The Revival of Levosimendan in Acute Heart failure ?

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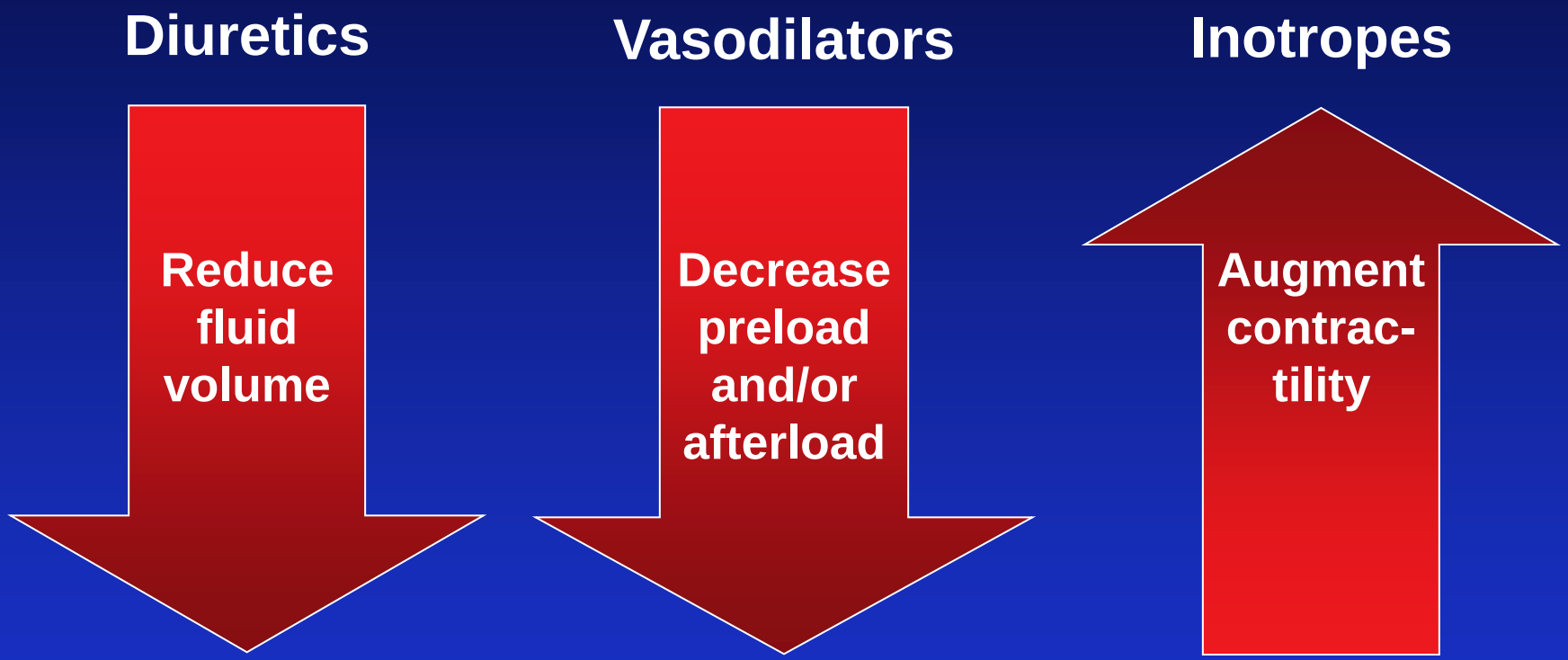
University of Athens, Greece

Disclosures: Received research grants and honoraria from Abbott USA and Orion Pharma, Finland

Conventional Treatments of Acute Heart Failure



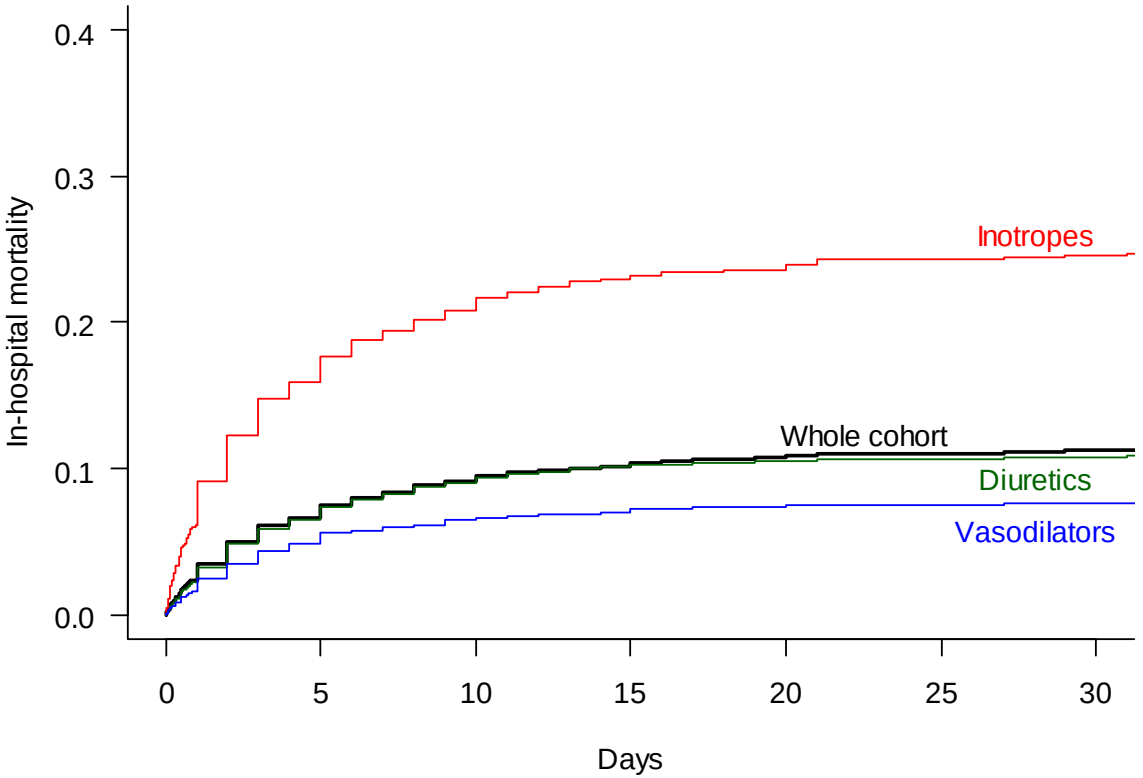
Fonarow GC. *Rev Cardiovasc Med.* 2001;2(suppl 2):S7–S12.

Inotropes in clinical practice

– Inotropic agents should be considered in patients with low output states, in the presence of signs of hypoperfusion or congestion despite the use of vasodilators and/or diuretics to improve symptoms

– **Class of recommendation IIa, level of evidence B**

Short-term Survival by Treatment Among Patients Hospitalized with Acute Heart Failure: The Global ALARM-HF Registry Using Propensity Scoring Methods



Mebazaa A, Parissis J, Porcher R, et al. Intensive Care Med 2011 Feb;37(2):290-301

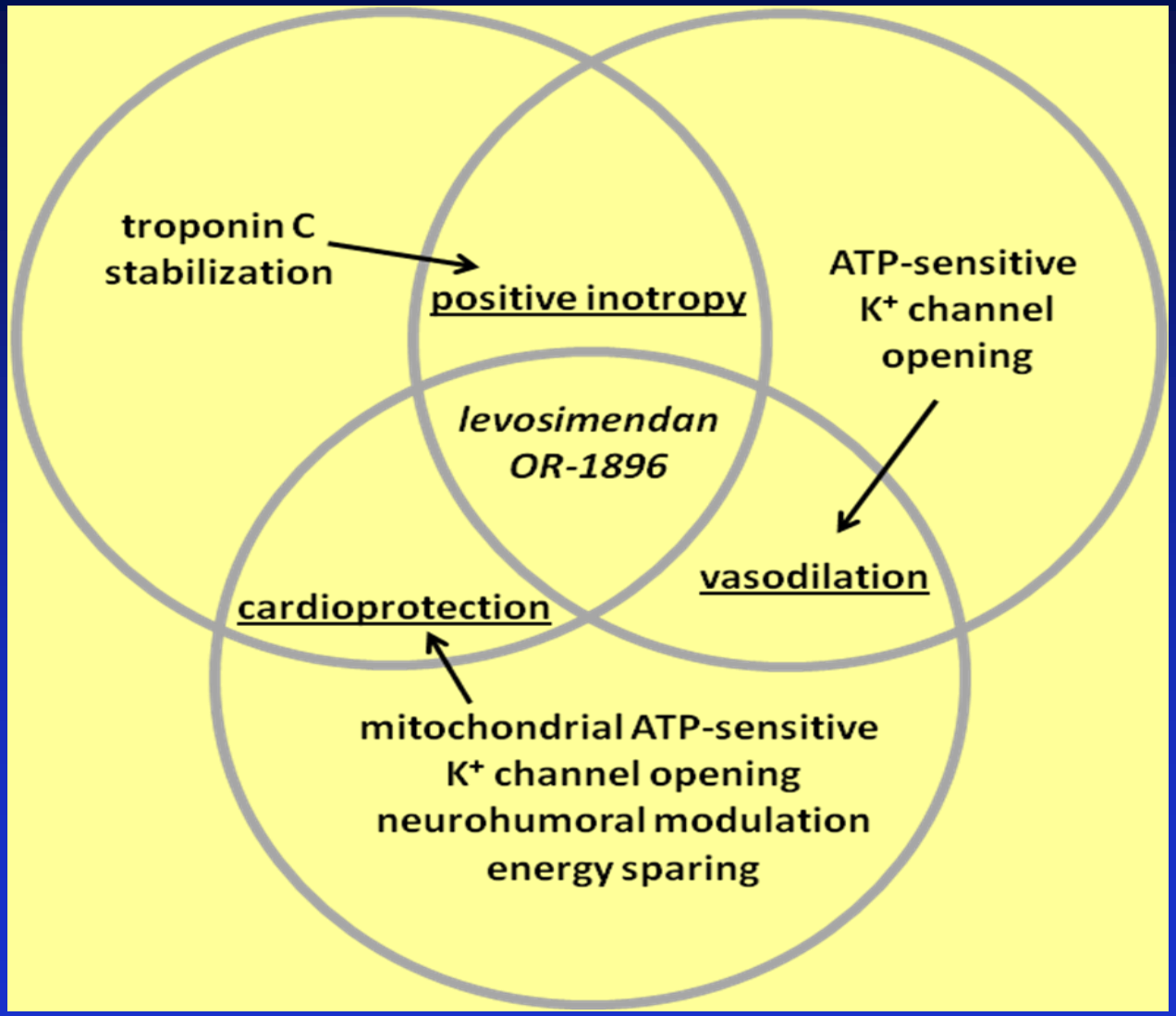
Table 2 A proposed inotrope treatment algorithm in acute heart failure (AHF) syndromes

AHF syndromes			
Edema (+) Warm extremities		Edema (±) Cool extremities	
SBP >100 mmHg	SBP 85–100 mmHg	SBP ≤85 mmHg	
IV Vasodilators (e.g., nitrates) + IV diuretics therapeutic optimization; adjust ACEI/oral vasodilator	Optimization of IV diuretics + adjustment of standard therapy; levosimendan (continuous 0.1–0.2 μg/kg/min) [If SBP <85 mmHg after the initiation of treatment, consider 0.05 μg/kg/min] or dobutamine or milrinone (in nonischemic HF) + vasopressor to maintain SBP >85 mmHg	Volume correction if no response: IV vassopressors (dobutamine, dopamine at vasoconstricting dosing and/or norepinephrine) If no response: mechanical support hemofiltration	If necessary, addition of levosimendan (continuous 0.05–0.1 μg/kg/min)

Parissis et al. Curr Opin Crit Care 2010

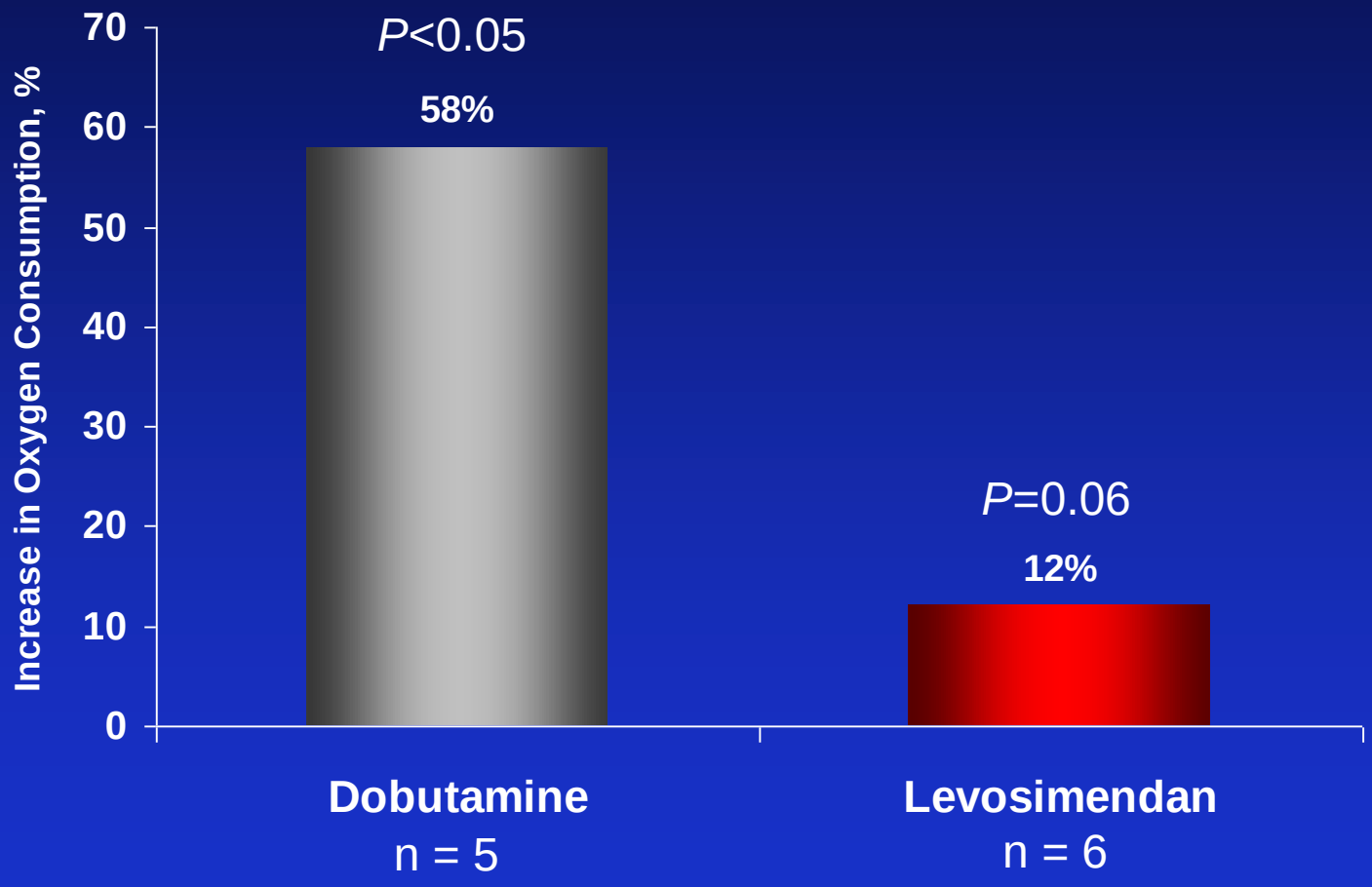
Levosimendan: biologic mechanisms and hemodynamic effects

Levosimendan: A Yellow Inodilator



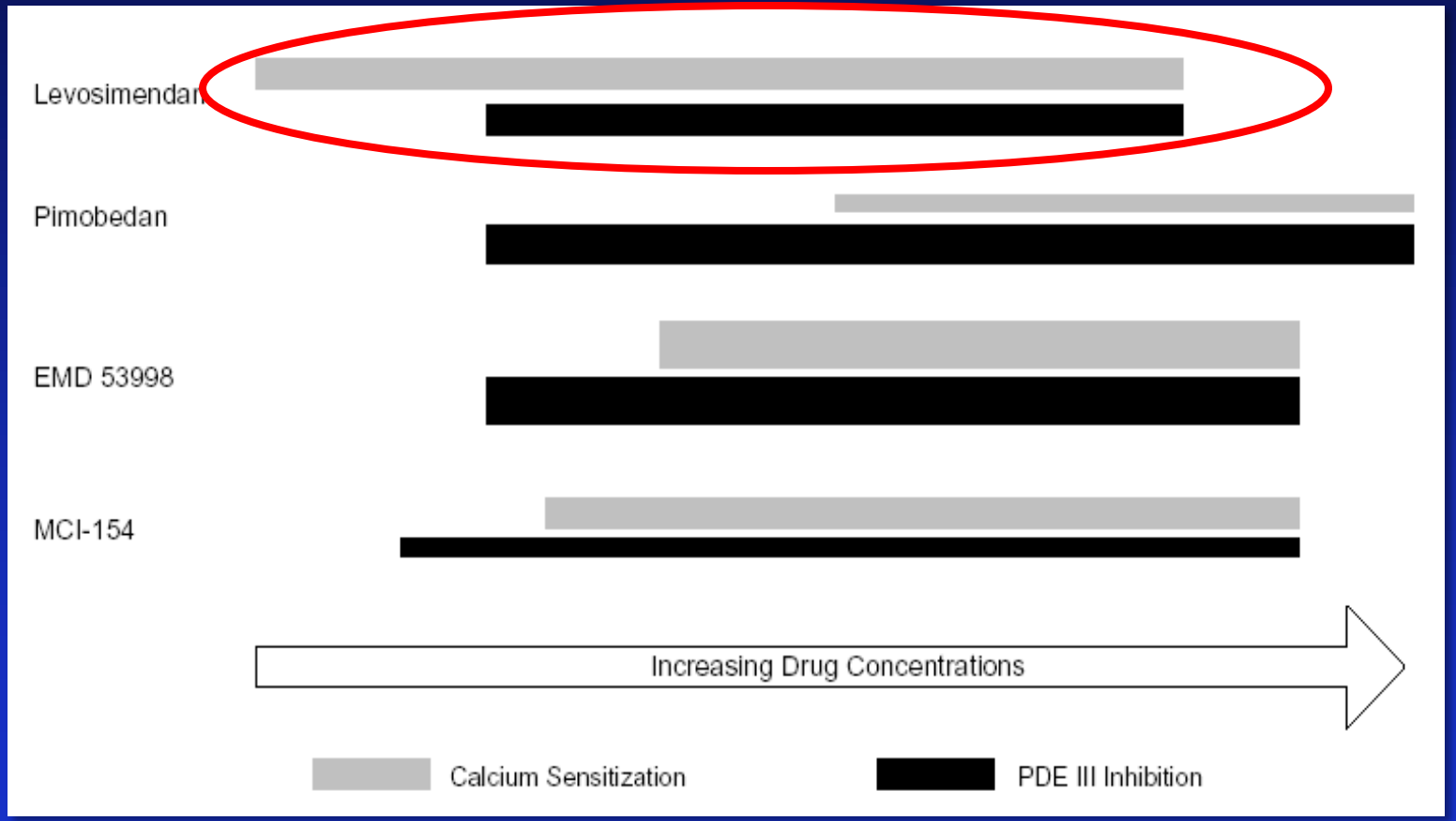
Expert Consensus Stockholm 2010; Papp Z, Parissis J et al. Int J Cardiol 2011 in press

Effects on Myocardial Oxygen Consumption



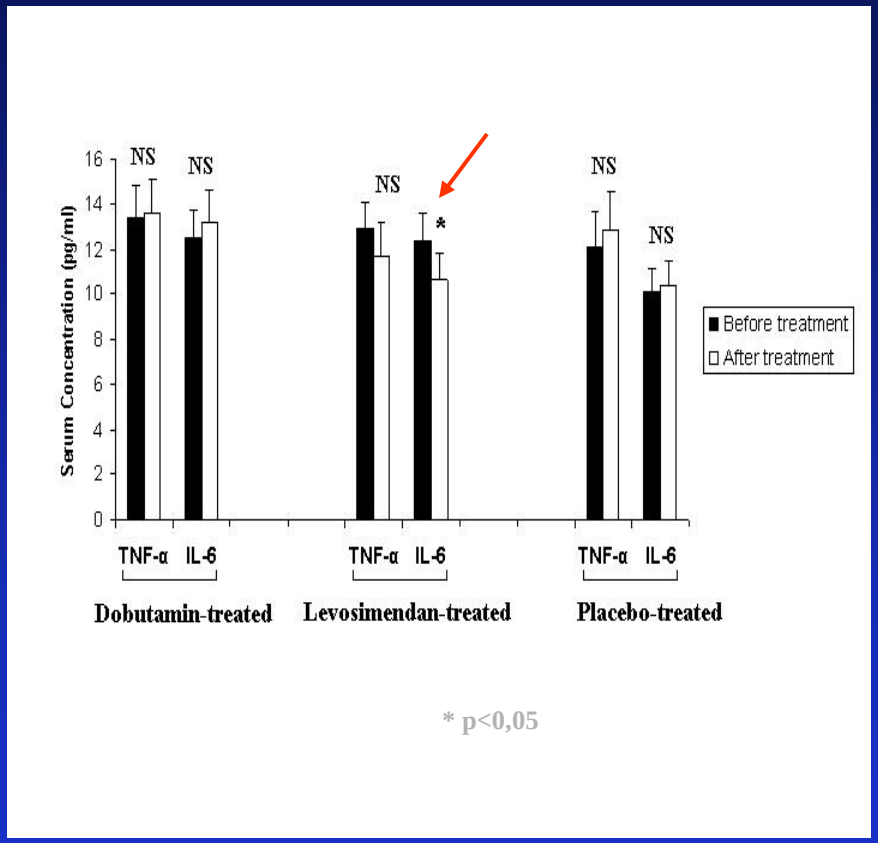
Ukkonen H, et al. Clin Pharmacol Ther. 1997;61:596-607.

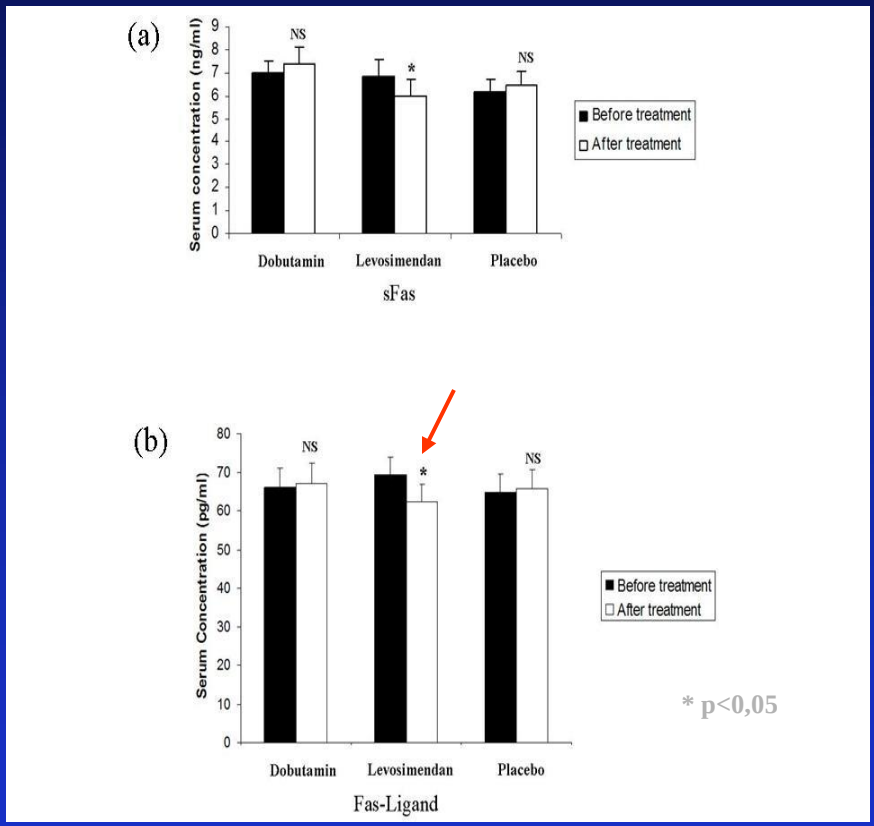
Intensity of the Calcium Sensitizer Effects and PDE III Inhibitor Effects in Different Calcium Sensitizer Compounds



Perrone SV. *Int J Cardiol* 2005;103:248-253.

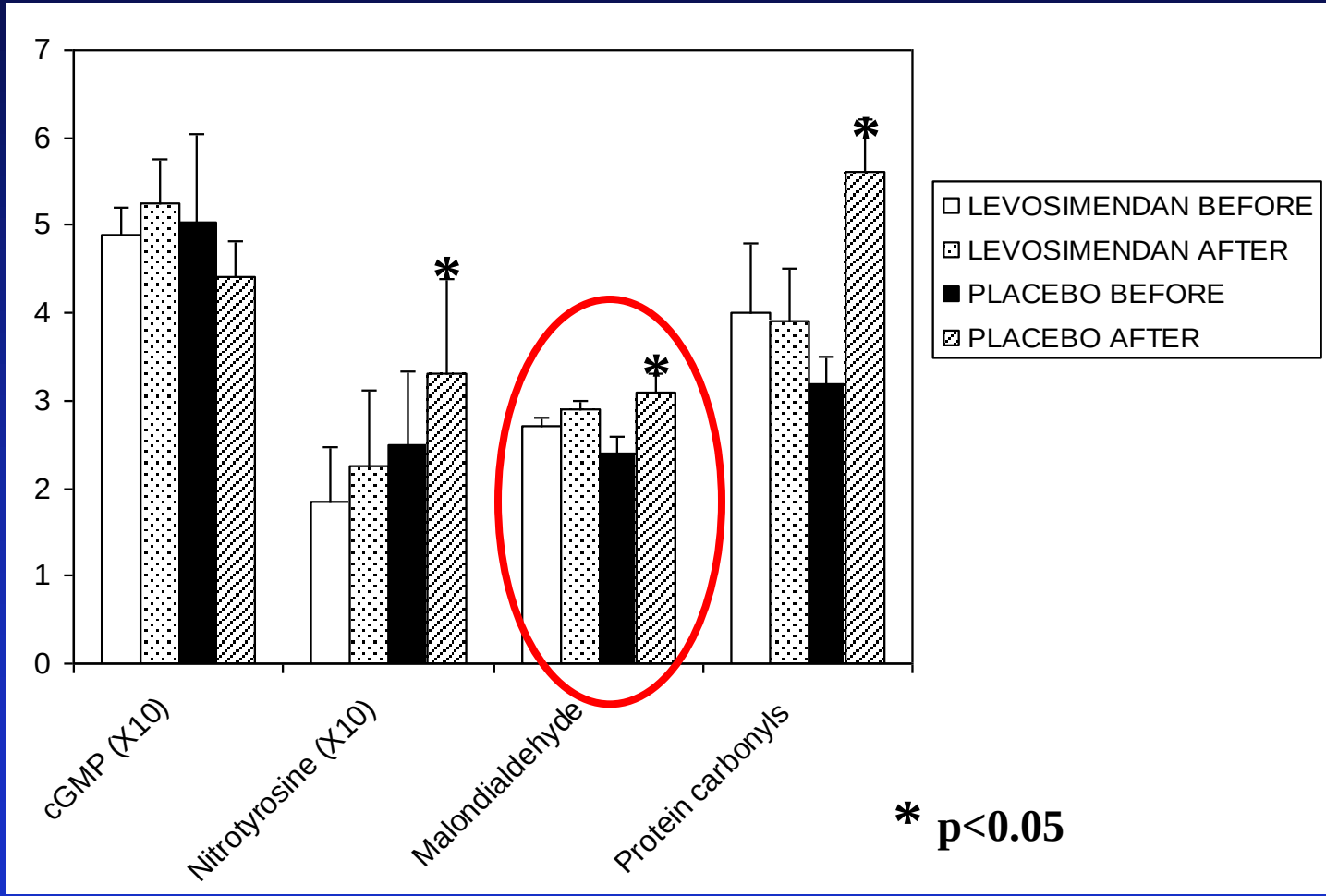
EFFECTS OF LEVOSIMENDAN ON PRO-INFLAMMATORY CYTOKINES IN ADHF





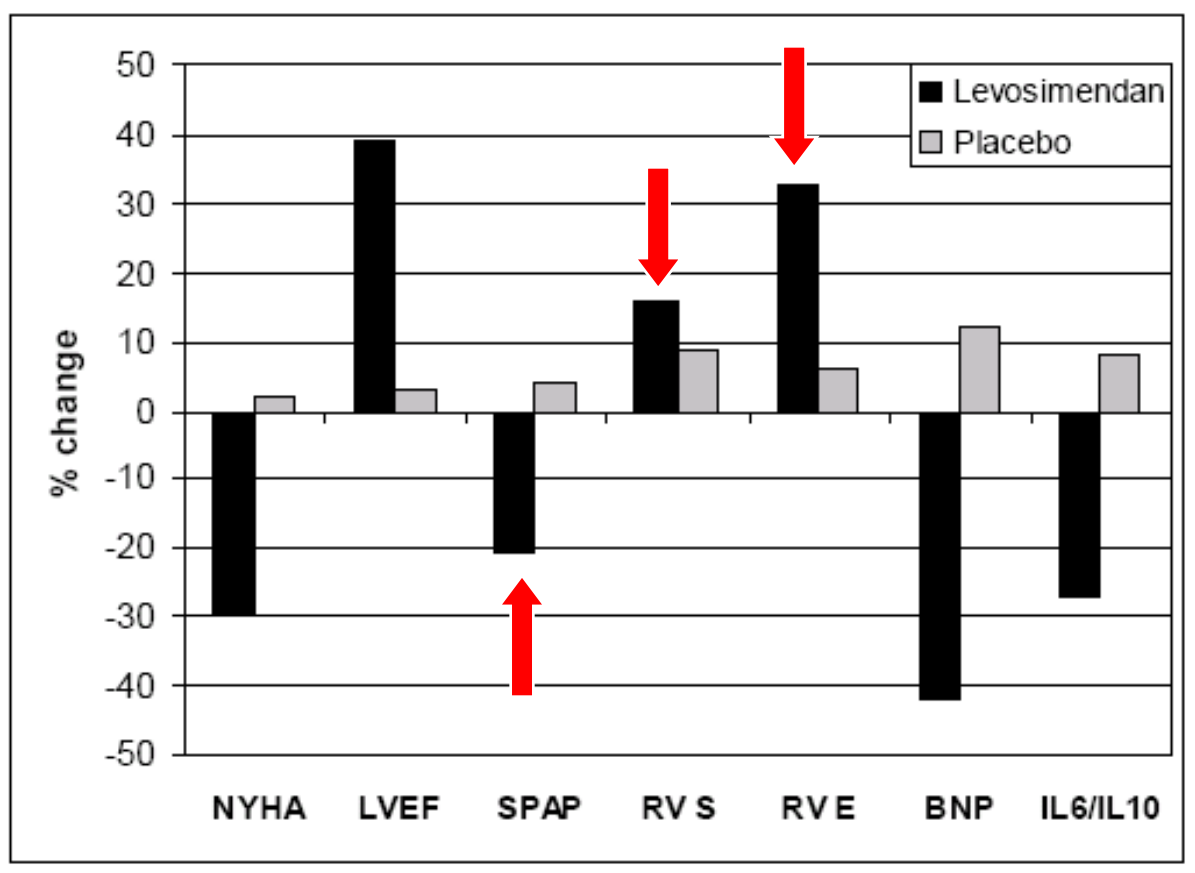
Parissis J, et al. Am J Cardiol 2004;93:1309

Levosimendan prevents oxidative damage in ADHF



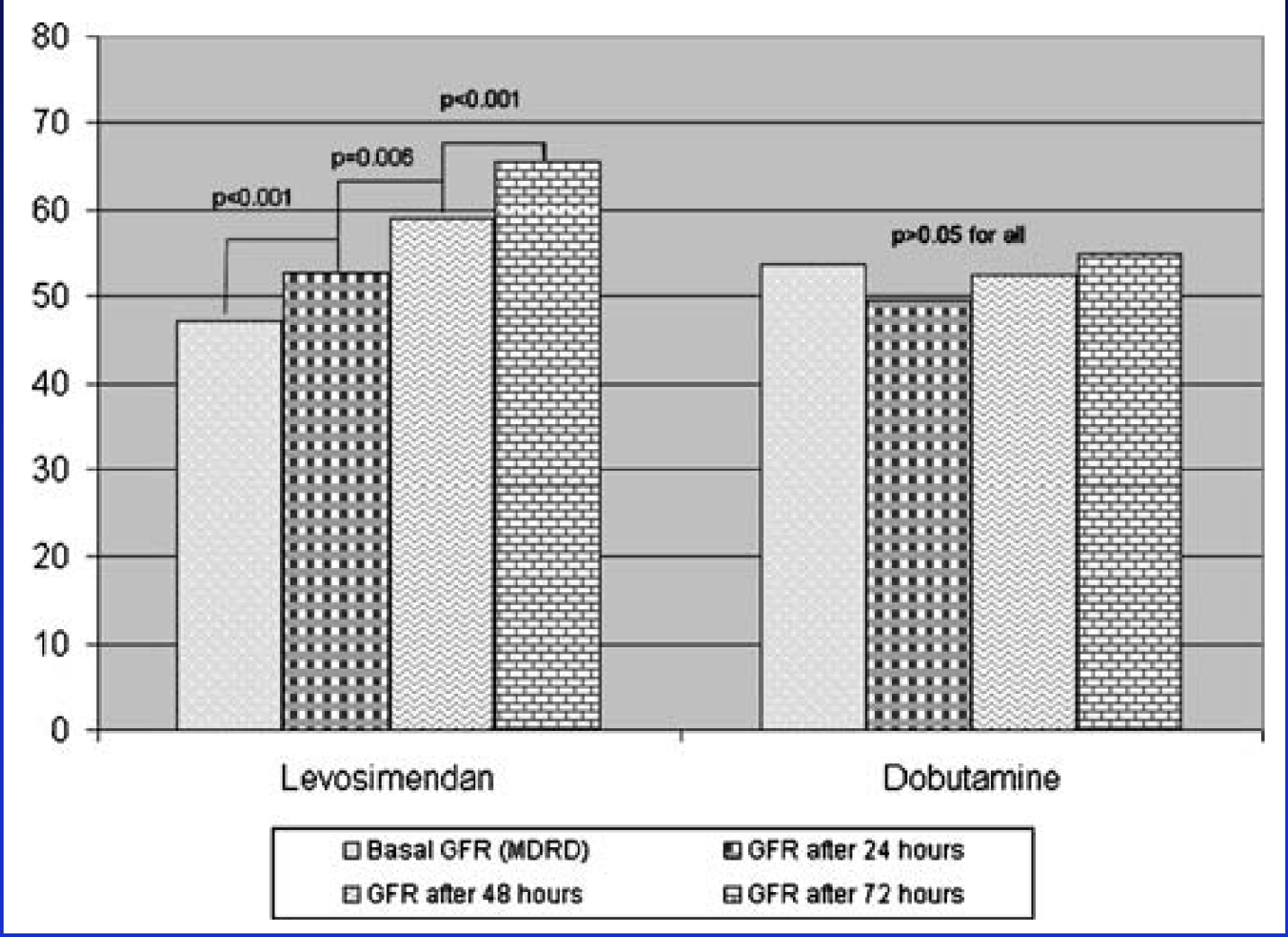
Parissis et al. Atherosclerosis 2007;195(2):e210-5.

Levosimendan and Right Ventricle in Advanced Heart Failure



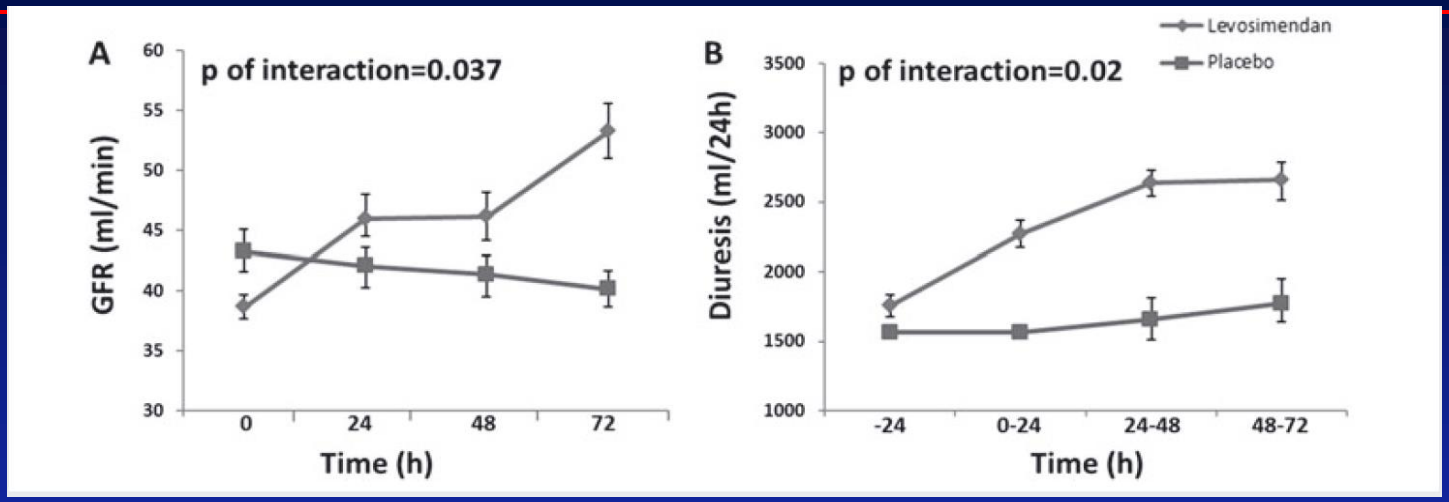
Parissis J, et al. Am J Cardiol 2006;98:1489

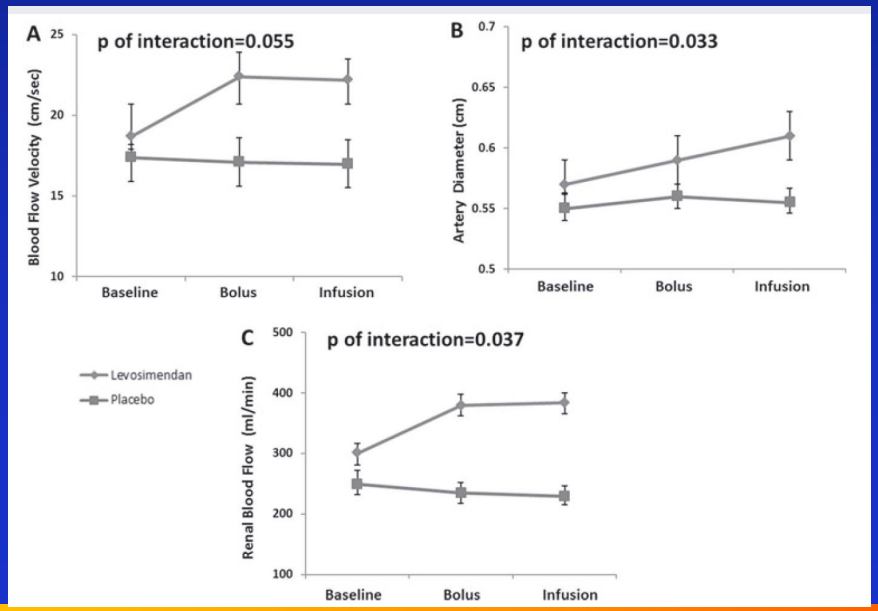
Levosimendan Improves Renal Function in Patients with ADHF: Comparison with Dobutamine



Yilmaz et al. Cardiovasc Drugs Ther 2007

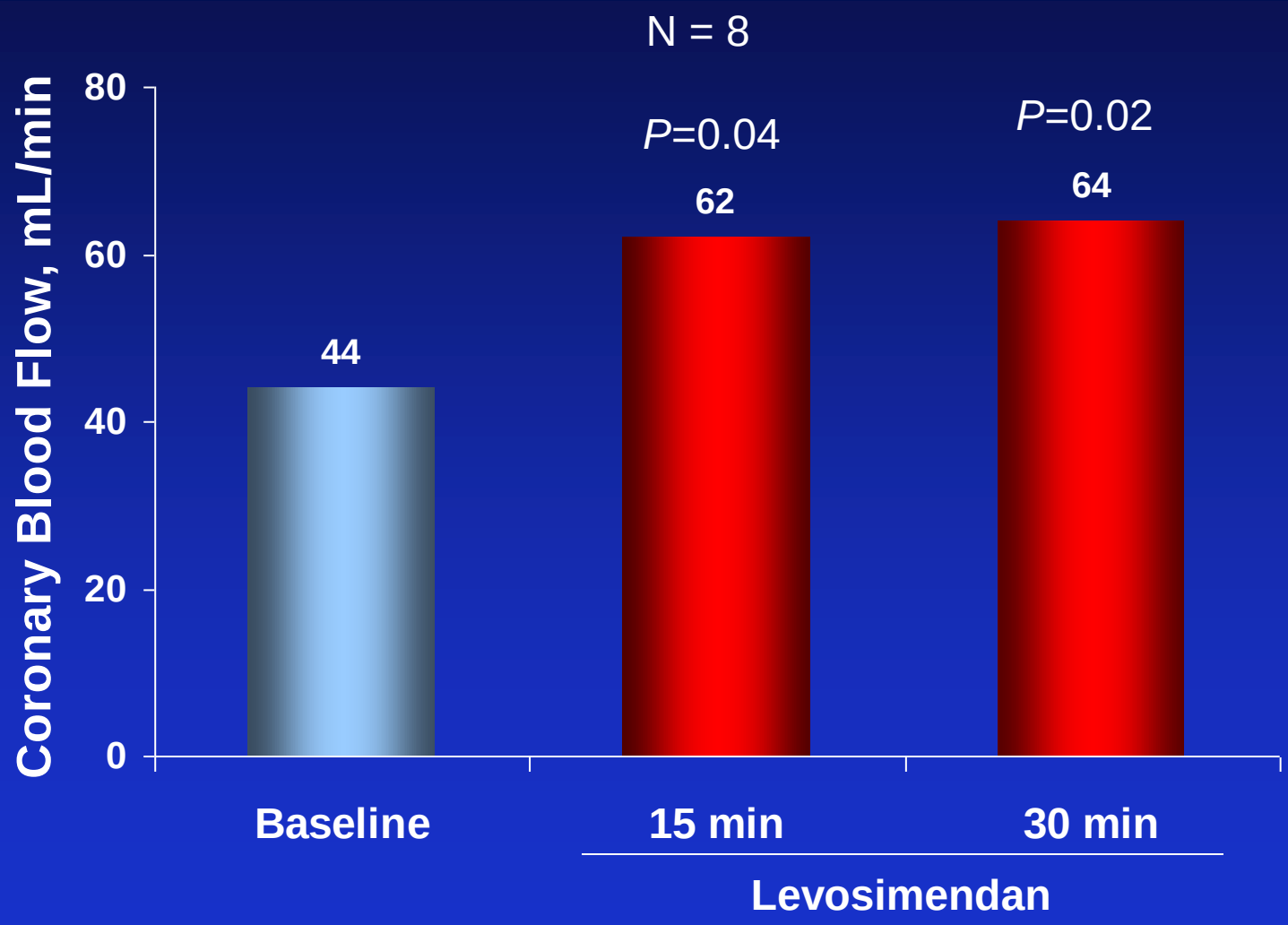
Levosimendan improves renal function in AHF: possible underlying mechanisms





Fedele et al. Eur J Heart Fail 2013

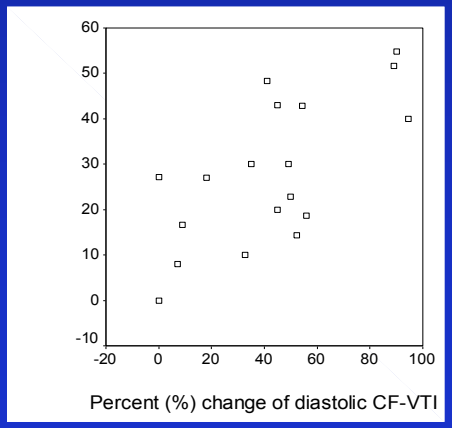
Effects of Levo on Coronary Blood Flow

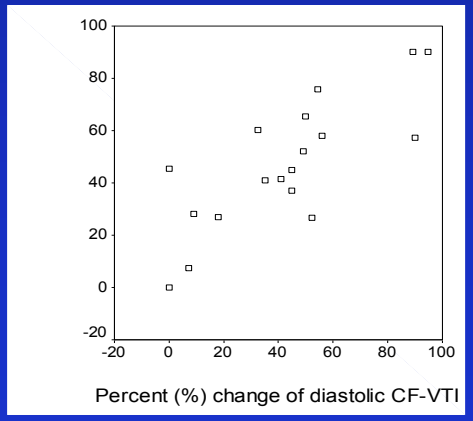


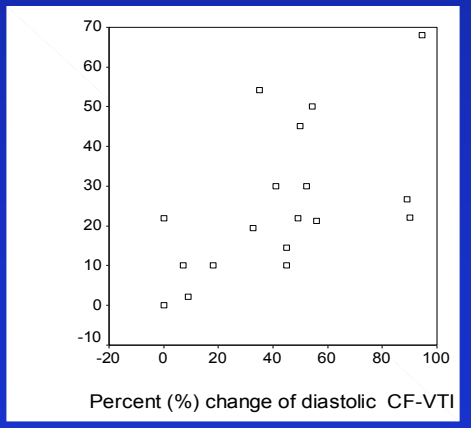
Michaels AD, et al. Circulation. 2005;111:1504-1509.

Increase of coronary flow after levosimendan infusion in patients with ADHF

	Max-CFV (m/sec)	VTI-CFV (m/sec)	RVSP(mm Hg)	E/e’	LVEF (%)	BNP (pg/ml)
LEVO baseline	0.29±0.1	10.3±2.6	59±8	26±21	25±7	1115±611
LEVO 48h post	0.43±0.2	16.3±6	51±7	13±5	33±4	588±471
p	0.017	0.002	0.002	0.014	<0.01	<0.01

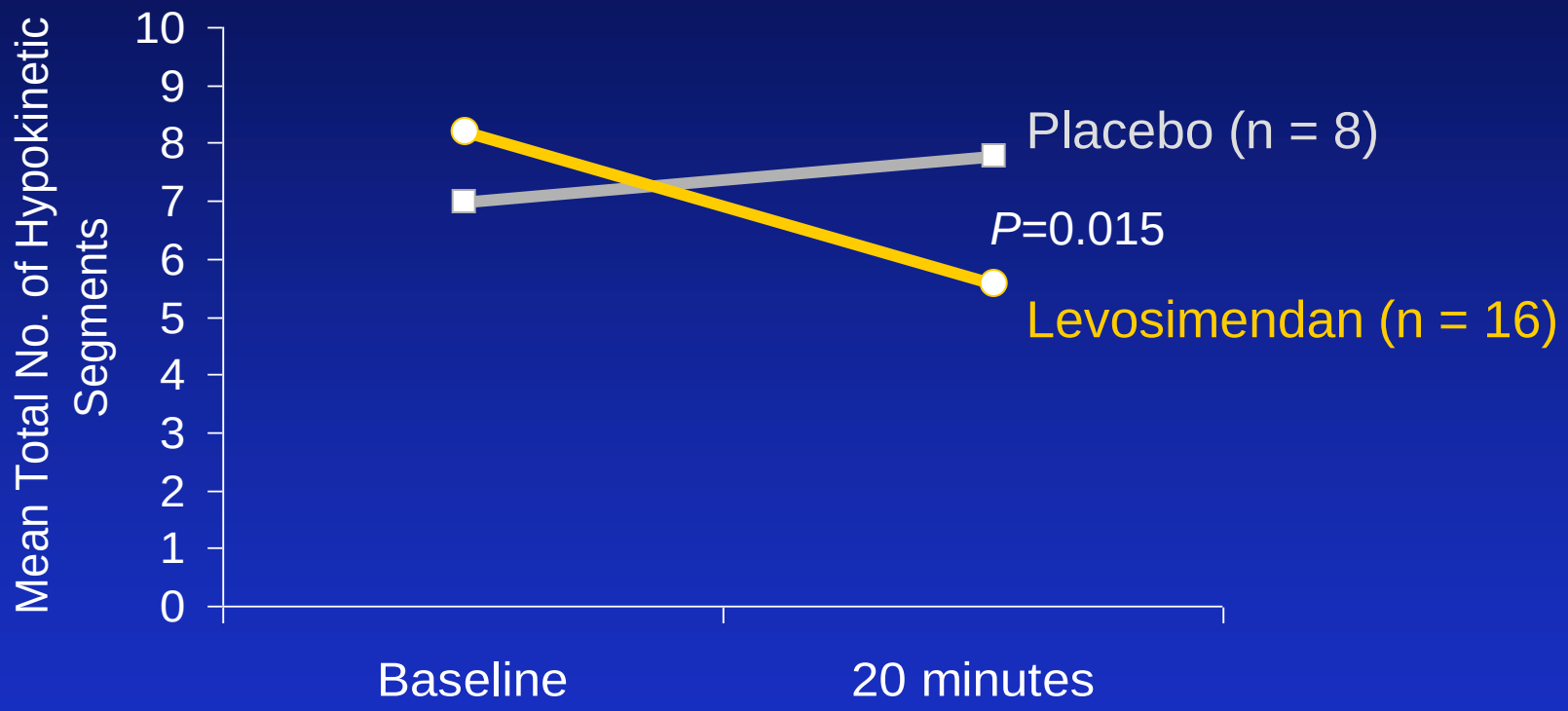






Ikonomidis I, Parissis J, Paraskevaidis I, et al.. Eur J Heart Fail 2007;9(12):1172-7.

Activation of Stunned Myocardium After Angioplasty



Sonntag S, et al. J Am Coll Cardiol. 2004;43:2177-2182.

Levosimendan improves hemodynamics and CFR after PCI in patients with post-MI LV dysfunction

	Levosimendan (n = 12)		Placebo (n = 14)	
	Baseline	After infusion	Baseline	After infusion
HR (beat/min)	68 ± 9	71 ± 11	65 ± 13	69 ± 8
Systolic BP (mm Hg)	105 ± 23	99 ± 19	107 ± 12	108 ± 16
PCWP (mm Hg)	24 ± 5	19 ± 5*	21 ± 7	22 ± 9
PAP (mm Hg)	12.7 ± 3.1	11.8 ± 2.7	14.1 ± 2.8	13.6 ± 3.3
SVR ([dyne · s]/cm^2)	1366 ± 329	1075 ± 258*	1311 ± 288	1329 ± 377
PVR ([dyne · s]/cm^2)	266 ± 30	265 ± 21	258 ± 18	256 ± 32
CI (L/[m^2 · min])	1.8 ± 0.4	2.4 ± 0.8*	1.7 ± 0.7	2.0 ± 0.9
Average systolic flow velocity (cm/s)	12.7 ± 5.8	12.1 ± 6.2	11.6 ± 6.3	11.8 ± 7.1
Average systolic flow velocity <6.5 cm/s (%)	4 (33.3)	4 (33.3)	5 (35.7)	5 (35.7)
Diastolic-systolic velocity ratio <3 (%)	8 (66.6)	8 (66.6)	9 (64.3)	10 (71.4)
CFR on reference vessel, ratio	2.1 ± 0.03	2.4 ± 0.06*	2.0 ± 0.04	2.1 ± 0.07

HR, Heart rate; *BP*, blood pressure; *PAP*, pulmonary artery pressure; *PVR*, pulmonary vascular resistance.
*$P < .05$ between parameters at baseline and after infusion in levosimendan group.

De Luca et al. Am Heart J 2005;150:563

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

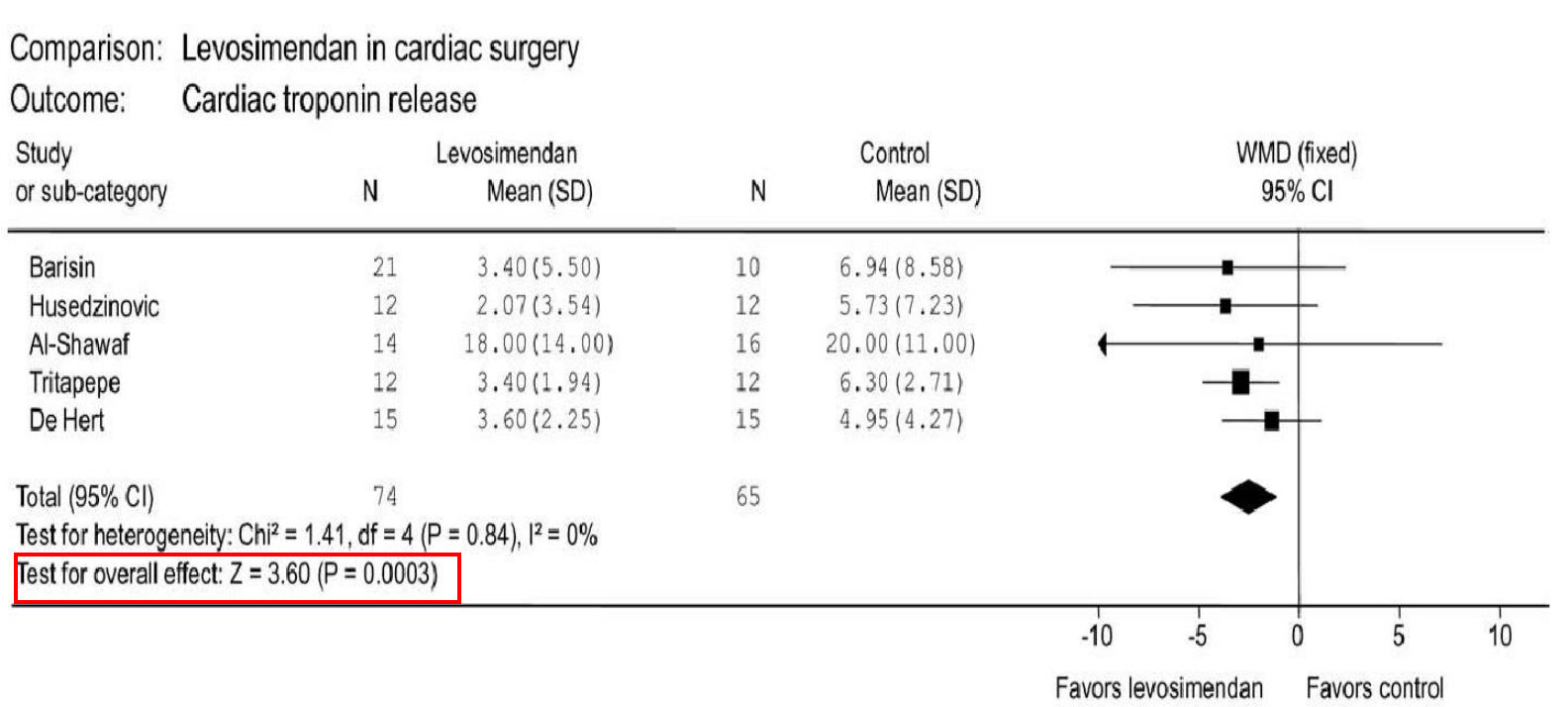


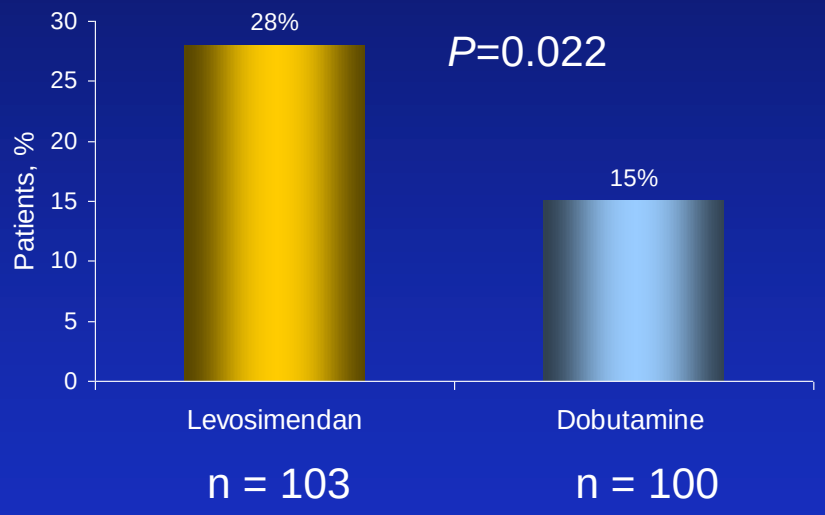
Fig 1. Pooled estimates of postoperative cardiac troponin release.

Zangrillo, et al. *Journal of Cardiothoracic and Vascular Anesthesia* 2009.

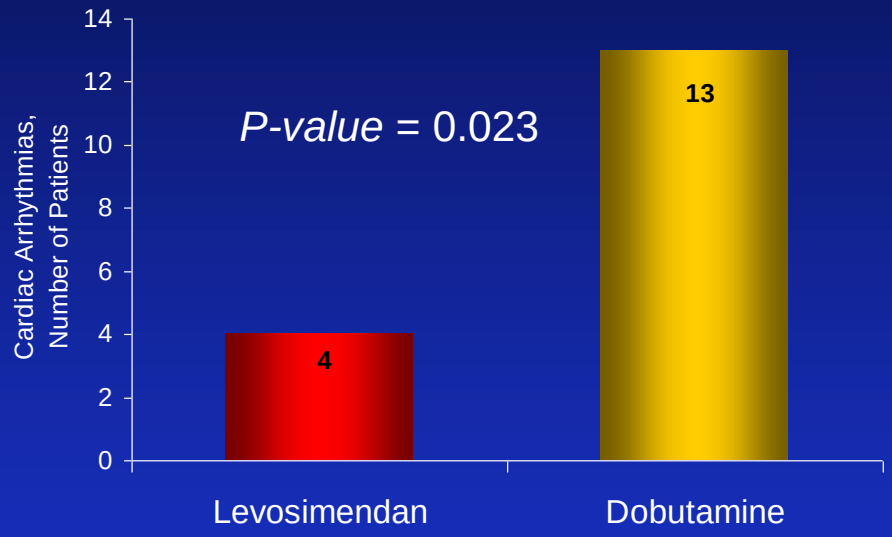
Levosimendan: Clinical Trials

Hemodynamic control in LIDO leaded to improvement of hemodynamics and prognosis without significant adverse effects

Increase in Cardiac Output ≥30% and a Decrease in PCWP ≥25%

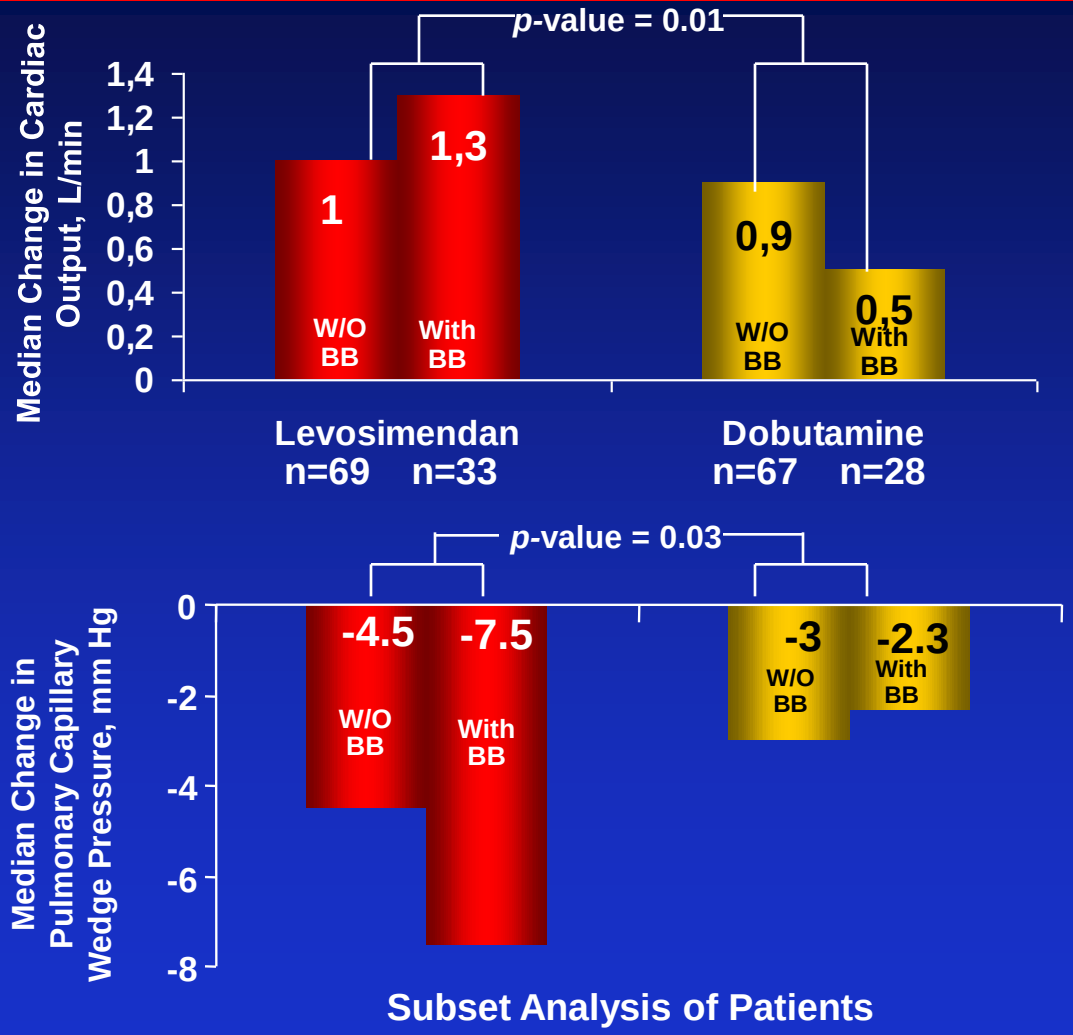


Lower percentage of arrhythmias in levosimendan arm



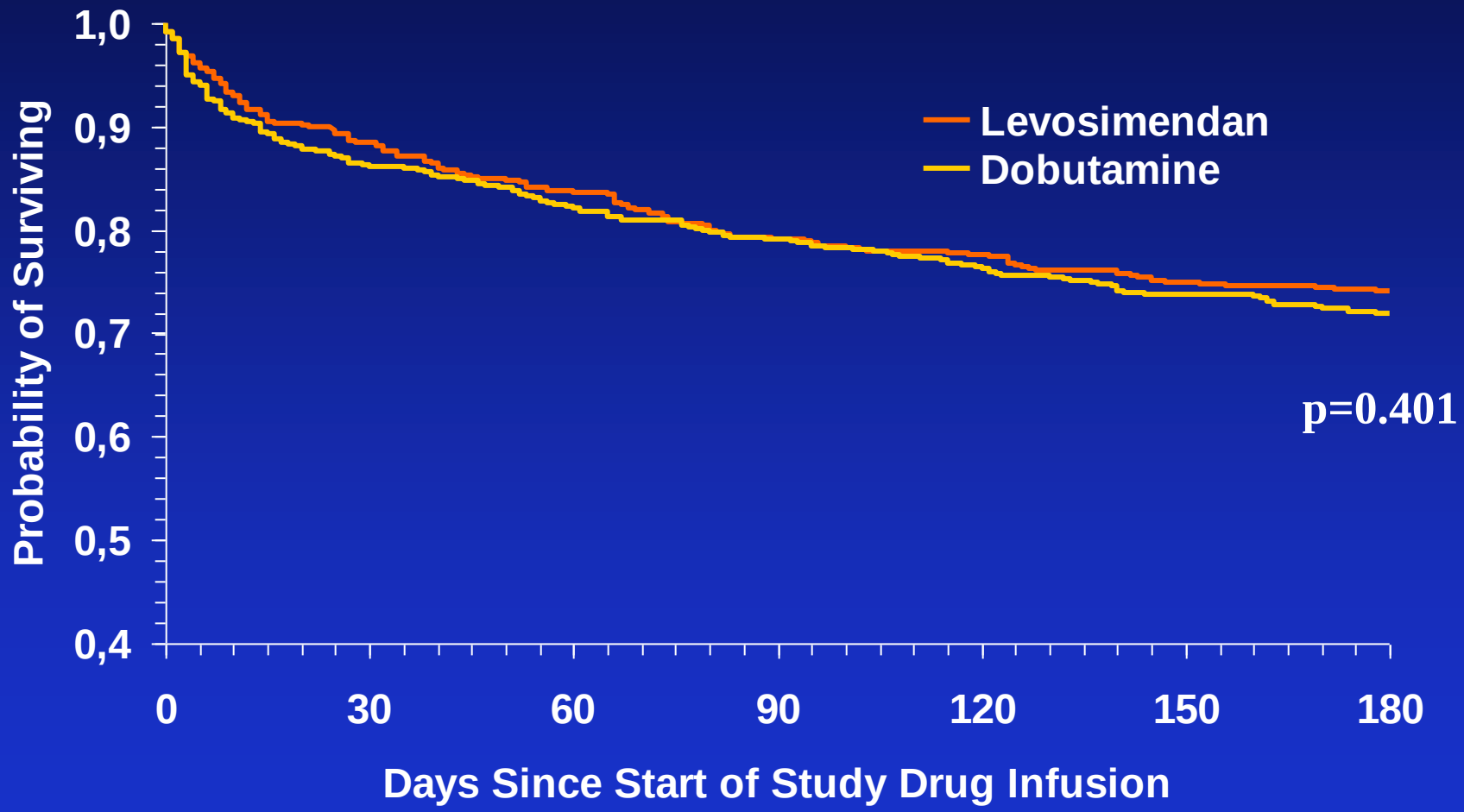
Follath F, et al. Lancet. 2002;360:196-202.

Effect of β-blockers on CO and PCWP Responses (LIDO)



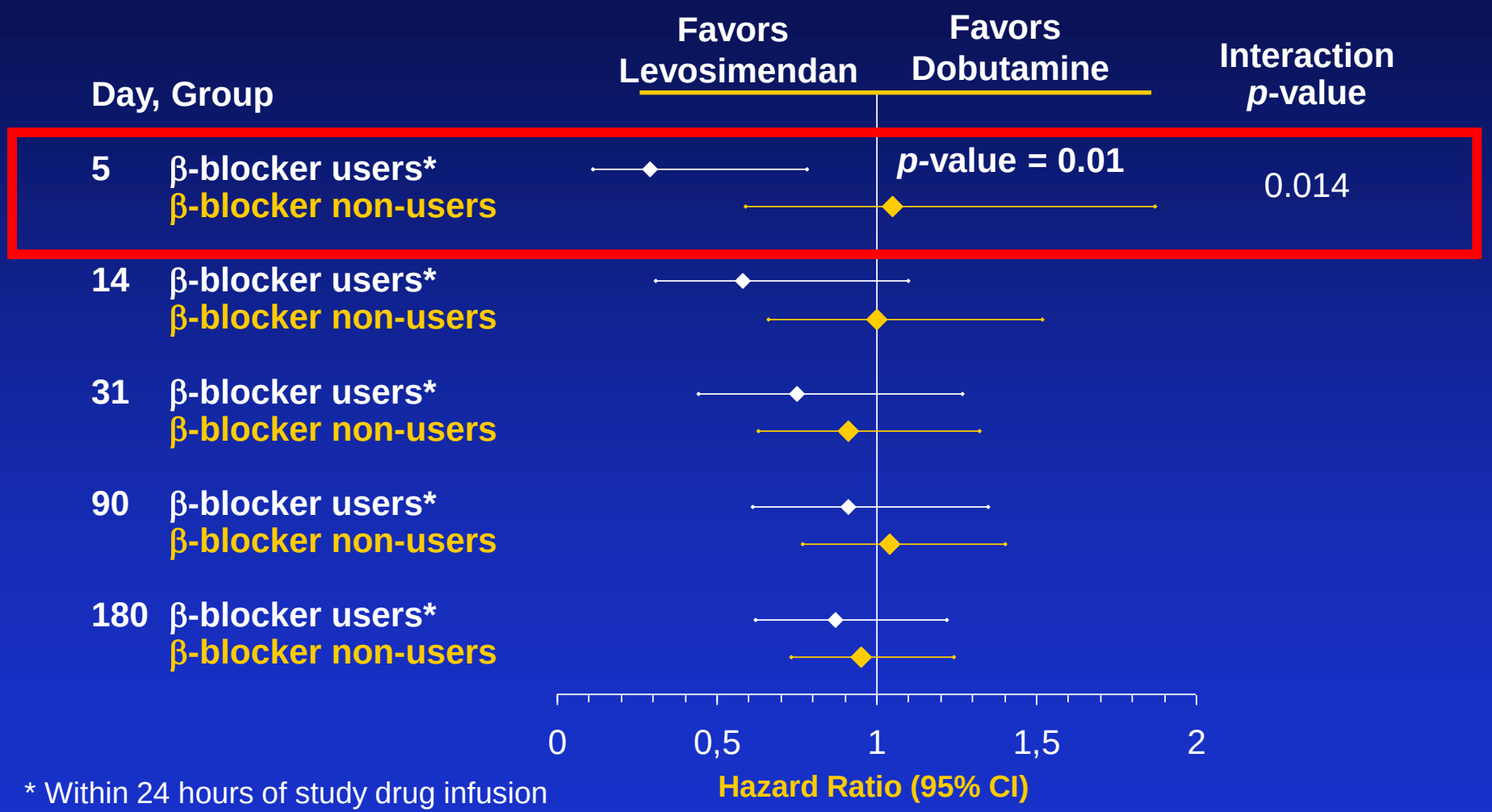
Follath F, et al. *Lancet.* 2002;360:196-202.

SURVIVE
180-day All-Cause Mortality



Mebazaa et al. JAMA 2007;297:1883-91.

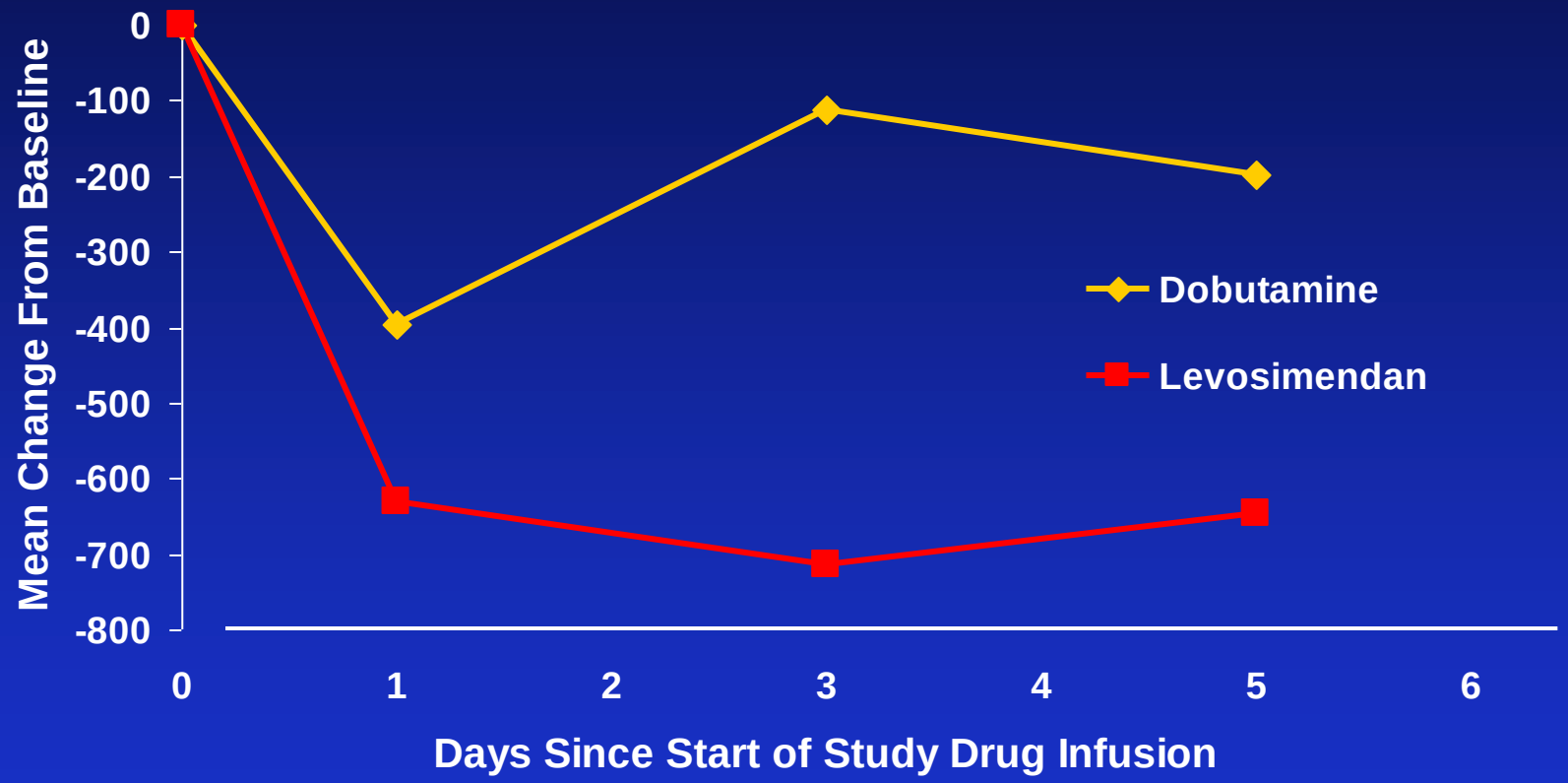
Hazard Ratios for Patients on β-Blockers at Baseline Appeared to Favor Levosimendan



* Within 24 hours of study drug infusion

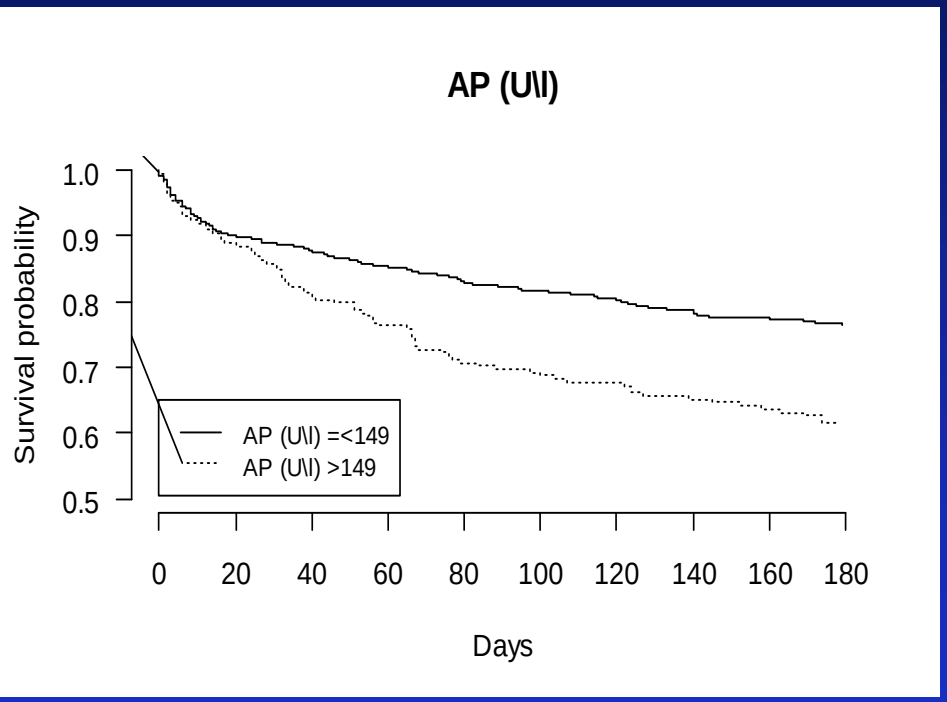
European Journal of Heart Failure Advance Access published January 21, 2009

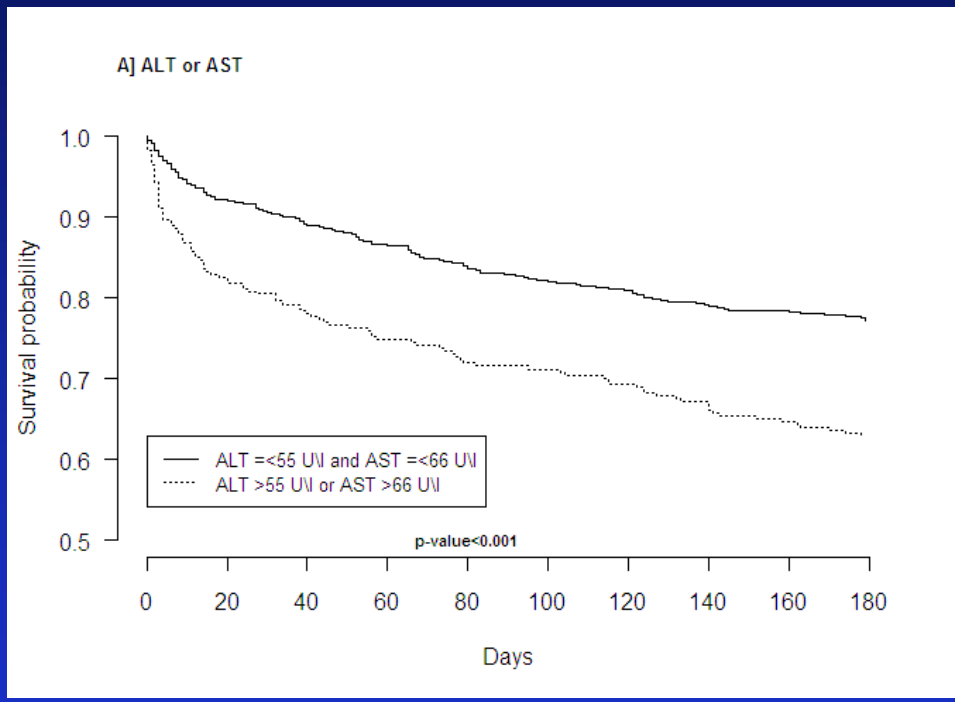
SURVIVE
Mean Change from Baseline in BNP



For comparison between treatment groups at all time points (***P*<0.0001**)
Due to the skewness in the data, median percent change is presented *versus* mean percent change from baseline

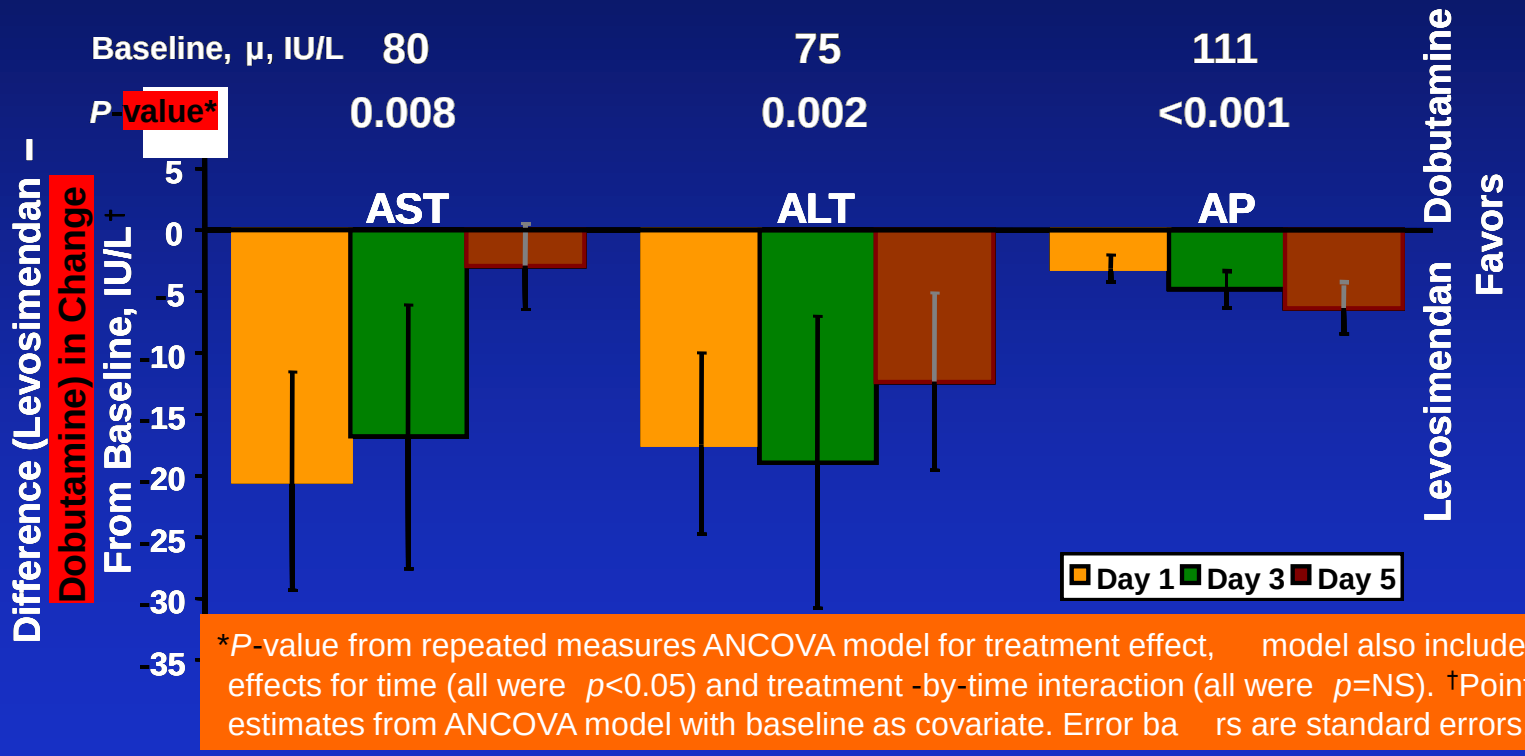
Prognostic role of liver congestion in ADHF: A SURVIVE subanalysis





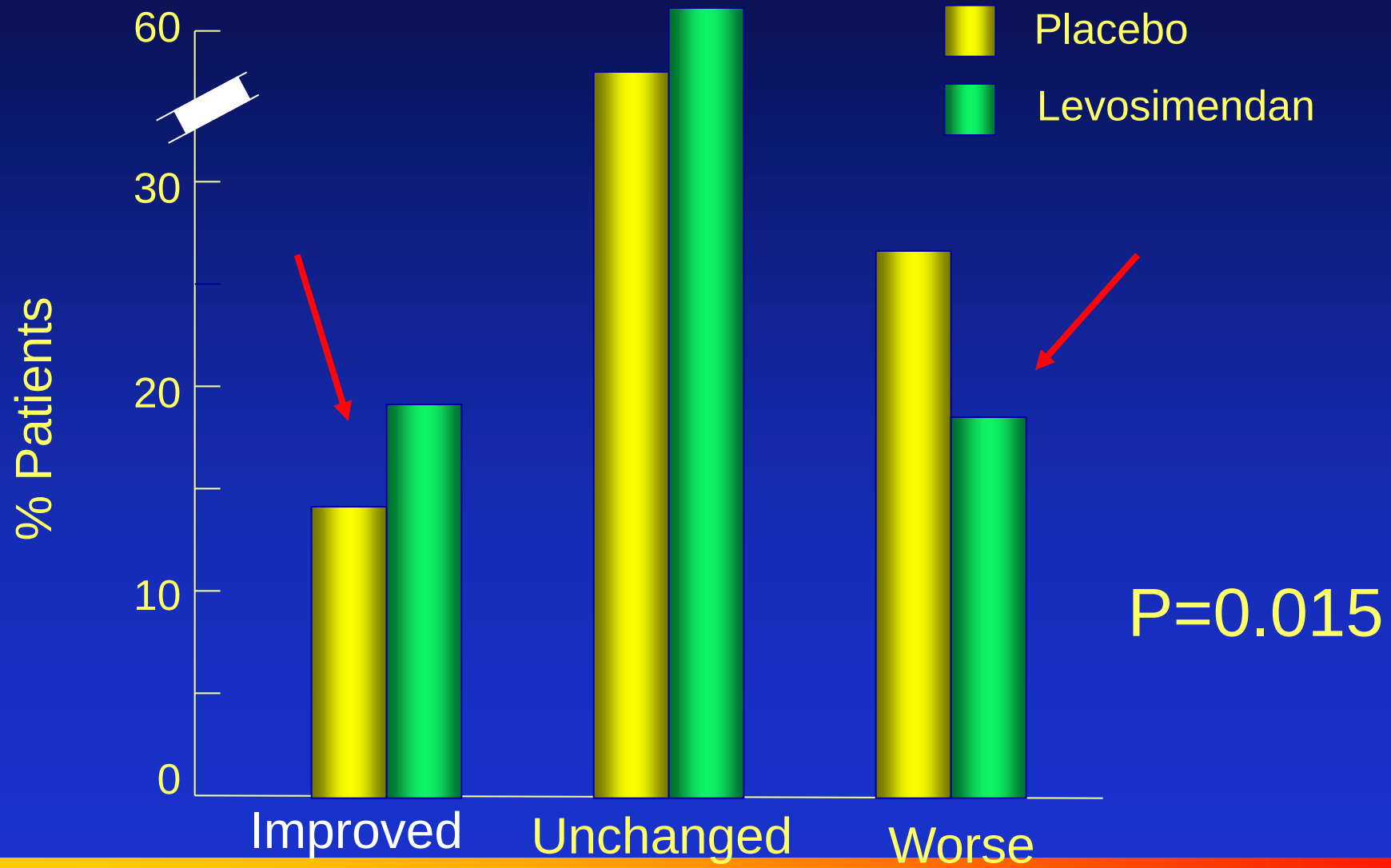
Nikolaou M, Parissis J,…, Mebazaa A, et al. Eur Heart J 2013

Levosimendan, compared to dobutamine, reduces markers associated with liver congestion and injury: A SURVIVE subanalysis



*P-value from repeated measures ANCOVA model for treatment effect, model also included effects for time (all were $p<0.05$) and treatment -by-time interaction (all were p=NS). †Point estimates from ANCOVA model with baseline as covariate. Error ba rs are standard errors.

REVIVE II: Primary Endpoint (n=600)



REVIVE: Effect of Levosimendan on Mortality

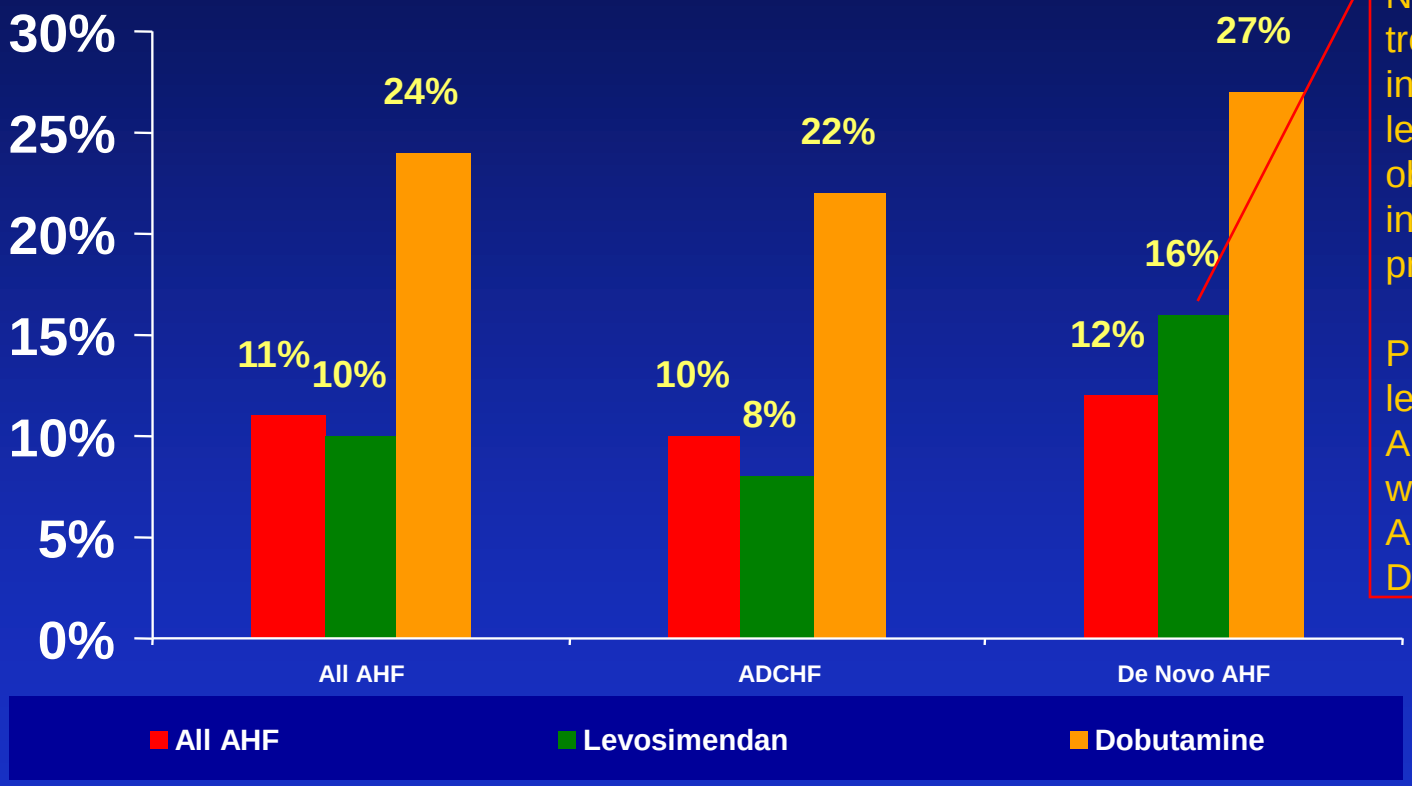
	Days Following Randomization			
	5	**14**	**31**	**90**
REVIVE II				
Placebo	1	5	12	35
Levosimendan	5	14	20	45
REVIVE I				
Placebo	0	1	4	5
Levosimendan	0	1	1	4
REVIVE I + II				
Placebo	1	6	16	40
Levosimendan	5	15	21	49

REVIVE II: Treatment Emergent Adverse Events of Interest in the Levosimendan and Placebo Arms

Adverse Event	Levosimendan + SOC (n = 293)	Placebo + SOC (n = 294)	p-value
	%	%	
Hypotension	50.2	36.4	<0.001
Ventricular tachycardia	24.6	17.3	0.031
Cardiac failure	22.9	27.2	0.225
Atrial fibrillation	8.5	2.0	<0.001
Ventricular extrasystoles	7.5	2.0	0.002
Sudden death	0.3	0	NS
Torsade de Pointes	0	0.3	NS

ALARM-HF data suggests a lower mortality rate in ADCHF patients receiving levosimendan compared to De Novo AHF patients

In-hospital mortality rate for levosimendan vs dobutamine* patients by main diagnosis



Note: in SURVIVE, treatment differences in favour of levosimendan were observed at 31 days in patients with a prior history of CHF

Prior BB usage in levosimendan ALARM-HF patients was 32% (36% in ADCHF vs 20% in De Novo AHF)

Sample = 318 Levo patients (of which ADCHF = 239 and De Novo AHF = 79) and 1,103 dobutamine patients (of which ADCHF = 680, and De Novo AHF = 423)

Mebazaa A, Parissis J, Porcher R, et al. Intensive Care Med 2011 Feb;37(2):290-301

Current IV Inotropic Therapies in AH: ESC recommendations

Dobutamine: cl IIa, Level evidence B

(prefereble agent due to lower cost)

Levosimendan: cl IIb, Level of evidence B

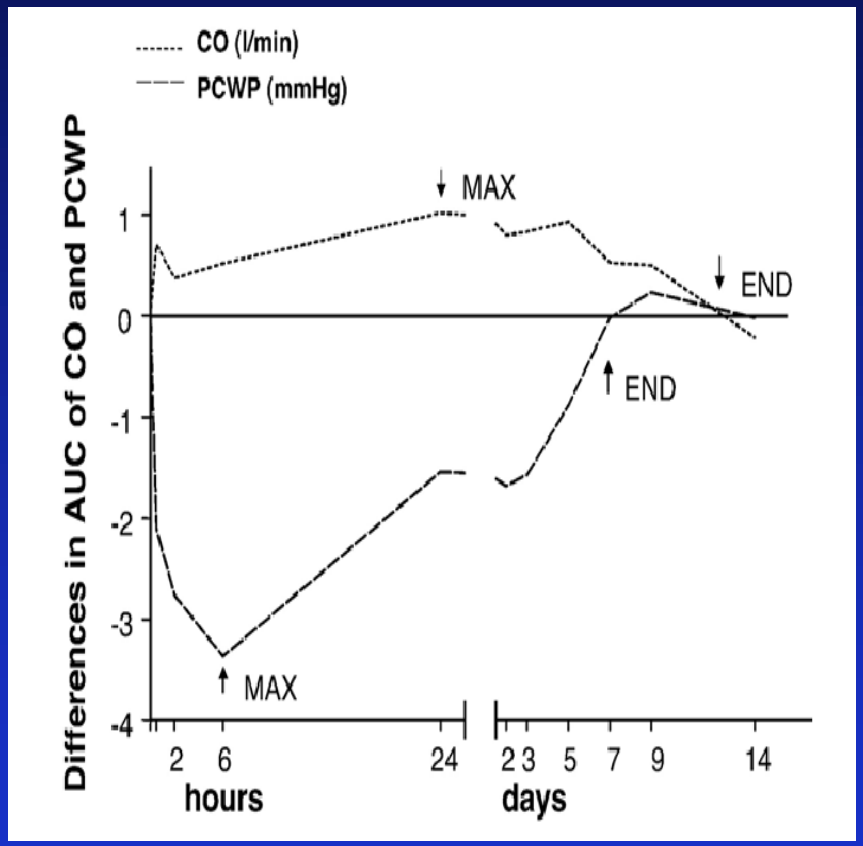
(preferable agent for patients on beta blocker)

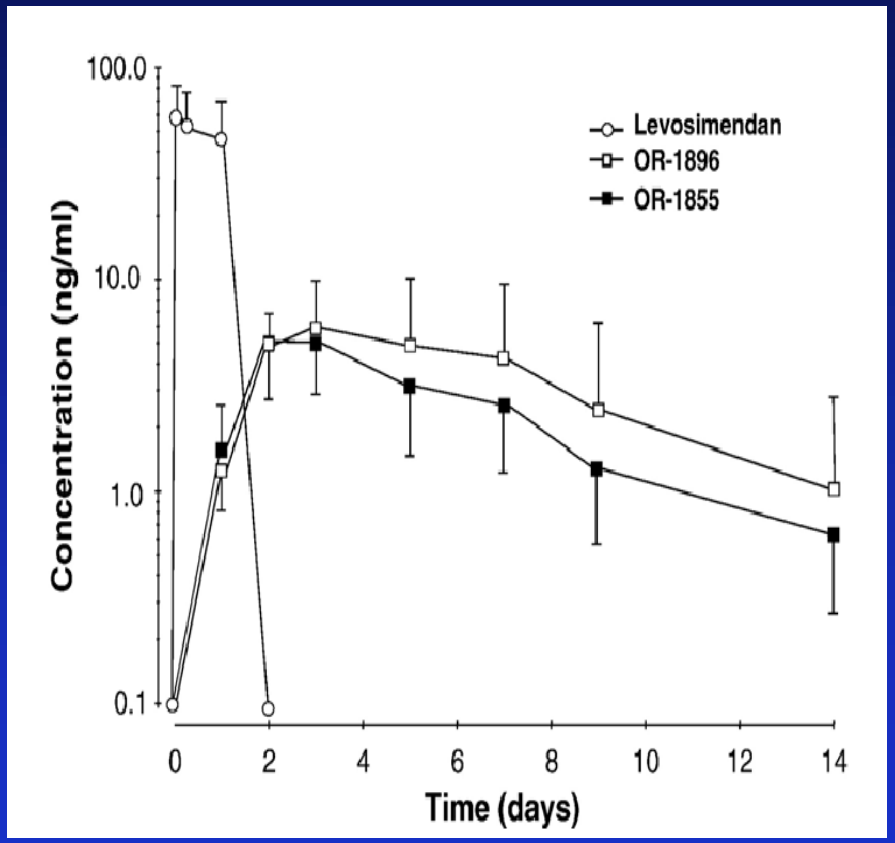
PDEIs: cl IIb, Level evidence B

Dopamine: cl IIb, Level evidence B

Pulsed Infusions in outpatients with advanced CHF

Duration of the Hemodynamic Action of a 24-h Infusion of Levosimendan in Patients with ADHF

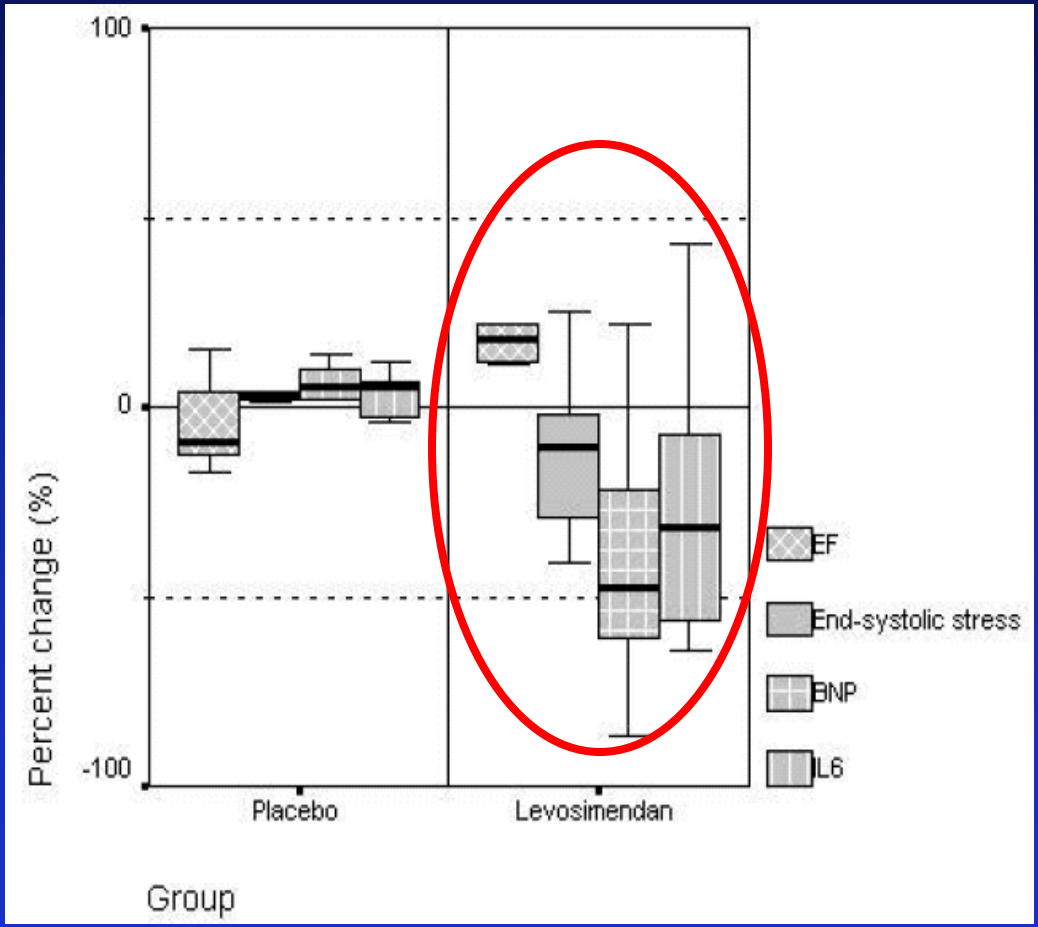


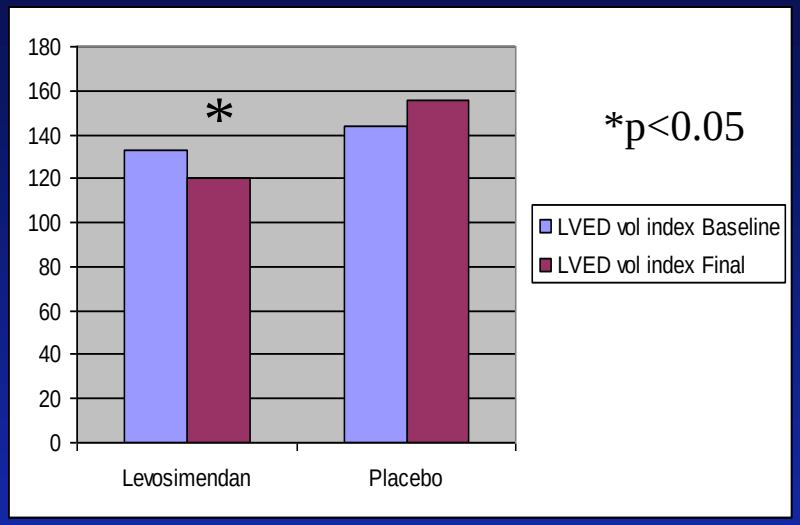


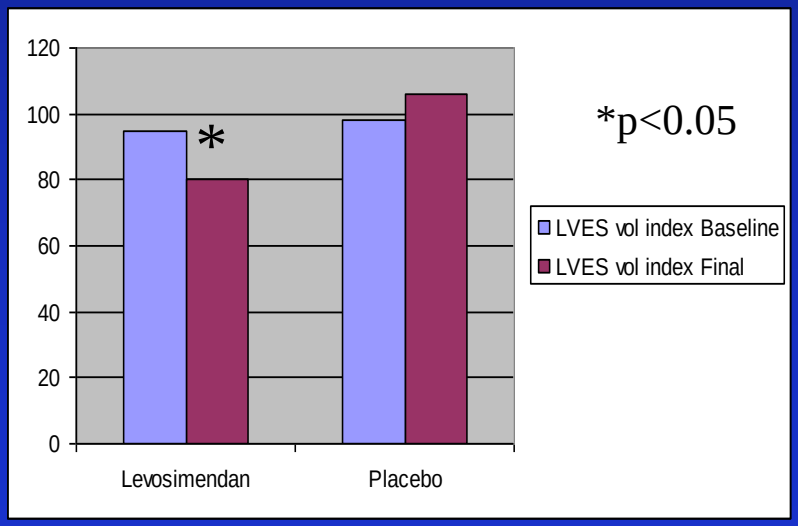
Lilleberg et al. Eur J Heart Fail 2007

Serial Levosimendan Infusions in ADHF: Results

N=25 pts



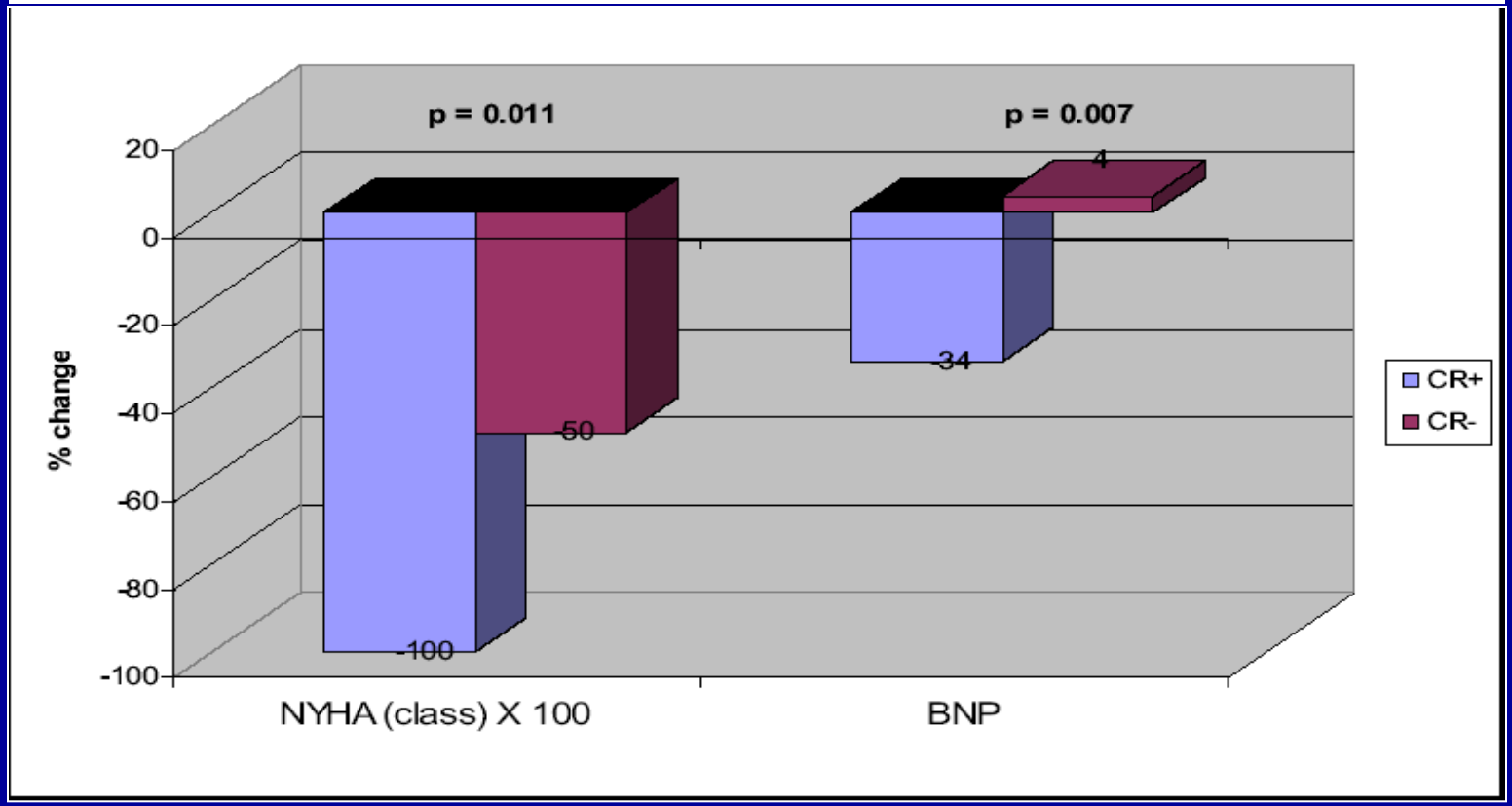




Parissis et al. Heart 2006;92(12):1768

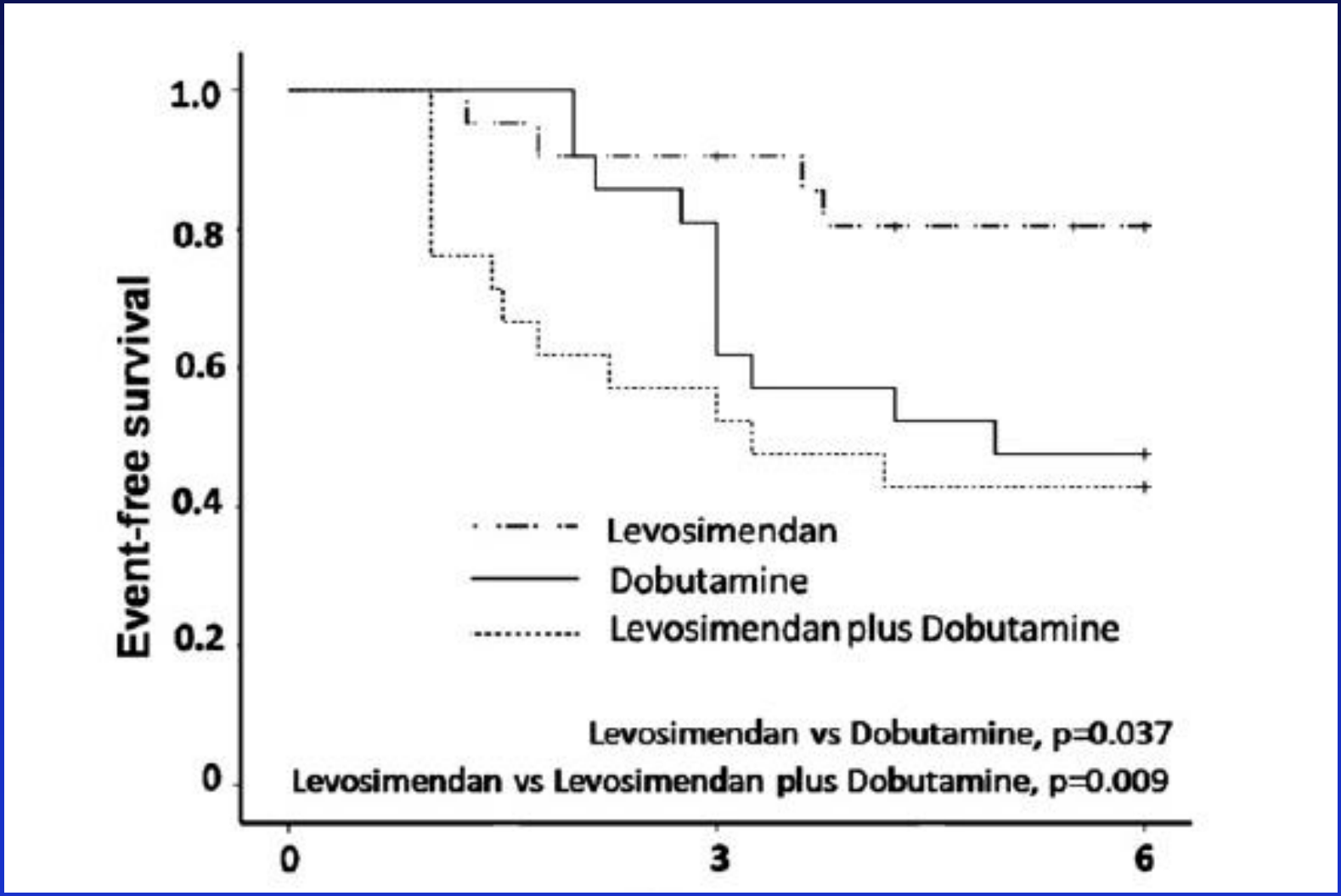
Usefulness of Dobutamine-Induced Changes of the Two-Dimensional Longitudinal Deformation Predict Clinical and Neurohumoral Improvement in Men After Levosimendan Treatment in ADHF

Ioannis A. Paraskevaidis, MD, Vassiliki Bistola, MD, Ignatios Ikonomidis, MD, John T. Parissis, MD*, Constantinos Papadopoulos, MD, Gerasimos Filippatos, MD, and Dimitrios T. Kremastinos, MD



Am J Cardiol 2008;102:1225-1229.

Comparison of three different regimens of intermittent inotrope infusions for end stage HF



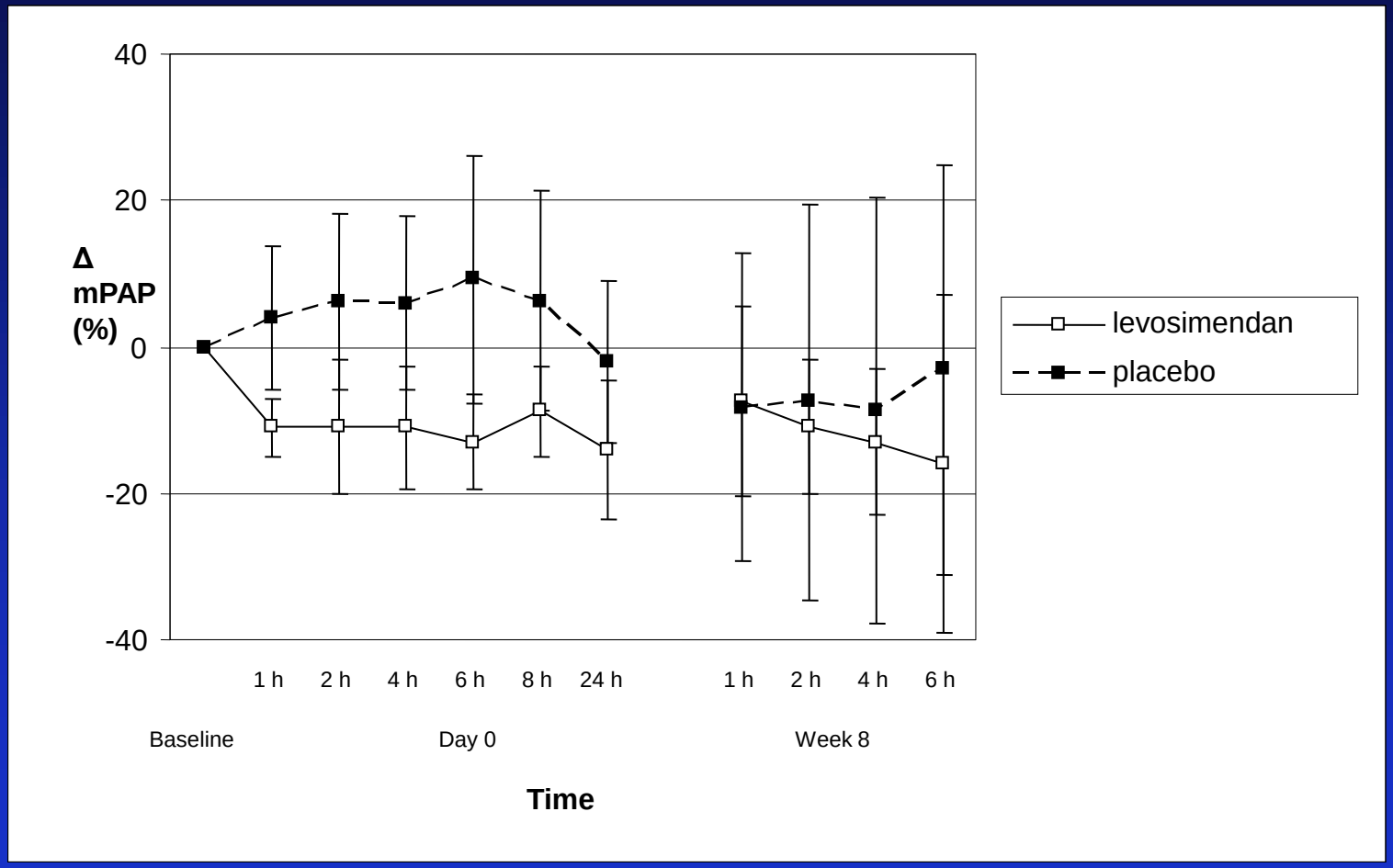
Bonios et al. Int J Cardiol 2012;159:225

Repetitive Levosimendan in pulm. hypertension

- Randomised, double-blind placebo-controlled parallel-group trial in patients with pulmonary hypertension
- 28 patients with pulmonary hypertension in four centres in Germany, one in Sweden
- Dosing:
  - initial: 12 mcg/kg/10 min bolus + 0.1 mcg/kg/min for 50 min + 0.2 mcg/kg/min up to 24 h
  - repeated doses: 0.2 mcg/kg/min for 6 h, in total 4 times with 2-week interval
- PEP: Change in pulmonary vascular resistance (PVR)

Kleber et al. J Clin Pharmacol 2009;49:109-115

Change in mPAP (mean ± SEM)



Kleber et al. J Clin Pharmacol 2009;49:109-115

LEVOREP – Studie

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2010) **12**, 186–192
doi:10.1093/eurjhf/hfp189

Rationale and design of the multicentre randomized trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep study)

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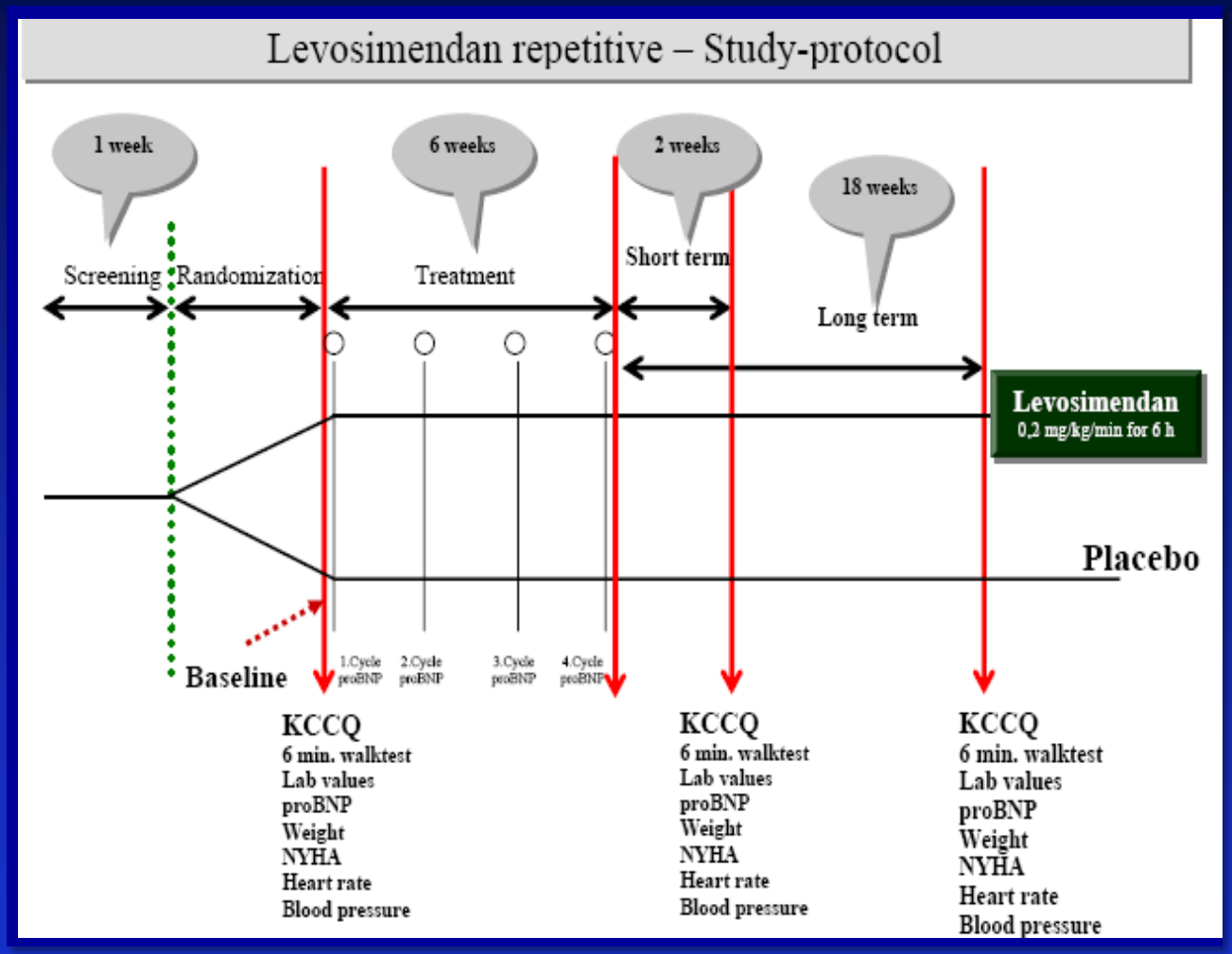
LEVOREP Trial: Design



Altenberger, Pöelzl, Parissis: Studienprotokoll 2008

LevoRep – Study

Inclusion criteria

- Chronic stable heart failure NYHA III/IV for >3 months
- Ejection fraction ≤ 35%
- Six-minute-walk test < 350 m
- Age > 20 years
- Individually optimized neurohormonal background therapy

Exclusion criteria

- Hospitalization for acute heart failure within the last 4 weeks
- Systolic blood pressure ≤ 100mmHg
- Potassium < 3.5 or > 5.5 mmol/l
- Creatinine clearance < 30 ml/min/qm
- History of torsade de pointes
- Surgical or percutaneous coronary revascularization or CRT implant within thelast 3 months

LevoRep - endpoints

Primary endpoint

Proportion of patients with ≥20% increase in the six-minute walking distance **and** ≥15% improvement in the KCCQ clinical summary score

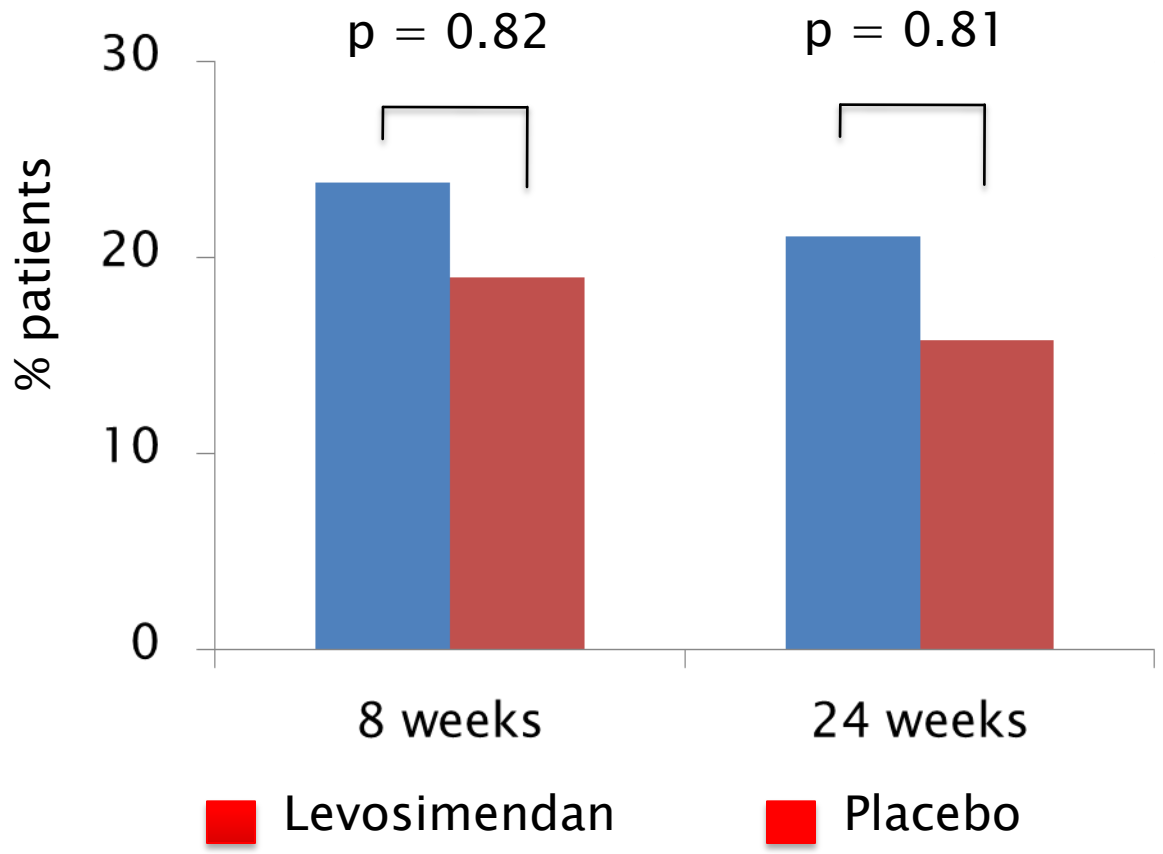
Secondary endpoint

Event-free survival (cardiac death, heart transplant or acute heart failure)

LevoRep – results

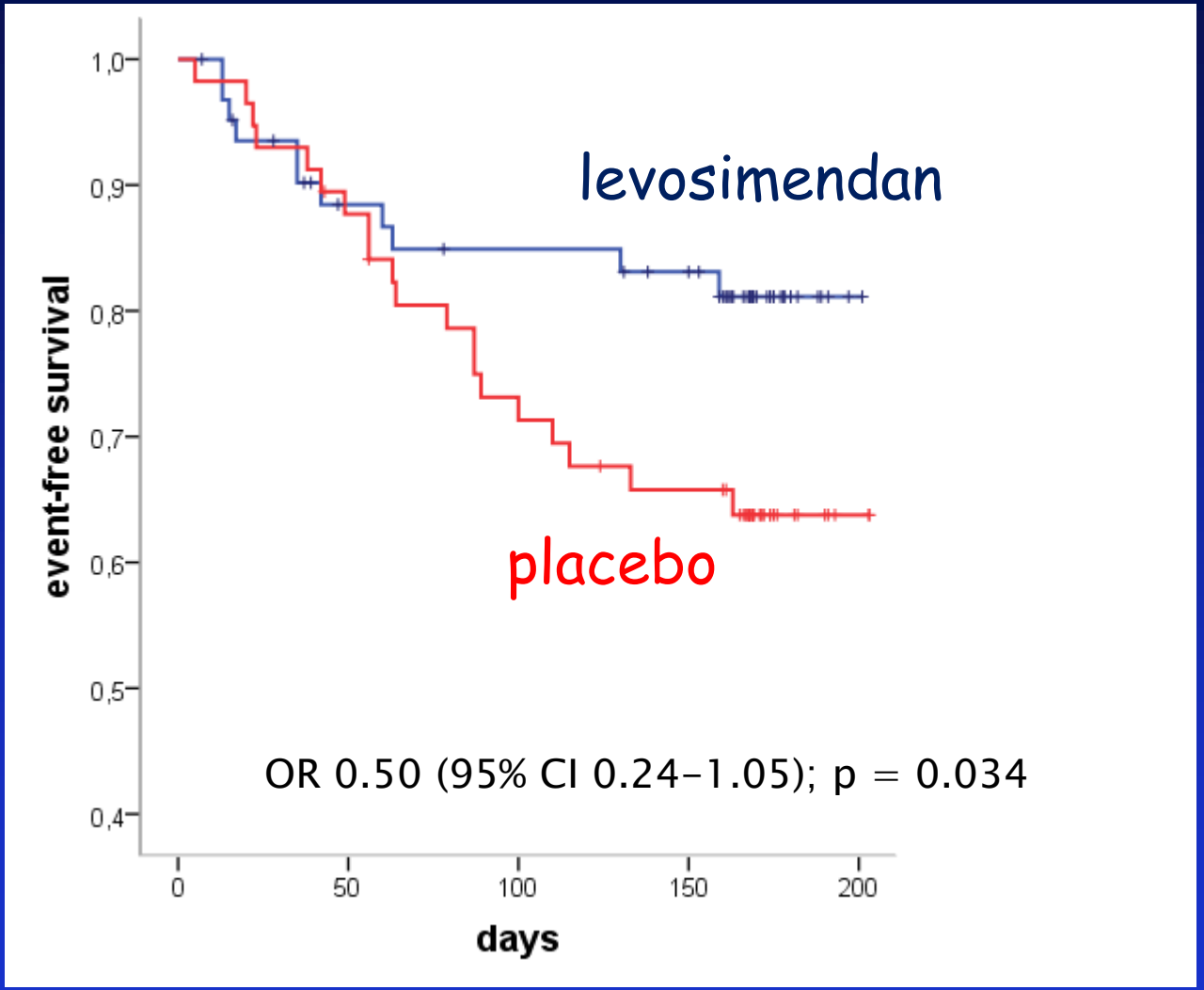
Primary endpoint

(Six min walk test ≥20% **and** KCCQ clinical summary score ≥15%)

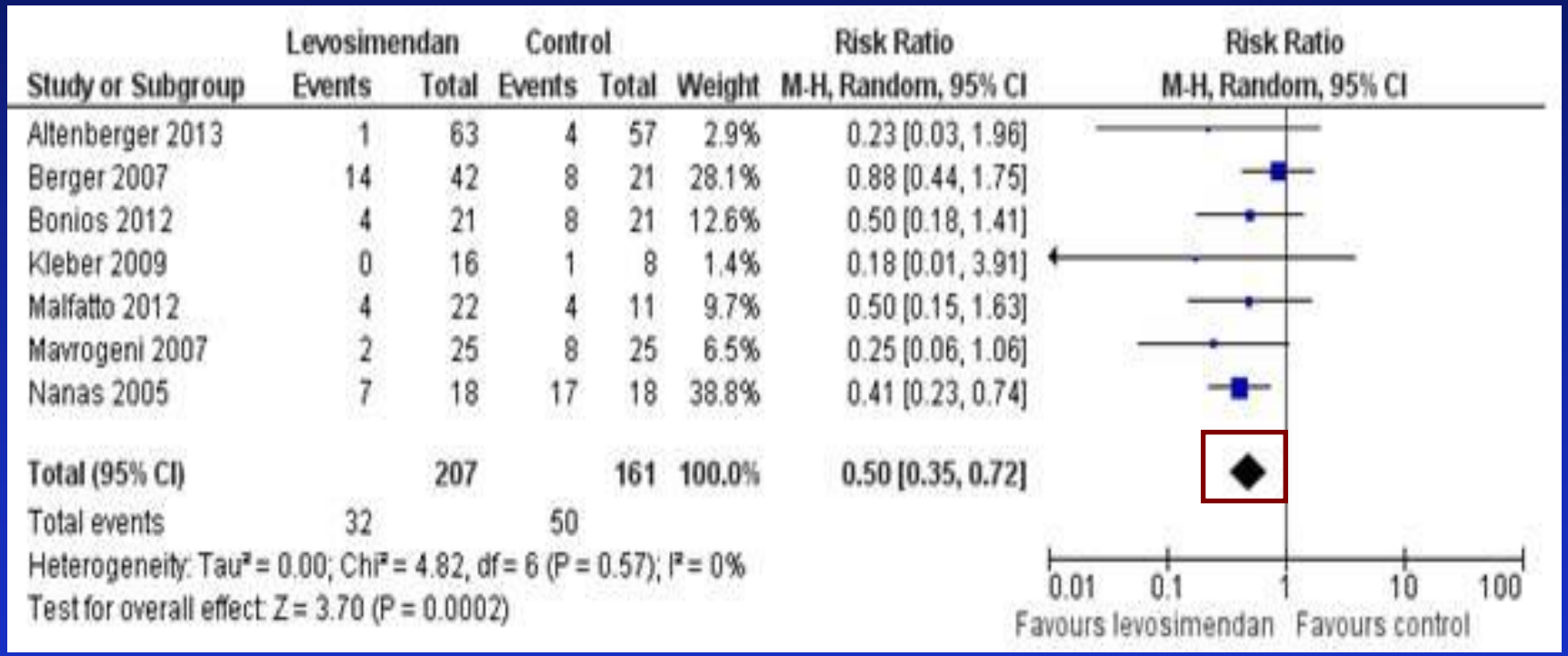


LevoRep – results

Secondary endpoint



Meta-analysis of pulsed infusion trials



Nieminen et al. Int J Cardiol 2014 submitted

SUMMARY (I)

- Traditional inotropes have several limitations in the real clinical practice (increase of myocardial oxygen uptake, myocardial injury, interaction with the oral medications).

- Levosimendan seems to be superior than traditional inotropes in improving hemodynamics and neurohormonal response but have failed to improve prognosis in AHF patients.

SUMMARY (II)

- Serial administration of levosimendan may improve long term outcomes in advanced CHF patients, without promoting mechanisms of cardiac injury.
- Optimum time interval and treatment duration remain to be determined (genetic factors, renal function, severity of disease).
- More randomized trials are needed in order to evaluate the safety and efficacy of this strategy.

(ongoing trials: LAICA, LION HEART, ELEVATE)

Practical recommendations for the safe use of levosimendan in ADHF patients

- Check for hypovolemia and correct volume
- Use hemodynamic monitoring in questionable cases (ECHO or PAC)
- Stop ACE inhibitor temporarily
- Keep beta-blocker
- Correct potassium (>4,0 mEq/l) and magnesium
- Avoid intensive diuresis and other iv vasodilators
- Avoid bolus dosing
- Use 0.1 µg/Kg/min (range: 0.05-0.2), uptitrating according to the patient response. In some cases, combine the drug with vasopressors (noradrenaline or dopamine).