JMC-5th JOINT MEETING WITH MAYO CLINIC:
GREAT INNOVATIONS IN CARDIOLOGY,
TURIN 15-16/10/2009

Acute and refractory heart failure: how to treat and what role for pharmacologic therapies?

Dr. Carlo Campana
U.O di Cardiologia
A.O. Sant'Anna Como

Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- INOTROPIC AGENTS: indicated in the presence of peripheral hypoperfusion with or without congestion or pulmonary oedema refractory to diuretics and vasodilators at optimal doses. Their use can be useful in the improvement of the hemodynamics

- Class IIa recommendation, level of evidence C

- **Their use is potentially harmful as they increase oxygen demand and calcium loading and they should be used with caution**

	SITE OF ACTION	MECHANISM	HEMODYNAMIC EFFECT	LIMITATIONS
DOBUTAMINE	β1-β2 adrenergic receptors	↑c AMP ↑ Ca release ↑ 02 demand	↑ contractility ↑Stroke volume ↑Arterial vasodilaton	β-blockers treatment tolerance (β-receptors down – regulation) tachycardia arrhythmias
DOPAMINE	Dopaminergic receptors β adrenergic receptors	↑c AMP ↑ Ca release (↑ O2 demand)	↑ contractility ↑Stroke volume Vasoconstriction (↑ afterload)	tachycardia arrhythmias
PDE III INHIBITORS	Inhibition of PDE III involved in breakdown of cAMP into AMP	↑ Ca release	↑ contractility vasodilation (↓pre-and afterload) in pts on β-blockade	hypotension
Ca SENSITIZERS LEVOSIMENDAN	↑sensitivity of troponinc to intracellular ionized Ca PDE III inhibition ATP-dependent K channels action	No ↑c AMP No ↑O2 demand	↑Stroke volume ↓SVR, ↓ PVR ↓ filling pressures	hypotension

Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- ***Dopamine***: may be used as an inotrope in AHF with hypotension, to improve renal blood flow and diuresis in decompensated HF with hypotension and low urine output
- Class of recommendation IIb, level of evidence C
- ***Dobutamine***: is currently indicated when there is peripheral hypoperfusion with or without congestion or pulmonary oedema refractory to diuretics and vasodilators at optimal doses; prolonged infusion is associated with tolerance; increased, dose-related incidence of arrhythmias
- Class of recommendation IIa,level of evidence C
- **For several years no controlled trials on DOB in AHF patients and some trials showed unfavourable effects with increased cardiovascular events**

Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- ***Phosphodiesterase inhibitors***: in presence of peripheral hypoperfusion with or without congestion refractory to diuretics and vasodilators at optimal doses and preserved systemic blood pressure
- Class of recommendation IIb, level of evidence C
- PDEIs type III: should be preferred to dobutamine in patients on concomitant beta-blocker therapy,and/or with an inadequate response to dobutamine
- Class of recommendation IIa,level of evidence C
- **The PDEIs effects on outcome of pts with AHF are insufficient but raise concerns about safety in pts with ischemic HF**

Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

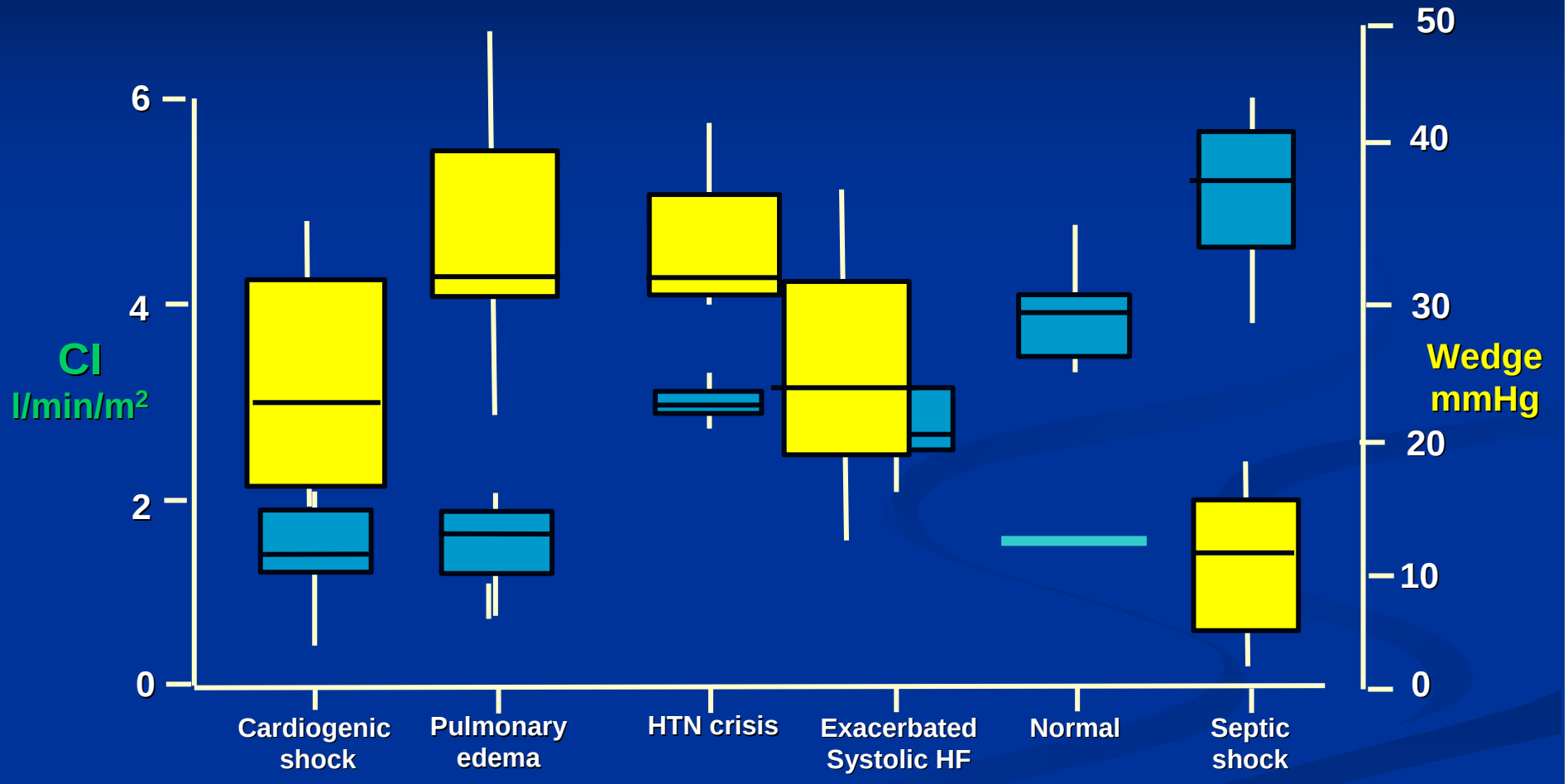
- ***Vasopressor therapy in cardiogenic shock***: is required when the combination of inotropic agents and fluid challenge fails to restore adequate arterial and organ perfusion despite an improvement in cardiac output
- In emergencies to sustain life and maintain perfusion in the face of life-threatening hypotension
- Epinephrine: can be used in case of dobutamine refractoriness and very low BP, with arterial and PAC monitoring
- Norepinephrine: used to increase SVR in presence of shock associated with low SVR

Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- ***Levosimendan***: in presence of symptomatic low cardiac output HF secondary to cardiac systolic dysfunction without severe hypotension
- Class of recommendation IIa, level of evidence B
- L. infusion in AHF with LV systolic dysfunction has been associated with a dose-dependent increase in CO and SV, a decrease in PWP, SVR and PVR
- A favourable outcome was shown in randomized clinical trials comparing L. with Dobutamine
- Hemodynamic response to L. Is maintained in patients on concomitant beta-blocker therapy

Hemodynamic patterns during acute HF



Cotter et al: Eur J Heart Fail, 2003; 5: 443-51

Italian Survey on Acute Heart Failure

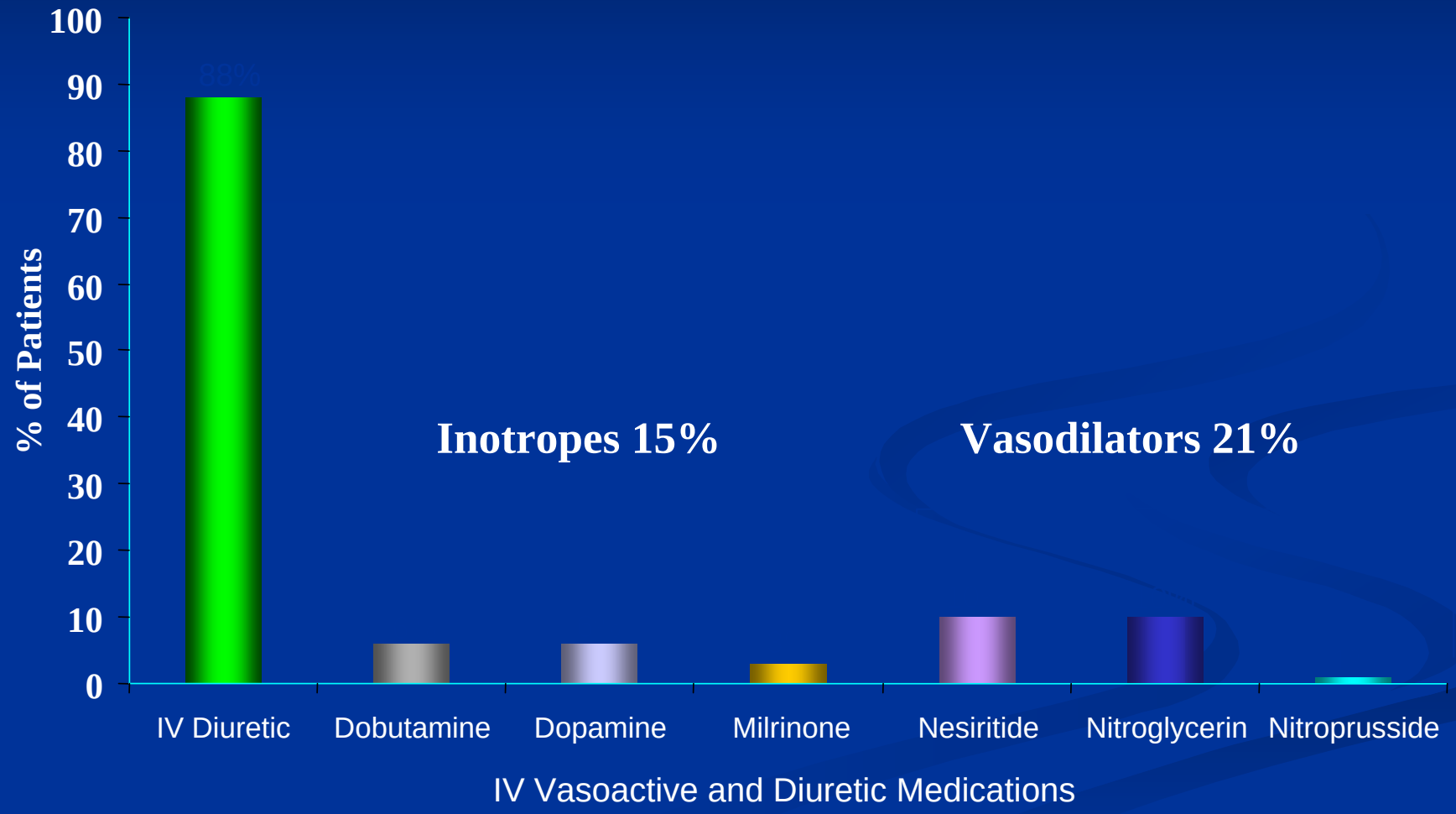
Tavazzi L et al. Eur Heart J 2006;27:1207-15.

IN-HOSPITAL IV MEDICATIONS

(2807 patients)

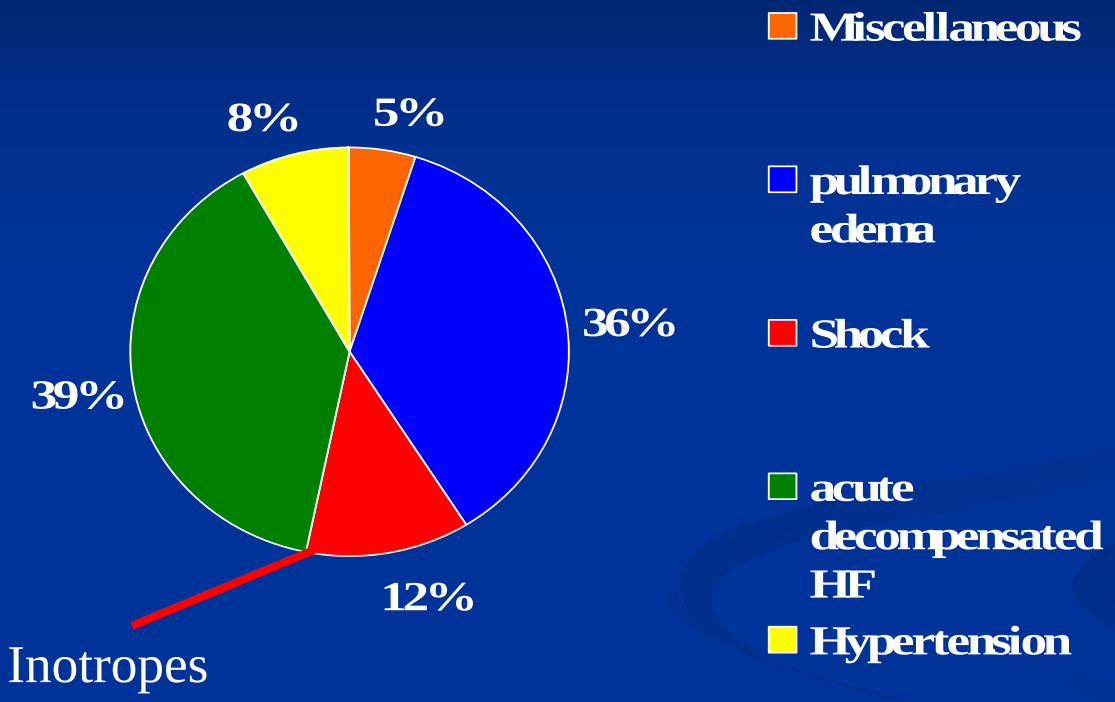
Nitrates	**51.3%**
Nitroglycerin	49.5%
Nitroprusside	2.7%
Inotropes	**24.6%**
Dopamine	18.5%
Dobutamine	12.9%
Enoximone	0.6%
Levosimendan	0.8%
Epinephrine	1.3%
Norepinephrine	0.6%

ADHERE
Most Common IV Medications N=105388 for AHFS



Alarm-HF Acute Heart Failure global Survey of Standard treatment Retrospective Study (8 countries)

4250 AHF pts (ADCHF 65%; de novo 35%)

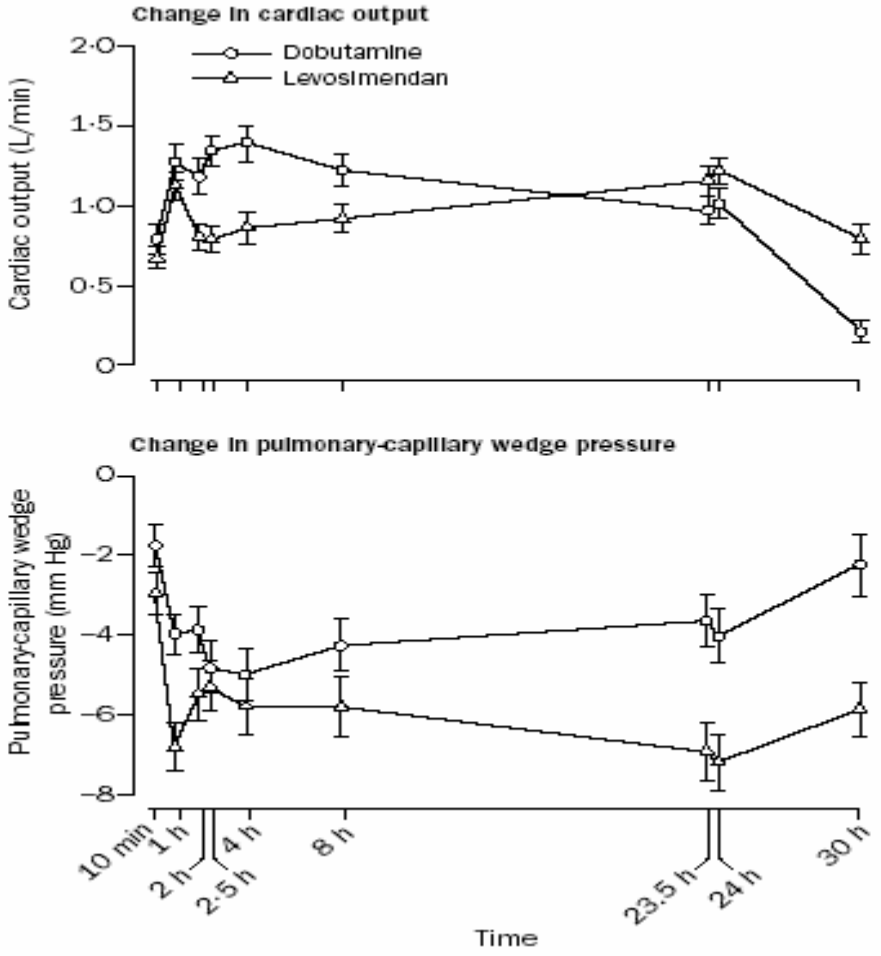


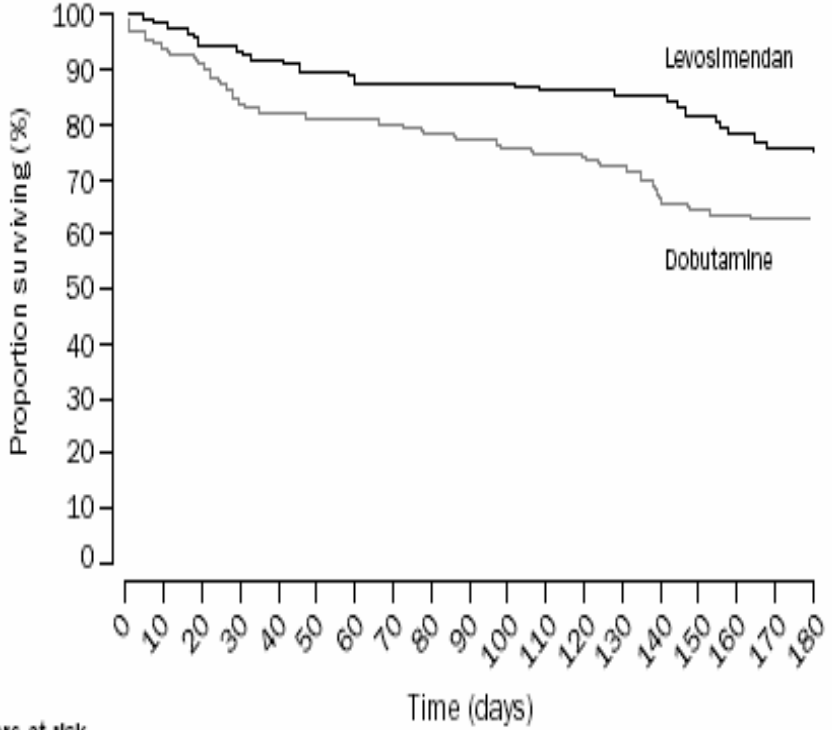
	ADCHF	SHOCK
Dobutamine	55%	60%
Dopamine	37%	45%
Levosimendan	18%	13%
Norepinephrine/Epinephine	18%	50%

Follath. Heart Failure Congress 2007; Hamburg

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

Follath F et al, 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)**

Esperienza multicentrica con LEVOSIMENDAN: confronto di variabili clinico strumentali

L Scelsi, C Campana, S Ghio, L Monti, C Opasich, S De Feo, F Cobelli, M Orlandi, G Di Pasquale, L Tavazzi. Una possibile alternativa alla terapia infusiva con i farmaci inotropi positivi tradizionali. Recenti progressi in medicina 2004;95:374-384.

	basale	Dopo 24 ore di levosimendan	Delta	95% C.I.		*p*
Peso *Kg*	73±10	70±9	+ 2,88	1,22	4,54	0,001
PASs *mmHg*	102±8	99±12	+ 2,64	-2,49	7,77	0,29
PASd	64±9	61±10	+ 3,2	-0,9	7,3	0,12
Creatininemia *mg%*	1,5±0,6	1,4±0,6	+ 0,03	-0,13	0,19	0,72
Natremia *mEq/L*	135±4	135±4	+ 0,66	-0,95	2,3	0,40
Potassiemia *mEq/L*	4,2±0,6	4,3±0,5	- 0.09	-0,42	0,23	0,55
BNP *pg/ml*	434±284	405±344	+ 28,61	-214	271	0,77
Log BNP	5,87±0,96	5,60±1,0	+ 0,22	-0,83	1,29	0,60
DTDVsx *mm*	71±10	70±11	+ 0,9	0,28	1,47	0,005
FE%	23±8	26±7	- 3,36	-4,69	–2,02	0,0000
Score CHF	5±2	2±2	+ 3,4	0,31	1,34	0,006

SURVIVE

Mortality Trial in ADHF

- **Design**
  - Randomized, double-blind, double-dummy
  - Multi-center, parallel-group
  - Levosimendan versus dobutamine
  - Primary end point: 180-day all-cause mortality

- **Assumptions**
  - Overall 180-day mortality rate: 25%
  - Levosimendan relative risk reduction: 25% (α = 0.05, power = 85%)
  - 330 events required (~1300 patients)

- **75 Sites in 9 countries**:

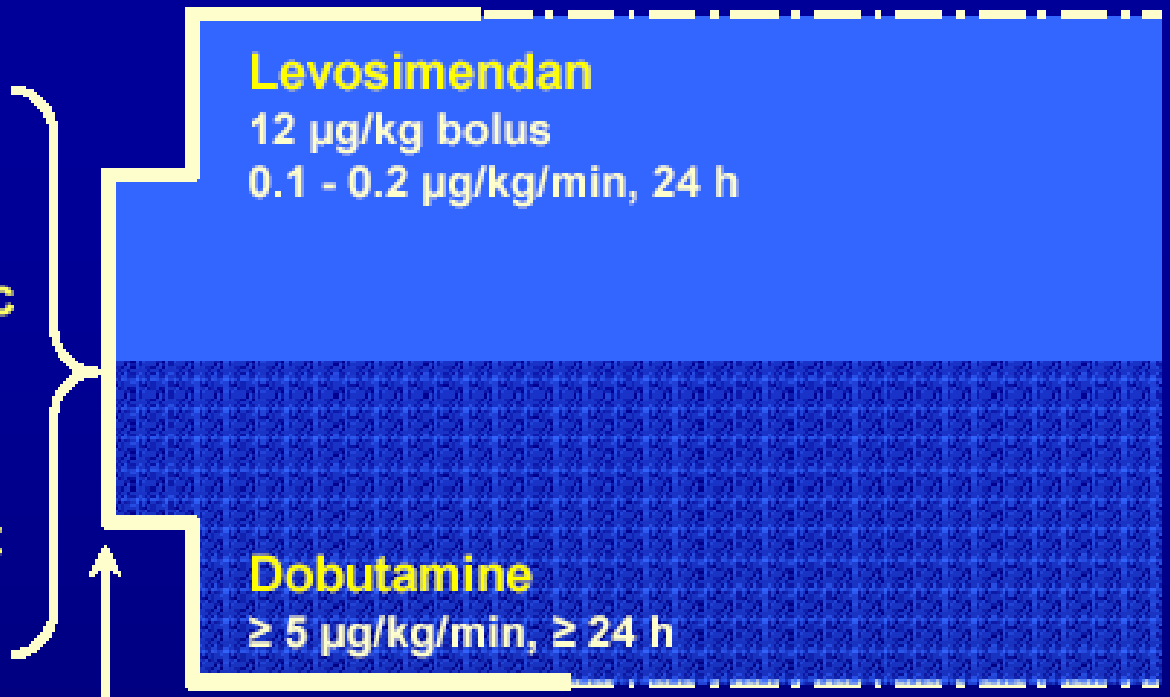
Austria, Finland, France, Germany, Israel, Latvia, Poland, Russia, and UK

JAMA 2007; 297:1883-91

SURVIVE

Study Design

- Hospitalized for ADHF
- LVEF ≤ 30%
- Clinical need for inotropic therapy after IV diuretics and/or IV vasodilators:
  - Oliguria,
  - And/or dyspnea at rest



Randomization
Balanced by country and previous heart failure

JAMA 2007; 297:1883-91

SURVIVE

Demographics and Characteristics

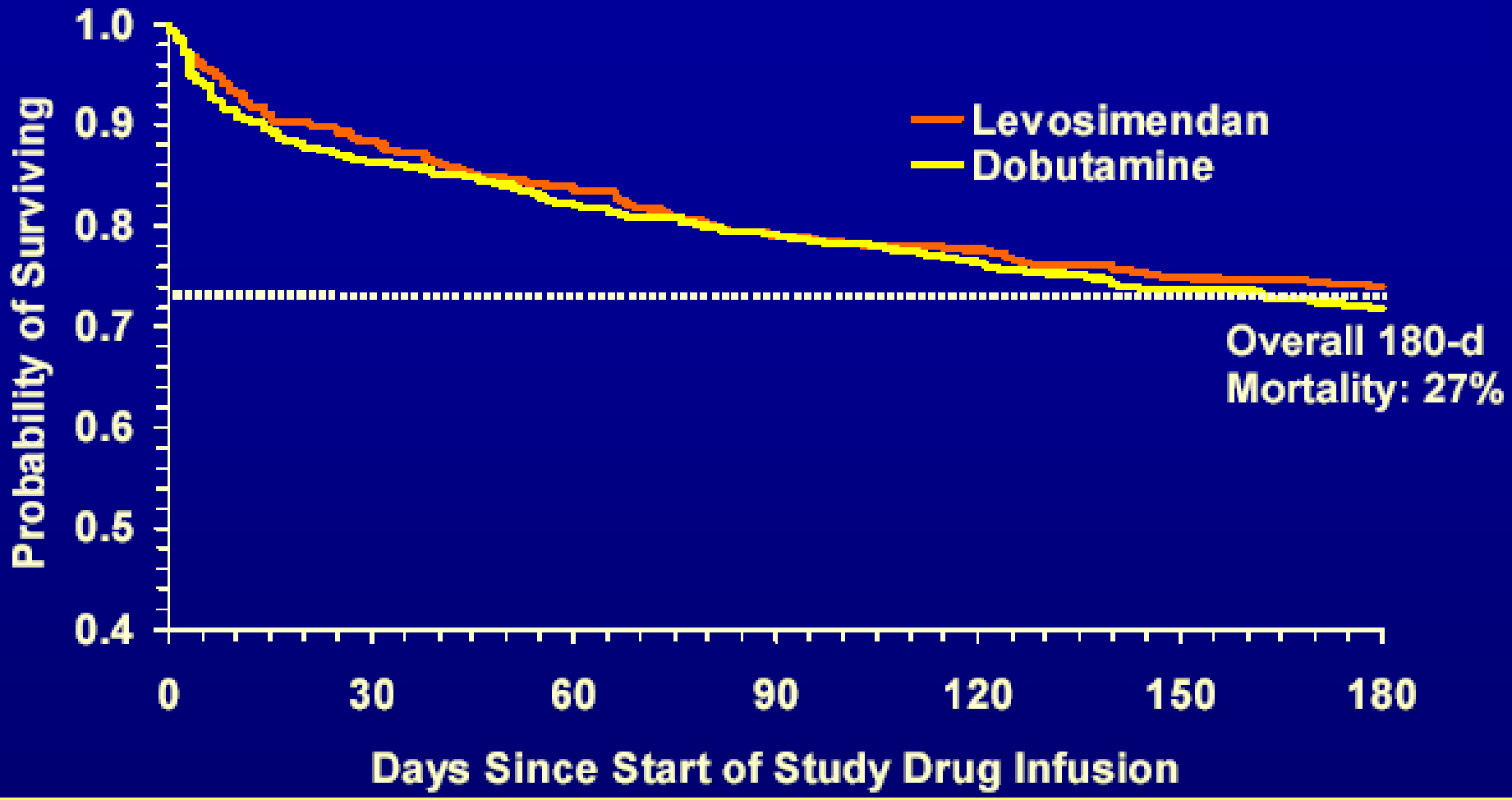
Variable	Levosimendan (n = 664)	Dobutamine (n = 663)
Male, %	74	70
Age, years, mean (SD)	67 (12)	66 (12)
Weight, kg	79 (18)	79 (16)
Previous history of HF, %	88	88
Ischemic etiology for acute HF, %	76	76
NYHA Class IV, %	86	85
LVEF, %	24 (5)	24 (5)
Median BNP*, pg/mL (Normal BNP in non-HF subjects < 135 pg/mL)	1178	1231
Heart rate, bpm	84 (17)	83 (17)
SBP, mm Hg	116 (18)	116 (19)

*AXSYM® BNP Assay

JAMA 2007; 297:1883-91

SURVIVE

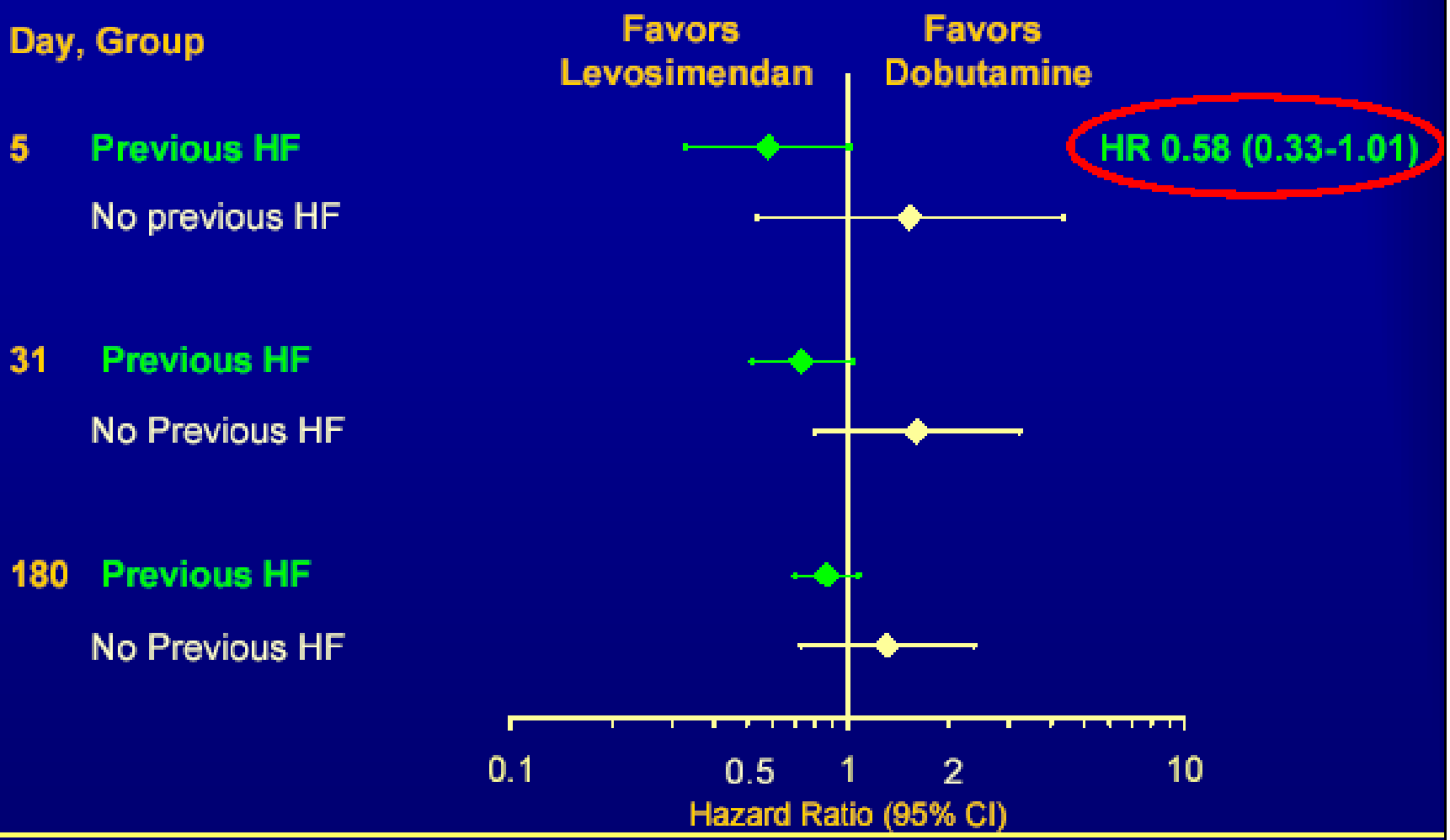
180-Day All-Cause Mortality



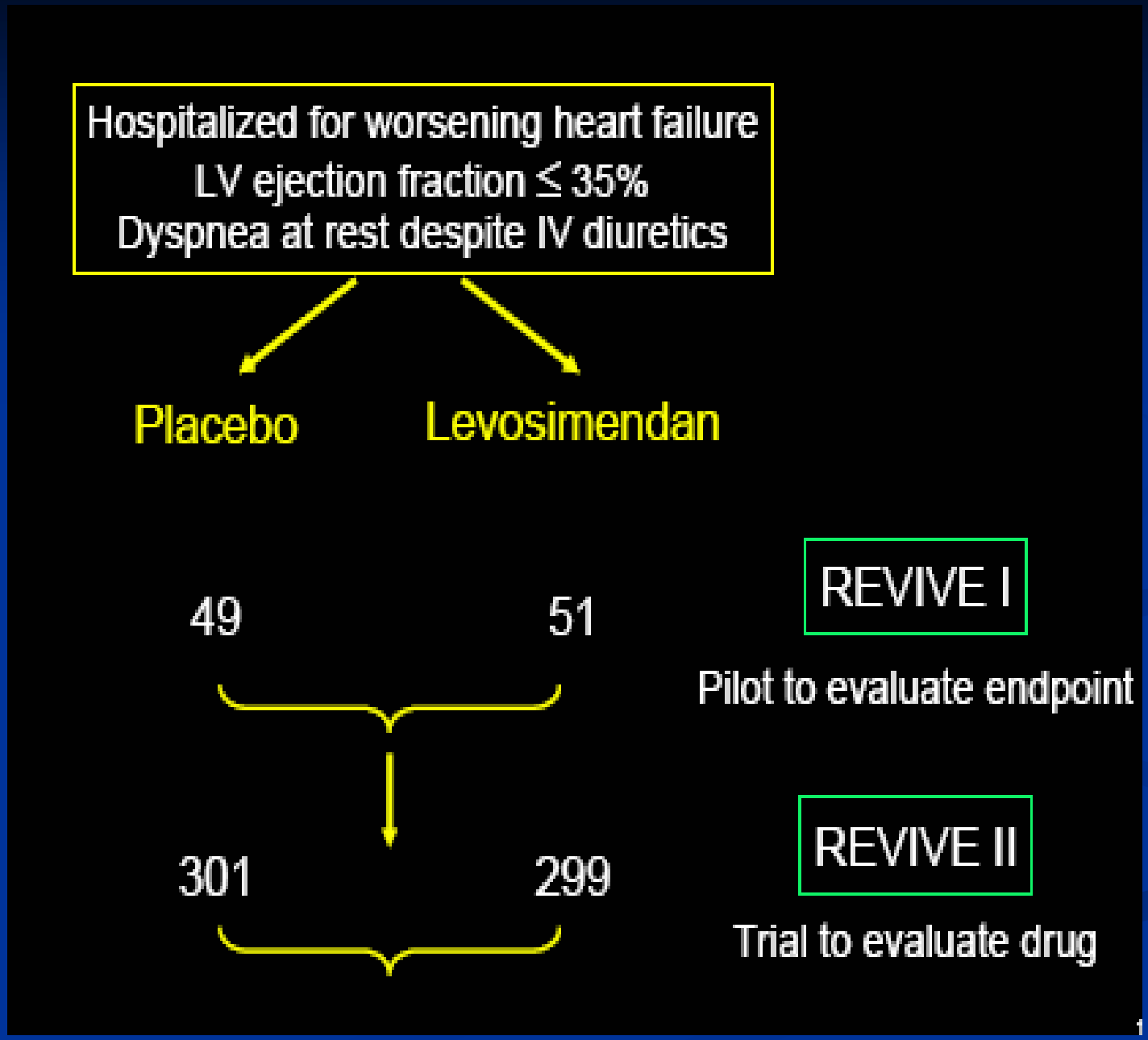
JAMA 2007; 297:1883-91

SURVIVE: Pre-Specified Stratum

All-Cause Mortality in Patients With / Without Previous HF



JAMA 2007; 297:1883-91


Hospitalized for worsening heart failure
LV ejection fraction ≤ 35%
Dyspnea at rest despite IV diuretics
Placebo
Levosimendan
49
51
REVIVE I
Pilot to evaluate endpoint
301
299
REVIVE II
Trial to evaluate drug

REVIVE II Trial: Study Endpoints

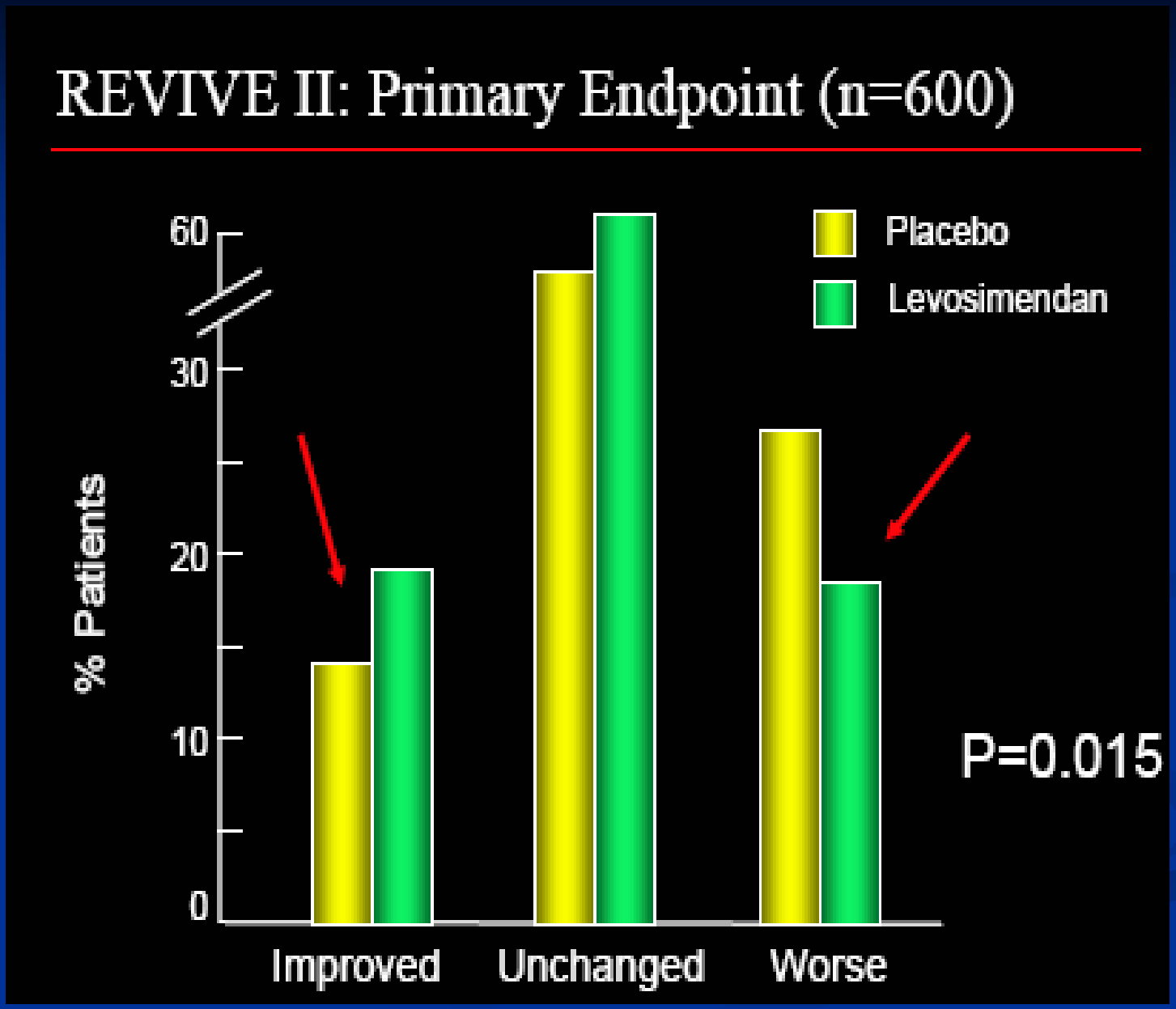
Primary Endpoint

- Clinical composite

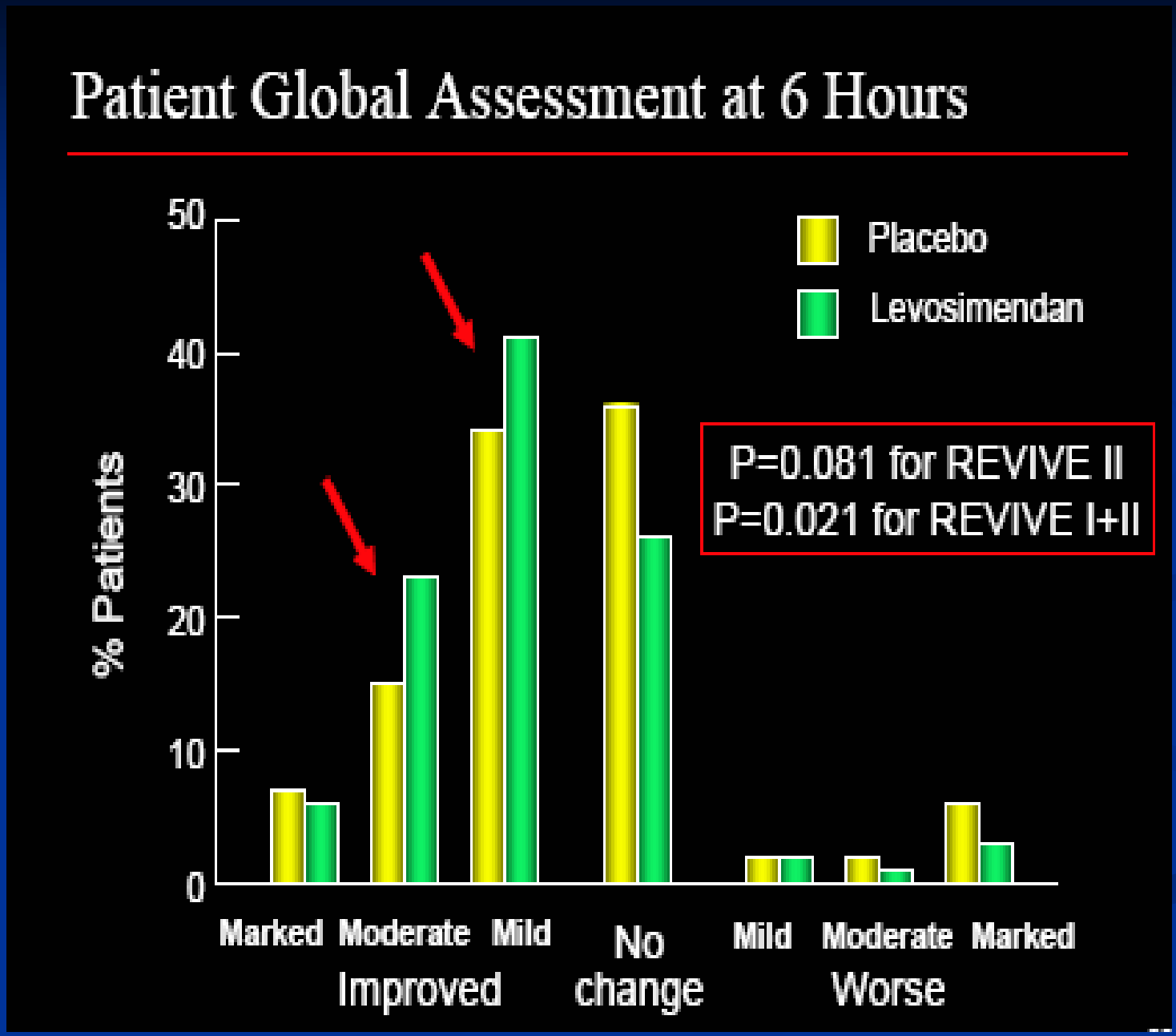
Secondary Endpoints

- B-Type natriuretic peptide (BNP) at 24 hours
- Patient global assessment at 6 hours
- Patient dyspnea assessment at 6 hours
- Days alive and out of hospital over 14 days
- Death or worsening heart failure over 31 days
- New York Heart Association class at 5 days
- All-cause mortality over 90 days

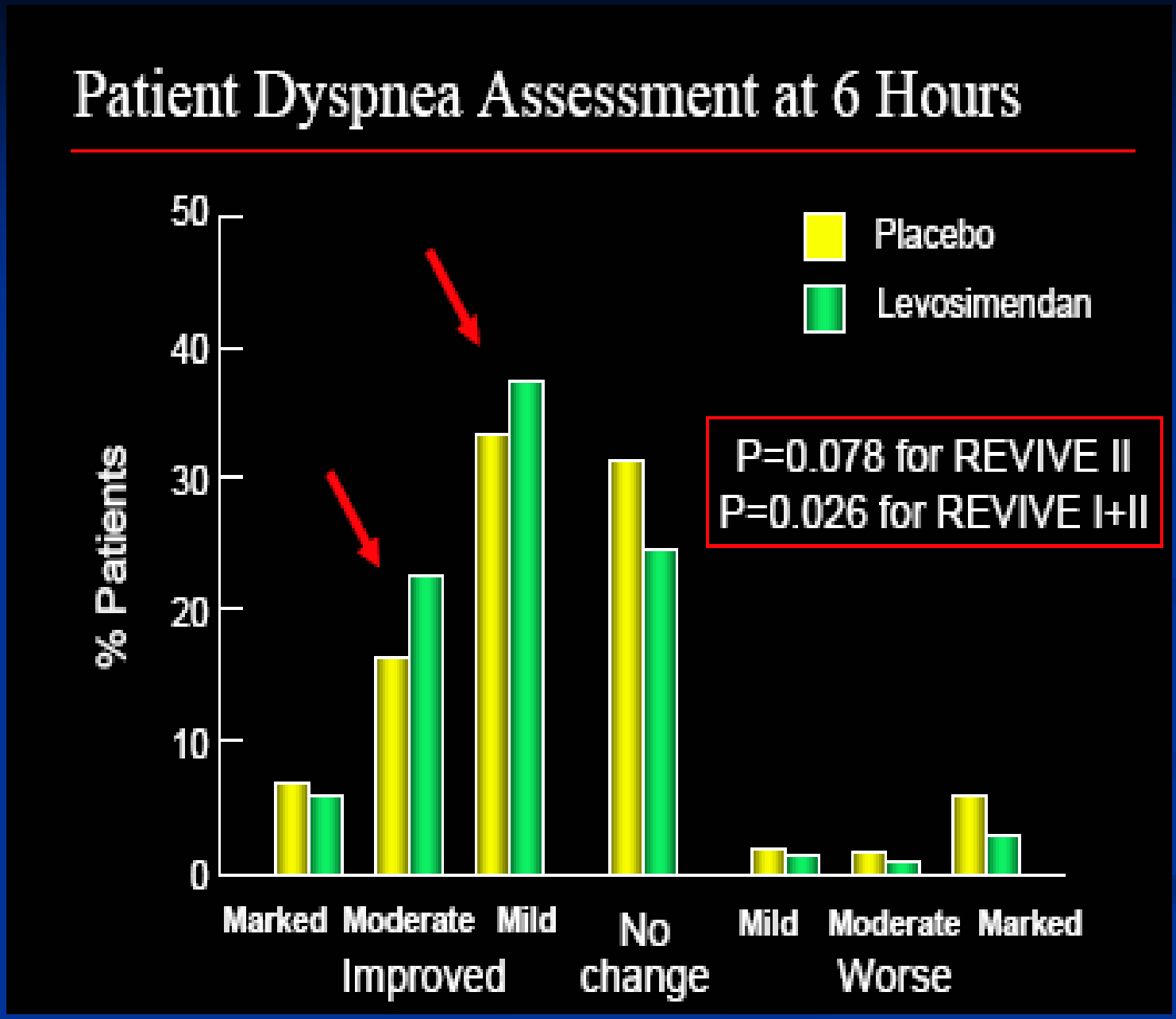
REVIVE II: Primary Endpoint (n=600)



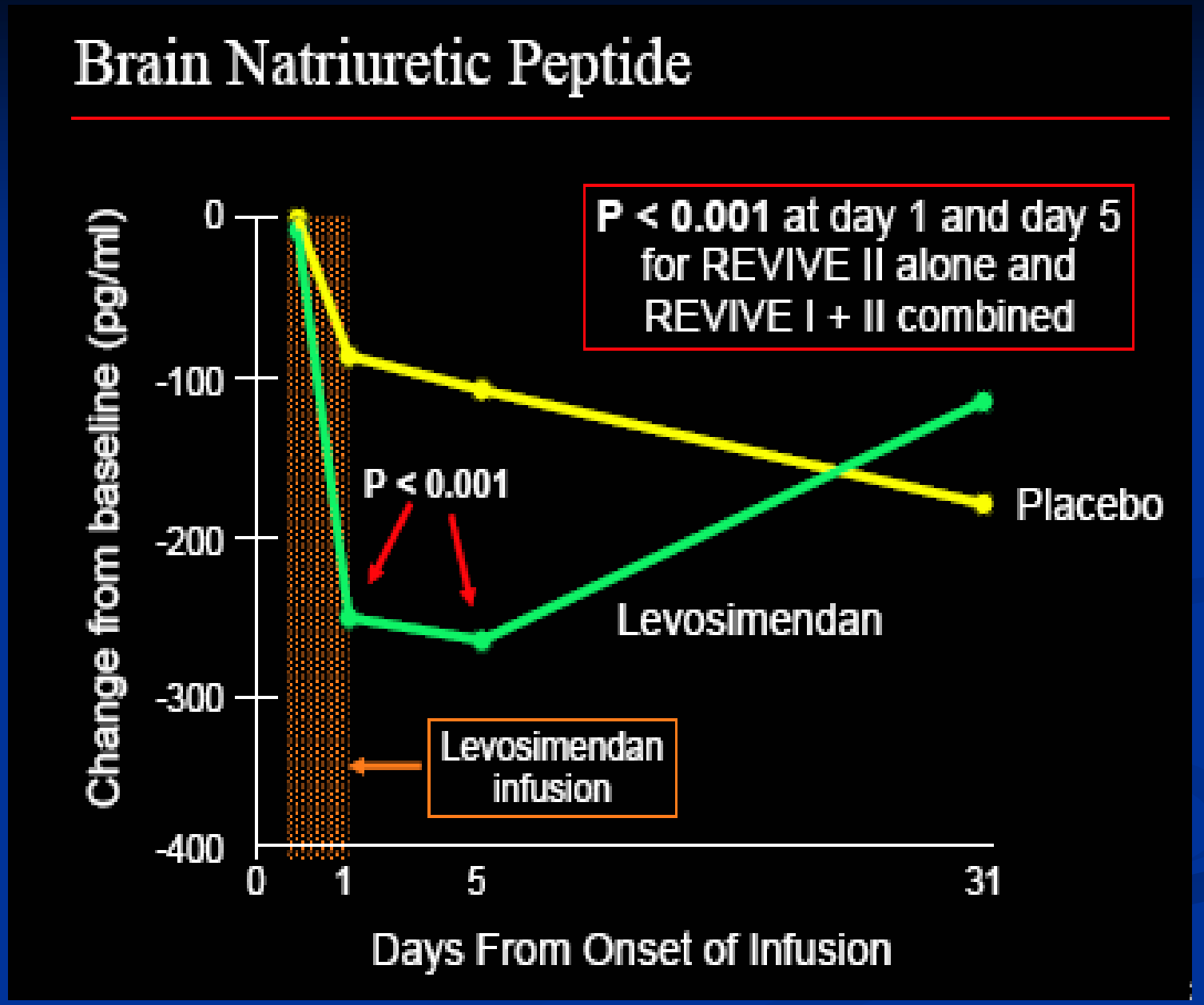
Patient Global Assessment at 6 Hours



Patient Dyspnea Assessment at 6 Hours



Brain Natriuretic Peptide



Duration of Initial Hospitalization

	Levosimendan (n=299)	Placebo (n=301)
Days for initial hospitalization		
Mean	7.0 ± 4.6	8.9 ± 8.6
Length of initial hospitalization		
1 to 5 days	129 (45.7%)	108 (37.0%)
6 to 10 days	109 (38.7%)	116 (39.7%)
> 10 days	44 (15.6%)	68 (23.3%)

P=0.006 for REVIVE II

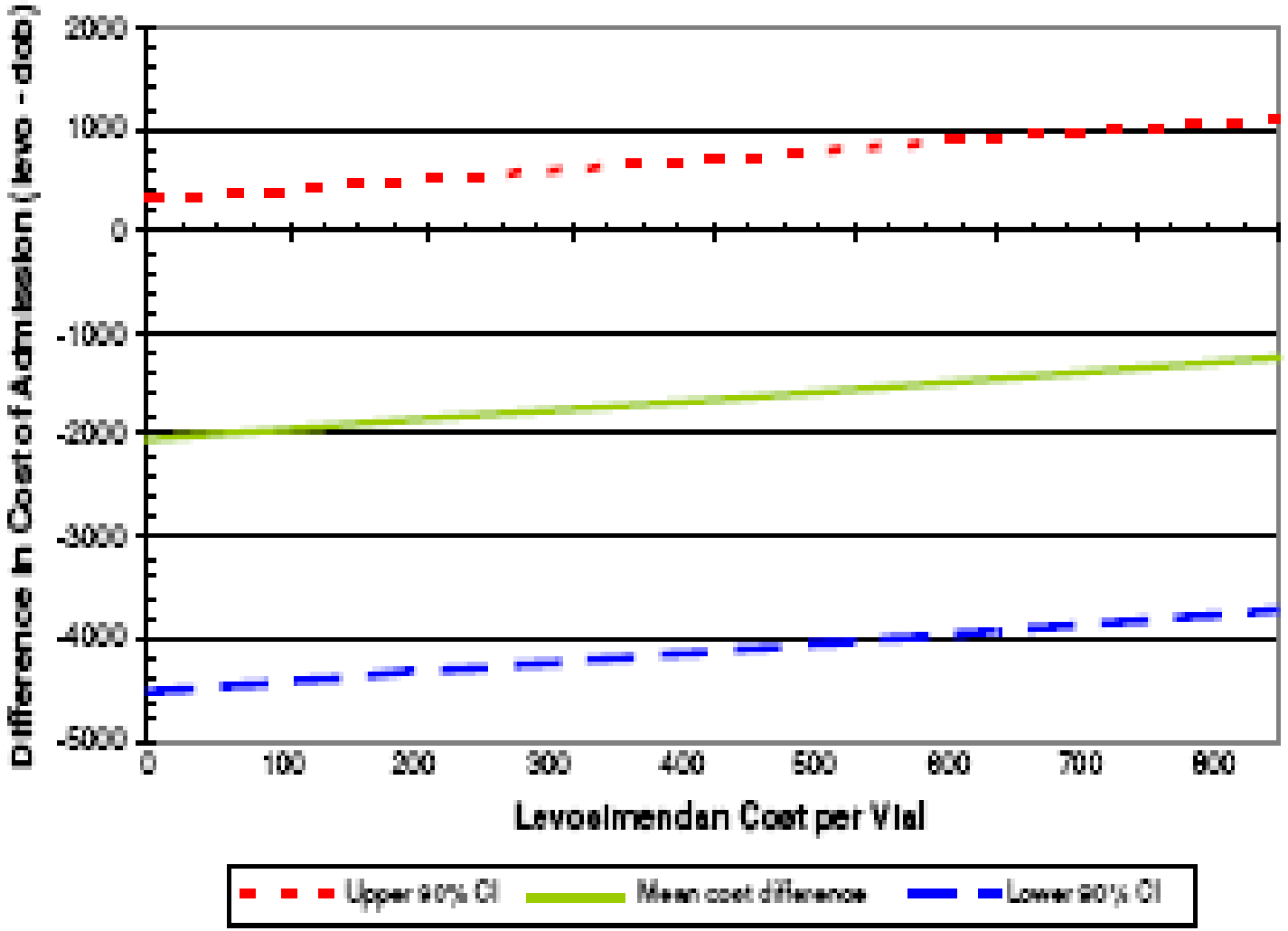
P=0.003 for REVIVE I+II

Eur J Health Econ
DOI 10.1007/s10198-009-0165-2

ORIGINAL PAPER

Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study

Greg de Lissovoy · Kathy Fraeman ·
John R. Teerlink · John Mullahy · Jeff Salon ·
Raimund Sietz · Amy Dardashi · Robert L. Padley



Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure

WS Colucci,U Elkayam, DP Horton, et al. N Engl J Med 2000;343:246-53.

TABLE 2. CHANGES IN BASE-LINE HEMODYNAMIC VALUES AT SIX HOURS IN THE EFFICACY TRIAL.*

VARIABLE	PLACEBO (N=42)	NESIRITIDE		P VALUE†
		0.015 μg/kg/min (N=43)	0.030 μg/kg/min (N=42)	
Pulmonary-capillary wedge pressure (mm Hg)	+2.0±7.2	−6.0±7.2‡	−9.6±6.2‡	<0.001
Right atrial pressure (mm Hg)	+0.4±4.6	−2.6±4.4‡	−5.1±4.7‡	<0.001
Systemic vascular resistance (dyn·sec·cm^{-5})	+161±481	−247±492‡	−347±499‡	<0.001
Cardiac index (liters/min/m^2)	−0.1±0.47	+0.2±0.49§	+0.4±0.69‡	<0.001
Systolic blood pressure (mm Hg)	+0.3±11	−4.4±10.2	−9.3±12.6‡	0.001
Systolic pulmonary-artery pressure (mm Hg)	+1.7±8.2	−9.4±10.3‡	−12.9±12.5‡	<0.001
Mean pulmonary-artery pressure (mm Hg)	+2.0±5.9	−7.0±6.9‡	−7.7±7.6‡	<0.001
Pulmonary vascular resistance (dyn·sec·cm^{-5})	+26±197	−62±100	−2±142	0.03
Heart rate (beats/min)	+1.4±7.5	−1.6±7.1	+0.0±8.8	0.22

*Plus–minus values are means ±SD. Plus signs denote an increase, and minus signs a decrease.

†P values are for the comparison among all three groups and were calculated with the omnibus F test.

‡P<0.001 for the pairwise comparison with placebo, by the F test.

§P<0.05 for the pairwise comparison with placebo, by the F test.

Risk of death associated with nesiritide in patients with acutely decompensated heart failure

KD Aaronson, J Sackner-Bernstein. JAMA 2006;296:1465-66

Table. Mortality Within 30 Days of Treatment Associated With Nesiritide or Control Therapy

	NSGET, VMAC, and PROACTION (N = 862)	*P* Value	VMAC and PROACTION (n = 735)	*P* Value
No. of deaths/total No. (%) of patients				
Nesiritide	37/485 (7.6)		31/400 (7.8)	
Control	15/377 (4.0)		13/335 (3.9)	
Unadjusted risks (95% CI)				
Crude risk ratio*	1.92 (1.07-3.44)	.03	2.00 (1.06-3.75)	.03
Hazard ratio†	1.97 (1.08-3.58)	.03	2.06 (1.08-3.93)	.03
Adjusted risks (95% CI)				
Relative risk‡	1.86 (1.05-3.27)	.03	1.93 (1.05-3.54)	.04
Hazard ratio§	1.93 (1.06-3.52)	.03	2.00 (1.05-3.83)	.04

Abbreviations: CI, confidence interval; NSGET, Nesiritide Study Group Efficacy Trial[2]; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor[4]; VMAC, Vasodilation in the Management of Acute Congestive heart failure.[3]

*Unadjusted and from pooled 2 × 2 table.

†Unadjusted and from univariable Cox proportional hazards model.

‡Adjusted for study by Mantel-Haenszel method (fixed-effects model).

§Adjusted for study by multivariable Cox proportional hazards model.

ASCEND-HF

ACUTE STUDY OF CLINICAL EFFECTIVENESS OF NESIRITIDE IN DECOMPENSATED HEART FAILURE

PRINCIPAL INVESTIGATOR

Robert M. Califf, M.D., Vice-Chancellor for Clinical Research, Director of Duke Clinical Research Institute (DCRI), Professor of Medicine, will chair the trial. DRCI, the academic clinical research organization within Duke University Medical Center, will collaborate with the Cleveland Clinic Cardiovascular Coordinating Center (C5) in managing the trial. In addition to Dr. Califf, the members of the ASCEND-HF executive committee include:

- **Paul W. Armstrong, M.D.,** Professor of Medicine at the University of Alberta in Edmonton, Alberta, Canada
- **Henry Dargie, M.D.,** Professor, Department of Cardiovascular Medicine at the Gardiner Institute in Glasgow, Scotland
- **Kenneth Dickstein, M.D., Ph.D.,** Professor, Institutt for indremedisin, University of Bergen, Central Hospital in Rogaland, Bergen, Norway
- **Brian Gibler, M.D.,** Professor and Chairman, Department of Emergency Medicine, University of Cincinnati
- **Michel Komajda, M.D.,** Professor, Pitie Salpetriere Hospital in Paris, France
- **Barry Massie, M.D.,** Chief, Cardiology Section, VA Medical Center, San Francisco
- **John J.V. McMurray, M.D., Ph.D.,** Professor of Medical Cardiology, University of Glasgow, Scotland
- **Markku S Nieminen, M.D.,** Professor, Chief, Department of Medicine, Helsinki University Central Hospital in Helsinki, Finland
- **Christopher O'Connor, M.D.,** Director, Duke Heart Failure Program, Associate Director of DCRI and Associate Professor of Medicine in the Division of Cardiology at Duke University Medical Center
- **Marc Alan Pfeffer, M.D., Ph.D.,** Professor, Senior Physician in Cardiology at Brigham and Women's Hospital in Boston
- **Jean-Lucien Rouleau, M.D.,** Professor, Dean of the Faculty of Medicine at the Université de Montréal-Pavillon in Montreal, Canada
- **Randall Starling, M.D., M.P.H.,** Section Head, Heart Failure & Cardiac Transplant Medicine at the Cleveland Clinic
- **Karl Swedberg M.D., Ph.D.,** Professor of Medicine at Sahlgrenska University Hospital/Östra, Goteborg University in Goteborg, Sweden

HOW TO BECOME A CENTER

DCRI, the clinical research organization within Duke University Medical Center, will collaborate with the Cleveland Clinic Cardiovascular Coordinating Center (C5) in managing the trial, and other leading medical centers around the world will participate. Duke Clinical Research Institute (DCRI) as the independent academic research organization that will lead the ASCEND-HF Trial. The ASCEND-HF study is managed outside North-America by Johnson & Johnson's Global Clinical Operations (GCO).

For more information regarding enrollment, please email the following information to WDrusedu@gcous.jnj.com or call 609-730-3396 (Attention: Barry Drusedum, Sr. Manager, Global Trial Manager):

- Name
- Telephone
- Fax
- Email
- Hospital Name
- Hospital Address

PROTOCOL DESIGN

As currently proposed, this randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of Nesiritide will include approximately 7,000 patients with ADHF. They will be randomized to receive Nesiritide or placebo as a bolus of 2 mcg/kg followed by continuous intravenous infusion of Nesiritide or placebo at 0.01 mcg/kg/minute for a minimum of 24 hours up to a maximum of seven days, in addition to standard care. The trial will be conducted at approximately 600 sites. Patient enrollment is expected to begin in the second quarter of 2007.

KEY OBJECTIVES

The study hypothesis is that Nesiritide given in addition to standard care is superior to placebo given in addition to standard care as measured by relief of breathing difficulties at 6 hours or 24 hours after Nesiritide administration, and reduction in rehospitalization due to heart failure and death from study drug administration through Day 30.

INCLUSION/ EXCLUSION CRITERIA

Inclusion Criteria:

- Men or women 18 years of age or older
- Hospitalized for the management of ADHF or diagnosed with ADHF within 48 hours after being hospitalized for another reason
- Diagnosis of ADHF is defined as dyspnea (difficulty breathing) at rest or dyspnea with minimal activity

Exclusion Criteria:

- At high risk for hypotension
- Acute coronary syndrome as primary diagnosis
- History of cardiac valvular stenosis, restrictive cardiomyopathy, hypertrophic cardiomyopathy, or pericardial tamponade
- Previous enrollment in a nesiritide study
- Persistent, uncontrolled hypertension (SBP[systolic blood pressure]> 180 mmHg)

CLINICAL ENDPOINTS

A number of safety and clinical outcomes endpoints are proposed, including:

- All-cause mortality through day 180
- Cardiovascular mortality through day 30
- Heart Failure rehospitalizations
- Renal impairment
- Hypotension

ABOUT NESIRITIDE

Nesiritide is indicated for the intravenous treatment of patients with ADHF who have dyspnea at rest or with minimal activity. In this population, the use of Nesiritide reduced pulmonary capillary wedge pressure and improved patient reported dyspnea. For Full Prescribing Information, visit www.natrecor.com. See Important Safety Information.

RECRUITMENT DATES

Second quarter of 2007

SOURCE OF FINANCIAL SUPPORT/SPONSOR

Scios Inc.

IMPORTANT SAFETY INFORMATION

HYPOTENSION

Nesiritide may cause hypotension and should be administered only in settings where blood pressure can be monitored closely. If hypotension occurs during administration of Nesiritide, the dose should be reduced or discontinued. At the recommended dose of Nesiritide, the incidence of symptomatic hypotension (4%) was similar to that of IV nitroglycerin (5%). Asymptomatic hypotension occurred in 8% of patients treated with either drug. In some cases, hypotension that occurs with Nesiritide may be prolonged. The mean duration of symptomatic hypotension was longer with Nesiritide than IV nitroglycerin (2.2 versus 0.7 hours, respectively). Nesiritide should not be used in patients with systolic blood pressure <90 mm Hg or as primary therapy in patients with cardiogenic shock. The rate of symptomatic hypotension may be increased in patients with a baseline blood pressure <100 mm Hg, and Nesiritide should be used cautiously in these patients. In earlier trials, when Nesiritide was initiated at doses higher than the 2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion, the frequency, intensity, and duration of hypotension were increased. The hypotensive episodes were also more often symptomatic and/or more likely to require medical intervention.

Nesiritide is not recommended for patients for whom vasodilating agents are not appropriate and should be avoided in patients with low cardiac filling pressures.

RENAL

Nesiritide may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with Nesiritide may be associated with azotemia. In the VMAC trial, through day 30, the incidence of elevations in creatinine to >0.5 mg/dL above baseline was 28% and 21% in the Nesiritide and nitroglycerin groups, respectively. When Nesiritide was initiated at doses higher than 0.01 mcg/kg/min, there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased.

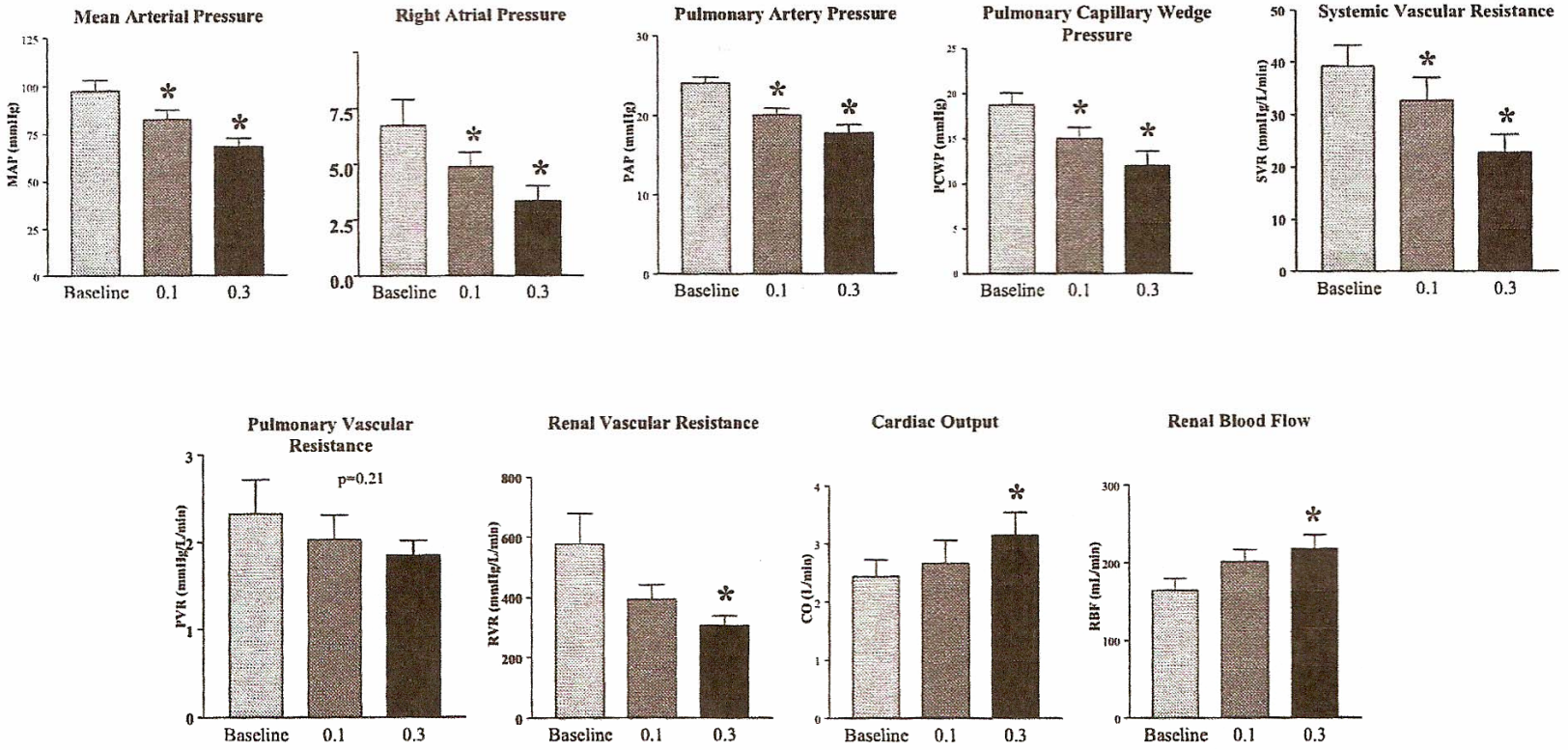
MORTALITY

In seven Nesiritide clinical trials, through 30 days, 5.5% in the Nesiritide treatment group died as compared with 4.3% in the group treated with other standard medications. In five clinical trials, through 180 days, 21.5% in the Nesiritide treatment group died as compared with 20.7% in the group treated with other medications. There is not enough information to know about the effect of Nesiritide on mortality.

See Full Prescribing Information at www.natrecor.com.

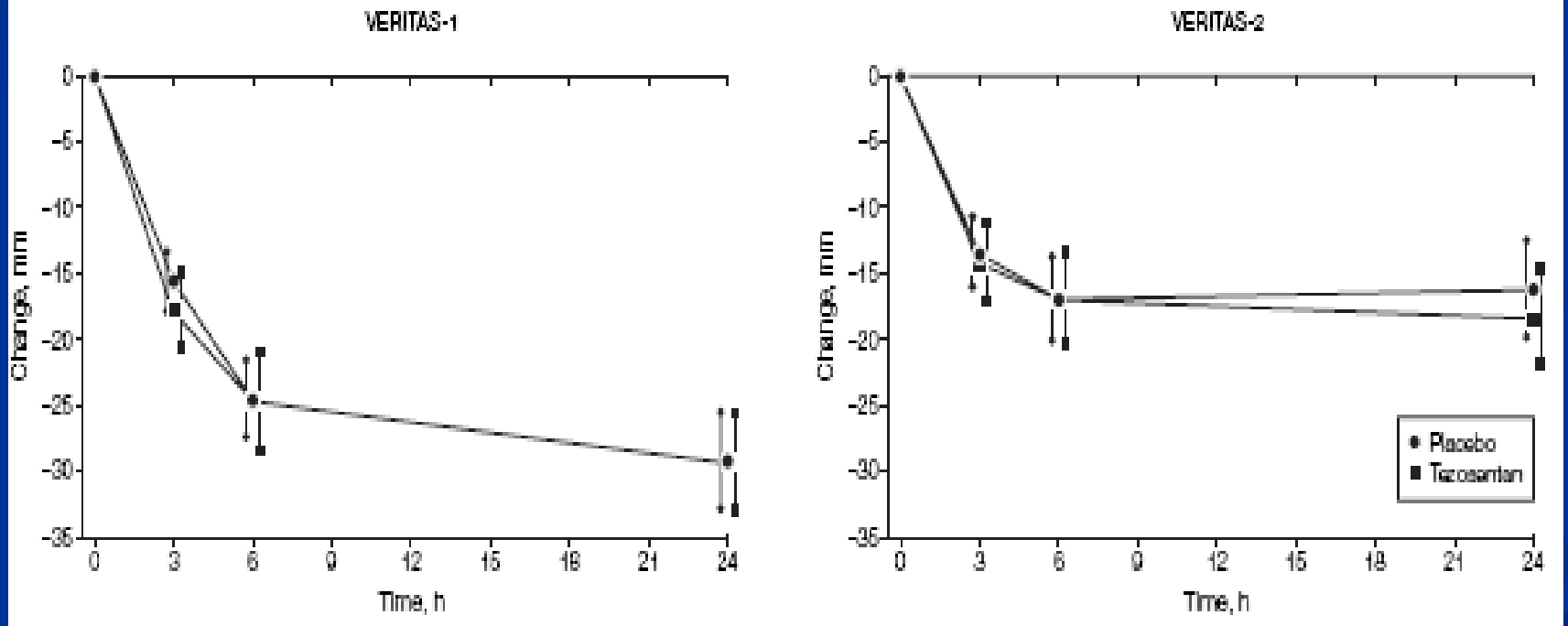
BAY 58-2667 is a nitric-oxide and heme-independent activator of soluble guanylate cyclase

Figure 4-5: The hemodynamic effects of intravenous administration of 2 doses of BAY 58-2667 were assessed in experimental heart failure in dogs. Heart failure was induced in 7 dogs by rapid ventricular pacing for 10 days



Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure

Figure 2. Change in Dyspnea in VERITAS-1 and VERITAS-2

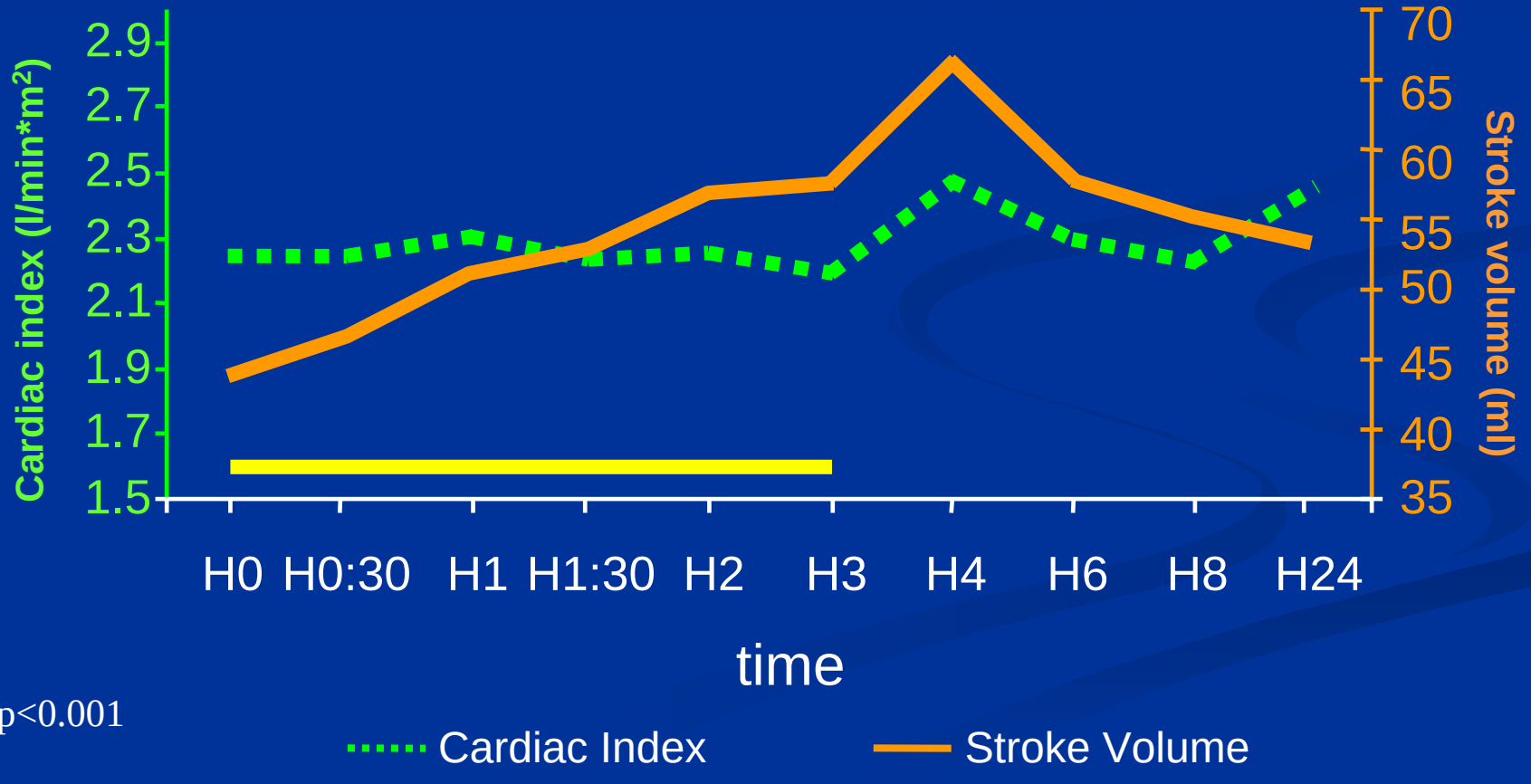


Change in dyspnea shown as the area under the curve. VERITAS Indicates Value of Endothelin Receptor Inhibition With Tezosentan In Acute Heart Failure Studies. Error bars indicate 95% confidence intervals.

McMurray JJV et al JAMA 2007;298:2009-19

Favorable Effects of Heart Rate Reduction with Intravenous Administration of Ivabradine in Patients with Advanced Heart Failure.

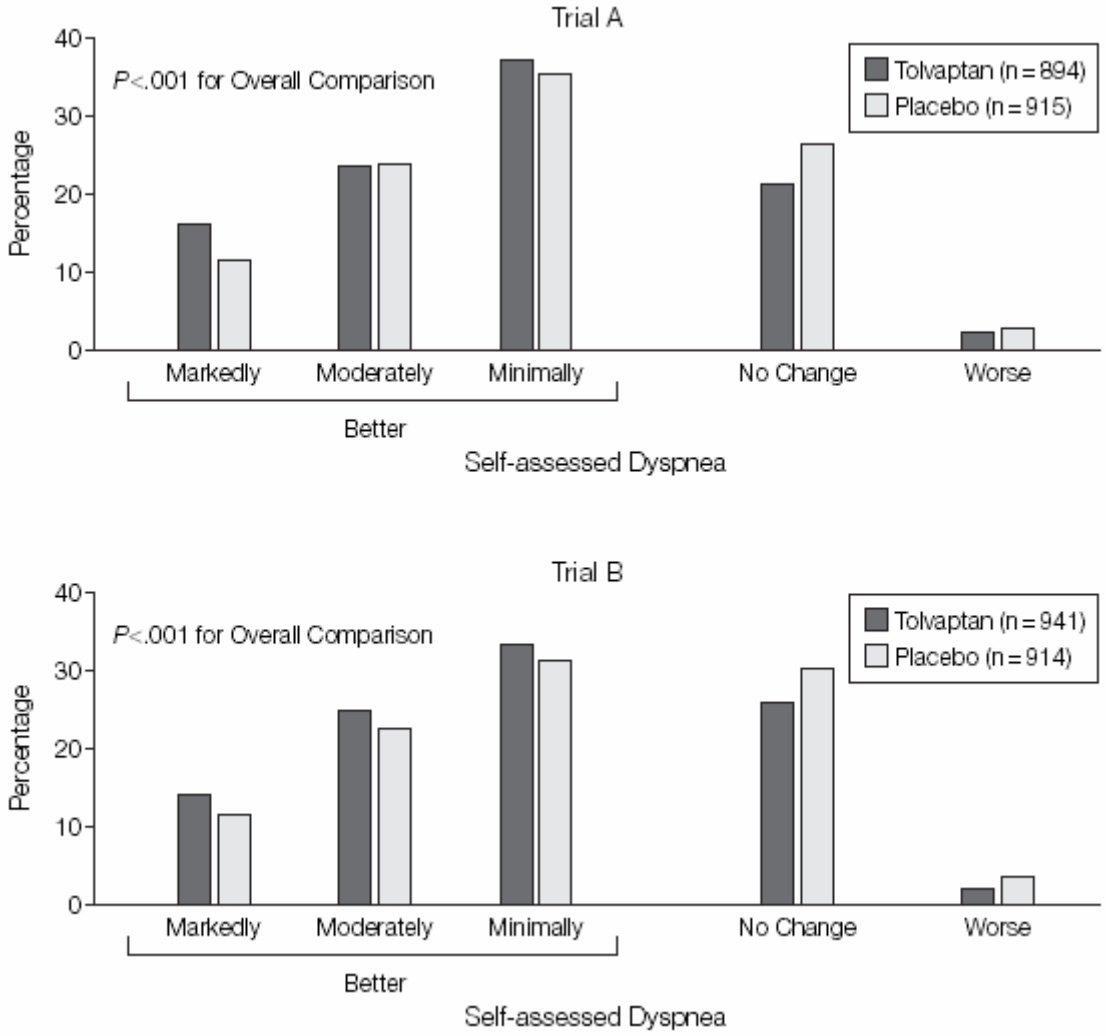
G M. De Ferrari, A Mazzuero, L Agnesina, A Bertoletti, M Lettino, C Campana, P J. Schwartz, L Tavazzi. JACC Submitted



Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure

The EVEREST Clinical Status Trials

M Gheorghiade, M A. Konstam, J C. Burnett, et al. *JAMA. 2007;297:1332-43*



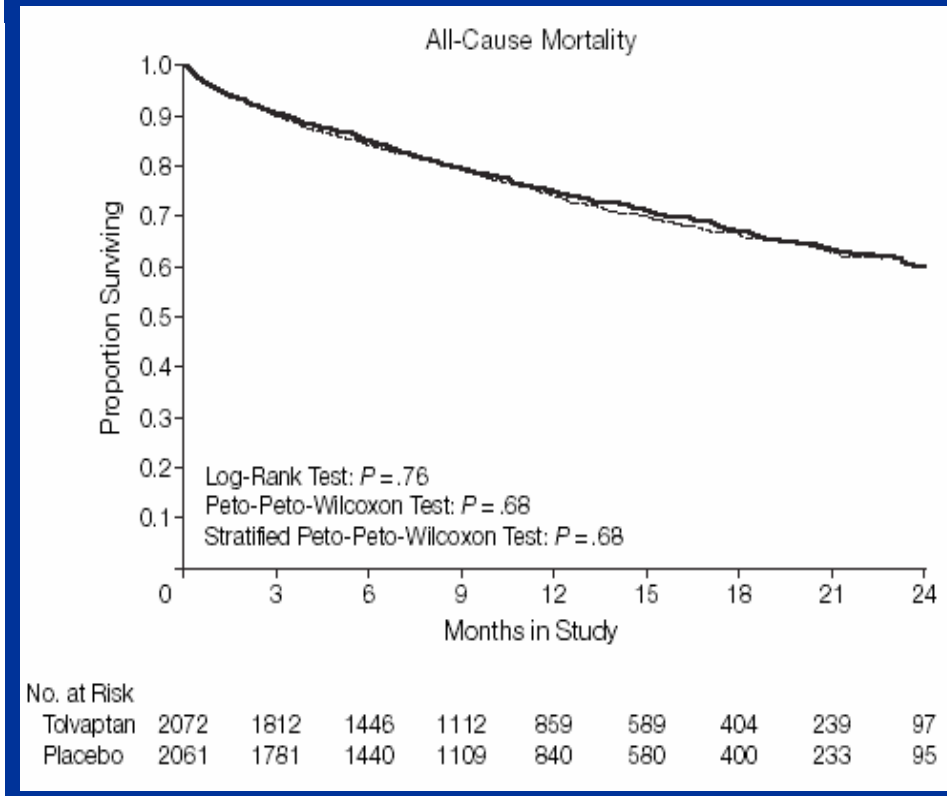
Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline

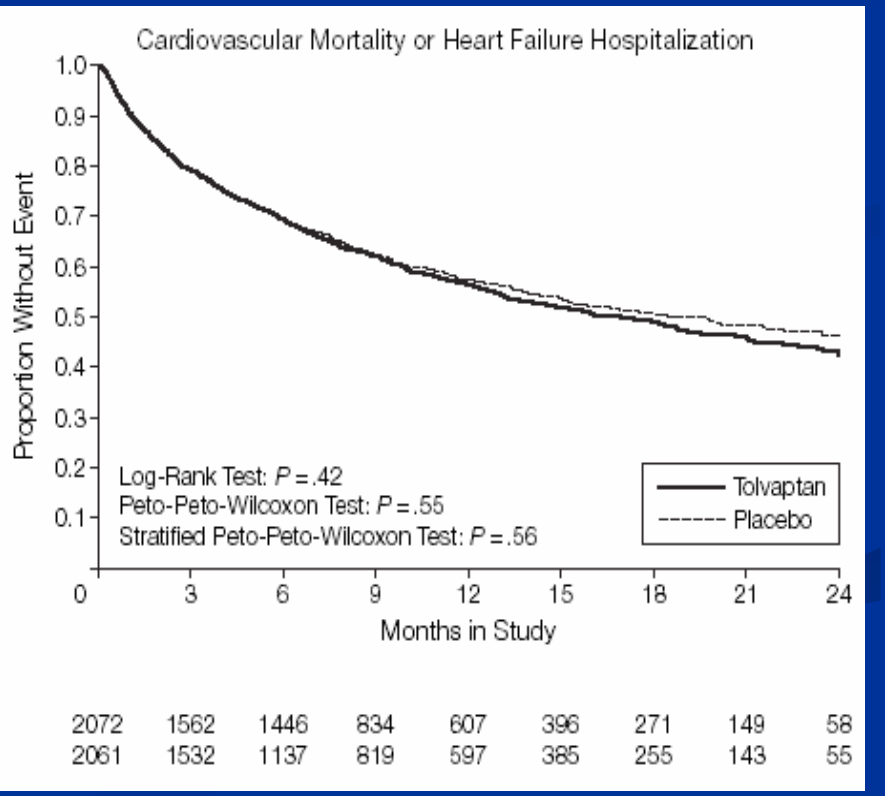
P value represents between-group comparison by van Elteren test.

Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

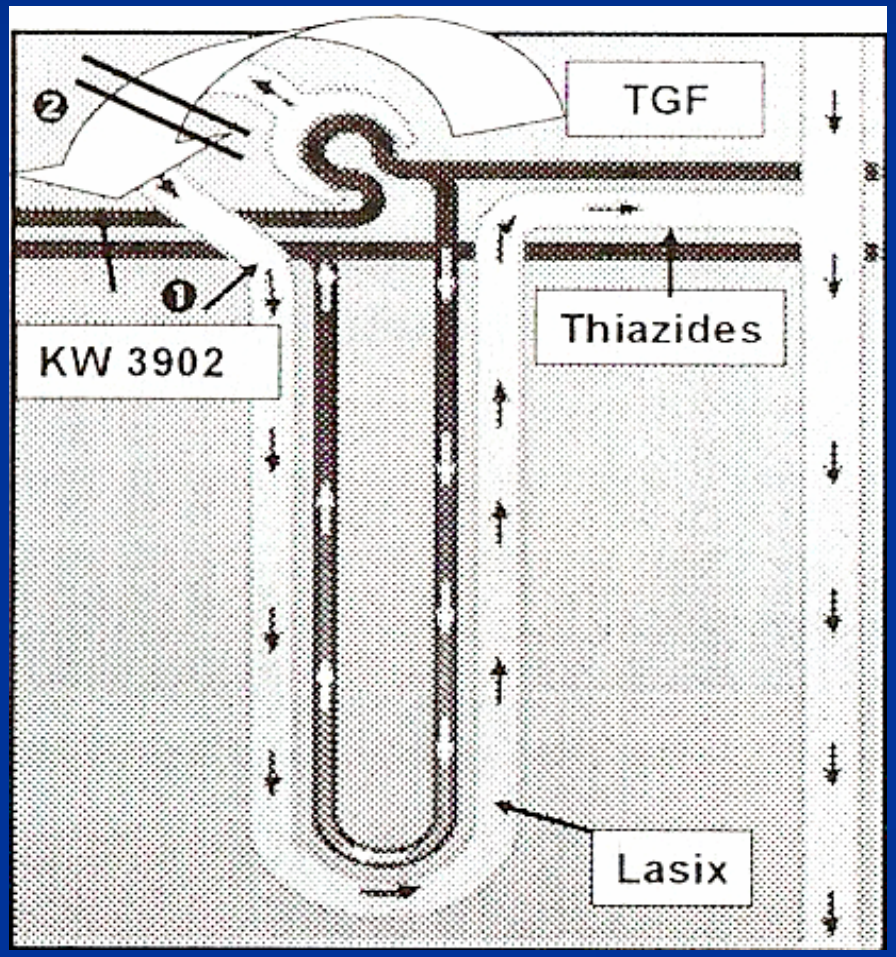
The EVEREST Outcome Trial

M A. Konstam, M Gheorghiade, JC. Burnett, et al. *JAMA. 2007;297:1319-31*





KW-3902:
Adenosine A1-Receptor Antagonist



Selective affinity for A1 vs. A2A receptors

1) Inhibits reabsorption of sodium and water in the proximal tubule → enhances diuresis

2) Blocks tubuloglomerular feedback (TGF) → reverses afferent arteriole vasoconstriction → maintains GFR

The PROTECT pilot study: a randomized placebo-controlled dose-finding Study of the Adenosine A1 receptor antagonist rolofylline in patients with Acute heart failure and renal impairment

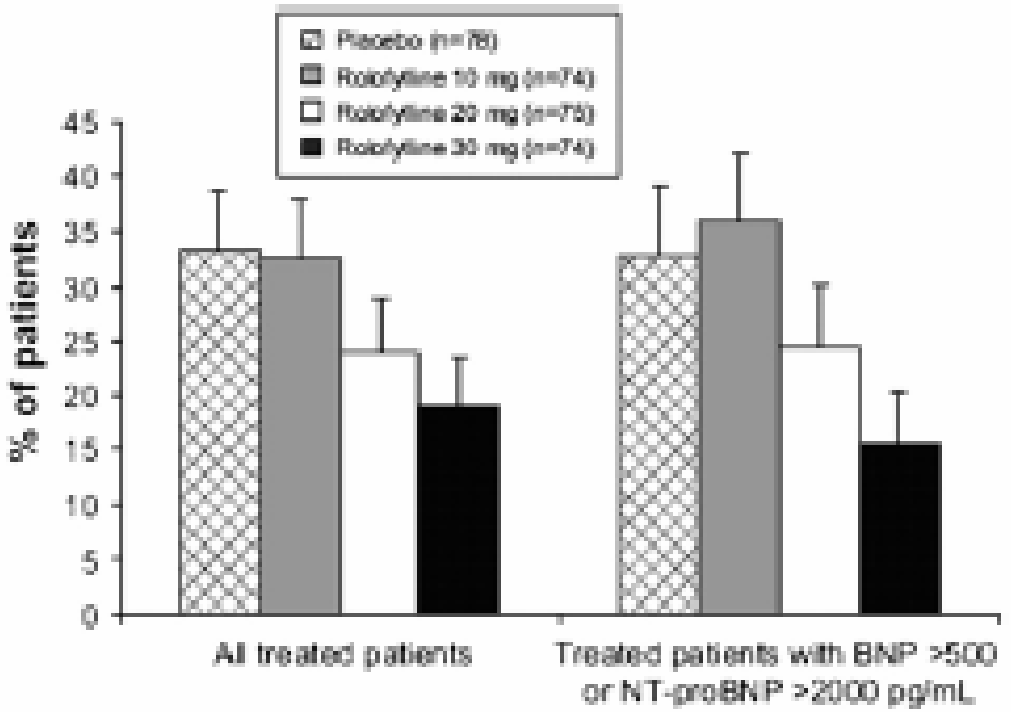


Fig. 4. Proportion of patients dying of any cause or rehospitalized for cardiovascular or renal causes during the 60-day follow-up period. (Bars represent standard errors of the proportions.)

Cotter G et al J Cardiac Failure 2008;14: 631-40

Feeling better, dying earlier

- Acute decompensated HF patients desperately ill
- Need new therapies, but the new agents must be viewed as cautiously as the positive inotropic strategy