

Heart Failure 2006

Helsinki, Finland

Acute heart failure

Which vasodilator in acute heart failure?

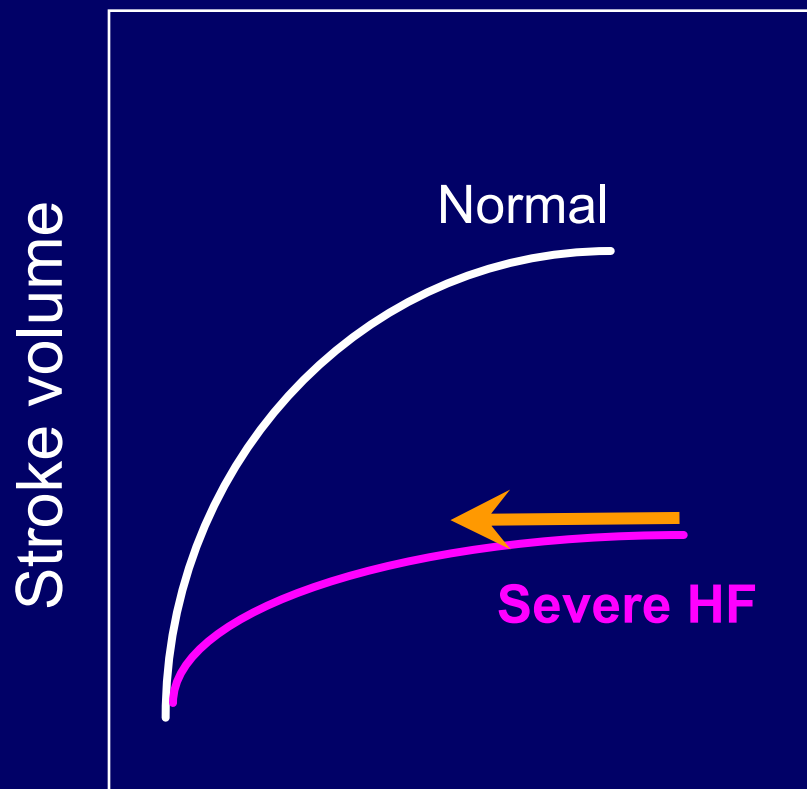
Marco Metra

Cattedra di Cardiologia

Università di Brescia

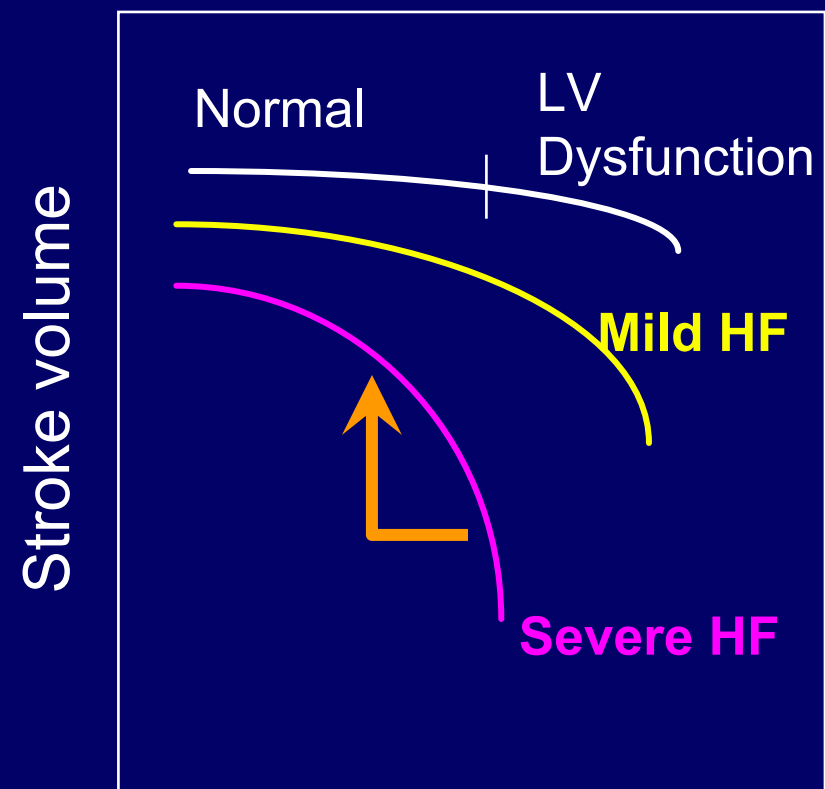
Hemodynamics of HF & vasodilator therapy

Venodilation



Preload

Arterial dilation



Afterload

From Cohn JN NEJM 1977;297:27

Vasodilators in AHF

Drug	PWP / RAP	SVR	CO / SV	Congest.	Hypoperf.
Nitrates (GTN, I-5MN, IDN)	↓ ↓ ↓ ↓	↓ ↓	↑	↓ ↓	↓
Nesiritide*	↓ ↓ ↓ ↓ ↓	↓ ↓	↑	↓ ↓ ↓	↓
Nitroprusside	↓ ↓	↓ ↓ ↓	↑ ↑ ↑	↓	↓
<i>Endothelin antagonists**</i>	↓ ↓	↓ ↓ ↓	↑ ↑ ↑	↓	↓

* Not approved in most European countries

** Not approved for clinical use

Nitrates

- **Indications**

- AHF with adequate BP

- **Effects**

- Venodilation only (low doses)
 - + arterial vasodilation at higher doses
- ↓ pulmonary congestion / \approx SV / \approx MVO₂
- ↓ congestion / ↑ peripheral perfusion
- Effects dependent on:
 - Pre- and afterload
 - Heart response to baroreceptor unloading

- **Class I recommendation**

- **Level of evidence B**

Clinical presentations of Acute HF (I)

Central mechanisms

1. Acute decompensated heart failure

- due to **Peripheral mechanisms** of chronic HF

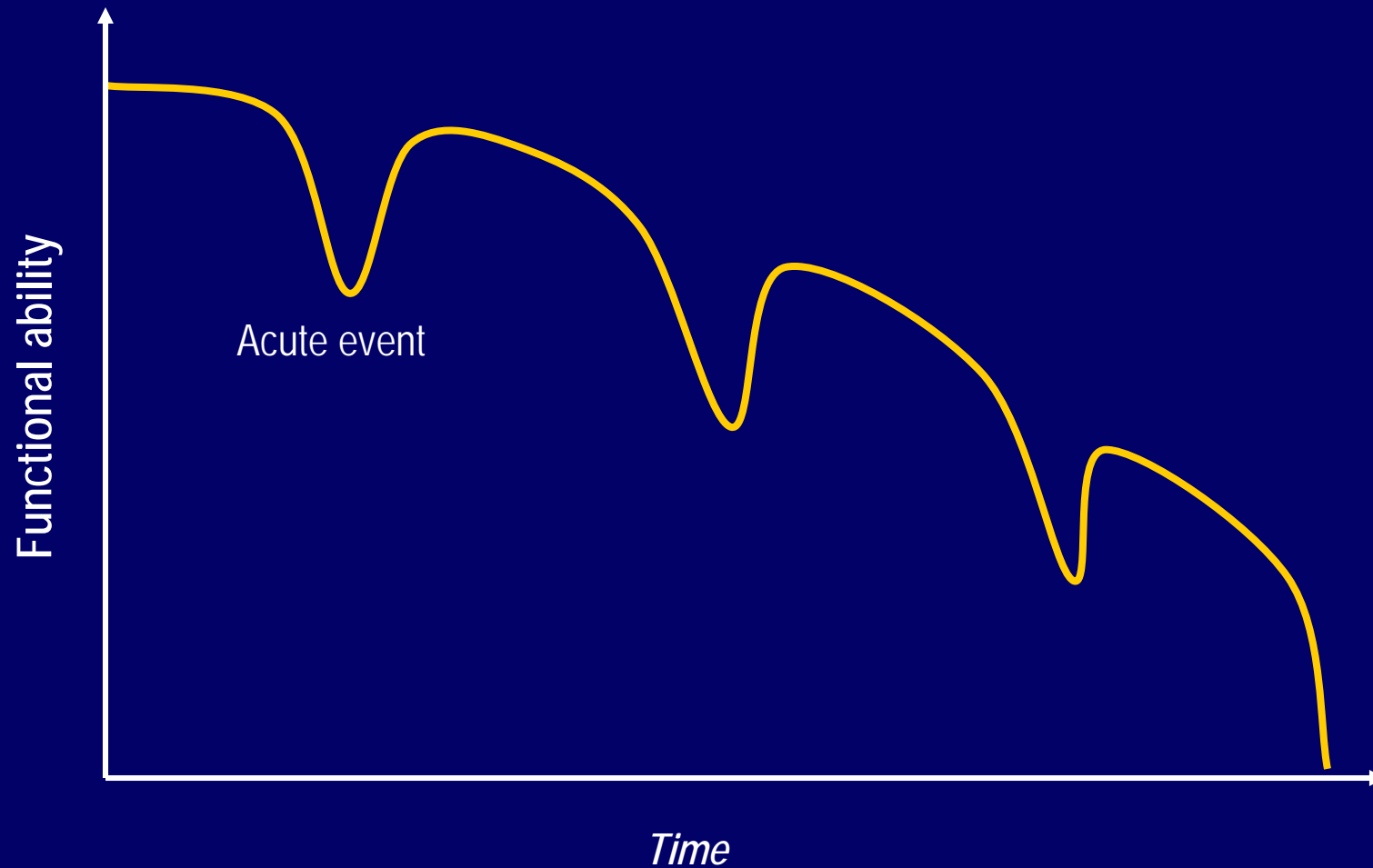
2. Hypertensive AHF

- Arterial hypertension
- Chest-Xray with pulmonary congestion / oedema
- LV systolic function may be normal

3. Pulmonary oedema

- Severe respiratory distress
- Lung rales & orthopnea
- O₂ saturation <90%
- Chest X-ray

Acute Exacerbations Contribute to the Progression of the Disease



Gheorghiade M et al. Am J Cardiol. 2005; 96 (6A)

Treatment of Acute Pulmonary Edema: Diuresis or Vasodilatation ?

Primary outcome	High dose IDN (n=52)	High dose furosemide (n=52)	P
IDN, mg	114 ± 6.8	1.4 ± 0.6	<0.001
Furosemide, mg	56 ± 28	200 ± 65	<0.001
Death	1 (2%)	3 (6%)	0.61
Mechanical ventilation	7 (13%)	21 (40%)	0.0041
Myocardial infarction	13 (25%)	24 (46%)	0.041
Any adverse event	13 (25%)	24 (46%)	0.041

Cotter G et al., Lancet 1998;351:389

Pathophysiologic mechanisms in acute HF

Therapy



```
graph LR; Therapy[Therapy] --> A[Myocardial injury – cell death – Ischaemia / Apoptosis]; Therapy --> B[Arrhythmias]; Therapy --> C[Renal dysfunction]; Therapy --> D[Hypotension / Hypoperfusion]; Therapy --> E[.....];
```

- **Myocardial injury – cell death**
– Ischaemia / Apoptosis
- **Arrhythmias**
- **Renal dysfunction**
- **Hypotension / Hypoperfusion**
- **.....**

Goals of Treatment of Acute Heart Failure: ESC Guidelines

- **Hemodynamic**

- ↓ PWP
- ↑ CO, SVI

- **Clinical**

- ↓ symptoms (dyspnoea, fatigue)
- ↓ clinical signs
- ↓ body weight
- ↑ diuresis
- ↑ SAO₂

- **Laboratory**

- S-Electrolytes normalization
- ↓ BUN, creatinine
- ↓ S-bilirubin
- ↓ S-BNP

- **Outcome**

- ↓ ICU length of stay
- ↓ duration of hospitalization
- ↑ time to readmission
- ↓ mortality

- **Tolerability**

- Low withdrawal rate
- Low incidence of AEs

Required

- ↓ of symptoms with = clinical course
- or ~ symptoms with ↑ clinical course

Pathophysiologic mechanisms in acute HF

Therapy

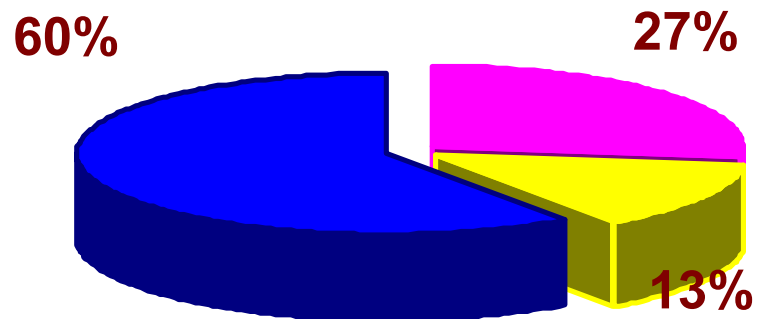


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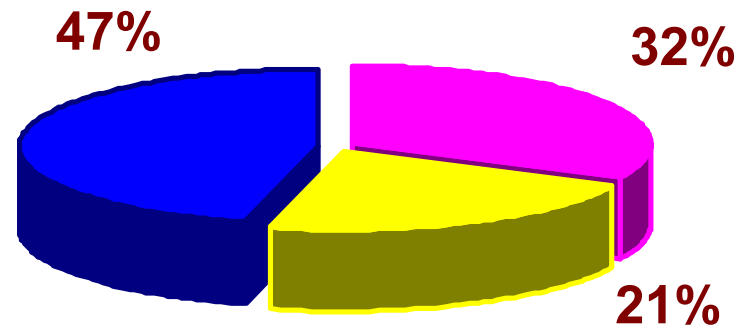
- **Myocardial injury – cell death**
– **Ischaemia / Apoptosis**
- **Arrhythmias**
- **Renal dysfunction**
- **Hypotension / Hypoperfusion**
- **.....**

Detectable cTnT and cause of HF

**Non-ischemic
cardiomyopathy
N=52**



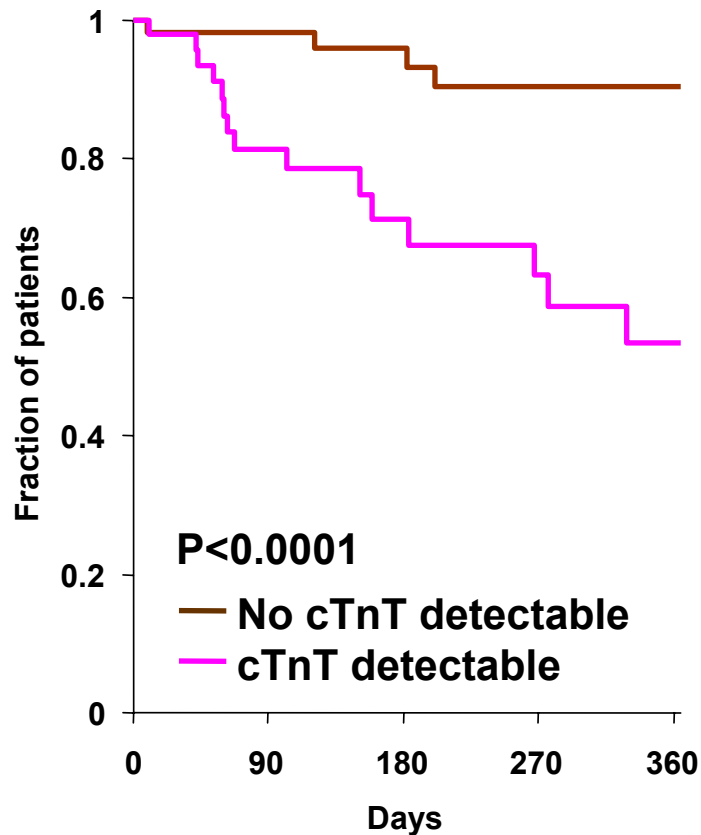
**Ischemic
cardiomyopathy
N=65**



- cTnT abnormal 6/6 samples
- cTnT abnormal 1-5/6 samples
- cTnT normal

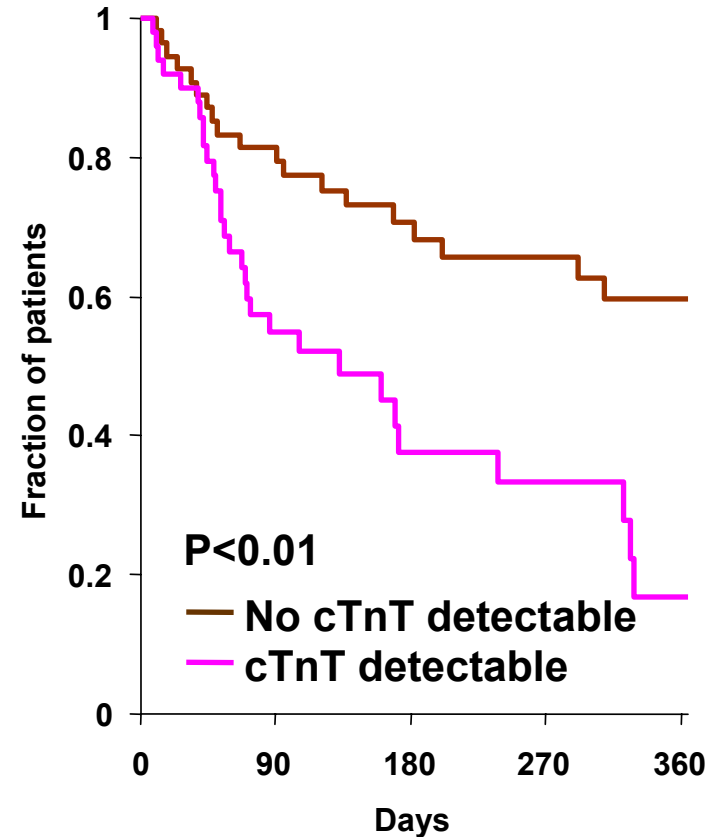
Freedom from Death or CV Hospitalization and cTnT plasma levels in Acute Heart Failure

Cardiac mortality



Patients at risk		Days				
	0	90	180	270	360	
No cTnT	56	55	44	35	33	
cTnT	51	34	21	15	11	

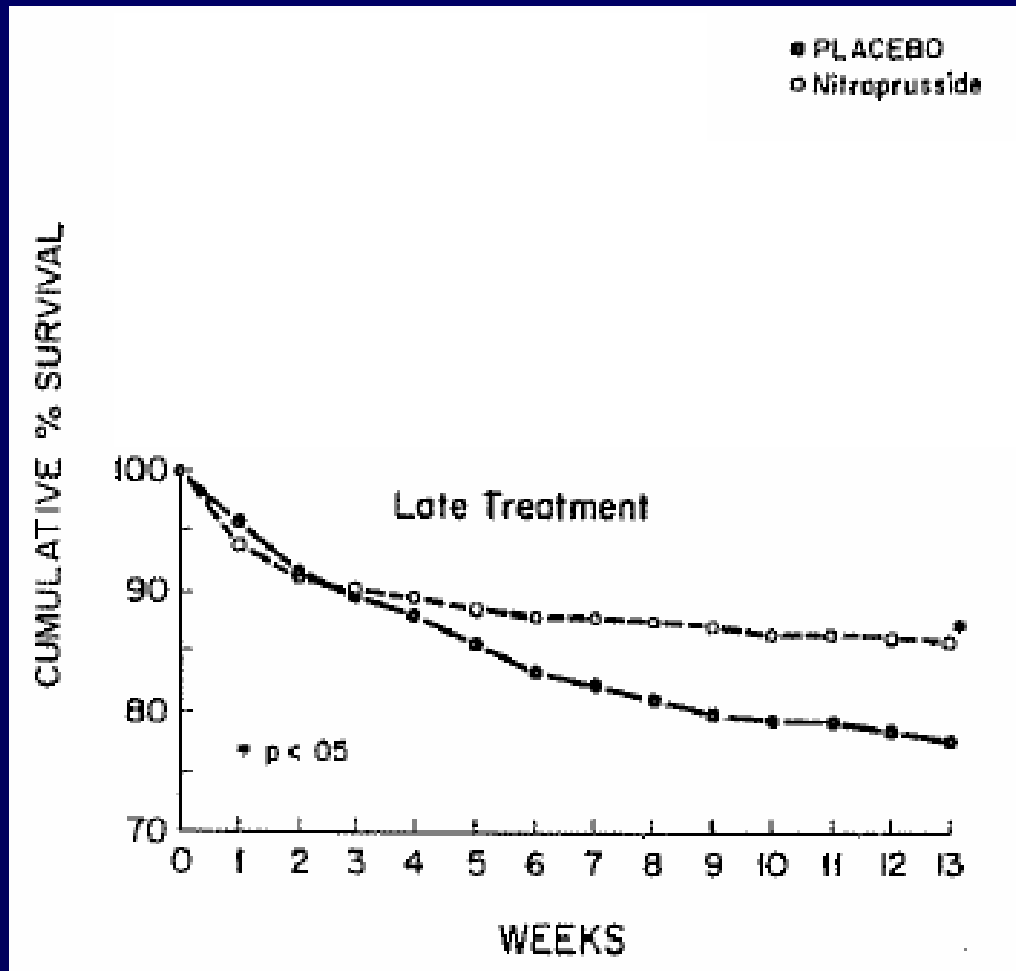
Cardiac mortality or CV hospitalizations



Patients at risk:		Days				
	0	90	180	270	360	
No cTnT	56	44	30	26	21	
cTnT	51	23	11	9	4	

Nitroprusside and Mortality

AMI + HF with PA Catheter

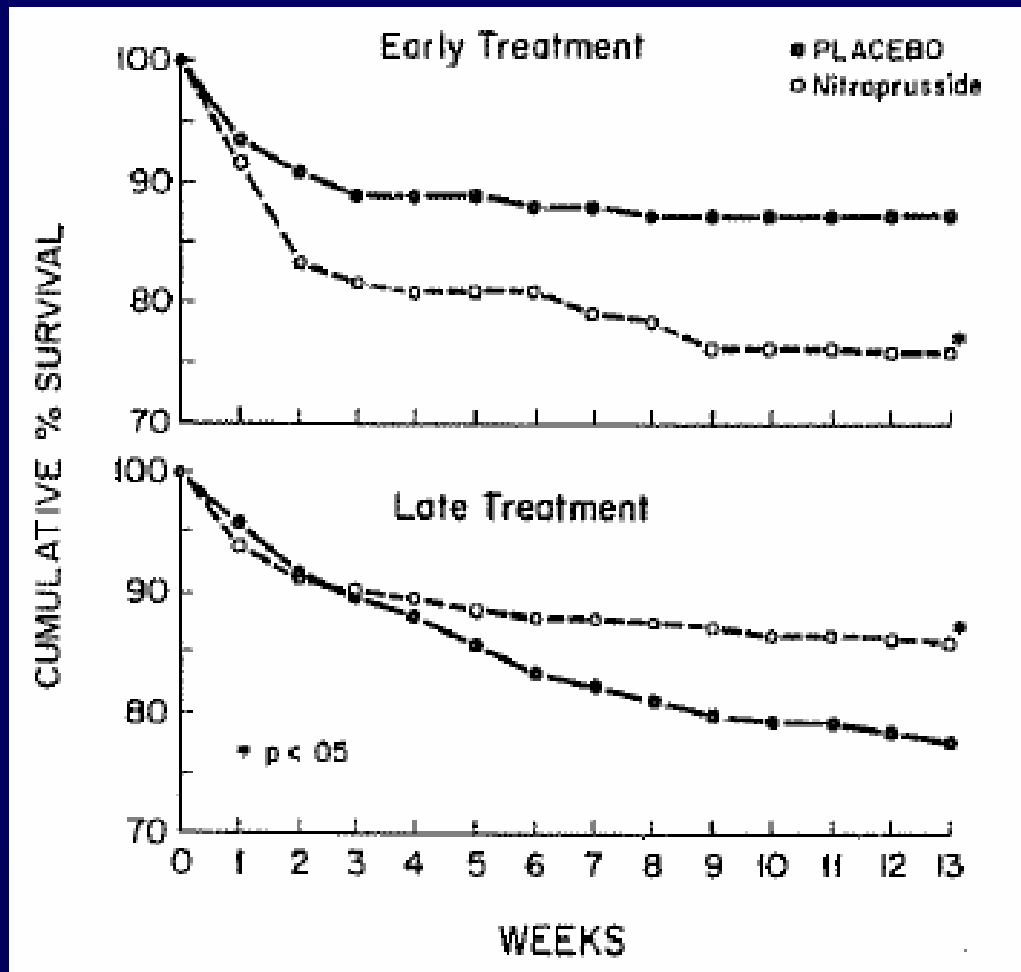


Placebo (n=405) & Nitroprusside (n=407) titrated to \downarrow PCWP

≥ 9 hrs.

Nitroprusside and Mortality

AMI + HF with PA Catheter



Placebo (n=405) & Nitroprusside (n=407) titrated to ↓ PCWP

< 9 hrs.

≥ 9 hrs.

Pathophysiologic mechanisms in acute HF

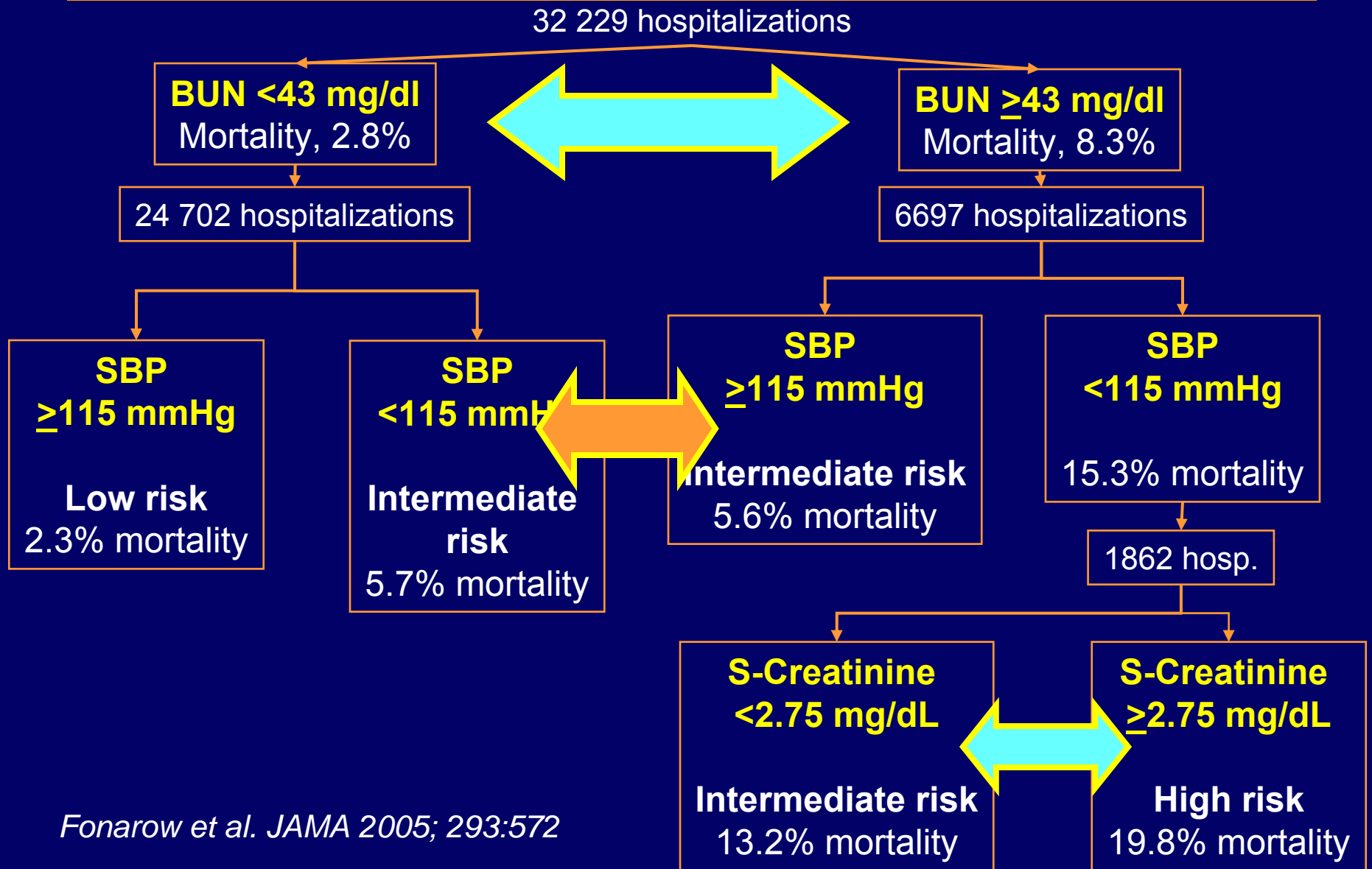
Therapy



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- **.....**

ADHERE: Risk Stratification for In-hospital Mortality in the Validation Cohort

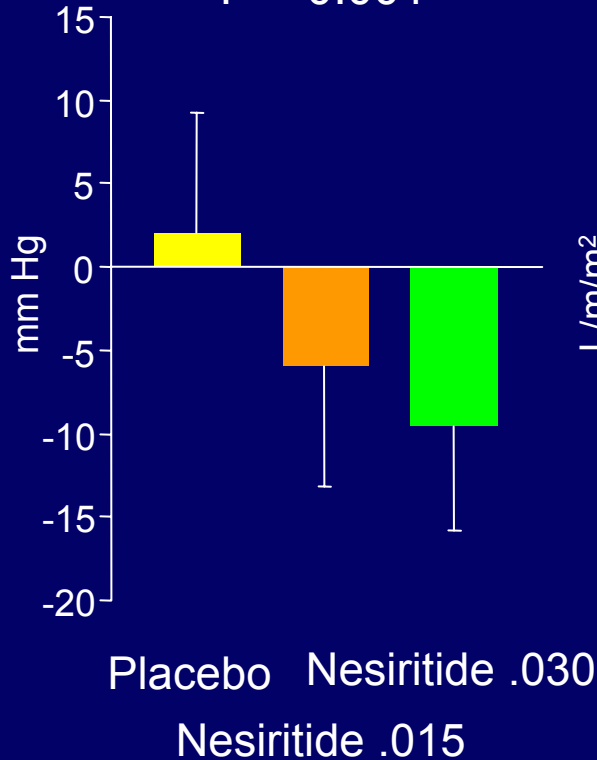


Fonarow et al. JAMA 2005; 293:572

Hemodynamic and Clinical Efficacy of Intravenous BNP (Nesiritide) in Patients with Decompensated Heart Failure

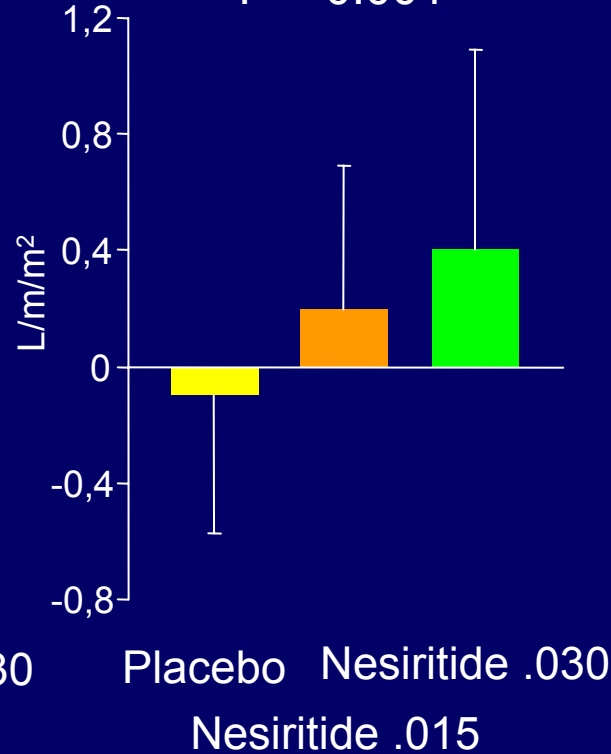
Pulmonary wedge pressure

P < 0.001



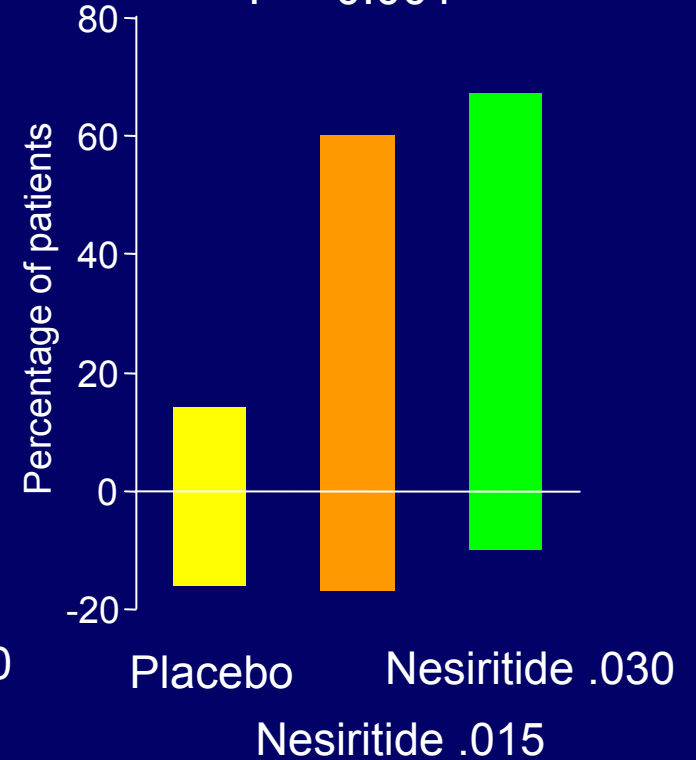
Cardiac index

P < 0.001



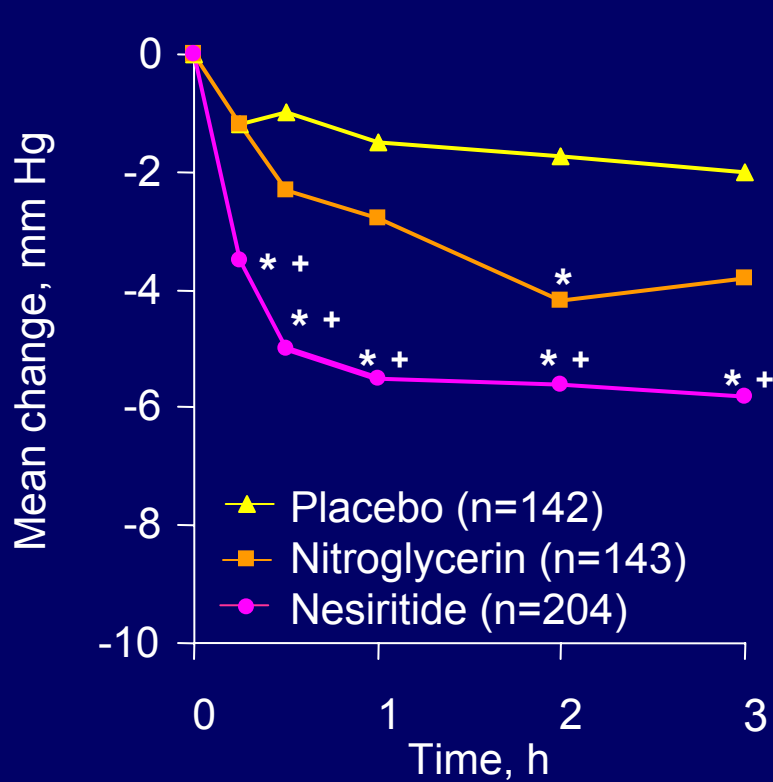
Global Clinical Status

P < 0.001

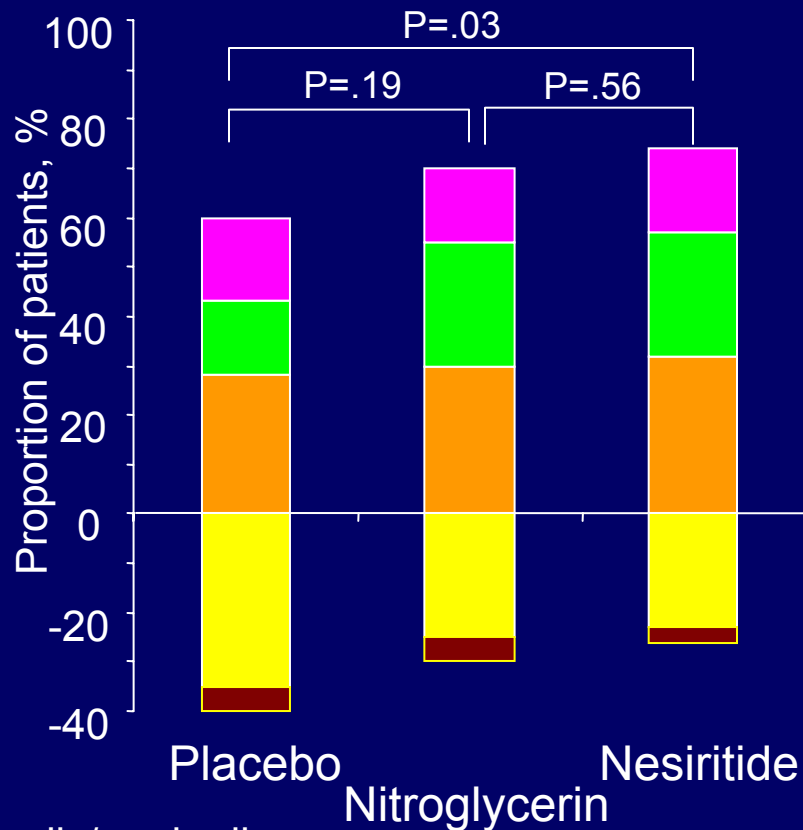


Intravenous Nesiritide versus Nitroglycerin for the Treatment of Decompensated Heart Failure

Pulmonary Wedge Pressure



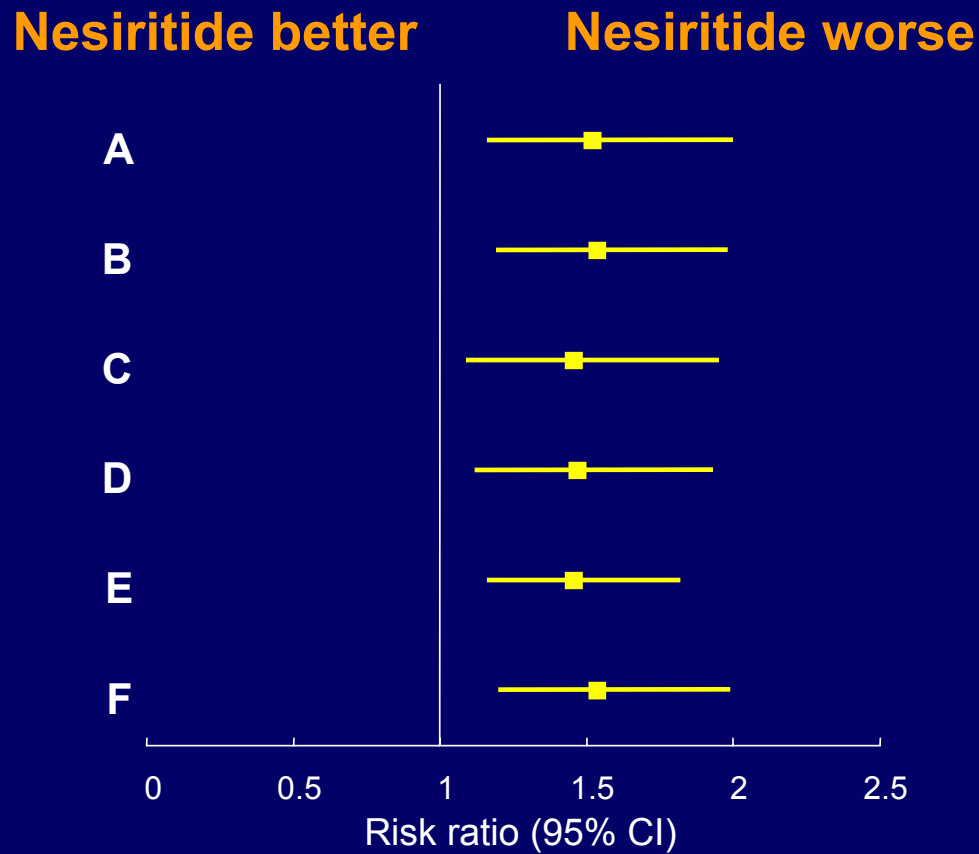
Dyspnea



VMAC Investigators,
JAMA 2002; 287:1531

- Minimally/markedly worse
- No change
- Minimally better
- Moderately better
- Markedly better

Risk of Worsening Renal Function with Nesiritide in Patients with ADHF



A, nesiritide ≤ 0.03 $\mu\text{g}/\text{kg}/\text{min}$ vs non-inotrope based controls; B, nesiritide ≤ 0.03 $\mu\text{g}/\text{kg}/\text{min}$ vs all controls; nesiritide ≤ 0.015 $\mu\text{g}/\text{kg}/\text{min}$ vs non-inotrope based controls; C, nesiritide ≤ 0.015 $\mu\text{g}/\text{kg}/\text{min}$ vs non-inotrope based controls; D, nesiritide ≤ 0.015 $\mu\text{g}/\text{kg}/\text{min}$ vs all controls; E, nesiritide ≤ 0.06 $\mu\text{g}/\text{kg}/\text{min}$ vs non-inotrope based controls; F, nesiritide ≤ 0.06 $\mu\text{g}/\text{kg}/\text{min}$ vs all controls

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

Table 2. Mortality Within 30 Days of Treatment Associated With Nesiritide or Control Therapy With Overall Risk Ratio Calculated by Mantel-Haenszel Test Using a Fixed-Effects Model

Study	No. of Deaths/Total No. (%) of Patients		Risk Ratio (95% CI)	P Value
	Nesiritide Therapy	Control Therapy		
NSGET	6/85 (7.1)	2/42 (4.8)	1.48 (0.31-7.03)	ND
VMAC	24/280 (8.6)	12/218 (5.5)	1.56 (0.80-3.04)	ND
PROACTION	5/120 (4.2)	1/117 (0.9)	4.88 (0.58-41.1)	ND
Total	35/485 (7.2)	15/377 (4.0)	1.74 (0.97-3.12)	.059

Abbreviations: CI, confidence interval; ND, not determined; NSGET, Nesiritide Study Group Efficacy Trial; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natreacor; VMAC, Vasodilation in the Management of Acute Congestive heart failure.

Sackner-Bernstein, J. D. et al. JAMA 2005;293:1900-1905.

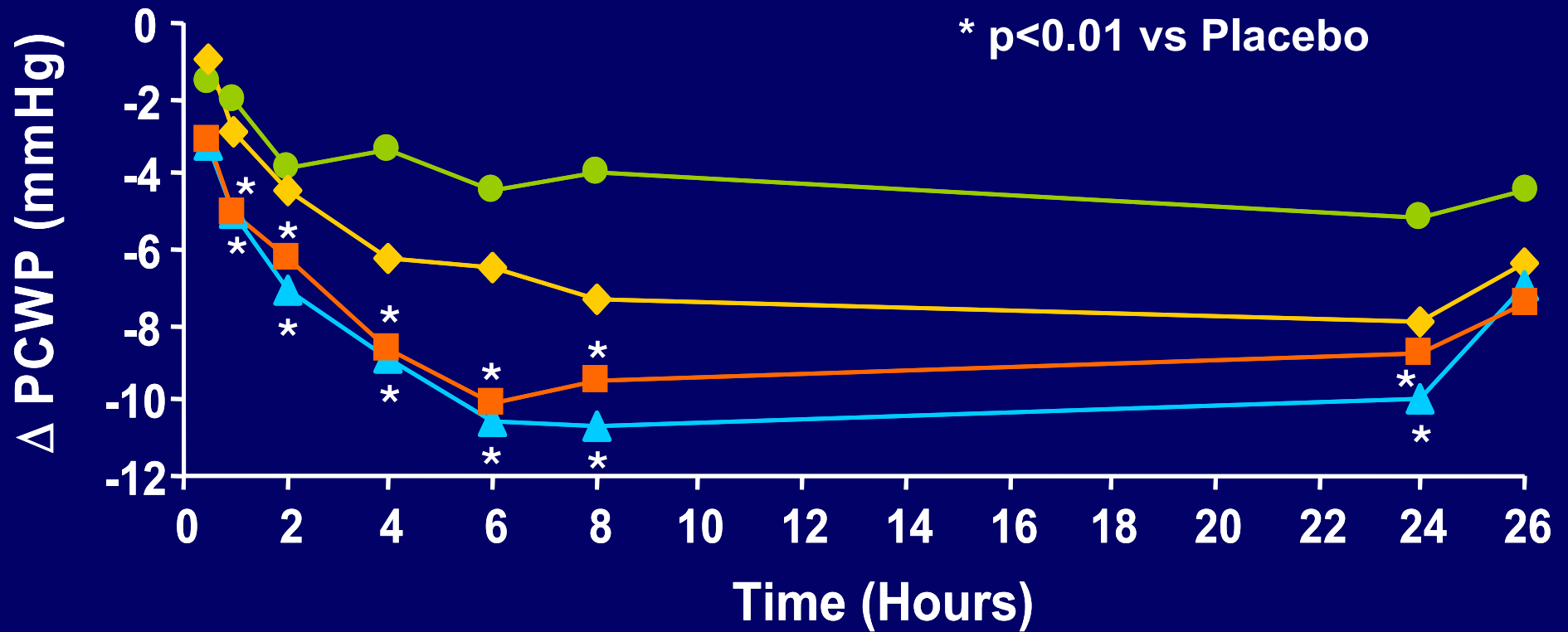
www.theheart.org

June 2, 2006

Huge nesiritide safety-efficacy study plans announced

... As announced by Scios, the planned US, Canadian, and European trial will randomize "as many as 7000" patients with acute decompensated HF and evaluate them for end points relating to dyspnea, rehospitalization, renal effects, mortality, quality of life, and treatment cost-effectiveness. ...

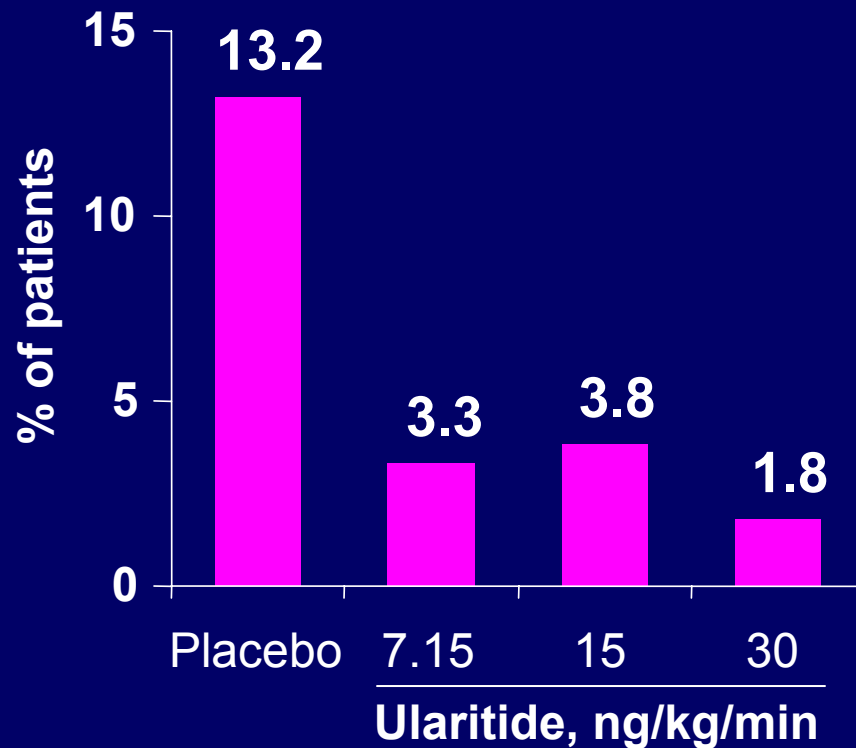
SIRIUS II: Ularitide Reduces PCWP



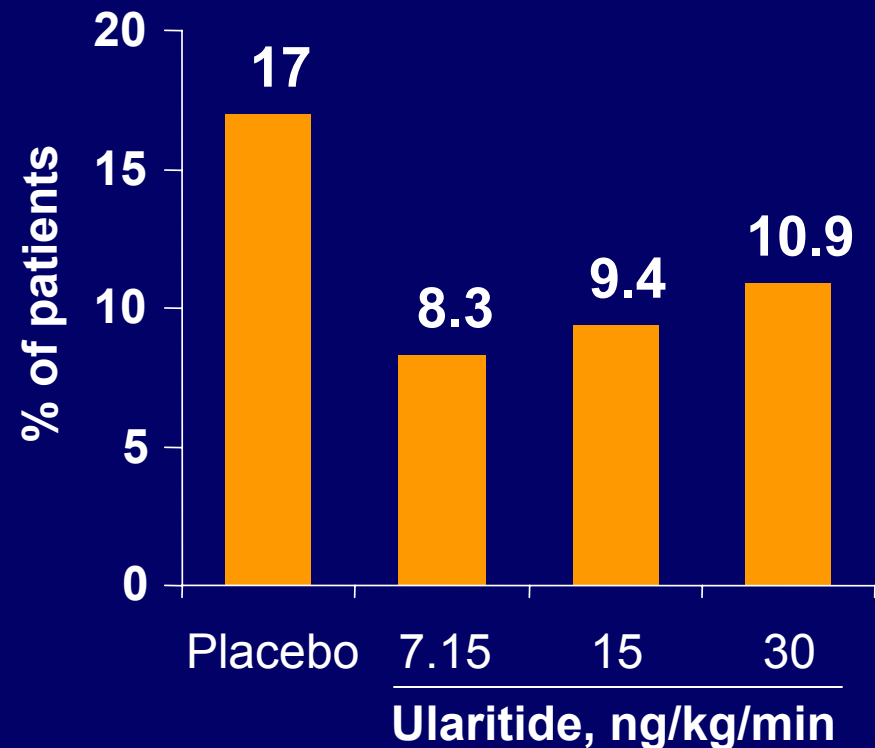
● Placebo ◆ 7.5 ng/kg/min ▲ 15 ng/kg/min ■ 30 ng/kg/min

Outcome in SIRIUS-II

Mortality



Adverse events



Mitrovic, Presented at ESC 2005

Pathophysiologic mechanisms in acute HF

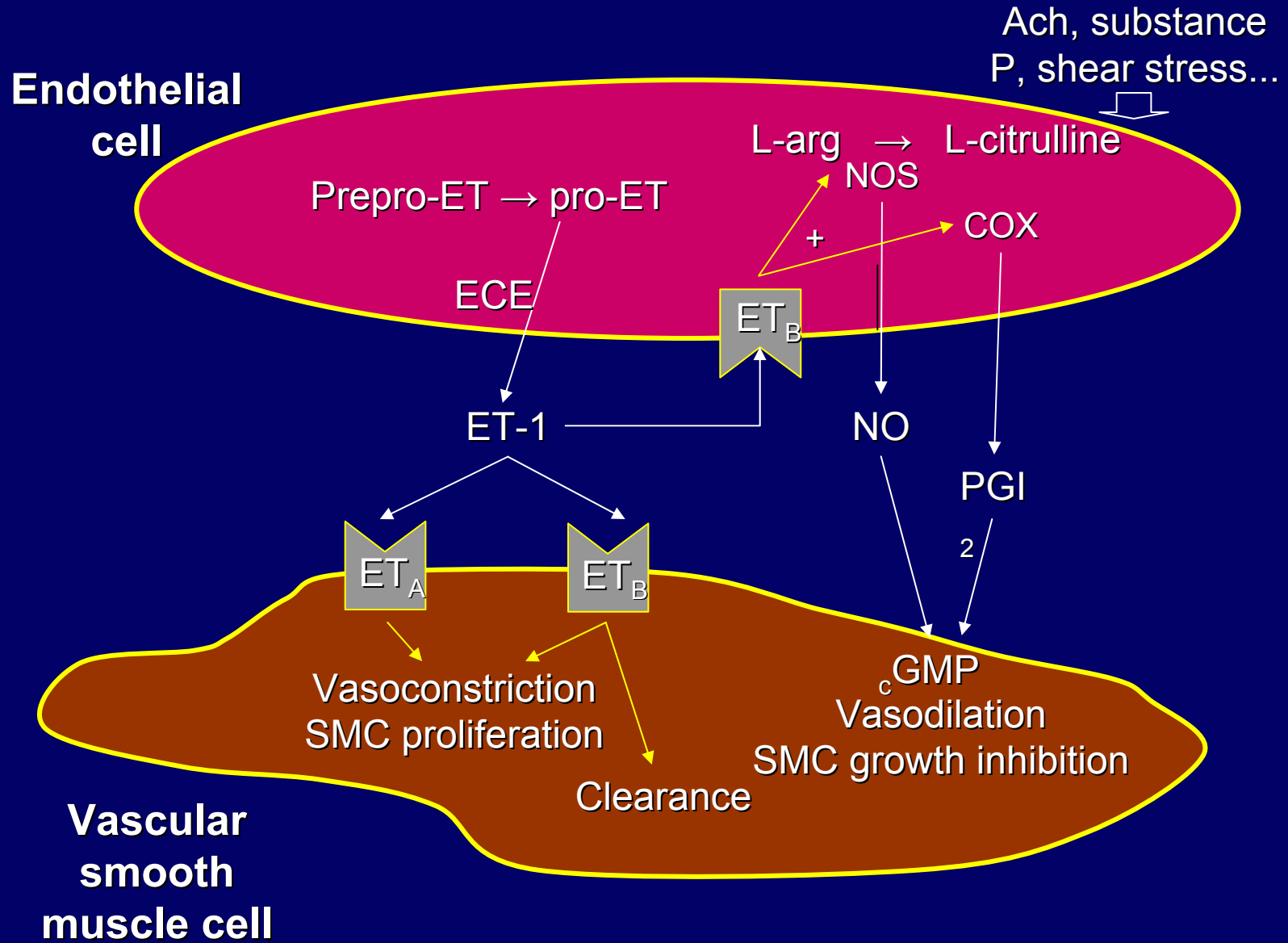
Therapy



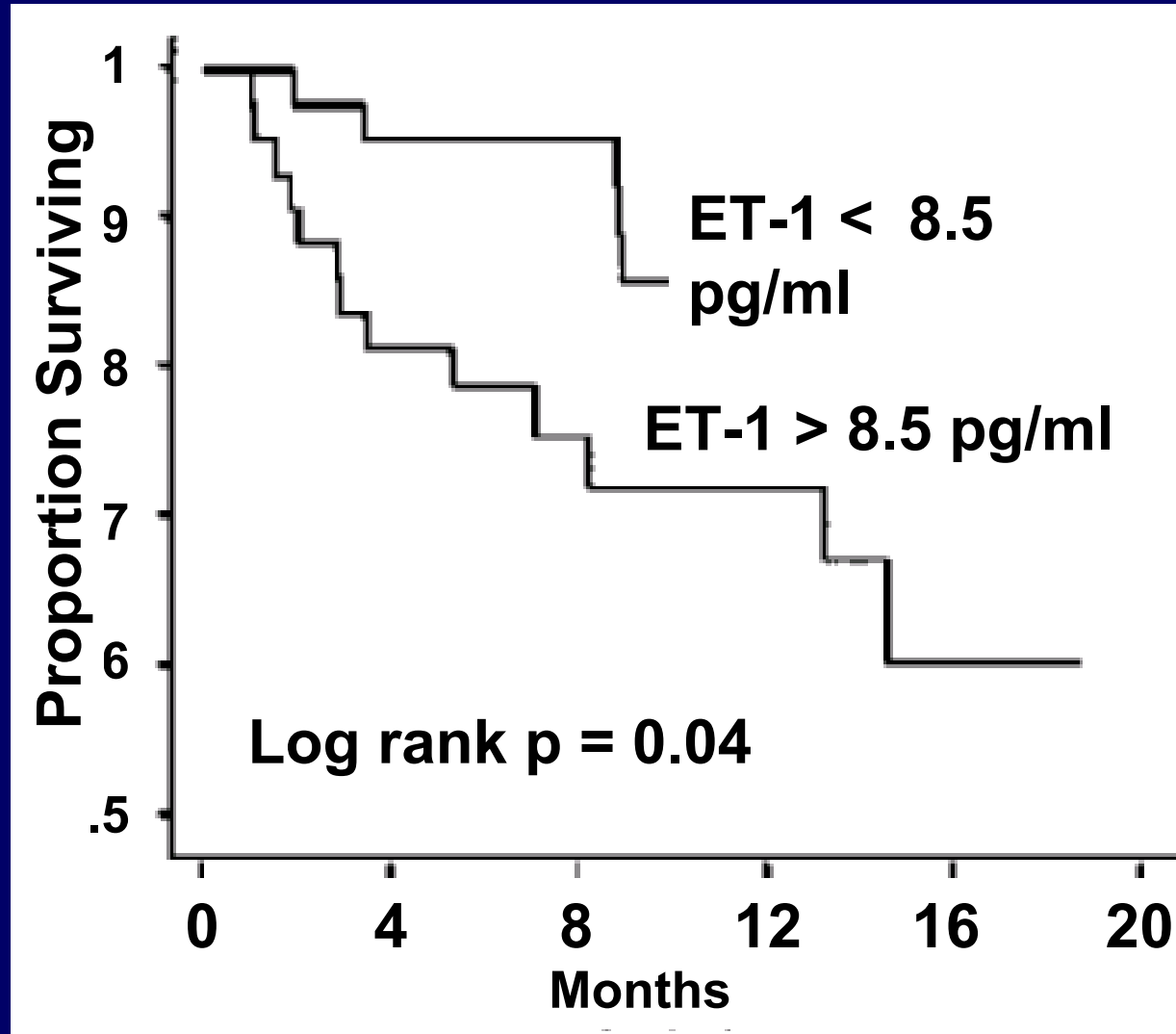
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```

- Myocardial injury – cell death
– Ischaemia / Apoptosis
- Arrhythmias
- Renal dysfunction
- Hypotension / Hypoperfusion
- Drug characteristics

Physiological Interaction Between Endothelial and Vascular Smooth Muscle Cells



6-Months Mortality in Patients with AHF by BL ET-1 (D. Aronson and A.J. Burger, *AJC* 91, Jan 15, 2003)



Primary Endpoints

VERITAS 1

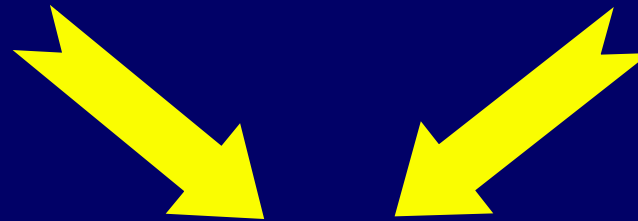
Dyspnea over 24 Hrs

n = 880, $\alpha = 0.04$

VERITAS 2

Dyspnea over 24 Hrs

n = 880, $\alpha = 0.04$



VERITAS 1 and 2

Death or WHF at 7 days

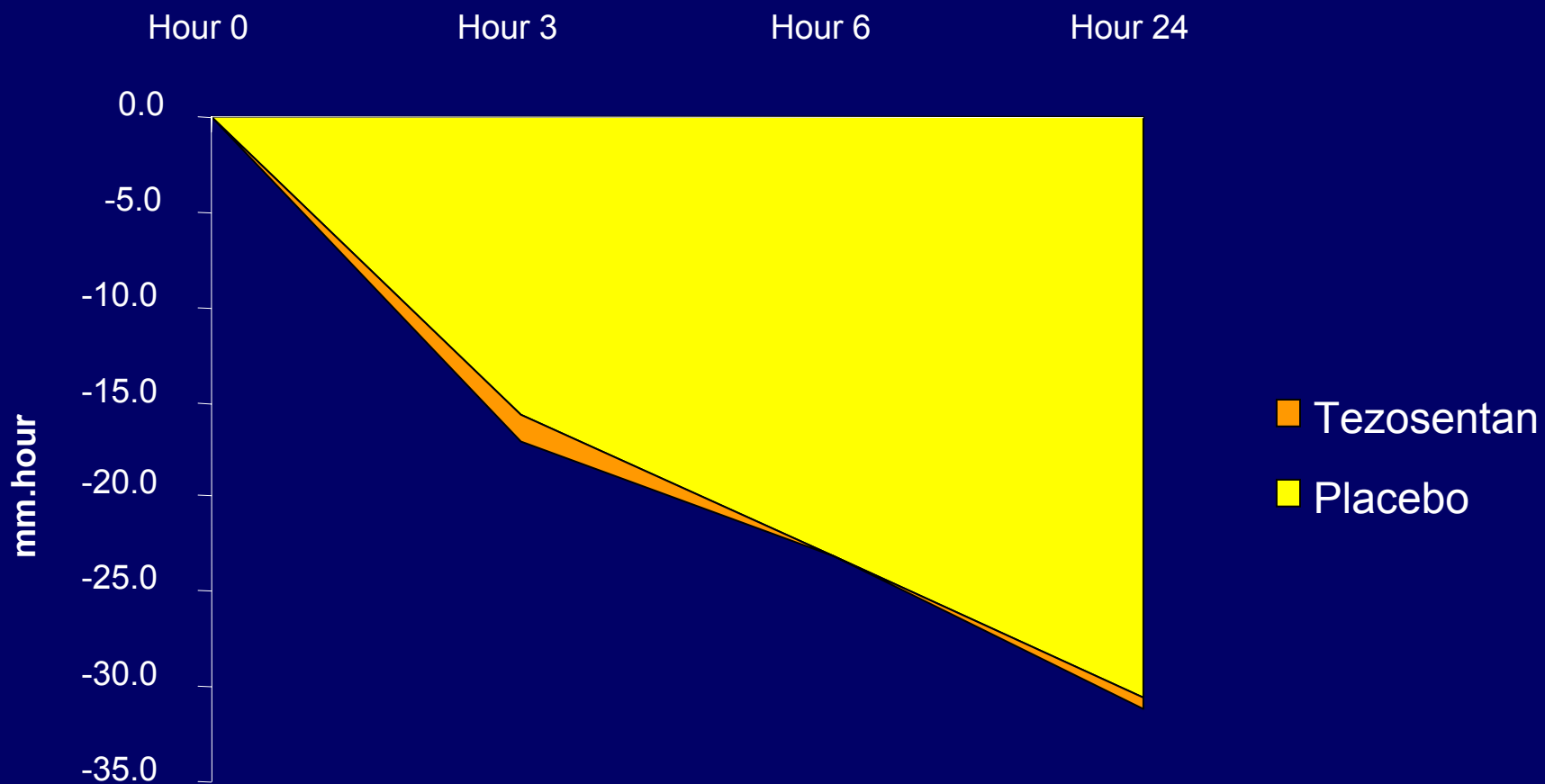
n = 1,760, $\alpha = 0.0092$

Incidence of Death or WHF (VERITAS 1 and 2 Combined)

	Placebo N = 708		Tezosentan N = 727		P-value *
	n	%	n	%	
Up to 7 days (primary endpoint)	187	26.4	191	26.3	0.95
Up to 30 days	235	33.2	232	31.9	0.61

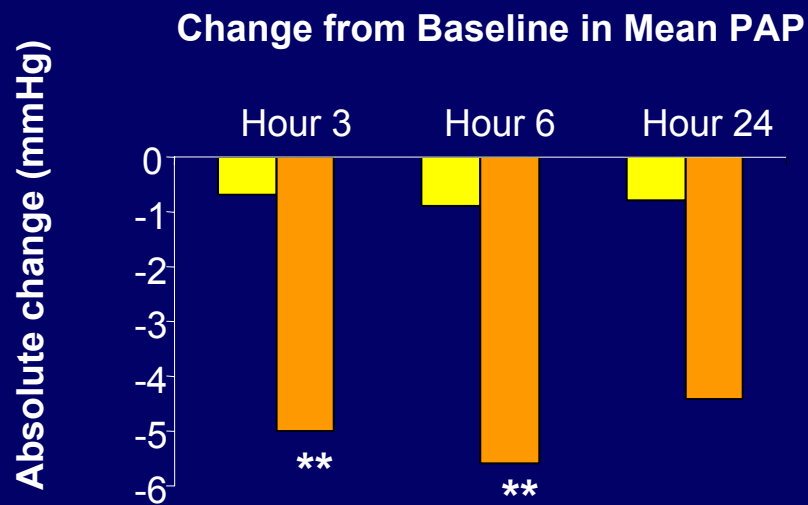
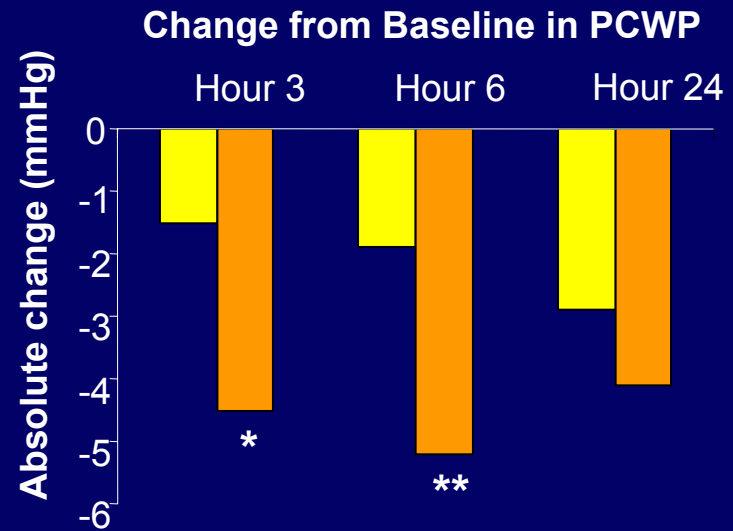
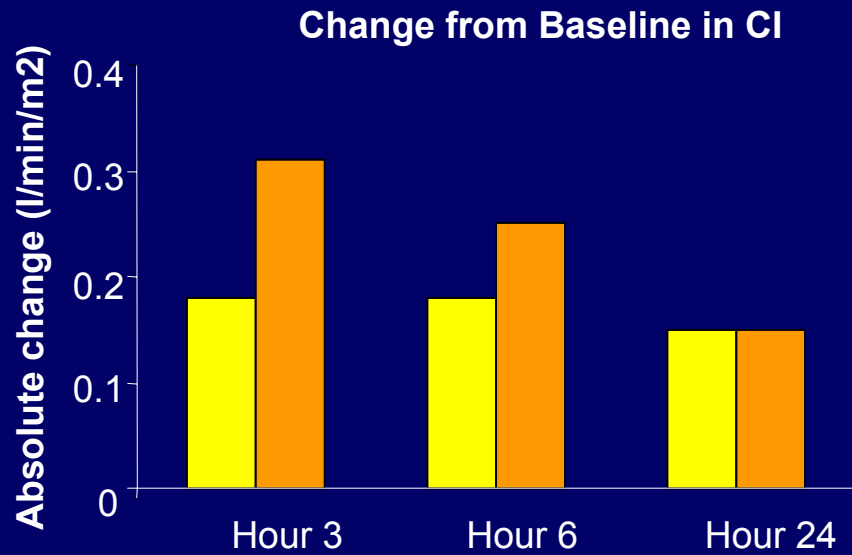
* Fisher's exact-test

AUC of Change in Dyspnea VERITAS 1 & 2

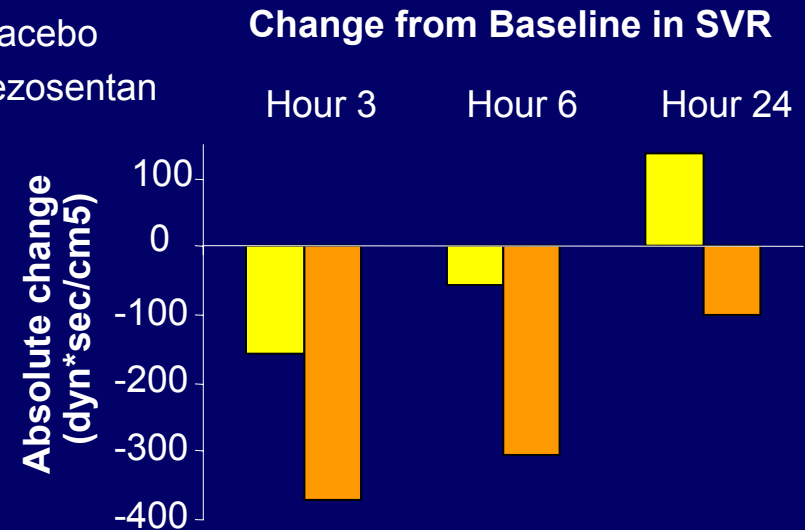


McMurray & Teerlink, ACC 2005

VERITAS Hemodynamic Substudy: Change From Baseline in Hemodynamic Parameters

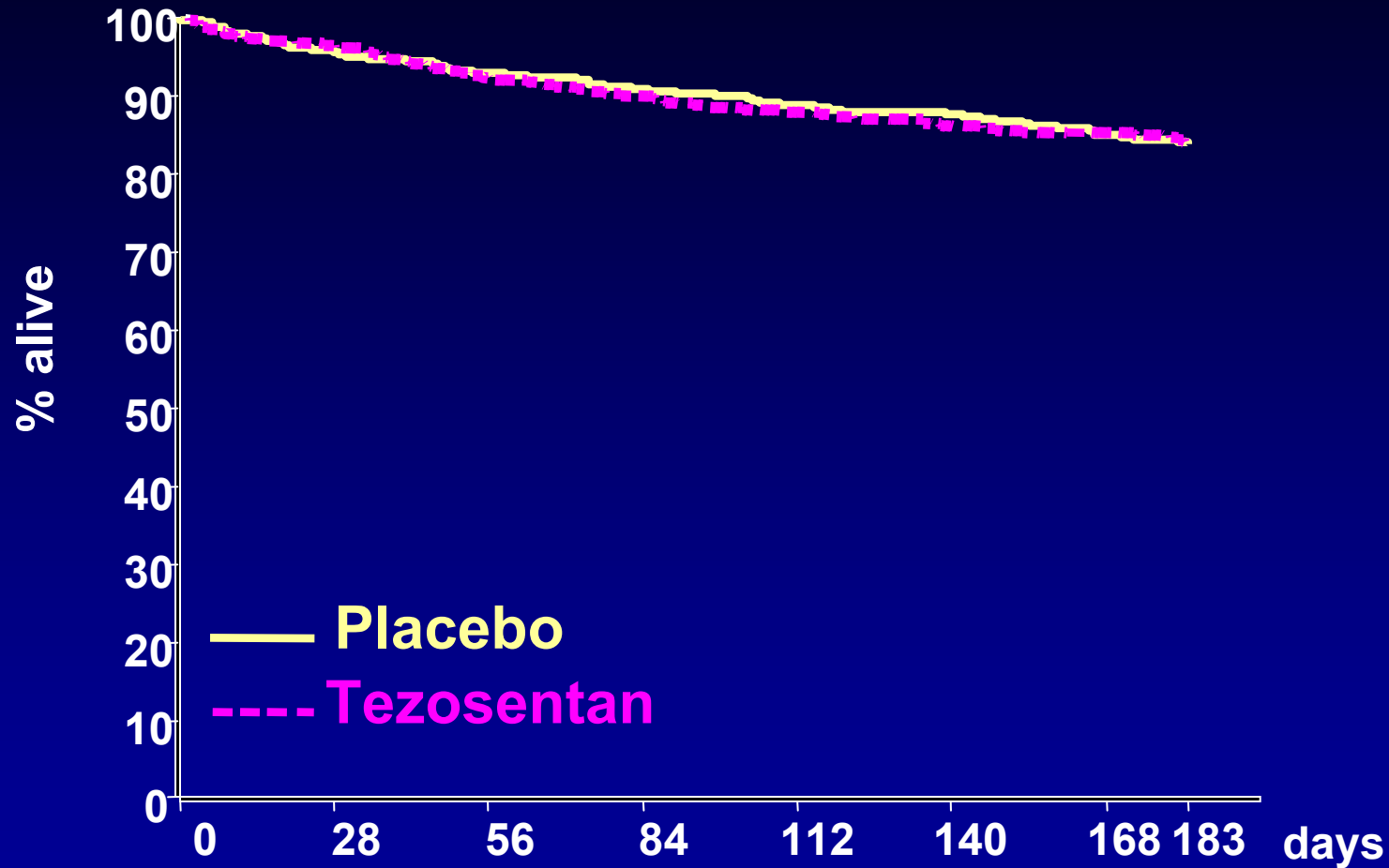


■ Placebo
■ Tezosentan



McMurray & Teerlink, ACC 2005

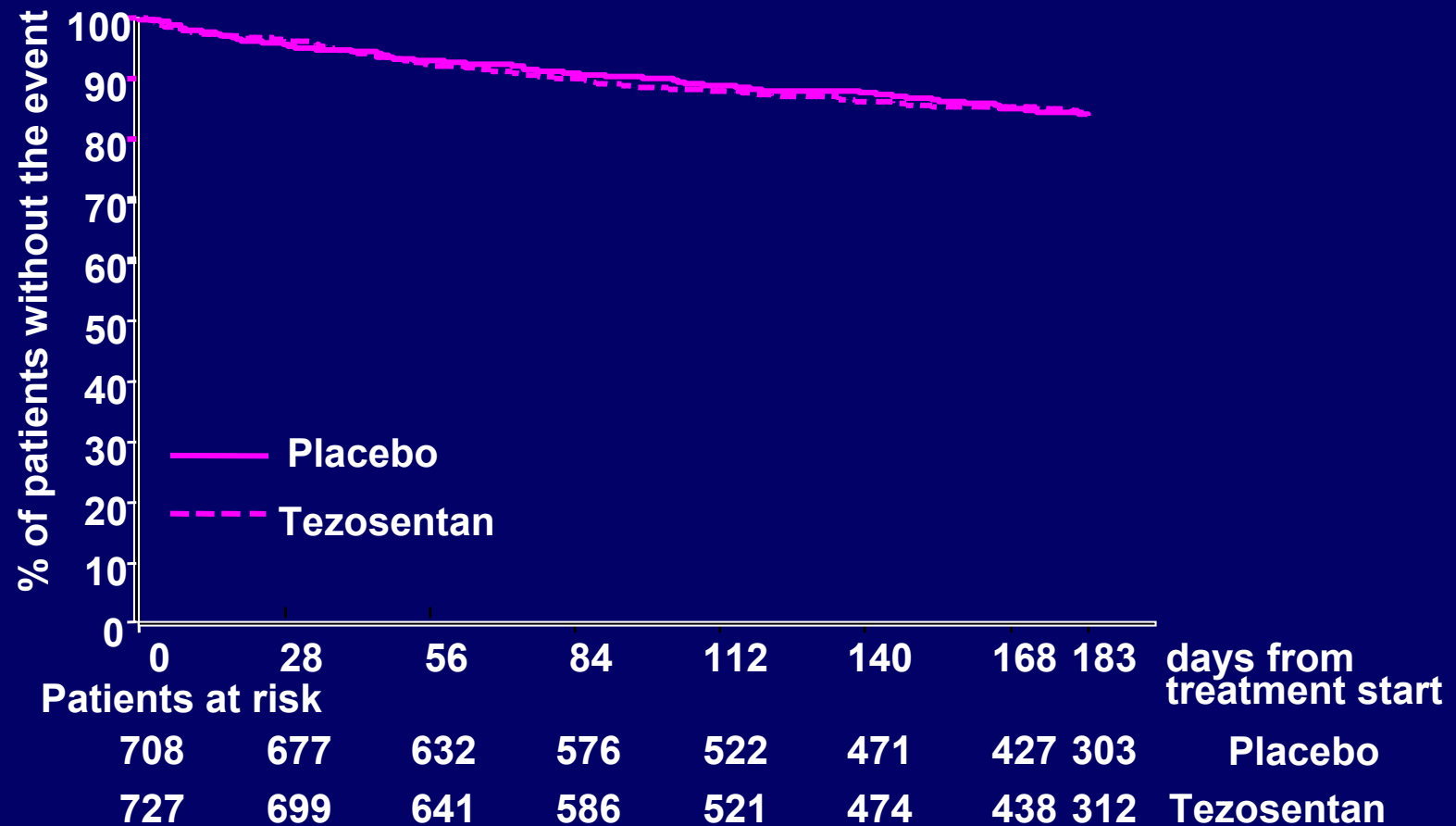
Survival Up to 6 months



Patients at risk	708	677	632	576	522	471	427	303	Placebo
	727	699	641	586	521	474	438	312	Tezosentan

McMurray & Teerlink, ACC 2005

Survival Up to 6 months



McMurray & Teerlink, ACC 2005

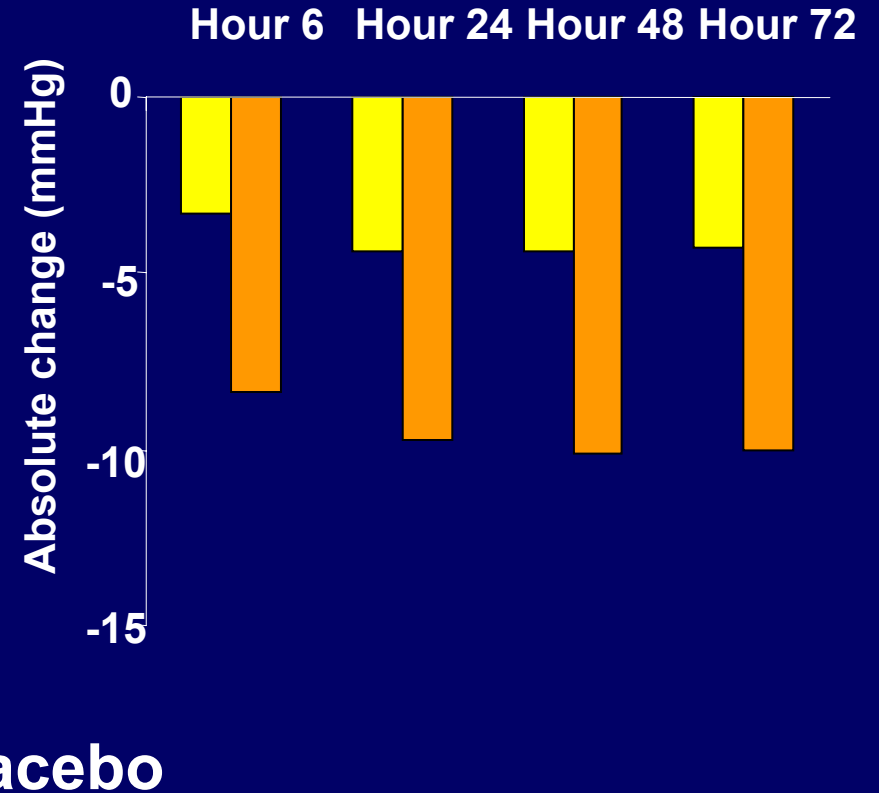
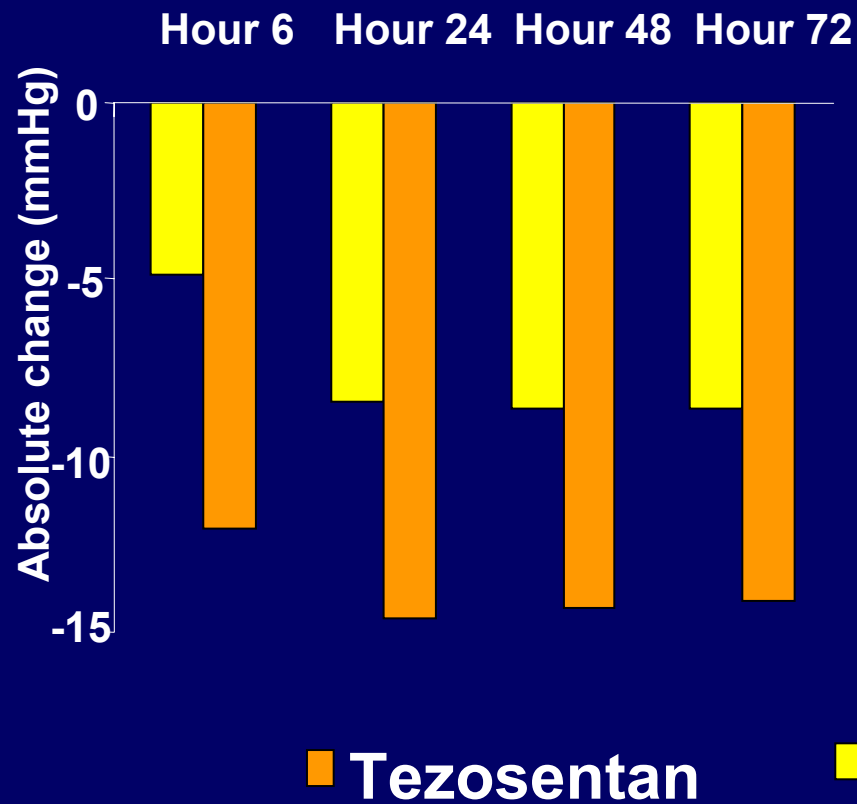
Explanations ?

- Excessive hypotension ?

Change From BL in Blood Pressures

Change from BL in SBP

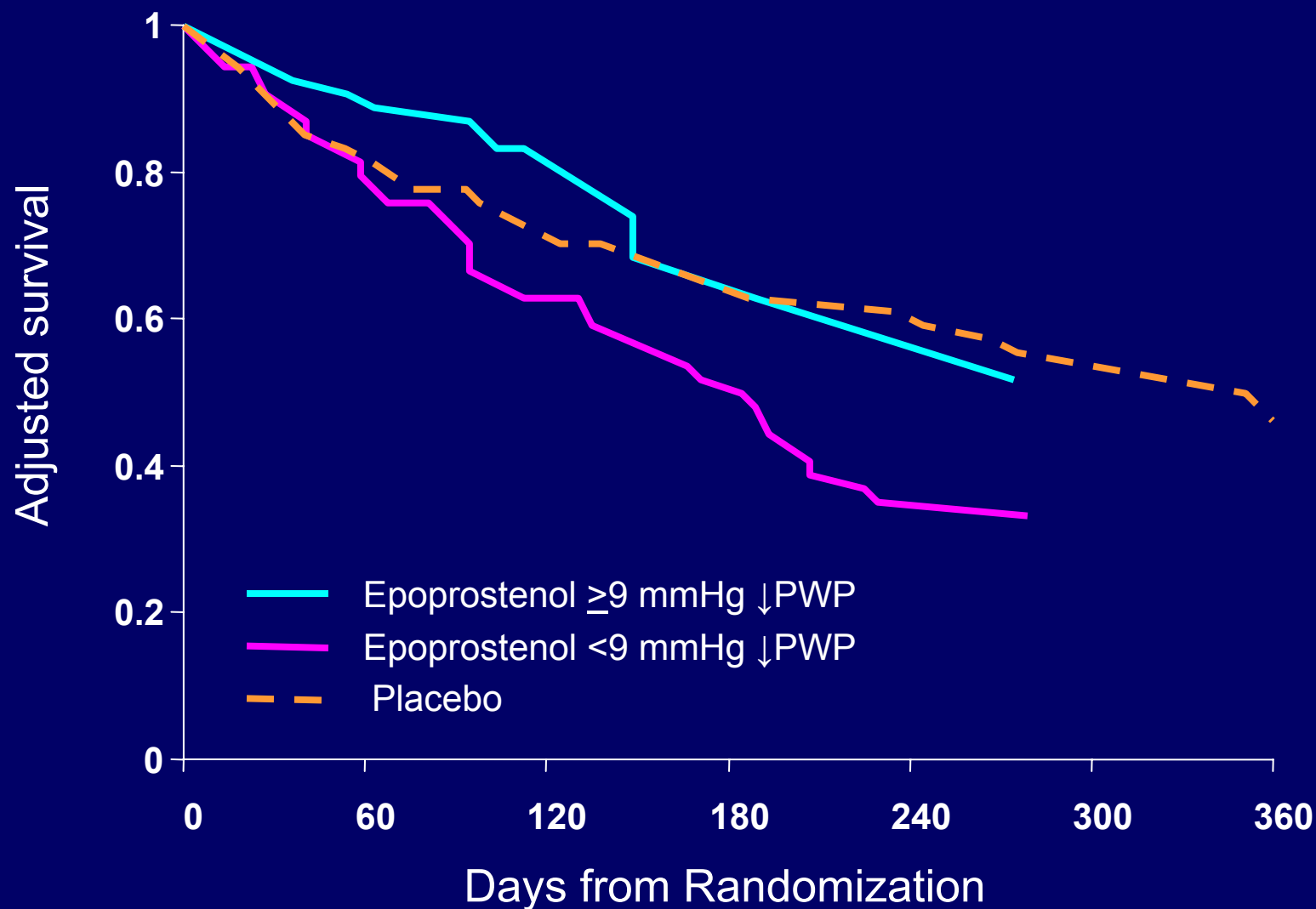
Change from BL in DBP



Explanations ?

- Excessive hypotension ?
- PAC effect ?
 - VMAC, RITZ-2...
- “Optimal effect” of diuretics and traditional vasodilators?
- Drug effect ?

Relationship Between Hemodynamic Changes and Survival in FIRST

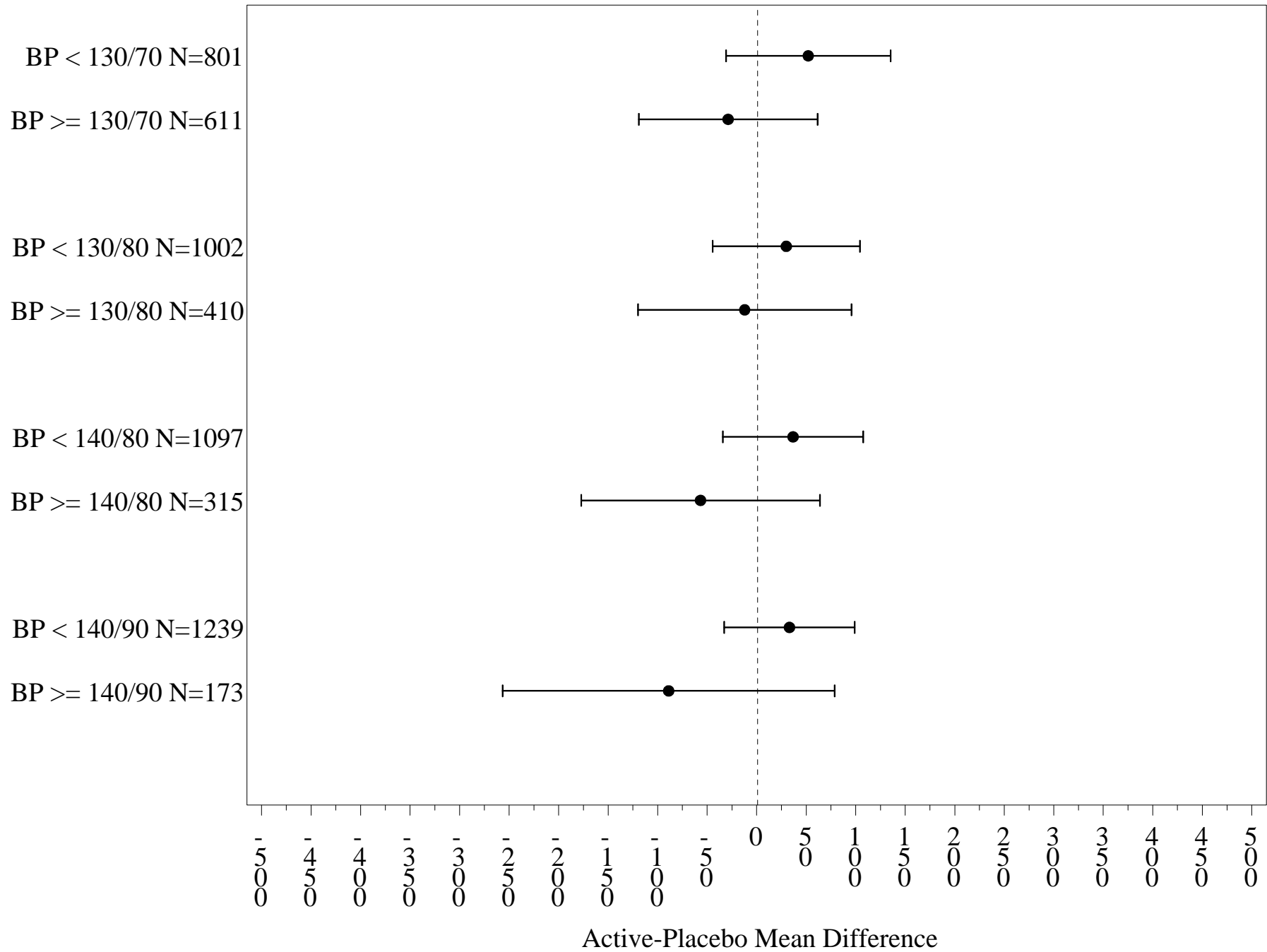


Shah et al. Am Heart J 2001; 141:908

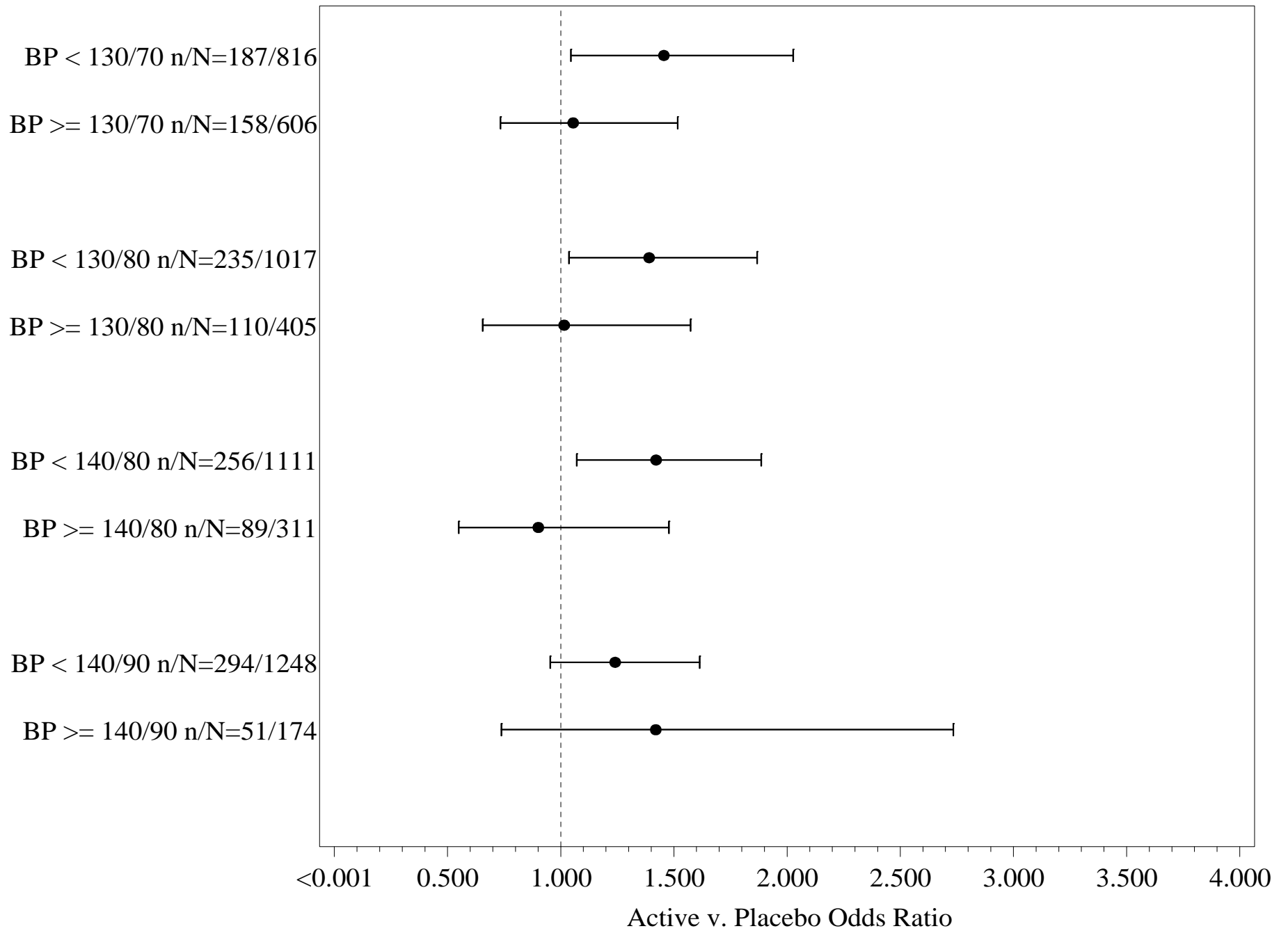
Explanations ?

- Excessive hypotension ?
- PAC effect ?
 - VMAC, RITZ-2...
- “Optimal effect” of diuretics and traditional vasodilators?
- Drug effect ?
 - “Excessive” \uparrow pulmonary blood flow ?
 - \uparrow pulmonary capillary permeability ?
 - ...

VAS AUC at 24 Hours



Creatinine Increase ≥ 0.3 mg/dL by 72 hours



Acute HF & Vasodilator treatment

- **Multiple pathophysiologic mechanisms**
- **Different clinical presentations**
- **Multiple effects of vasodilator therapy**

Acute HF & Vasodilator treatment

- Multiple physiopathologic mechanisms
- Different clinical presentations
- Multiple effects of vasodilator therapy
- We remain with
 - Nitrates
 - Nitroprusside in patients without active ischemia
 - Need of other agents or trials