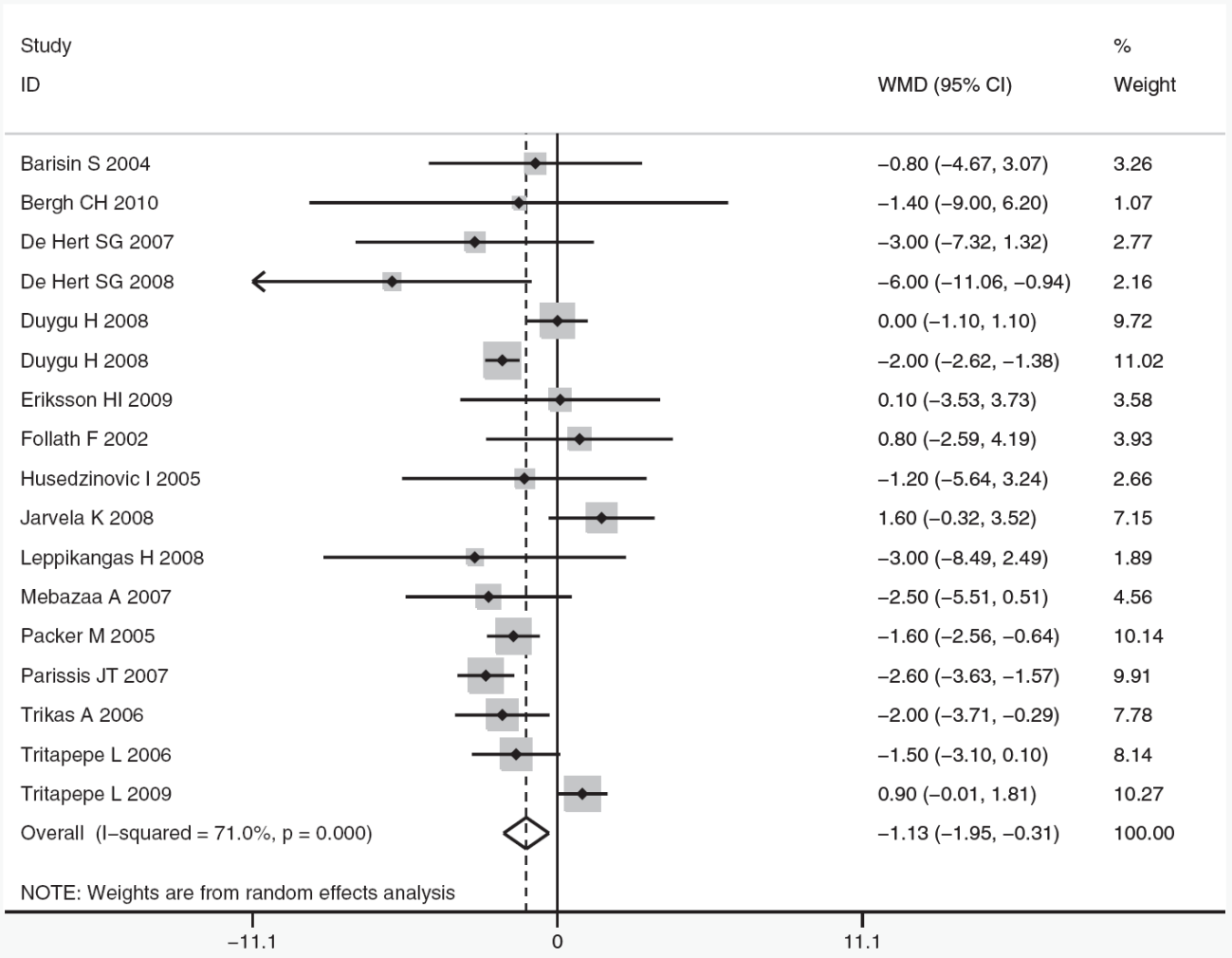
Table 1 Baseline demographic profiles and characteristics of patients stratified according to use of β-blockers

Variable[a]	β-blocker users (n = 669)		β-blocker non-users (n = 658)	
			Levosimendan (n = 328)	Dobutamine (n = 330)
			232 (71%)	224 (68%)
			69 (12)	68 (11)
			78 (18)	78 (16)
			169 (9)	168 (8)
			309 (94%)	311 (94%)
			24 (6)	24 (5)
			268 (82%)	261 (79%)
			33 (10%)	48 (15%)
			262 (80%)	266 (81%)
			40 (12%)	43 (13%)
			16 (5)	14 (4%)
			282 (86%)	286 (87%)
			164 (50%)	164 (50%)
			32 (10%)	32 (10%)
			12 (4%)	12 (4%)
			206 (63%)	212 (64%)
			102 (31%)	108 (33%)
			194 (59%)	189 (57%)
Aldosterone antagonists	188 (56%)	210 (63%)	148 (45%)	156 (47%)

Hazard ratios for all-cause mortality up to 31 days according to β-blocker status



How can you mend a broken heart?*



Levosimendan reduced the length of hospital stay

Novidades na IC – Levosimendan: regresso ao Futuro?

Study or Subgroup	Levosimendan Events	Total	Dobutamine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adamopoulos *et al.*, 2006	2	23	5	23	1.5%	0.40 [0.09, 1.86]
Alhashemi *et al.*, 2009	10	21	13	21	3.9%	0.77 [0.44, 1.35]
Alvarez *et al.*, 2005	1	15	0	15	0.2%	3.00 [0.13, 68.26]
Alvarez *et al.*, 2006	1	25	1	25	0.3%	1.00 [0.07, 15.12]
Bergh *et al.*, 2010	2	29	1	31	0.3%	2.14 [0.20, 22.34]

Study or Subgroup	Levosimendan Events	Total	Dobutamine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adamopoulos *et al.*, 2006	2	23	5	23	2.0%	0.40 [0.09, 1.86]
Bergh *et al.*, 2010	2	29	1	31	0.4%	2.14 [0.20, 22.34]
Bonios *et al.*, 2012	4	21	8	21	3.2%	0.50 [0.18, 1.41]

Study or Subgroup	Levosimendan Events	Total	Dobutamine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alvarez *et al.*, 2005	1	15	0	15	1.7%	3.00 [0.13, 68.26]
Alvarez *et al.*, 2006	1	25	1	25	3.5%	1.00 [0.07, 15.12]
Levin *et al.*, 2008a	2	36	9	35	31.8%	0.22 [0.05, 0.93]
Levin *et al.*, 2008b	6	69	17	68	59.6%	0.35 [0.15, 0.83]
Levin *et al.*, 2009	2	30	1	32	3.4%	2.13 [0.20, 22.33]
Total (95% CI)		**175**		175	**100.0%**	**0.43 [0.23, 0.81]**
Total events	12		28			

Heterogeneity: Chi² = 4.73, *df* = 4 (*P* = 0.32); I^2 = 15%

Test for overall effect: *Z* = 2.60 (*P* = 0.009)

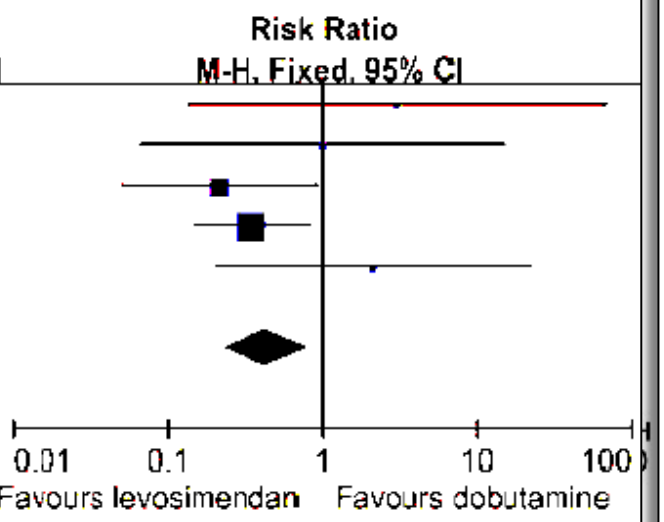


Fig. 3 Forest plot for the risk of mortality in the cardiac surgery setting

Novidades na IC – Levosimendan: regresso ao Futuro?

Levosimendan Reduces Cardiac Troponin Release After Cardiac Surgery: A Meta-analysis of Randomized Controlled Studies

Alberto Zangrillo, MD,* Giuseppe Biondi-Zoccai, MD,† Anna Mizzi, MD,* Giovanna Bruno, MD,* Elena Bignami, MD,* Chiara Gerli, MD,* Vincenzo De Santis, MD,‡ Luigi Tritapepe, MD,‡ and Giovanni Landoni, MD*

Objectives: **The authors performed a meta-analysis to investigate the effects of levosimendan in cardiac surgery. data. The endpoint was postoperative cardiac troponin release. Levosimendan was associated with a significant re-**

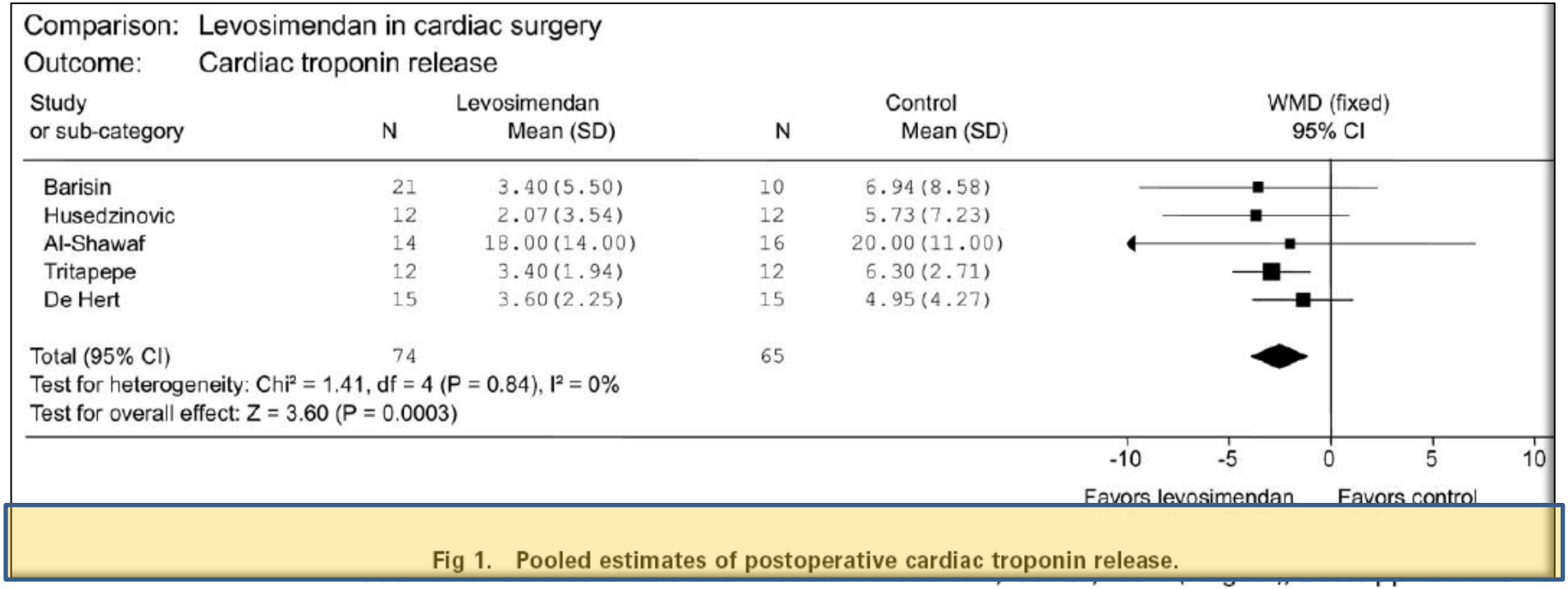


Fig 1. Pooled estimates of postoperative cardiac troponin release.

Novidades na IC – Levosimendan: regresso ao Futuro?

Reducing Mortality in Cardiac Surgery With Levosimendan: A Meta-analysis of Randomized Controlled Trials

Journal of Cardiothoracic and Vascular Anesthesia, Vol 24, No 1 (February), 2010: pp 51-57

Table 1. Description of the 10 Studies Included in the Meta-analysis

First Author	Journal	Year	Cardiac Surgery Procedures	Characteristics of Included Patients	Control	Follow-up

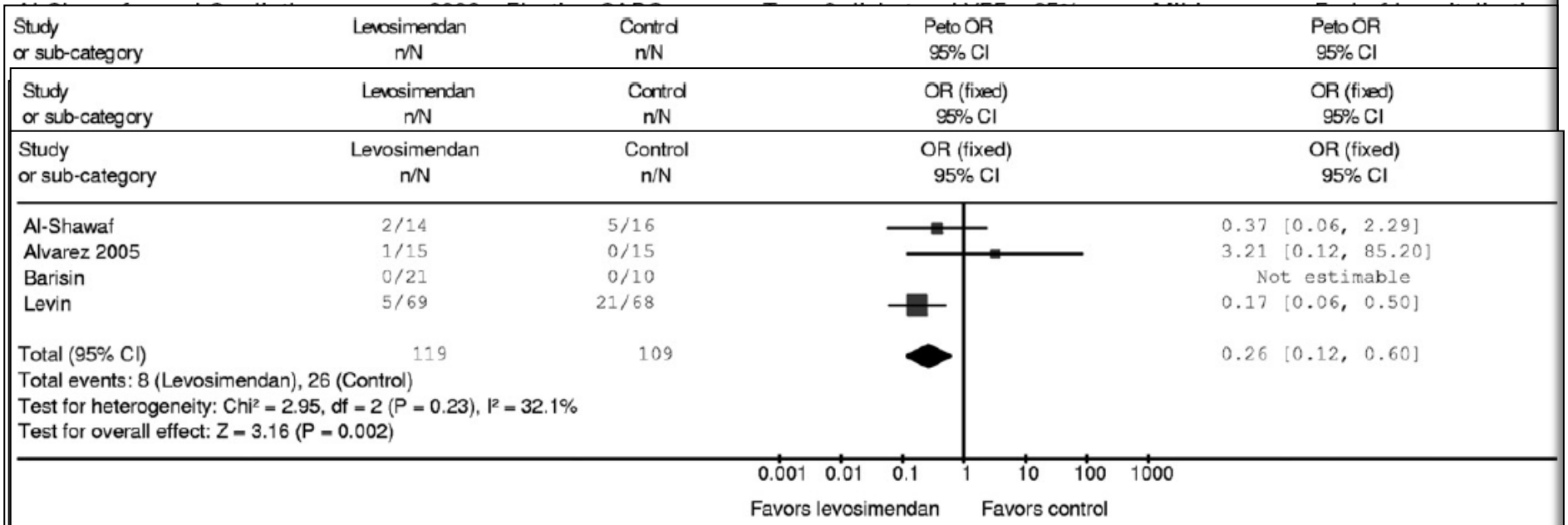
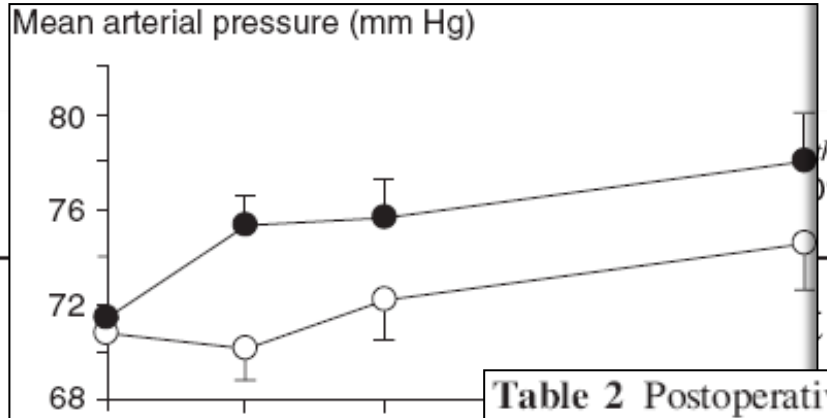
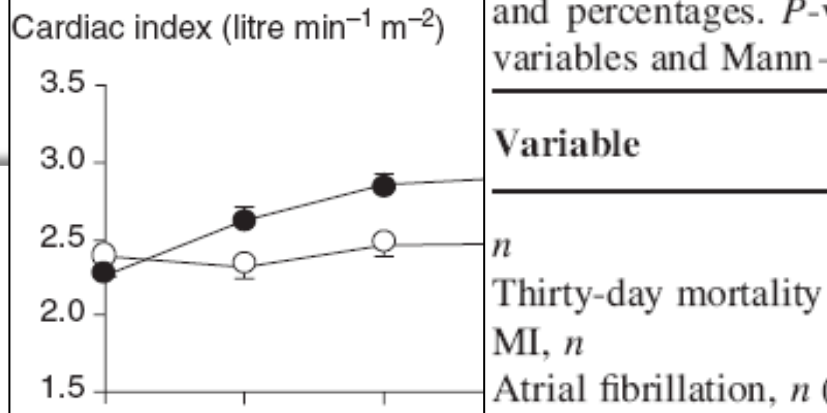
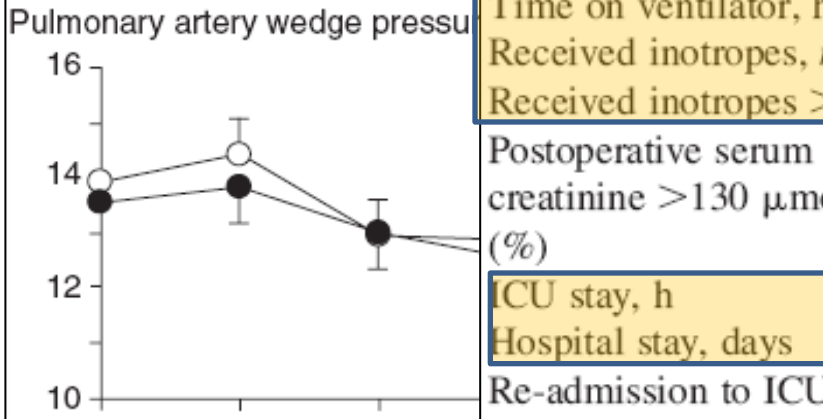


Fig 5. A Forest plot for the risk of postoperative acute renal failure comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

Novidades na IC – Levosimendan: regresso ao Futuro?







hesia **102** (2): 198–204 (2009)
)93/bja/aen367

BJA

improves outcomes in patients

Table 2 Postoperative results. Data are reported as mean (SD), or frequencies and percentages. *P*-values refer to χ^2 or the Fisher exact test for categorical variables and Mann–Whitney *U*-test for continuous ones

Variable	Control	Treatment	*P*-value
n	50	52	
Thirty-day mortality	0	0	NS
MI, *n*	1	0	0.5
Atrial fibrillation, *n* (%)	10 (20.0)	12 (23.1)	0.7
Time on ventilator, h	13.6 (4.5)	11.3 (2.5)	0.02
Received inotropes, *n* (%)	17 (34.0)	9 (17.3)	0.053
Received inotropes >12 h, *n* (%)	9 (18.0)	2 (3.8)	0.02
Postoperative serum creatinine >130 μmol litre^{-1}, *n* (%)	4 (8)	2 (3.8)	0.4
ICU stay, h	32.7 (12.9)	24.8 (7.1)	0.002
Hospital stay, days	12.0 (2.5)	11.1 (2.3)	0.09
Re-admission to ICU, *n* (%)	1 (2.0)	0	0.5
Re-exploration for bleeding, *n* (%)	1 (2.0)	1 (1.9)	0.9

Original Article

Table 1 - Baseline characteristics of the patients with and without worsening renal function

	Patients with worsening renal function (n=14)	Patients without worsening renal function (n=31)	p

Table 2 - Parameters of renal and cardiac functions in patients with and without worsening renal function

	Baseline GFR level (mL/min/m²)	GFR level after infusion (mL/min/m²)	p	Baseline creatinine level (mg/dL)	Creatinine level after the infusion (mg/dL)	p	Baseline EF level (%)	EF level after infusion (%)	p
Patients with worsening renal function (n=14)	48.9 ± 15	59.3 ± 21.8	0.011	1.40 ± 0.16	1.21 ± 0.23	0,001	25 ± 6	29 ± 6	0.018
Patients without worsening renal function (n=31)	53.7 ± 17.6	52.9 ± 21.4	0,850	1.29 ± 0.33	1.37 ± 0.66	0,240	25 ± 9	27 ± 6	0.002

Novidades na IC – Levosimendan: regresso ao Futuro?

Cardiovasc Drugs Ther (2007) 21:431–435
DOI 10.1007/s10557-007-6(

Age (years)
Sex (male/female)
Basal creatinine (mg/dl)
Basal blood urea nitrogen
Basal 24-h urine output (r
24-h urine output after 24
Basal calculated glomerula
(ml/min/1.73 m2)
Calculated glomerular filtr
of infusions (ml/min/1.7
Systolic BP before infusio
Diastolic BP before infusi
Systolic BP after infusion
Diastolic BP after infusior

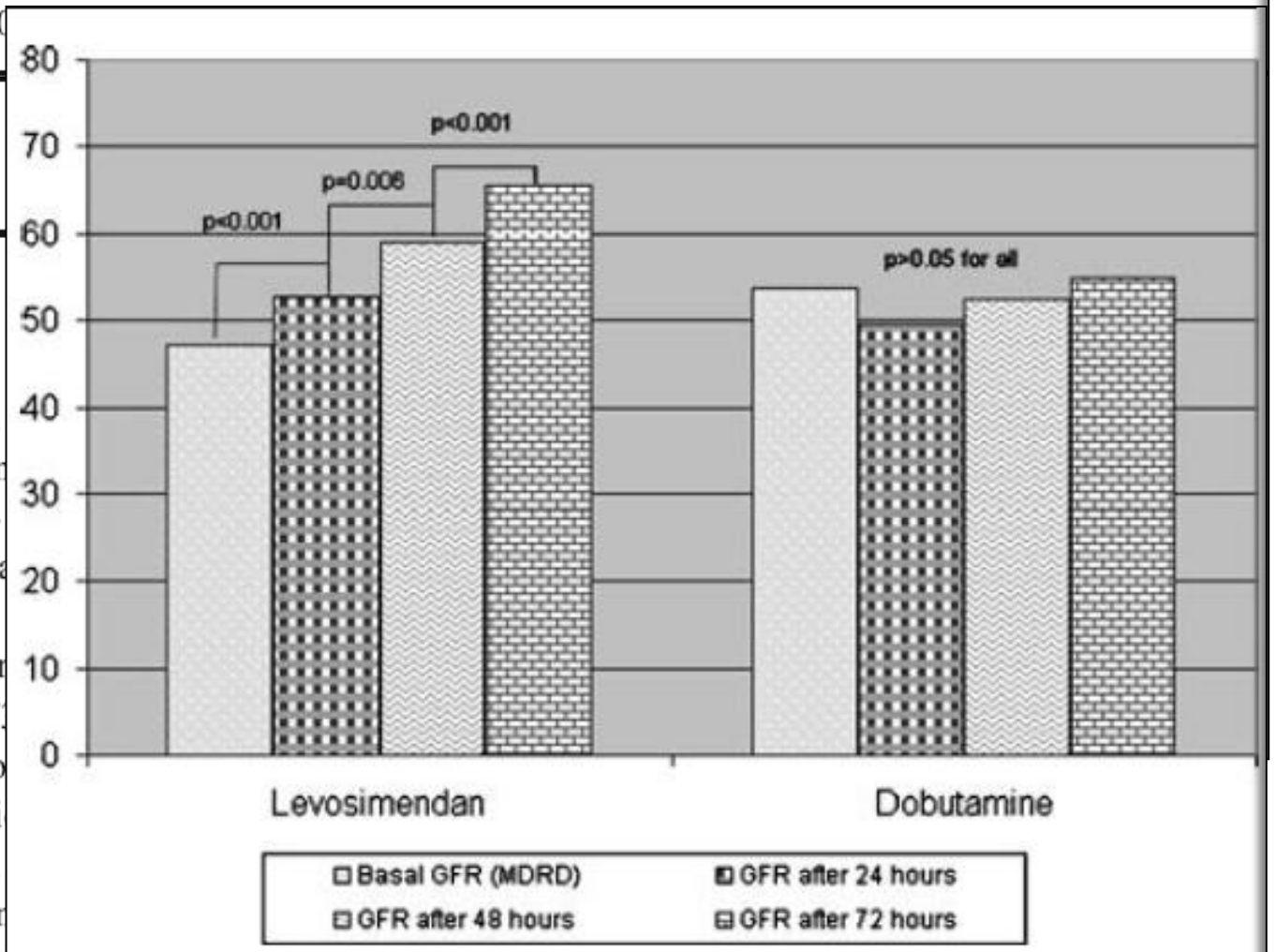


Fig. 1 Temporal change of glomerular filtration rate in the follow up group (n=27 in levosimendan, n=14 in dobutamine). Vertical axis denotes for calculated glomerular filtration rate by MDRD formula

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2010) **12**, 404–410
doi:10.1093/eurjhf/hfq032

Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers

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Novidades na IC – Levosimendan: regresso ao Futuro?

Heart Fail Rev (2009) 14:265–275
DOI 10.1007/s10741-008-9128-4

Levosimendan: from basic science to clinical practice

John T. Parissis · Pinelopi Rafouli-Stergiou ·
Ioannis Paraskevaidis · Alexandre Mebazaa

Table 3 Clinical criteria assessing response to levosimendan therapy in acute heart failure syndromes (modified from the reference [64])

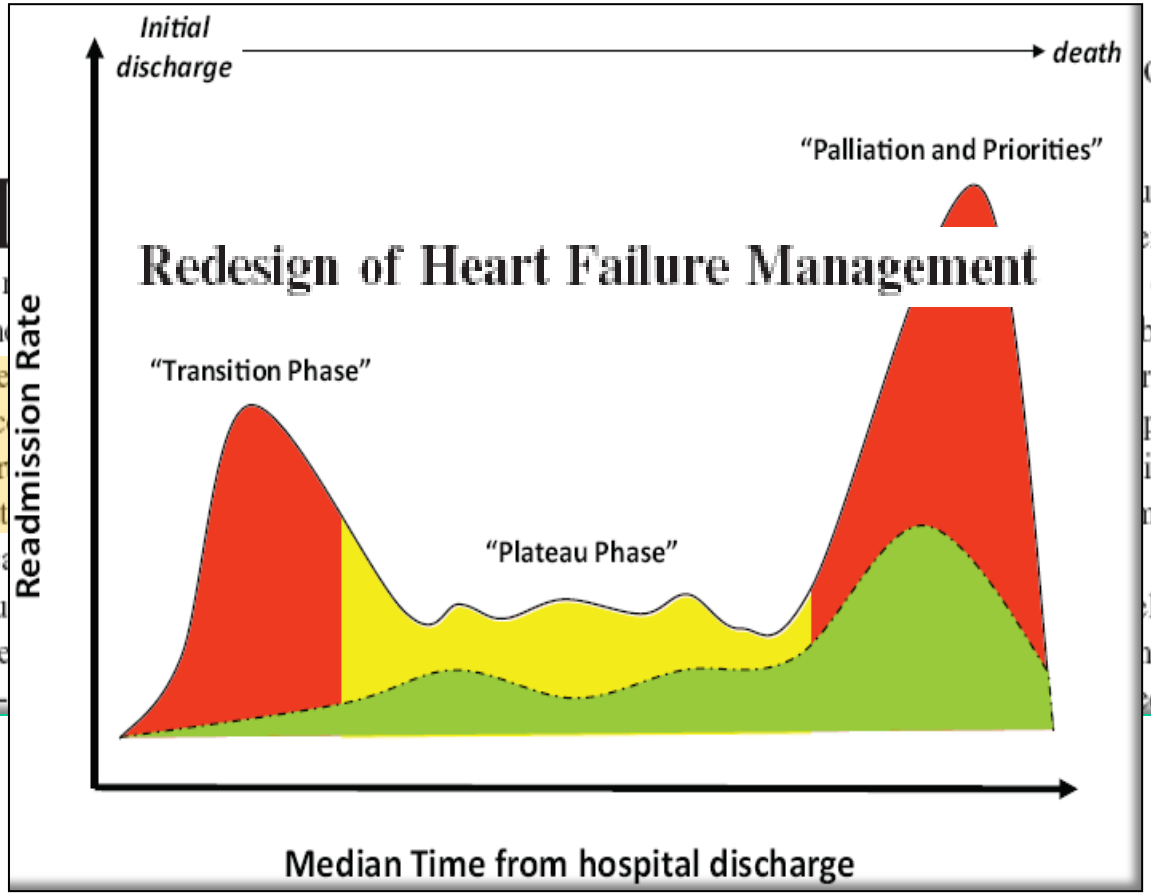
Responders	Non-responders
Acutely decompensated heart failure	De novo acute heart failure
NYHA class III/IV	End-stage disease
Congestive	Hypovolemic
Ischemic (hibernating, stunning)	Ischemic (no contractile reserve)
Systolic blood pressure > 100 mm Hg	Systolic blood pressure < 100 mm Hg
No concomitant therapies (excessive diuresis, vasodilators, inotropes)	Concomitant therapies (excessive diuresis, vasodilators, inotropes
NT-proBNP: >30% reduction after 48 h	NT-proBNP: <30% reduction after 48 h
Rapid acetylation of parent drug to active metabolites (genetically determined)	Slow acetylation of parent drug to active metabolites (genetically determined)
On beta-blocker treatment at admission	No concomitant beta-blocker treatment

Special Report

Circulation. 2012;126:501-506

Rehospitalization for Heart Failure

Predict or Prevent?



on, MD

ures at which clinical decompensation
r in the patients with heart failure with
exceeds the median daily levels during
bility.[16] Data from trials of implantable
rs confirm that the risk for heart failure
pled to the degree of chronic filling
ith progressively higher risk once the
monary artery diastolic pressure rises

legantly outlined a 3-phase terrain of
nission based on analysis of a cohort of
d Canadian patients with heart failure

Clinical trials that have assessed the repetitive use of levosimendan.

Study (ref)	Patients, study design	Comparator	Planned cumulative dose (mg×kg-1)	Number of cycles / duration	lenght of treatment (+follow up)	Main results described
Altenberger et al., 2012.[62]	120, randomised	LS vs Placebo	up to 0,29	4 / 6 h / bi-weekly	6 w (+20 w)	Primary endpoint not met, secondary endpoint (morbidity and mortality) met
Malfatto et al., 2012.[61]	33, not randomised	LS vs Furosemide	up to 2,11	4 / 24 h / monthly	3 m (+ 1 m + 1 y)	Favourable effects on LVEF, neurohormonal balance and 1-year survival
Bonios et al., 2012.[60]	63, randomised	LS vs Dobutamine vs Dob + LS	2,92	24 / 6 h / weekly	6 m	Survival and haemodynamic benefits
Mavrogeni et al., 2007.[57]	50, randomised, open	LS vs Placebo	1,73	6 / 24 h / monthly	6 m	Improvement in symptoms and LVEF
Nanas et al., 2005.[55]	36, open	LS+dobutamine vs dobutamine alone	1,15	4 / 24 h / bi-weekly	6 w (+3 d)	Improvement in 45-day survival rate
Parissis et al., 2006.[56]	25, randomised	LS vs Placebo	0,75 to 2,66	5 / 24 h / 3-weekly	12 w (+ 30 d)	Improvement in LVEF, modulation of neurohormonal and immune activation
Berger et al., 2007.[58]	75, randomised	LS vs Prostaglandin E1	up to 0,62	4 / 24 h / monthly	3 m (+9 m)	Inferior facilitation of up-titration of beta-blockers and worse clinical outcome, equal effect on mortality.
Papadopoulou et al., 2009.[59]	30, open	LS (no comparator)	0,86	6 / 24 h / monthly	6 m	Improvement in objective echocardiographic measures and subjective quality-of-life questionnaires
Kleber et al., 2009.[38]	28, randomised	LS vs Placebo	up to 0,58	1×24 then 4×6 h bi-weekly	8 w (+4 w)	Improvement in pulmonary vascular resistance and mean pulmonary artery pressure

Clin Res Cardiol
DOI 10.1007/s00392-013-0649-z

REVIEW

Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials

Simona S
Marta M
Mara Sca

Received: 2

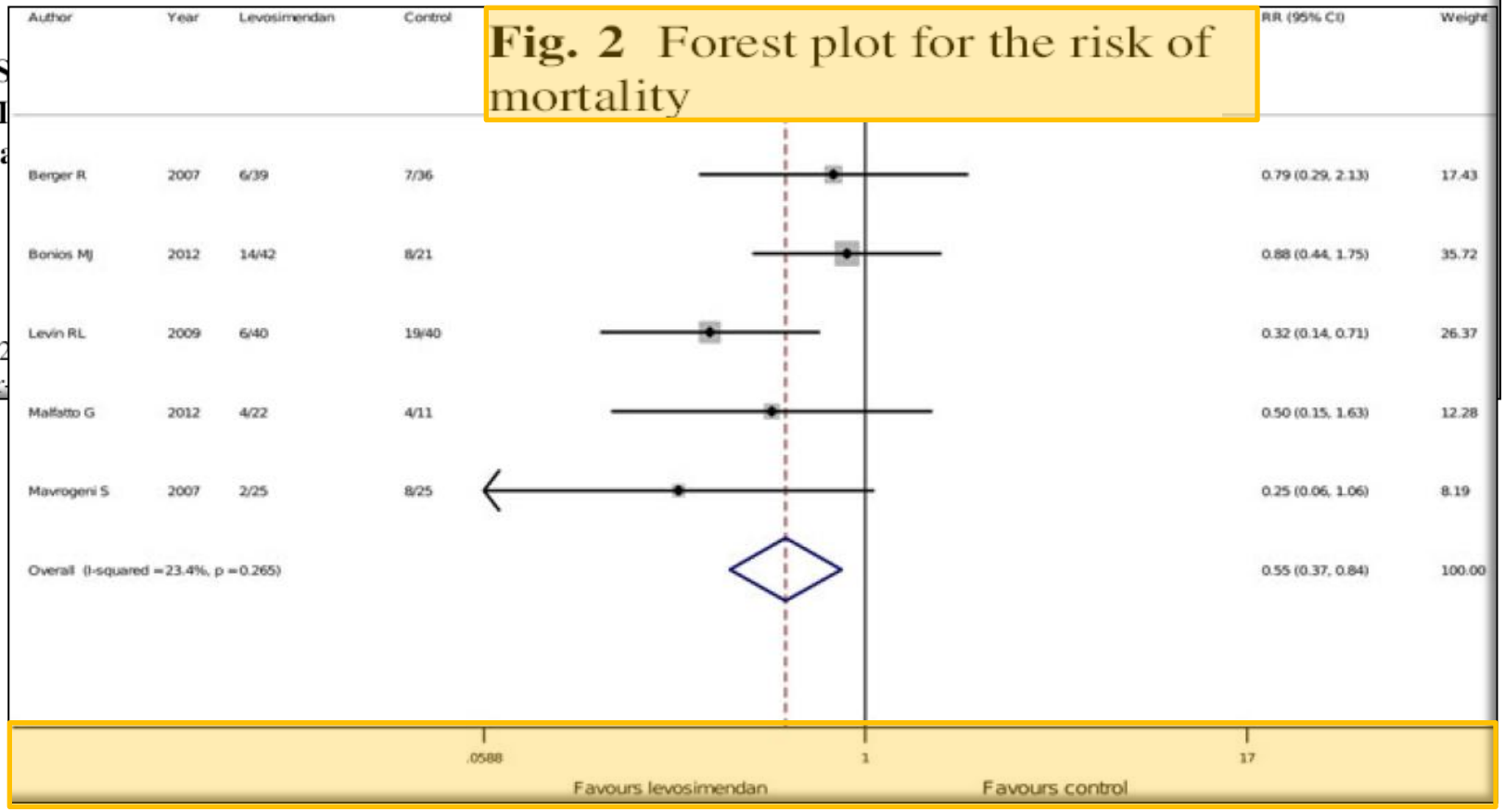


Fig. 2 Forest plot for the risk of mortality

Novidades na IC – Levosimendan: regresso ao Futuro?

Ongoing trials that are assessing intermittent or repetitive levosimendan treatment

Name of the trial (acronym, NCT code)	**Expected N** (design)	**Dose** ($\mu g \times kg^{-1} \times min^{-1}$)	**Infusion Length** (h)	**Treatments** (study duration)
The Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients study (LION-HEART, NCT01536132)	69 (1:1 vs placebo)	0.2	6	every two weeks (per 3 months)
The Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial to Study Efficacy, Security, and Long-Term Effects of Intermittent Repeated Levosimendan Administration in Patients with Advanced Heart Failure (LAICA, NCT00988806)	213 (1:1 vs placebo)	0.1	24	every 15 or 30 days (per 12 months)
The Early LEvosimendan *Versus* Usual Care in Advanced Chronic hearT failurE (ELEVATE, NCT01290146)	134 (1:1 vs furosemide)	0.05 or 0.1	24	at early signs of deterioration (per 12 months)

Repetitive use of levosimendan for treatment of chronic advanced heart failure: clinical evidence, practical considerations, and perspectives: an expert panel consensus

Indication for levosimendan use in advanced heart failure

- Severe systolic dysfunction (LVEF <35%)
- NYHA IIIb-IV and/or INTERMACS levels 4, 5, 6
- Repeated hospitalisation or emergency department visits (≥2 in the past year)
- All of the above despite optimal treatment for heart failure

Submitted 2014

Novidades na IC – Levosimendan: regresso ao Futuro?