Therapy for acute heart failure – time for change?!

Chaired by Professor Stefan Anker

Charité Medical School, Berlin, Germany
President of the ESC Heart Failure Association (HFA)

14th February 2013

A satellite symposium sponsored by Cardiorentis at *Cardiology Update 2013,* Davos, Switzerland

ESC Guidelines for the treatment of AHF

Professor Piotr Ponikowski

Head of Heart Diseases, Medical University, Wroclaw, Poland and past President of the HFA

Why to treat acute heart failure early: similarities to the acute coronary syndrome

Professor Alexandre Mebazaa

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Conflicts of interest

- Alere
- Bayer
- Cardiorentis
- Edwards
- Novartis
- Orion

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
Nigel Burrows
A. Mclean
F. Vilas-Boas
A. Mebazaa

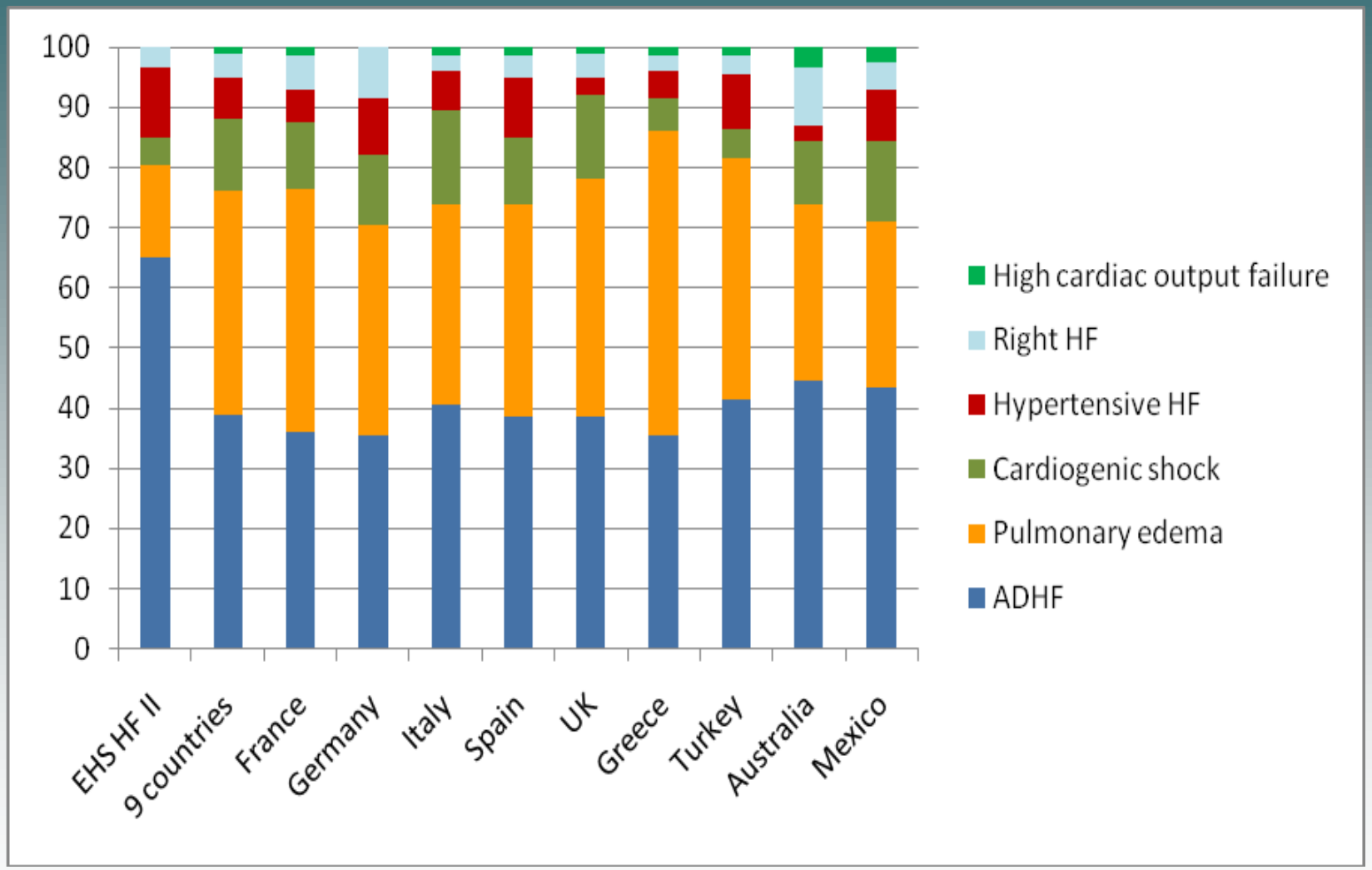
Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)

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

ORIGINAL

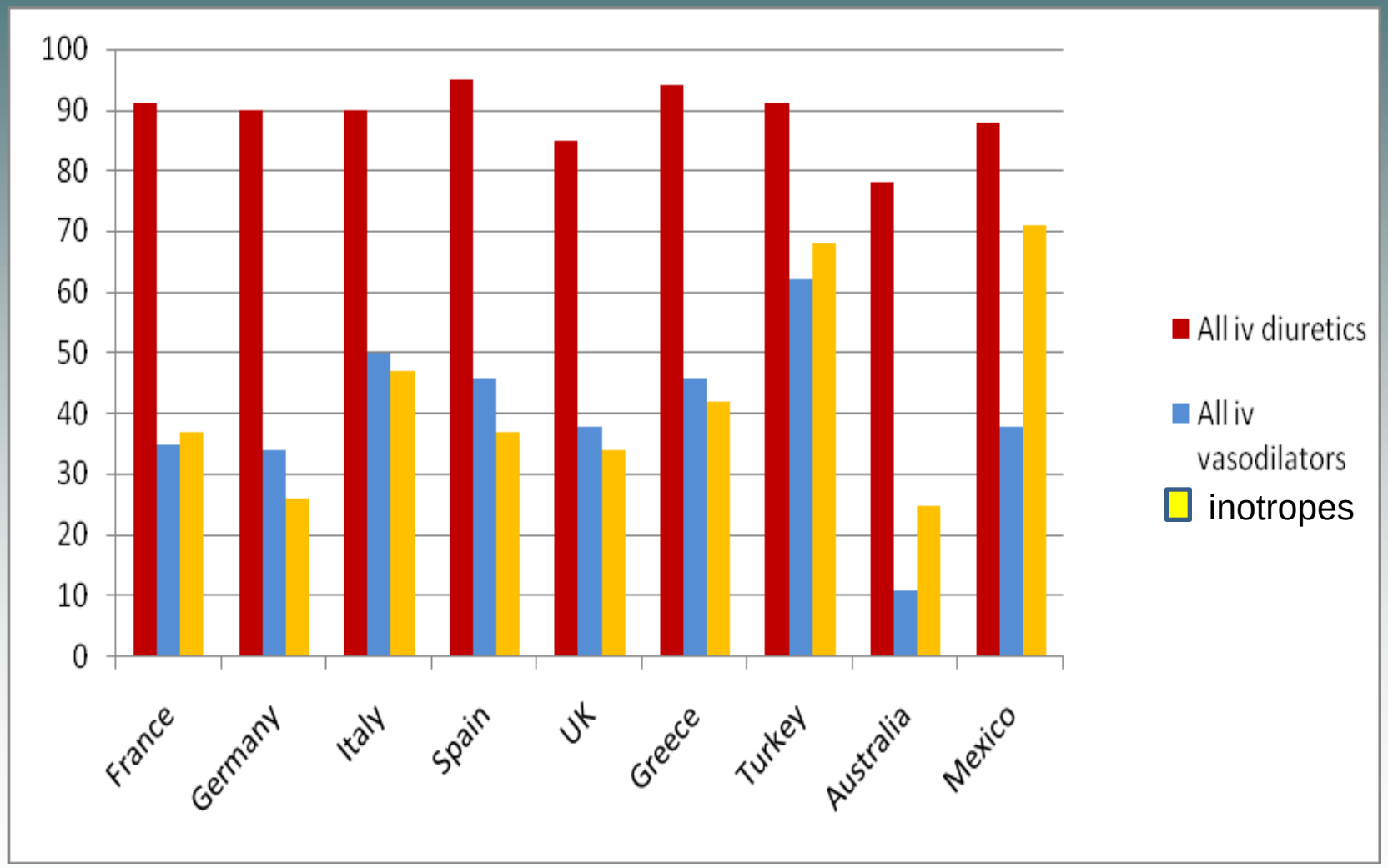
Alexandre Mebazaa
John Parissis
Raphael Porcher
Etienne Gayat
Maria Nikolaou
Fabio Vilas Boas
J. F. Delgado
Ferenc Follath

Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods



Mebazaa et al *Intensive Care Medicine* 2011

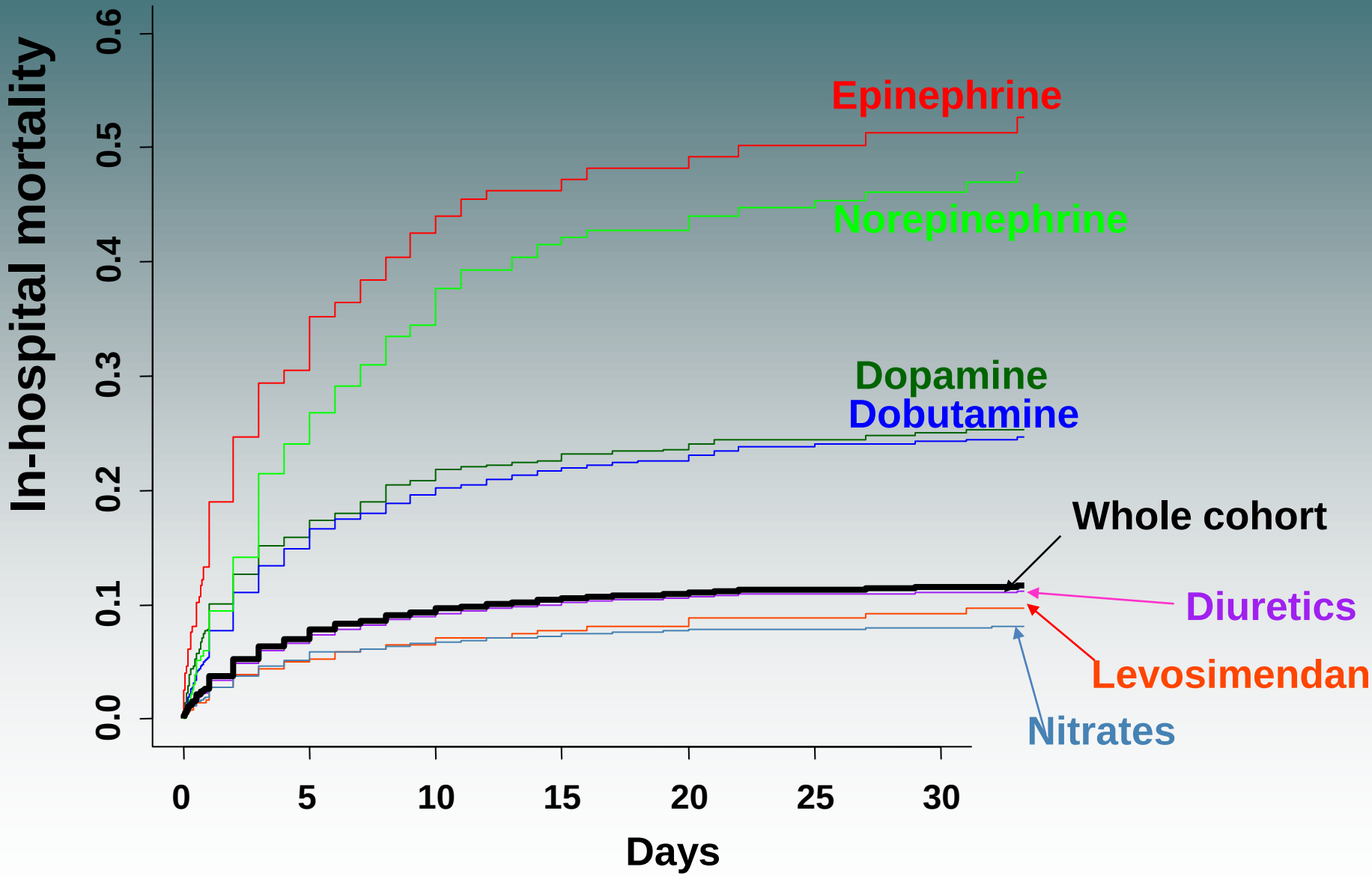
ALARM-HF: IV treatment at admission



Mebazaa et al *Intensive Care Medicine* 2011

ALARM results

- **IV diuretics and IV vasodilators were started at a median of 0.5 [0.0 – 1.0] hour and 0.5 [0.0 – 2] hour respectively after admission.**
- **IV vasodilators were quasi-exclusively nitrates: nitroglycerine in 76 % and isosorbite dinitrate 19 %**
- **In-hospital mortality:**
- **- *Before matching* 7.6 vs 14.2 % with and without vasoD**
- **- *After matching* 7.8 versus 11 % with and without vasoD**



Mebazaa et al *Intensive Care Medicine* 2011

Think outside the box

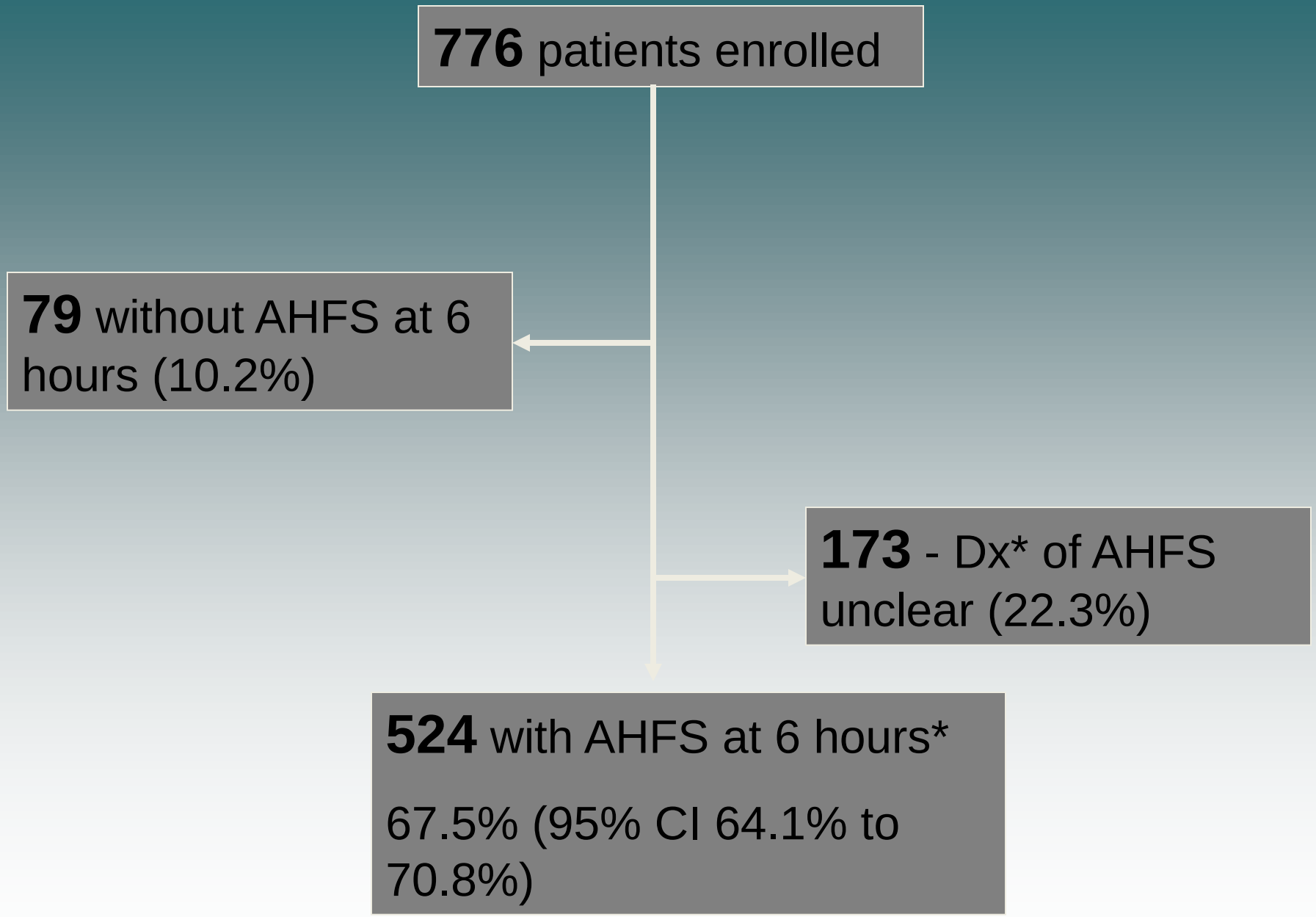
- **Use agents with vasodilator properties**

- **Treat at admission: the TTU concept**
  - ***Including patients >12-24 hours of admission was wrong!***

URGENT objectives

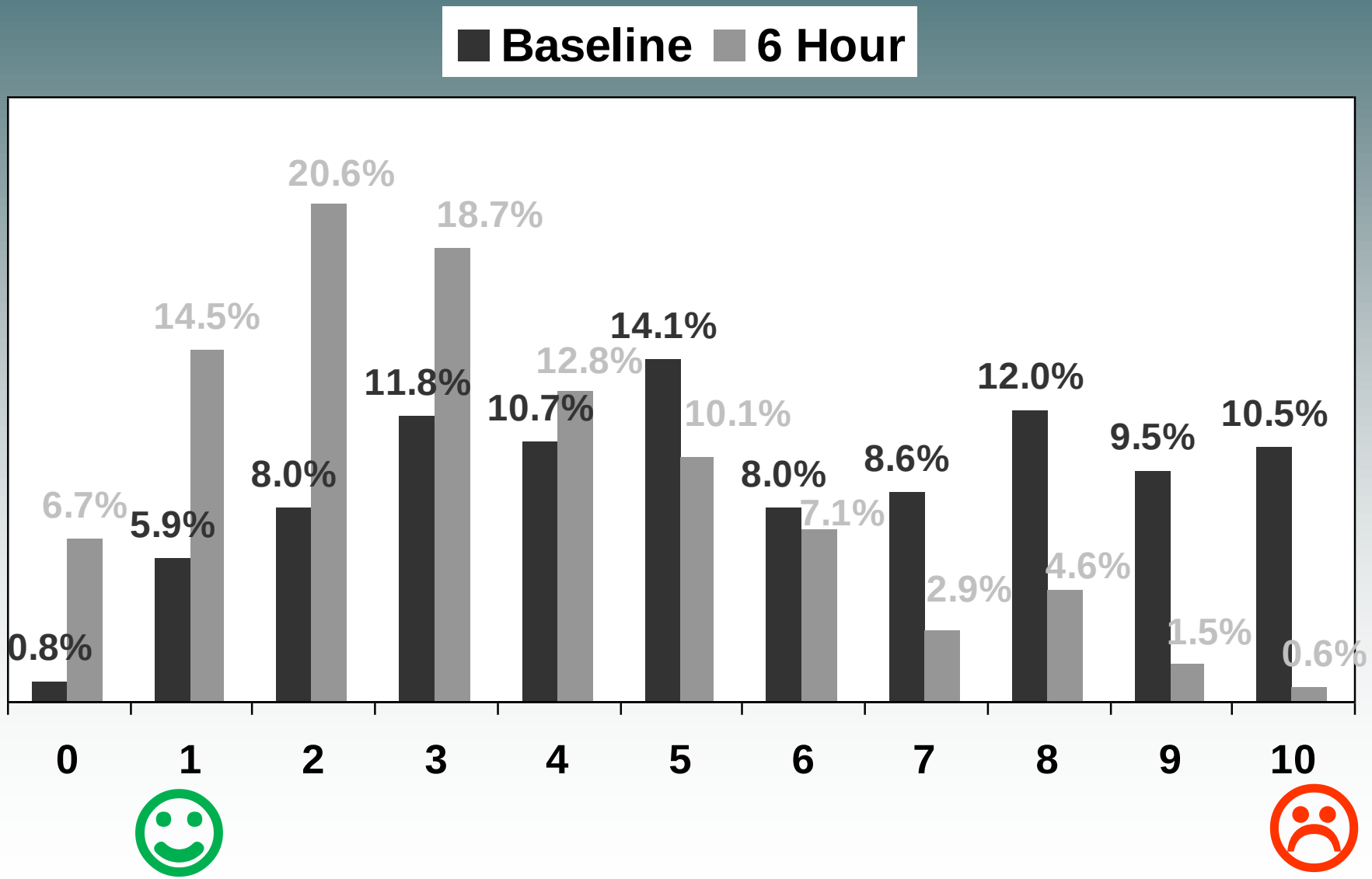
- **Define what is the optimal tool**
  - **To measure dyspnea at admission**

- **Assess how much dyspnea is altered by:**
  - **The ‘conventional’ treatment**
  - **in AHF patients**

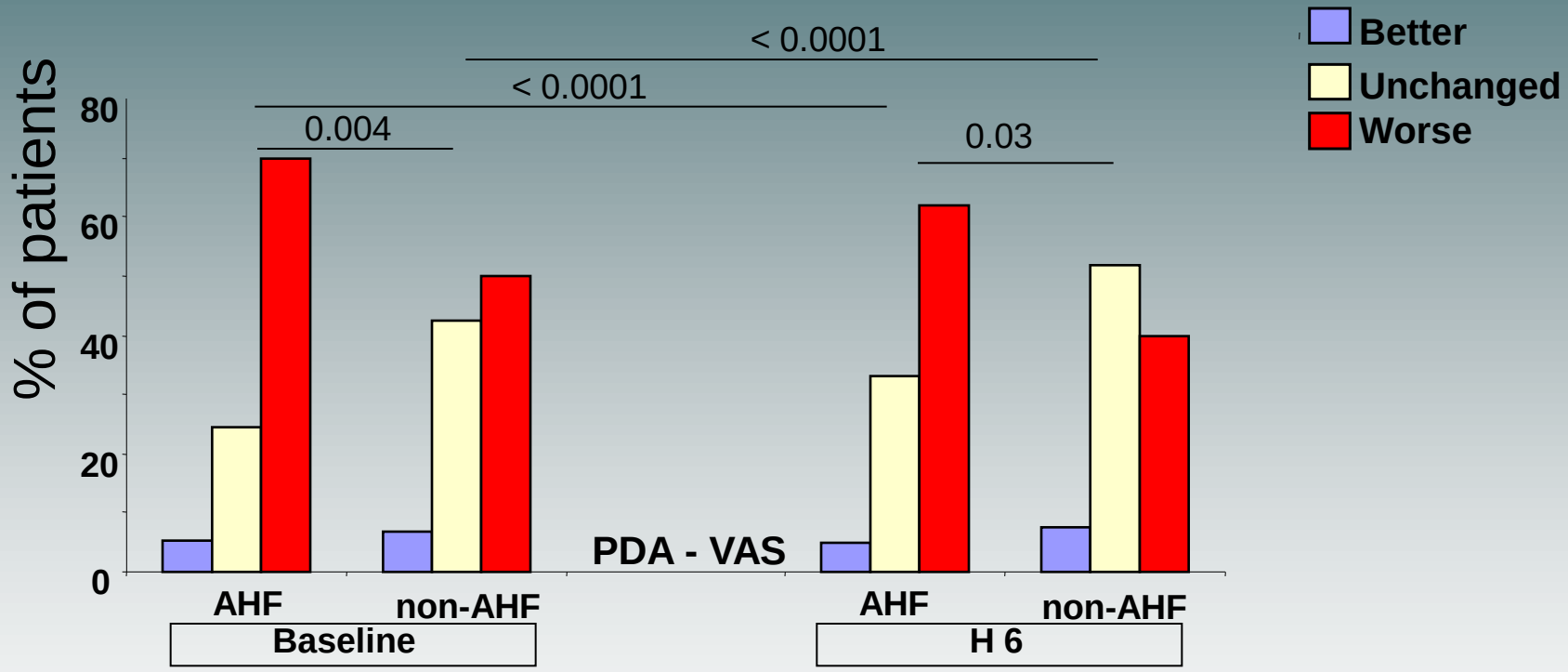


Mebazaa et al. *Eur Heart J* 2010

Acute dyspnea measured by Visual Analog Score



Effect of orthopnea on acute dyspnea



Mebazaa et al. *Eur Heart J* 2010

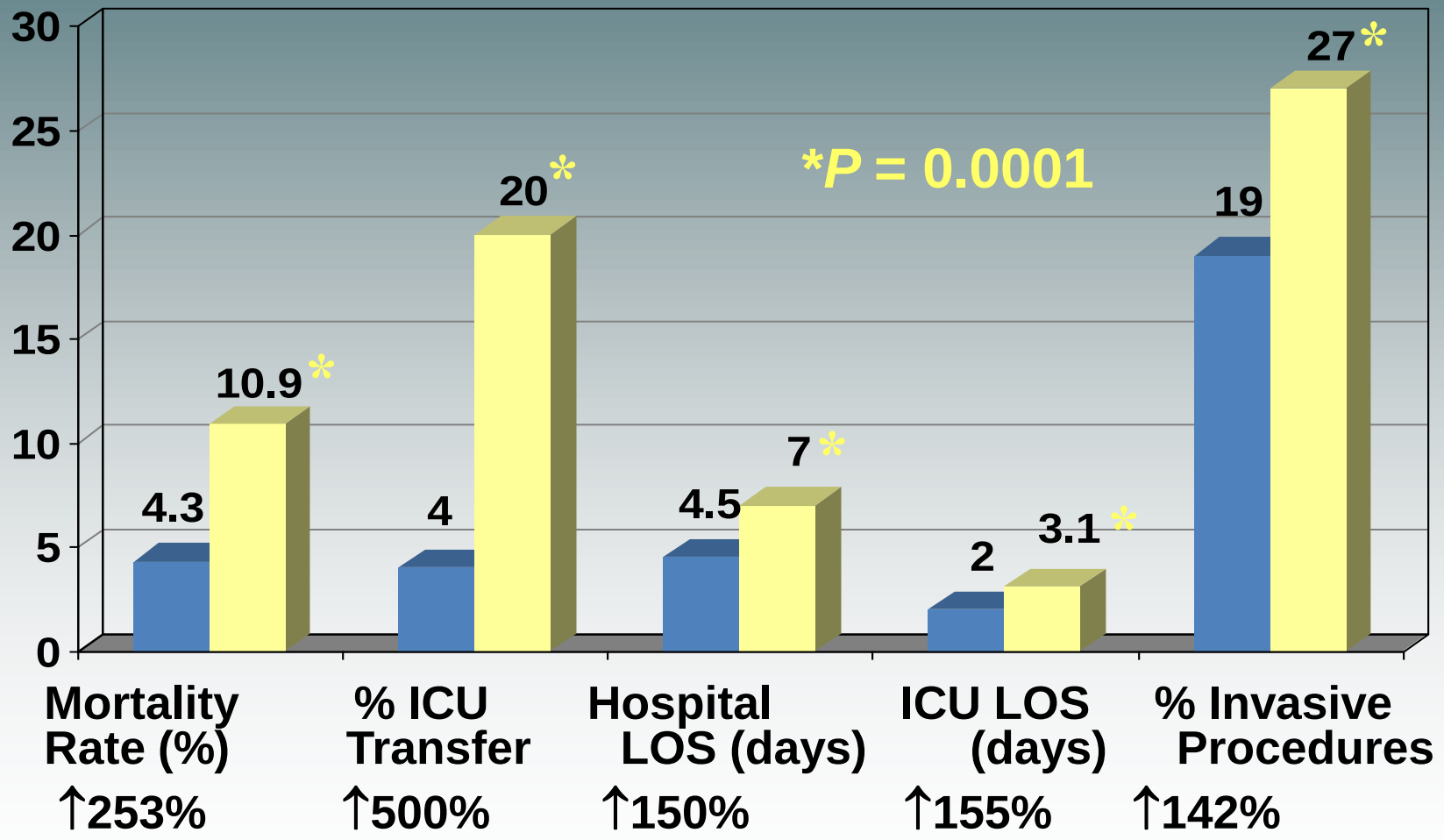
Treatment of acute heart failure

The earlier the better

46,599 ED ADHF

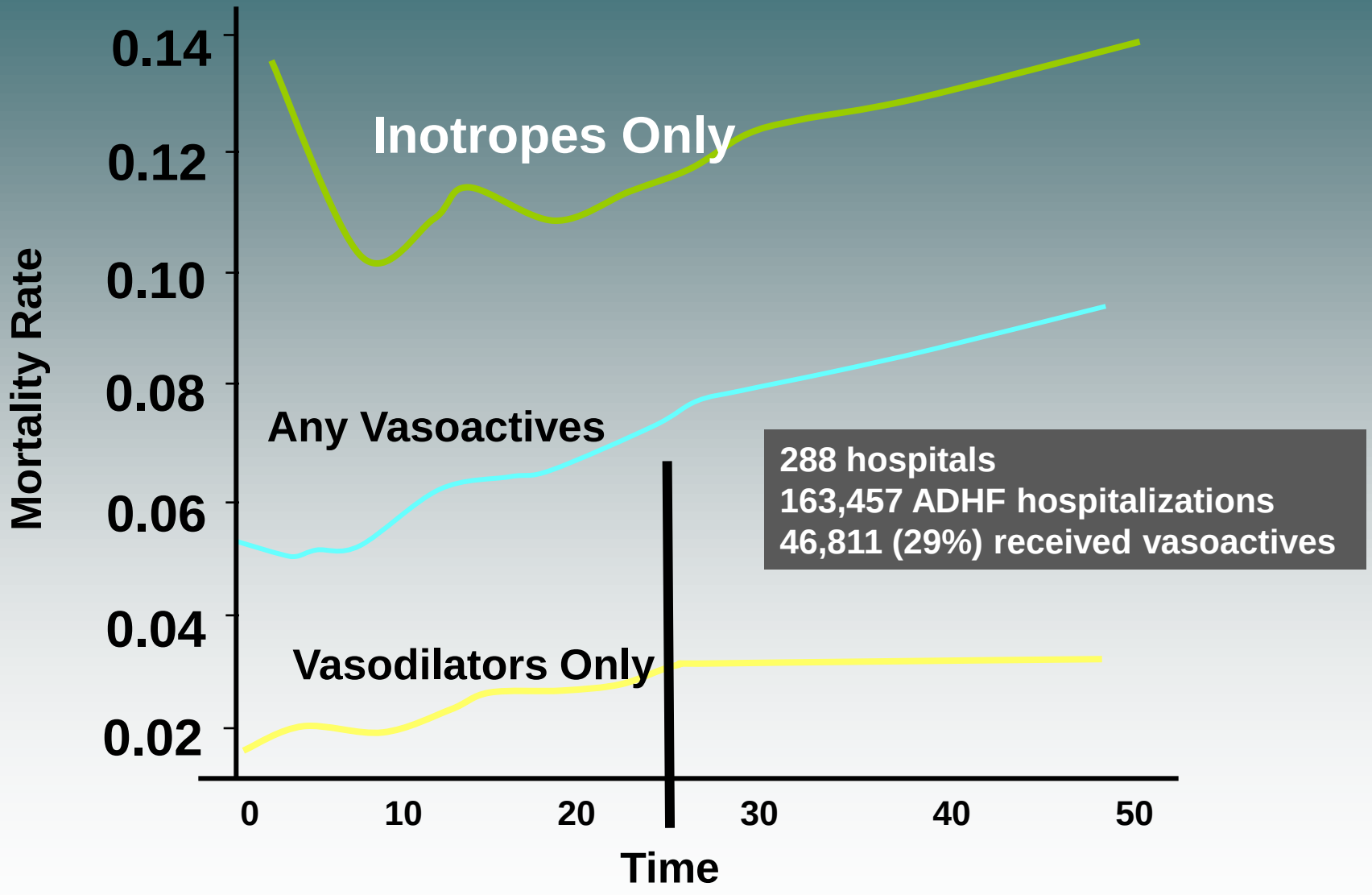
Vasoactive by location

- 4,096 in ED — 1.1 hr
- 3,499 inpatient — 22 hr



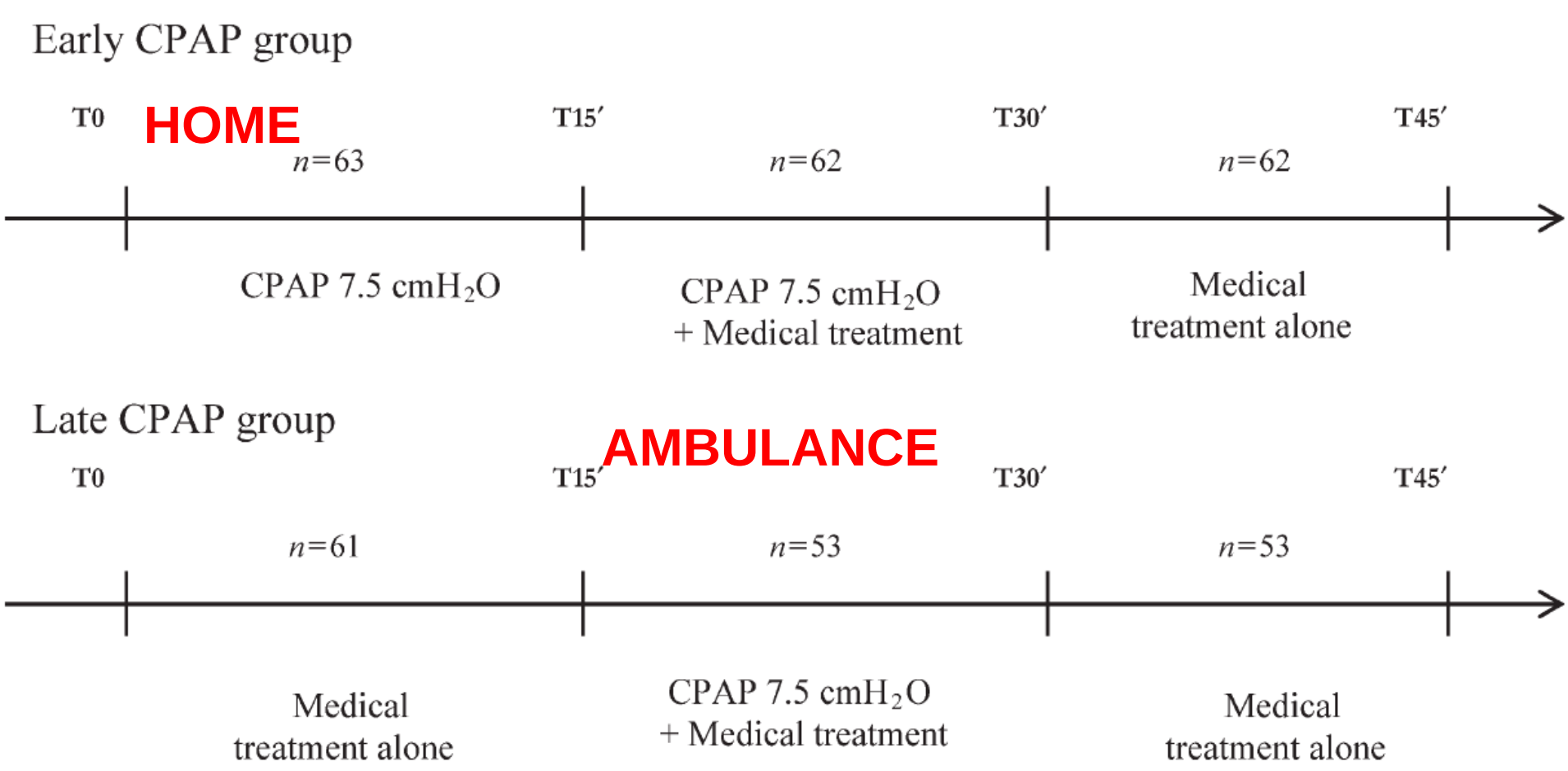
Peacock WF. *Ann Emerg Med*. 2003;42(4):S26.

Time to Vasoactives vs. Mortality



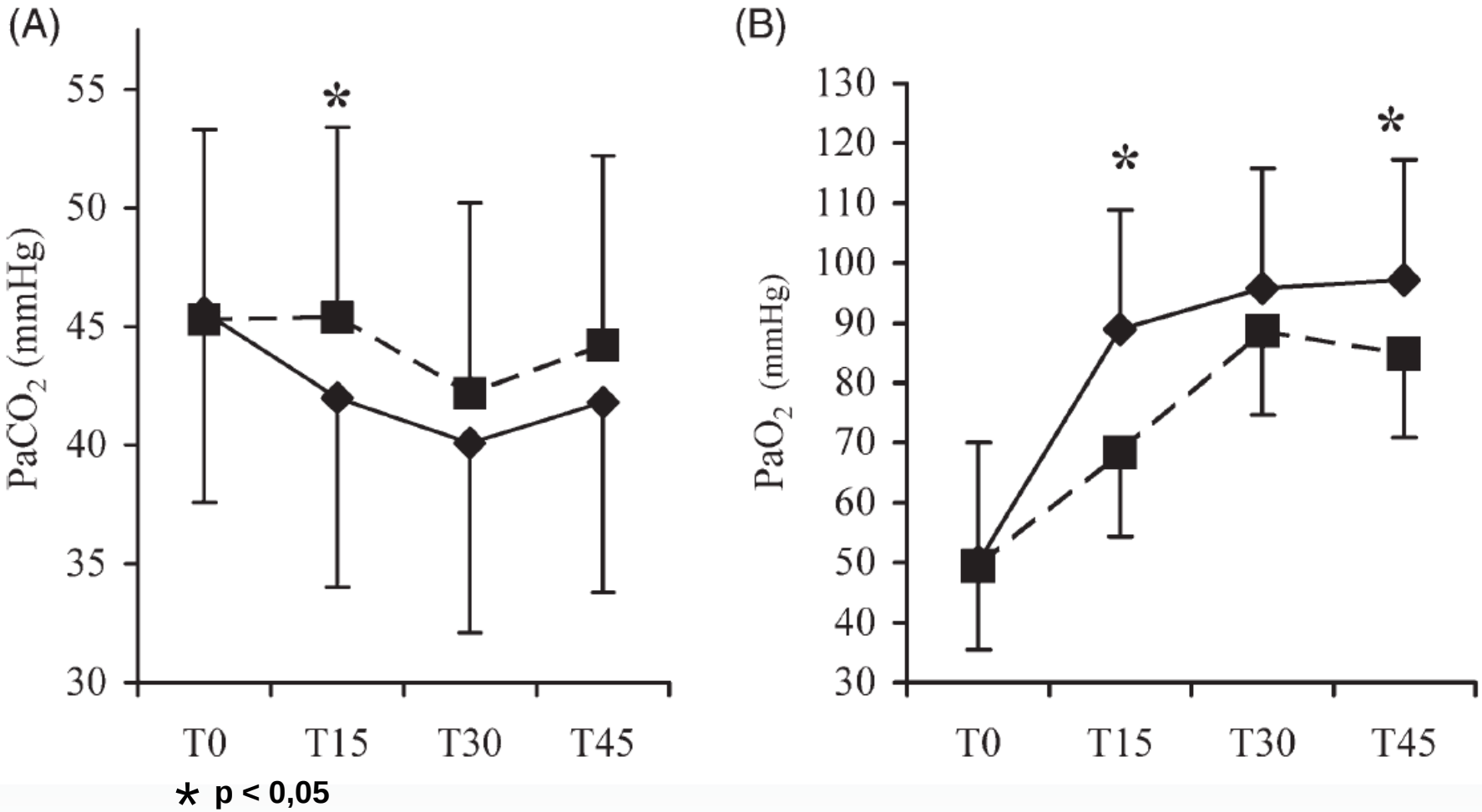
Peacock WF. *Ann Emerg Med*. 2003;42(4):S26.

Early CPAP vs Late CPAP



Plaisance P et al. *Eur. Heart J.* 2007; 28:2895

Early CPAP vs Late CPAP



Plaisance P et al. *Eur. Heart J.* 2007; 28:2895

Early CPAP vs Late CPAP

	Early CPAP	Late CPAP	p-value
Intubation Rate	6	16	0.01
Intubation between T0 and T15	1	8	
Need for Dobutamine	0	5	0.02
In-hospital Mortality	2	8	0.05

Plaisance P et al. *Eur. Heart J.* 2007; 28:2895

Treatment developments in AHF trials

The **TTU**: **T**ime **T**o **U**laritide should be **3 to 6 hours !**

We need to involve ED doctors in AHF trials **!**

Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes

Alexandre Mebazaa, MD, PhD; Mihai Gheorghiade, MD, FACC; Ileana L. Piña, MD, FACC; Veli-Pekka Harjola, MD; Steven M. Hollenberg, MD; Ferenc Follath, MD; Andrew Rhodes, MD; Patrick Plaisance, MD; Edmond Roland, MD; Markku Nieminen, MD; Michel Komajda, MD; Alexander Parkhomenko, MD; Josep Masip, MD; Faiez Zannad, MD, PhD; Gerasimos Filippatos, MD

Mebazaa et al. *Critical Care Medicine*, 2008, Suppl 36:129-139

Initial 90-120 minutes

Next 6 – 12 hours

Management at admission

- Non-invasive monitoring
- (SaO_2, BP, temperature)
- Lab tests
- BNP or NT-pro BNP

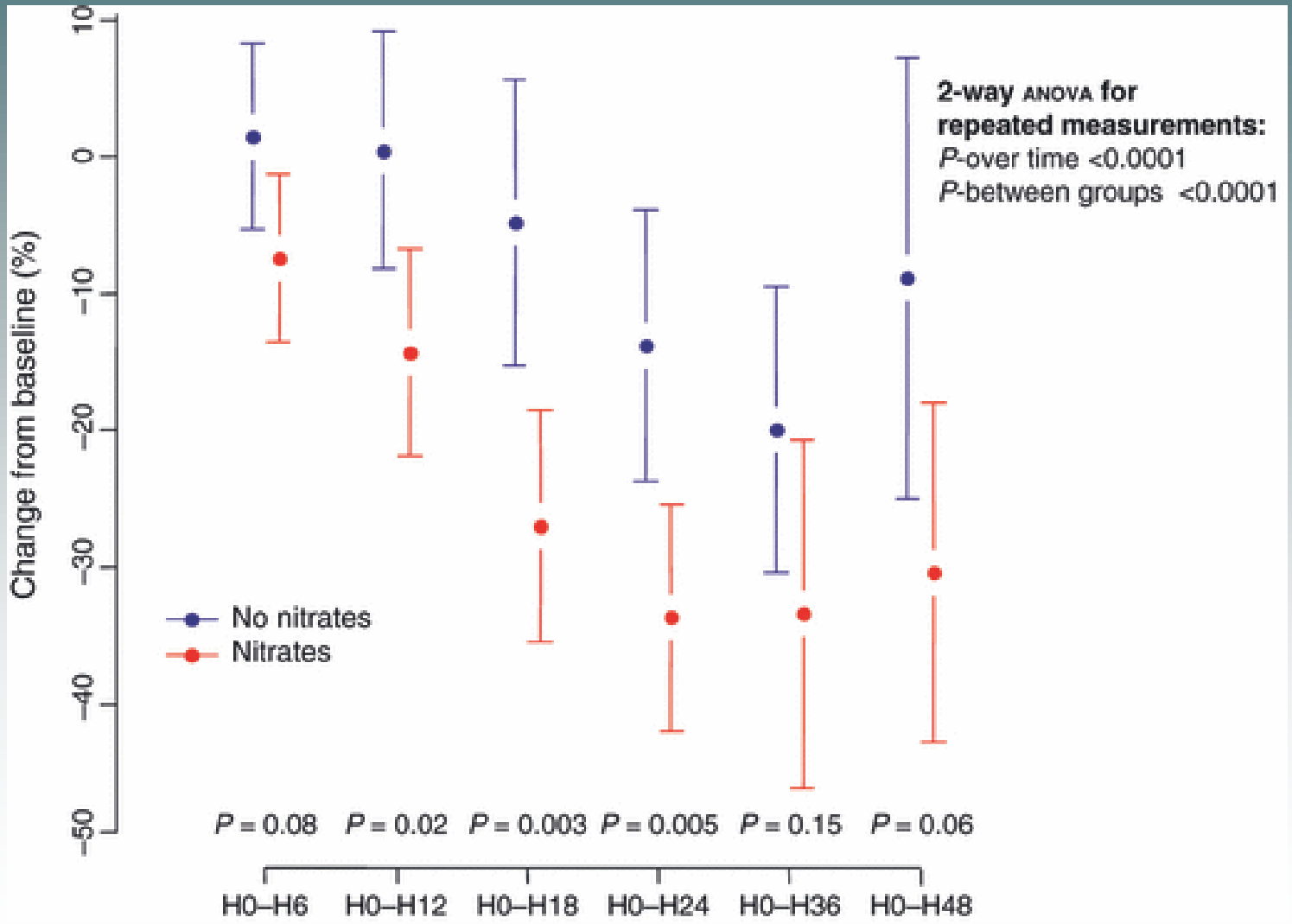
Tailored therapy

- **CS1 (SBP > 140 mmHg):** NIV and Nitrates; diuretics are rarely indicated unless volume overload
- **CS2 (SBP 100-140 mmHg):** NIV and Nitrates; diuretics if systemic chronic fluid retention
- **CS3 (SBP < 100 mmHg):** Volume loading with initial fluid challenge if no overt fluid retention; inotrope; PAC if no improvement; if BP fails to improve above 100 mmHg and hypoperfusion persits, then consider vasoconstrictors
- **CS4 (ACS):** NIV; Nitrates; Cardiac catheterization lab, follow guideline recommended management for ACS (aspirin, heparin, reperfusion therapy); IABP
- **CS5 (RVF):** Avoid volume loading; diuretics if SBP >90 mmHg and systemic chronic fluid retention; inotropes if SBP <90 mmHg; If SBP fails to improve above 100 mmHg, then begin vasoconstrictors

•Transfer to tertiary care center

Mebazaa et al. *Critical Care Medicine*, 2008, Suppl 36:129-139

Change of BNP from baseline during high-dose nitrate strategy (nitrates) vs standard therapy (no nitrates)

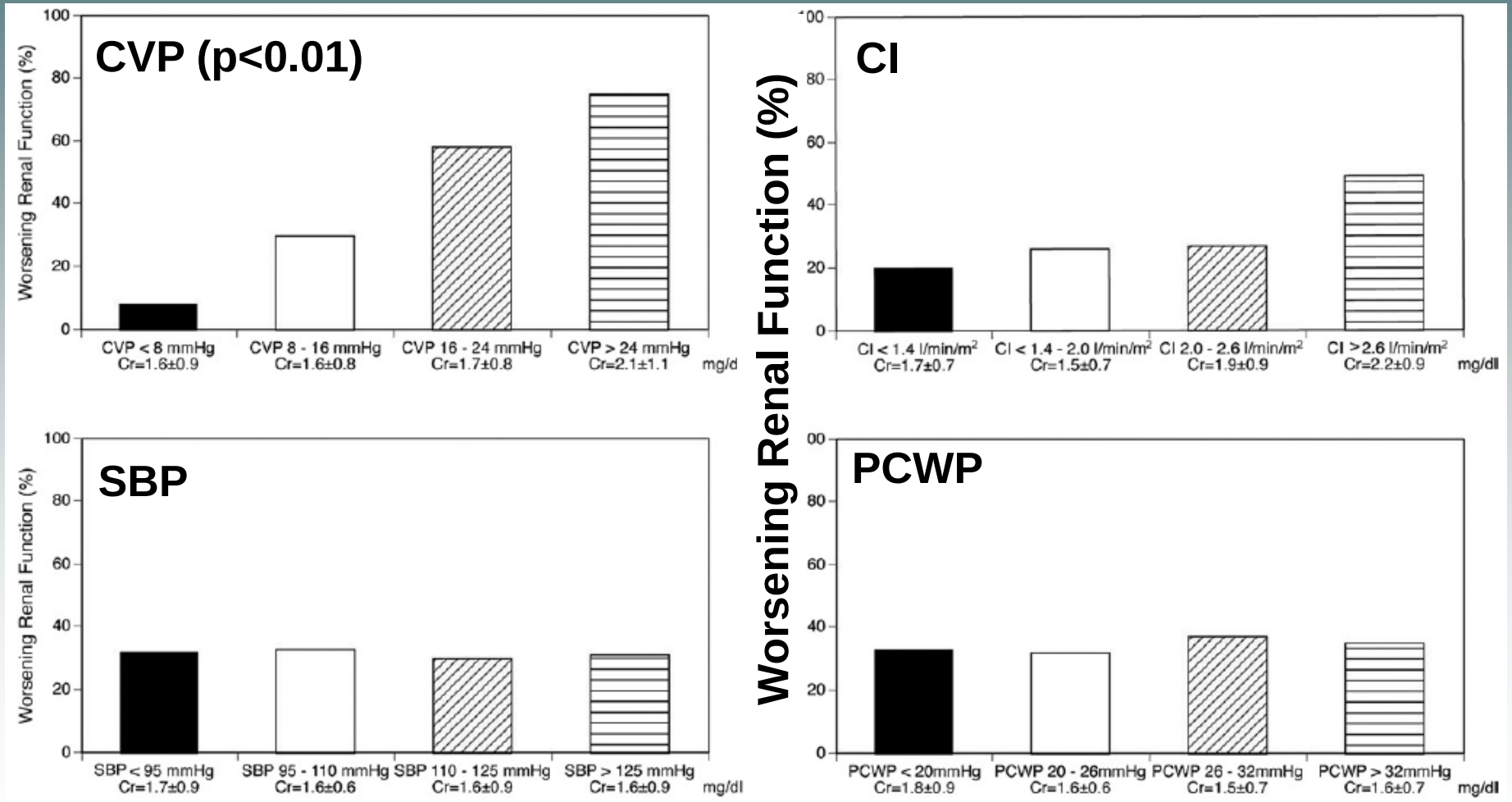


Breidthardt et al *J of Internal Medicine*, 2010: 267:322-330

Why should we start AHF treatment as early as possible?

- Very early **prevention of worsening organ damage**
  - Heart function (troponin, ischemia)
  - Other organ's function
- Restoring organ damage ?

Effects of CVP, CI, SBP and PcwP on worsening renal functionIn Acute Heart Failure patients



European Heart Journal Advance Access published October 22, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs332

CLINICAL RESEARCH

Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure

Maria Nikolaou[1,2,3], John Parissis[3], M. Birhan Yilmaz[1,15], Marie-France Seronde[1,2,4], Matti Kivikko[5,6], Said Laribi[1,2,7], Catherine Paugam-Burtz[2,8], Danlin Cai[9], Pasi Pohjanjousi[6], Pierre-François Laterre[10], Nicolas Deye[1,11], Pentti Poder[12], Alain Cohen Solal[1,2,13], and Alexandre Mebazaa[1,2,14]*

[1]UMRS 942 Inserm, F-75010 Paris, France; [2]Univ Paris Diderot, Sorbonne Paris Cité, F-75205 Paris, France; [3]Heart Failure Unit, 2nd Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; [4]Department of Cardiology, University Hospital Jean-Minjoz, Besançon, France; [5]Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland; [6]Orion Pharma, Kuopio, Finland; [7]AP-HP, Department of Emergency Medicine, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [8]AP-HP, Department of Anesthesiology and Critical Medicine, Hôpital Beaujon, F-92110 Clichy, France; [9]Abbott Laboratories, Abbott Park, IL, USA; [10]Department of Critical Care Medicine, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; [11]AP-HP, Medical ICU, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [12]First Department of Cardiology, North Estonia Medical Center, 12419 Tallinn, Estonia; [13]AP-HP, Department of Cardiology, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [14]AP-HP, Department of Anesthesiology and Critical Care Medicine, Hôpital Lariboisière, 2 Rue A Paré F-75475 Paris Cedex 10, France; and [15]Cumhuriyet University School of Medicine, Department of Cardiology, Sivas, Turkey

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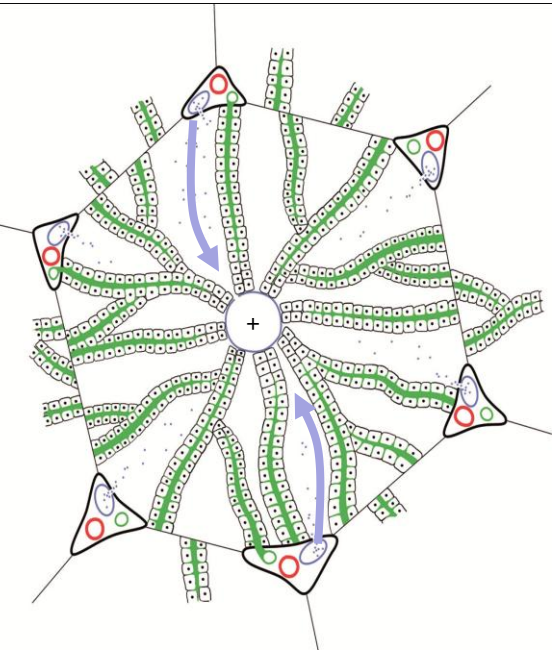
Normal liver lobule

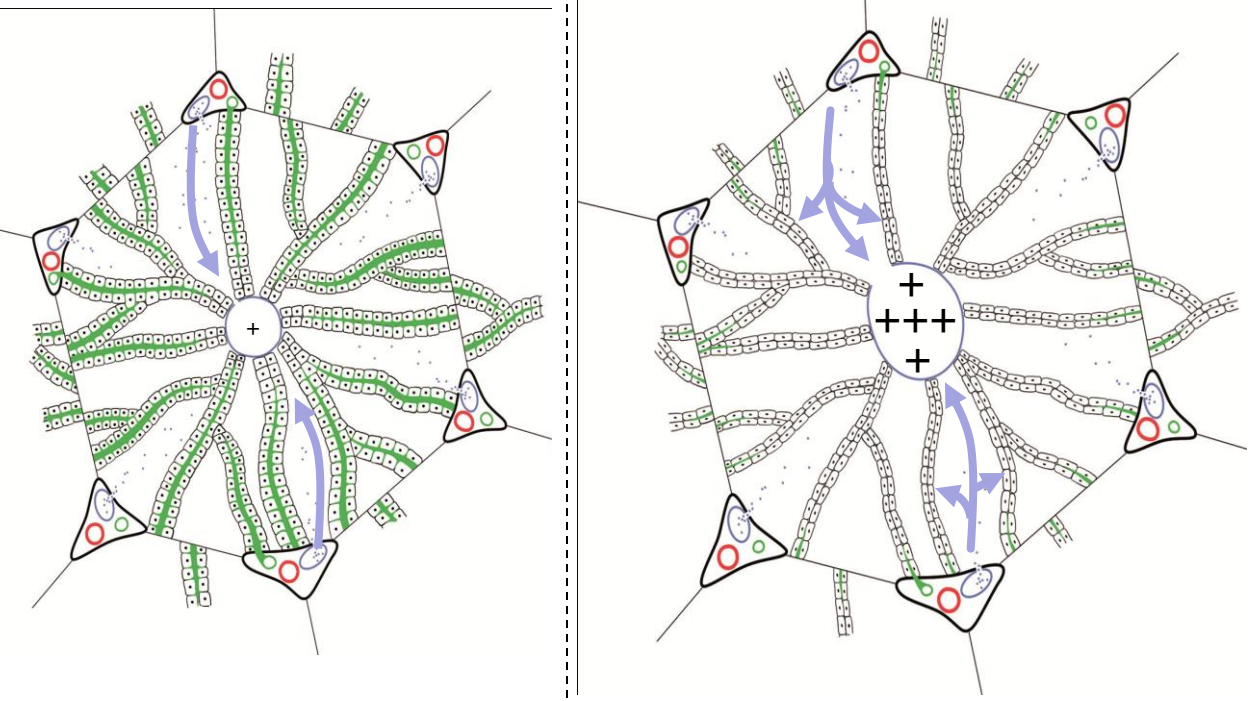


Nikolaou et al *Eur Heart Journal* 2013 (in press)

AHF-induced liver congestion
(increased BNP)

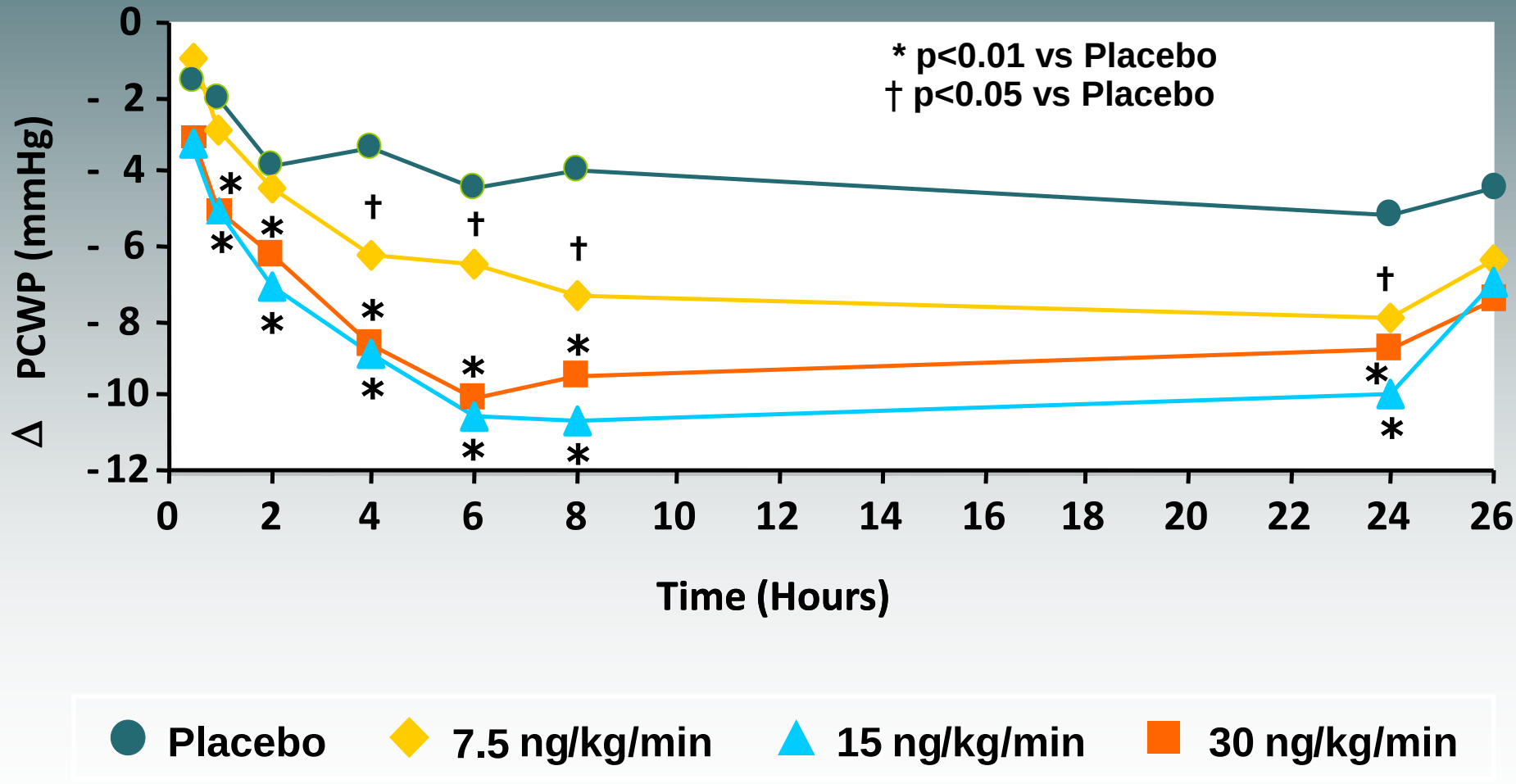
Normal
liver lobule

bile duct
compression
(increased AP)

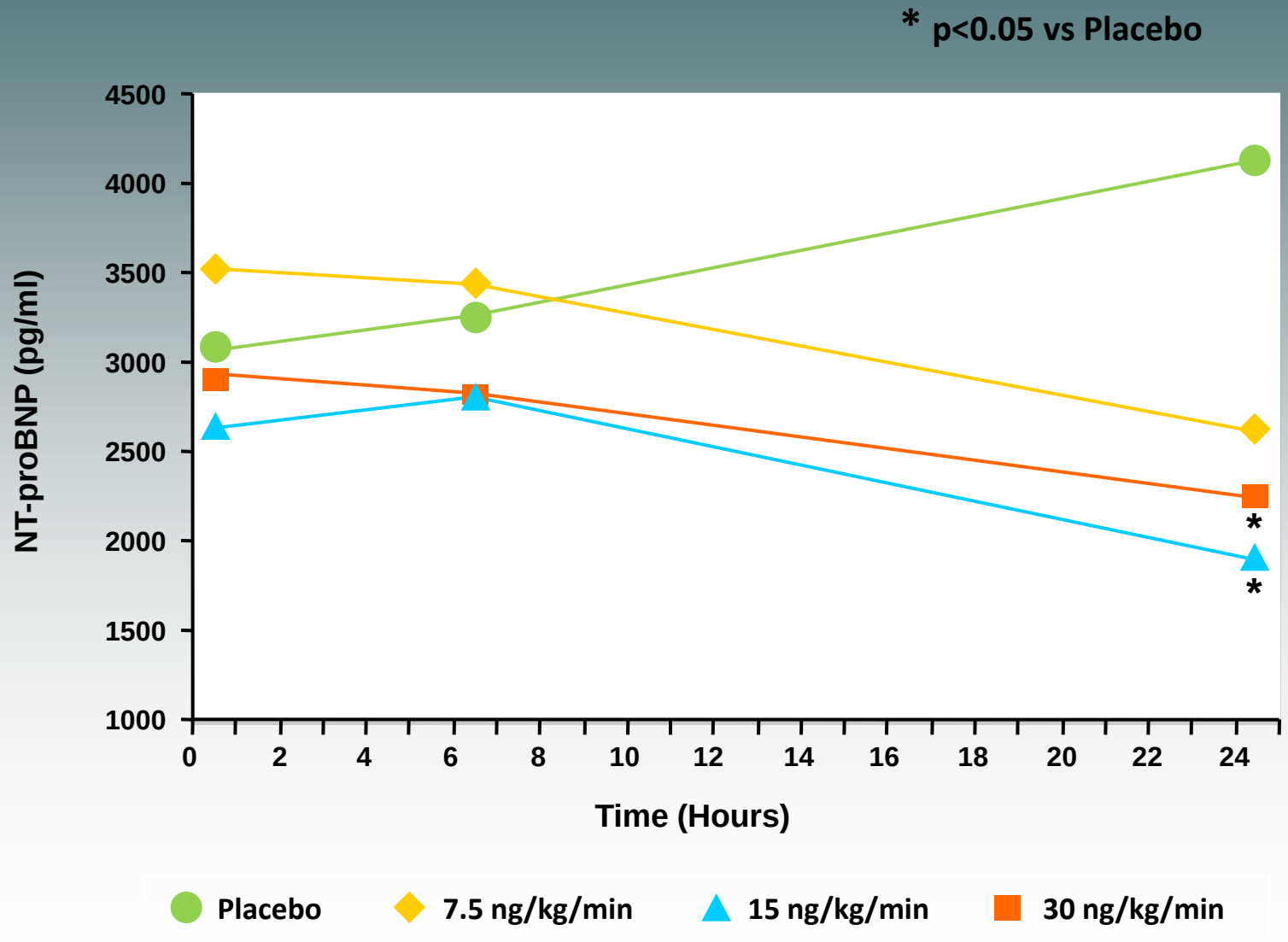


Nikolaou et al *Eur Heart Journal* 2013 (in press)

Ularitide Reduces PCWP



Ularitide Reduces NT-pro BNP Levels



AHF should be treated with the same delay as ACS

- Better symptom relieve
- Prevent worsening organ’s function
- Improve AHF survival rate

The TRUE-AHF programme: ularitide in patients with AHF

Pr Gerasimos Filippatos

Chief, Heart Failure Unit, Department of Cardiology, Athens University Hospital, Greece, President-elect of the ESC Heart Failure Association (HFA)

The facts…

- **25+ million people** affected worldwide[1,2]

- Heart failure affects:
  - **6-10% of elderly people** [3]
  - **4.3 million hospitalisations** in the **USA**[4]
  - **3.5 million hospitalisations** in **Europe**[4]

- Heart failure hospitalisations have **tripled over last three decades**[5]
- **2% of health care expenditure** in European countries[1]
  - **~75% relating to inpatient care**[1]

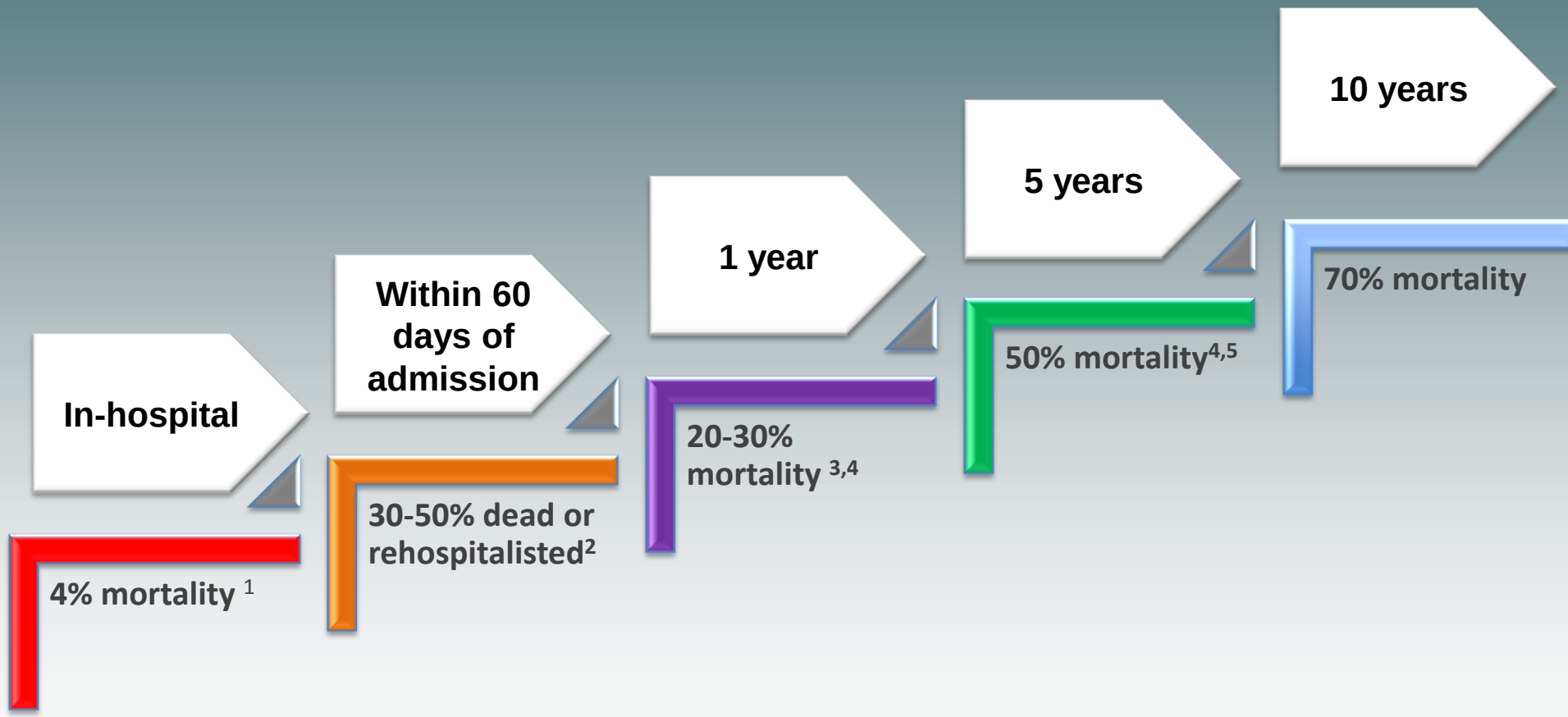
1. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S.,1979 to 2004. J Am Coll Cardiol 2008;52(6):428–34.
2. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J 1998; 19 Suppl P:P9.
3. WRITING GROUP MEMBERS, Lloyd-Jones D, Adams RJ, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010; 121:e46.
4. Decision Base 2009; Acute Heart Failure, p 50, Decision Resources, 260 Charles Street, Waltham, Massachusetts, USA
5. Eur Heart J Supplements 2002; 4 (Suppl D):D50-D58 - http://eurheartjsupp.oxfordjournals.org/content/4/suppl_D/D50.full.pdf
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2801958/

Management of heart failure

- Despite advances in therapy, QoL is very poor and the outcome is ominous.
- **~45% of patients** hospitalised with AHF will be **rehospitalised at least once** (and 15% twice) within twelve months[1]
- Prognosis substantially **worse than with most cancers** and experience a mortality risk **5 times greater** than that of **heart attack patients**[2]

1. ESC guidelines - http://www.escardio.org/guidelines-surveys/esc-guidelines/Documents/AHF/guidelines-AHF-ES-2005.pdf
2.Eur Heart J Supplements 2002; 4 (Suppl D):D50-D58 - http://eurheartjsupp.oxfordjournals.org/content/4/suppl_D/D50.full.pdf

Impact of acute heart failure

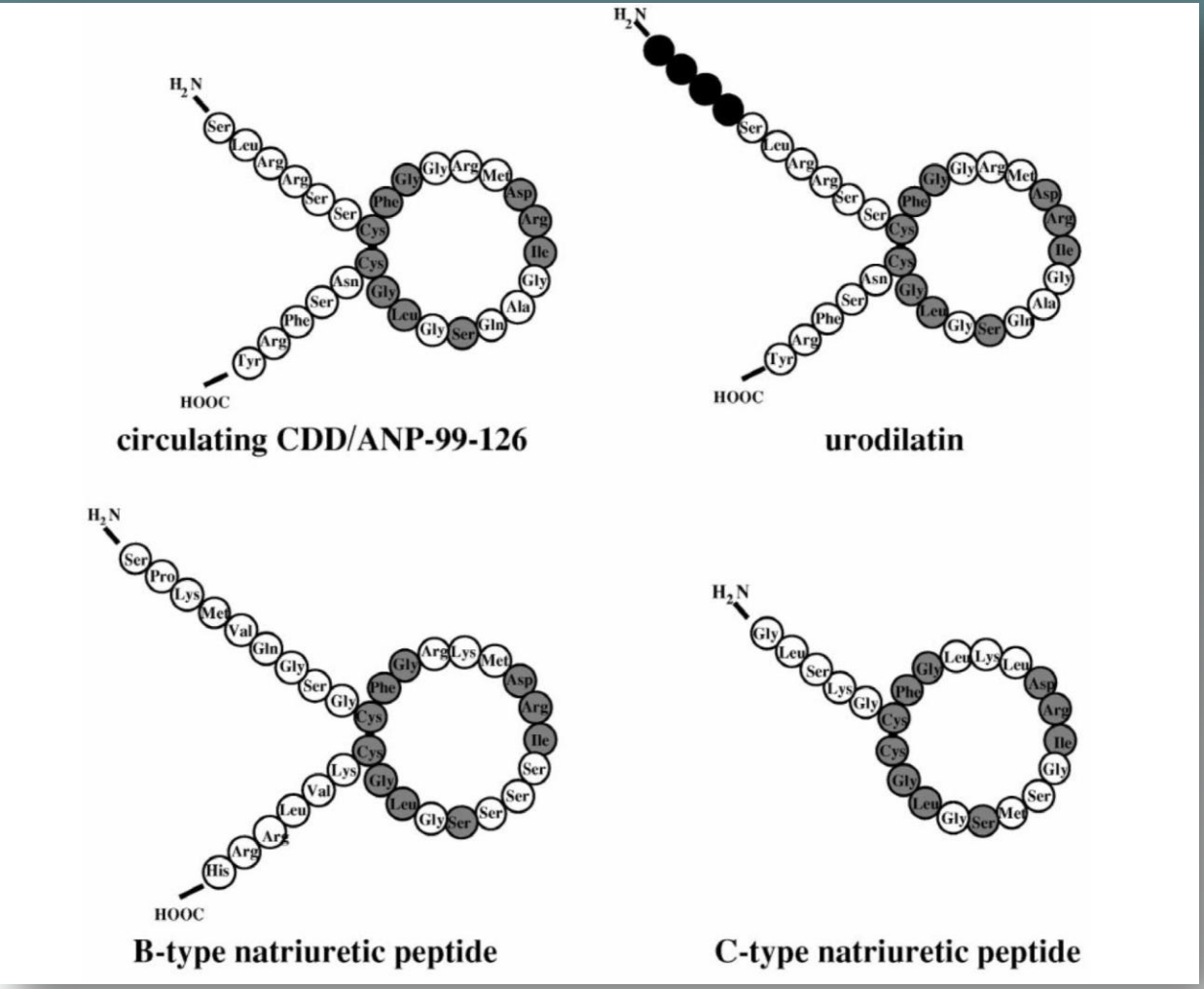


1. Adamsa et al. Am Heart J 2008;149 209-16
2. Dickenstein et al/ Eur Heart J 2008; 29:2388-442
3. Chen et al. JAMA 2011;306:1669-78
4. Loehr et al. Am J Cardiol 2008; 101: 1016-22
5. Roger et al. Circulation 2012;125:e2-220

Based on previous study results…

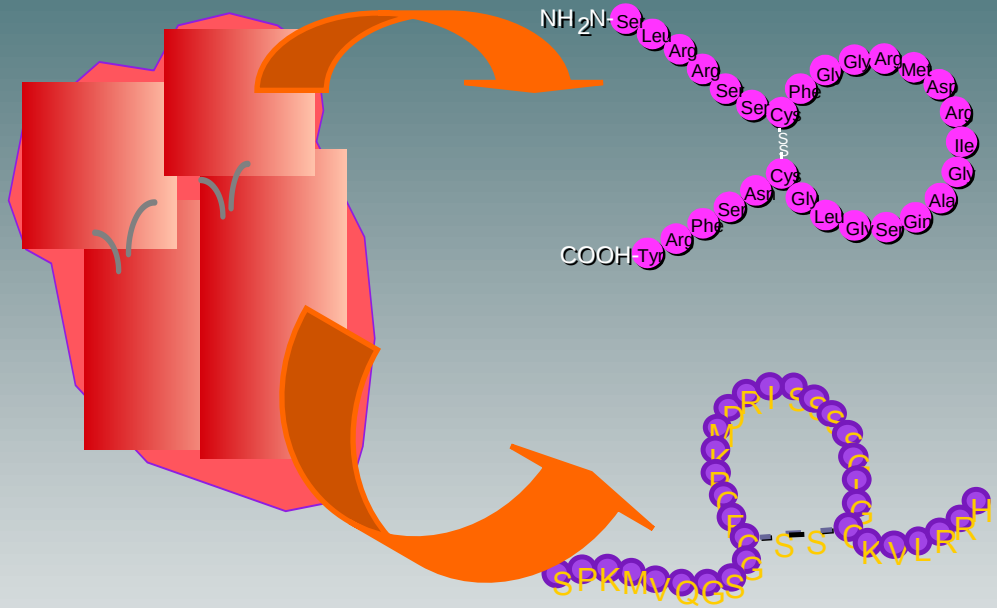
Patients suffering with acute heart failure should be treated as early as possible

All Natriuretic Peptides Are Not Created Equal

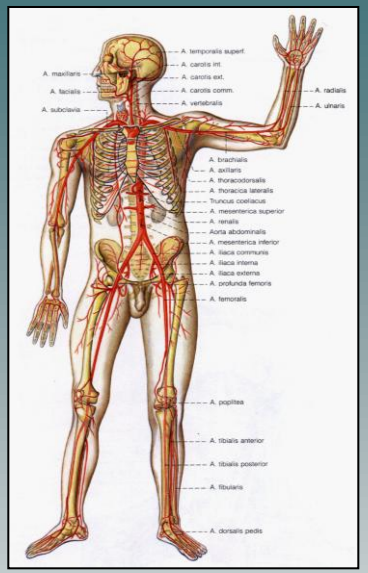


Forssmann et al - Cardiovasc Res 2006

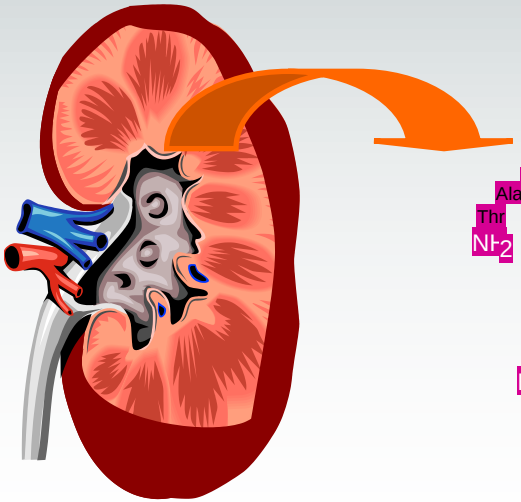
Synthesis Sites of the Natriuretic Peptides

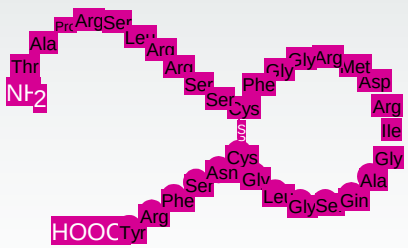


ANP



BNP





Urodilatin

Physiology of Urodilatin

Urodilatin is synthesized in the distal tubule cells

⇓

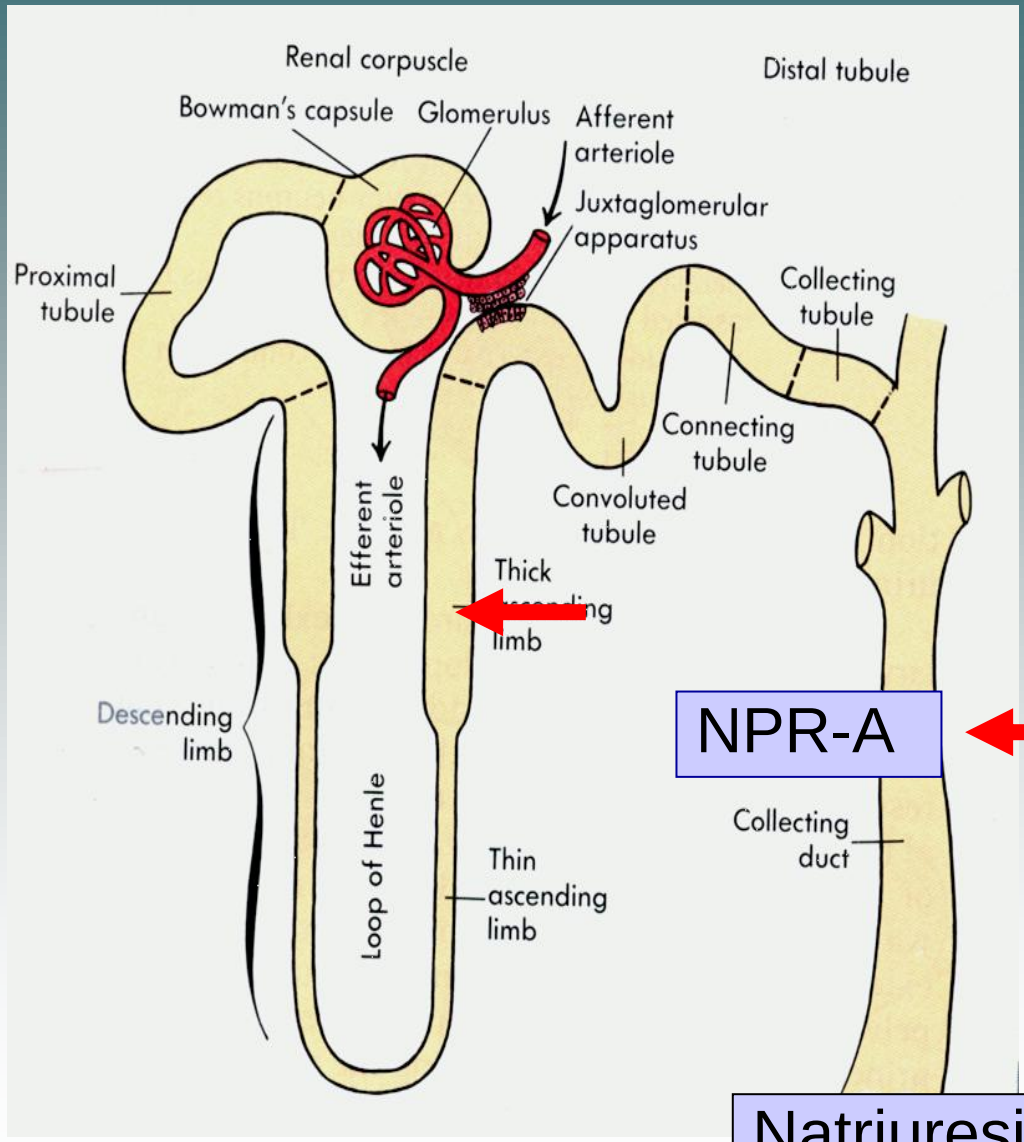
...is luminally secreted

⇓

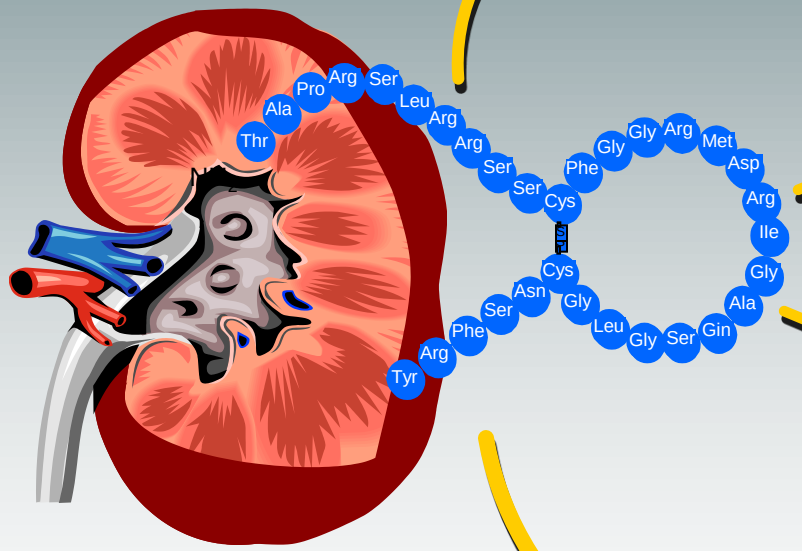
...binds downstream in inner medullar-collecting duct to NPR-A and acts via cGMP

⇓

...and inhibits Na-reabsorption



Summary of the Pharmacological Effects of Urodilatin ("Ularitide")



Hemodynamic (vasodilation)

- veins
- arteries

Bronchodilation

Neurohumoral

↓ RAAldosteroneS

Renal

↑ diuresis

natriuresis

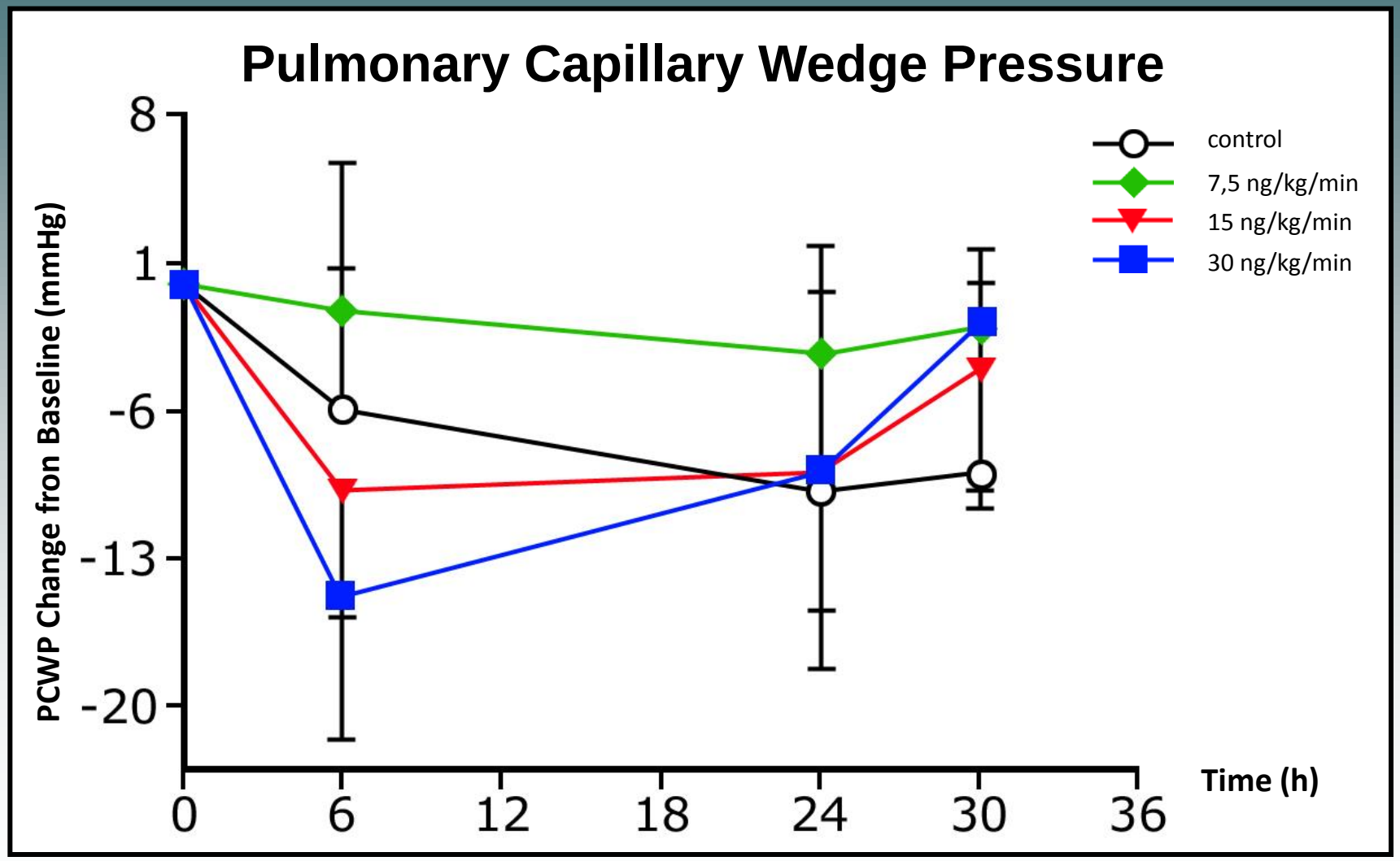
SIRIUS I

Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: A double-blind, placebo-controlled, ascending-dose trial

Veselin Mitrovic, MD, Hartmut Luss, MD, Klaus Nitsche, MD, Kristin Forssmann, MD, Erik Maronde, PhD, Katrin Fricke, PhD, Wolf-Georg Forssmann, MD, and Markus Meyer, MD

Am Heart J 2005; 150:1239.e1-1239.e8

SIRIUS I


Pulmonary Capillary Wedge Pressure
PCWP Change fron Baseline (mmHg)
8
1
-6
-13
-20
0
6
12
18
24
30
36
Time (h)
control
7,5 ng/kg/min
15 ng/kg/min
30 ng/kg/min

SIRIUS II

Safety and efficacy of an Intravenous placebo controlled Randomised Infusion of Ularitide in a prospective double-blind Study in patients with symptomatic, decompensated chronic heart failure (Phase IIb)

Veselin Mitrovic MD, Petar Seferovic MD, Dejan Simeunovic MD, Milutin Miric MD, Valentin S. Moiseyev MD, Zhanna Kobalava MD, Klaus Nitsche MD, Wolf-Georg Forssmann MD, Hartmut Lüss MD and Markus Meyer MD

European Heart Journal 2006; 27:2823–2832

SIRIUS II – study endpoints

Primary Endpoints:

- Change in PCWP at 6 hrs compared to placebo
- Change in patient-assessed dyspnea at 6 hrs compared to placebo

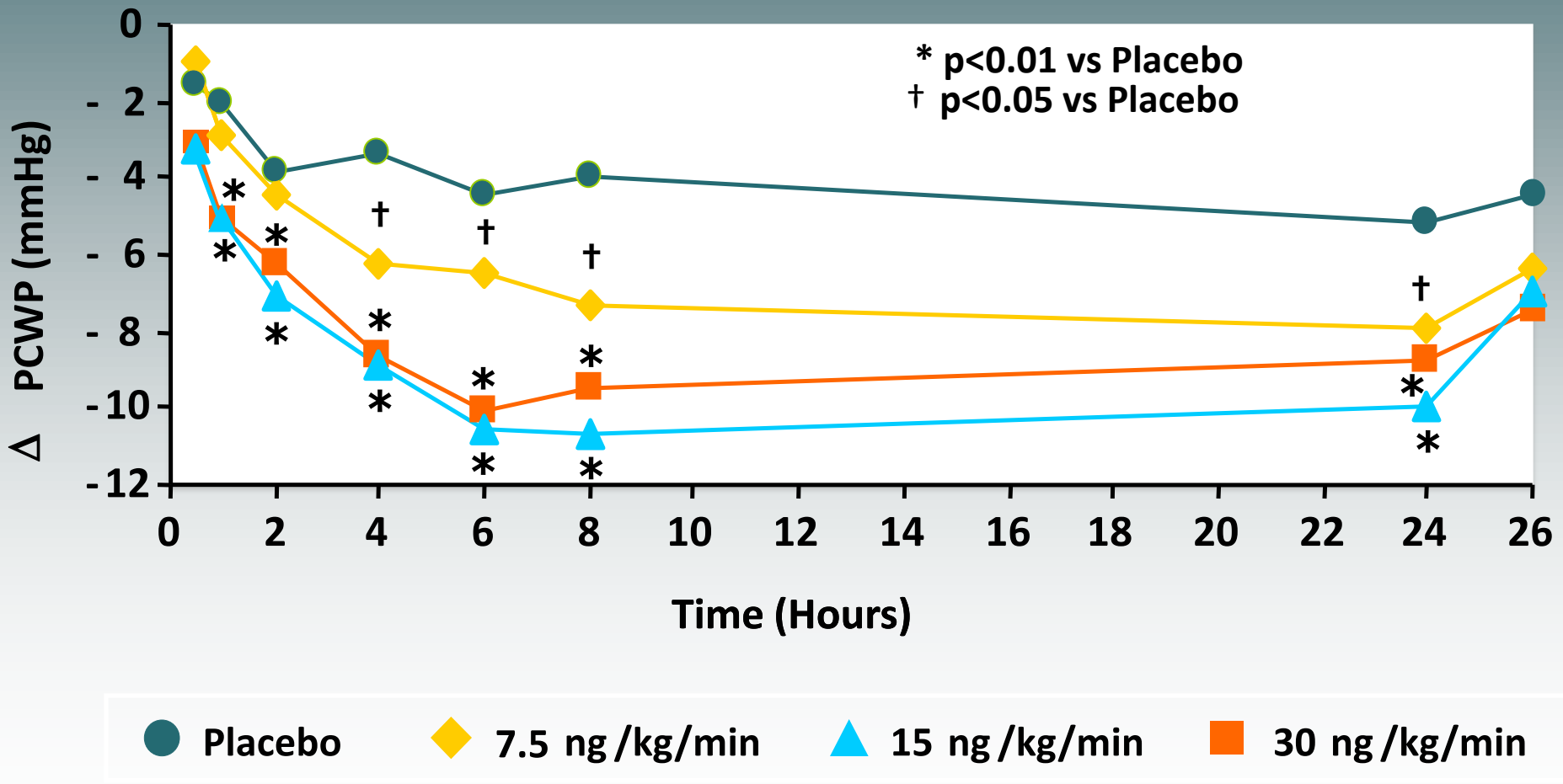
Main Secondary Endpoints:

- Hemodynamic parameters (RAP, PAP, CI, SVR, SV)
- Renal function (through 72 hrs)
- Safety
- 30-day mortality

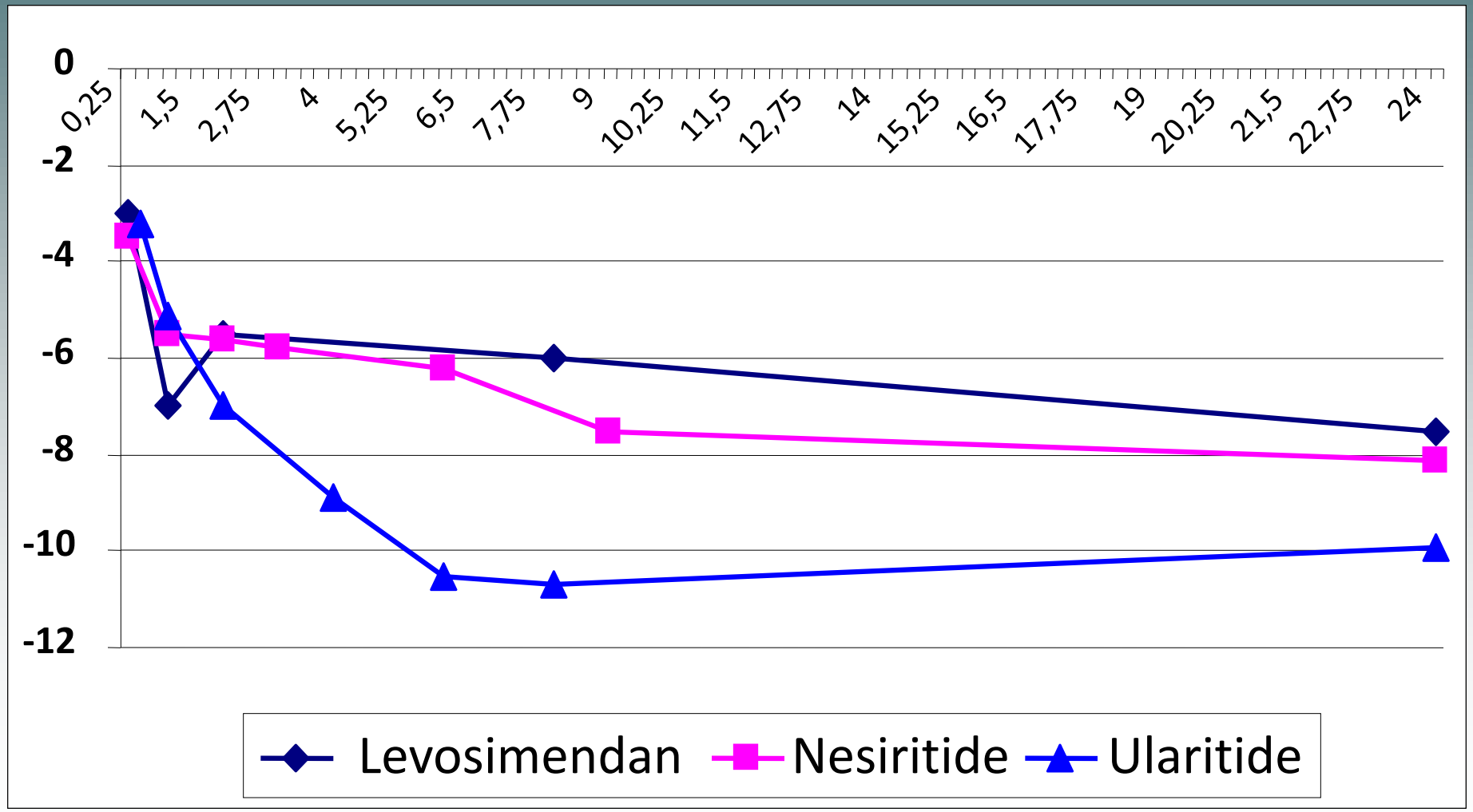
Baseline Characteristics

	LIDO N=203	VMAC N=204	SIRIUS II N=221
Age (yrs)	**58**	**62**	**60**
Male (%)	**91**	**73**	**70**
PCWP (mmHg)	**25**	**28**	**26**
CI (L $min^{-1}m^{-2}$)	**1.9**	**2.2**	**1.9**
RAP (mmHg)	**10.4**	**15**	**10.0**
Sys BP (mmHg)	**112**	**120**	**125**

Ularitide Reduces PCWP

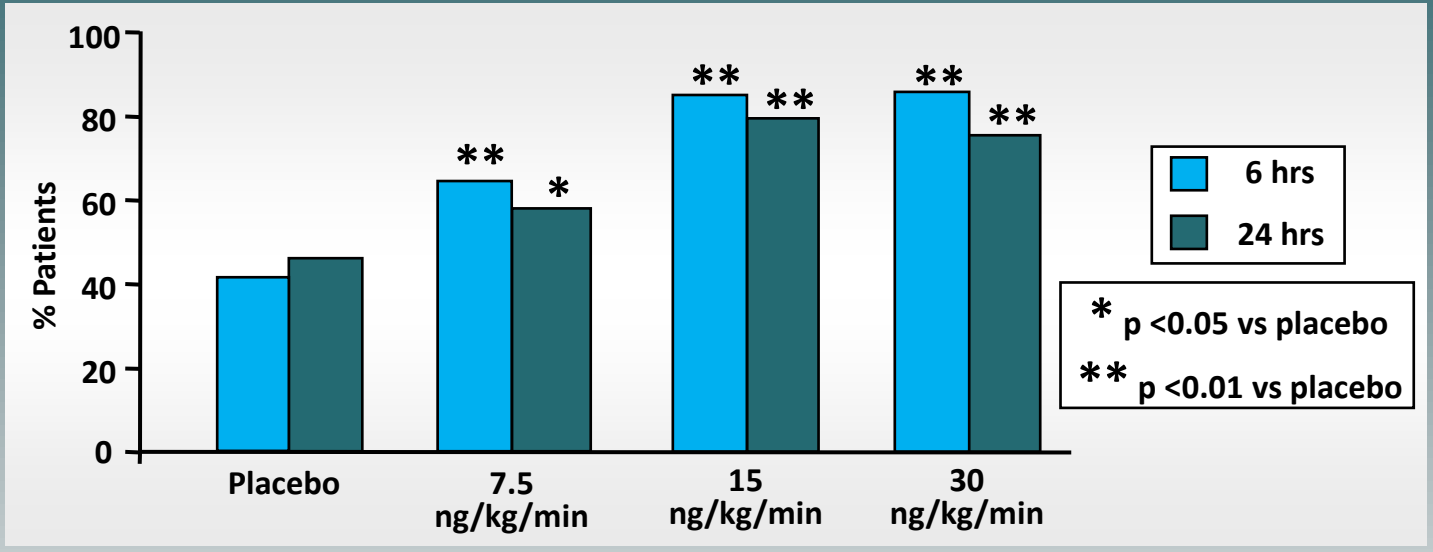


Comparative PCWP Changes
Mean Change from Baseline (mmHg)

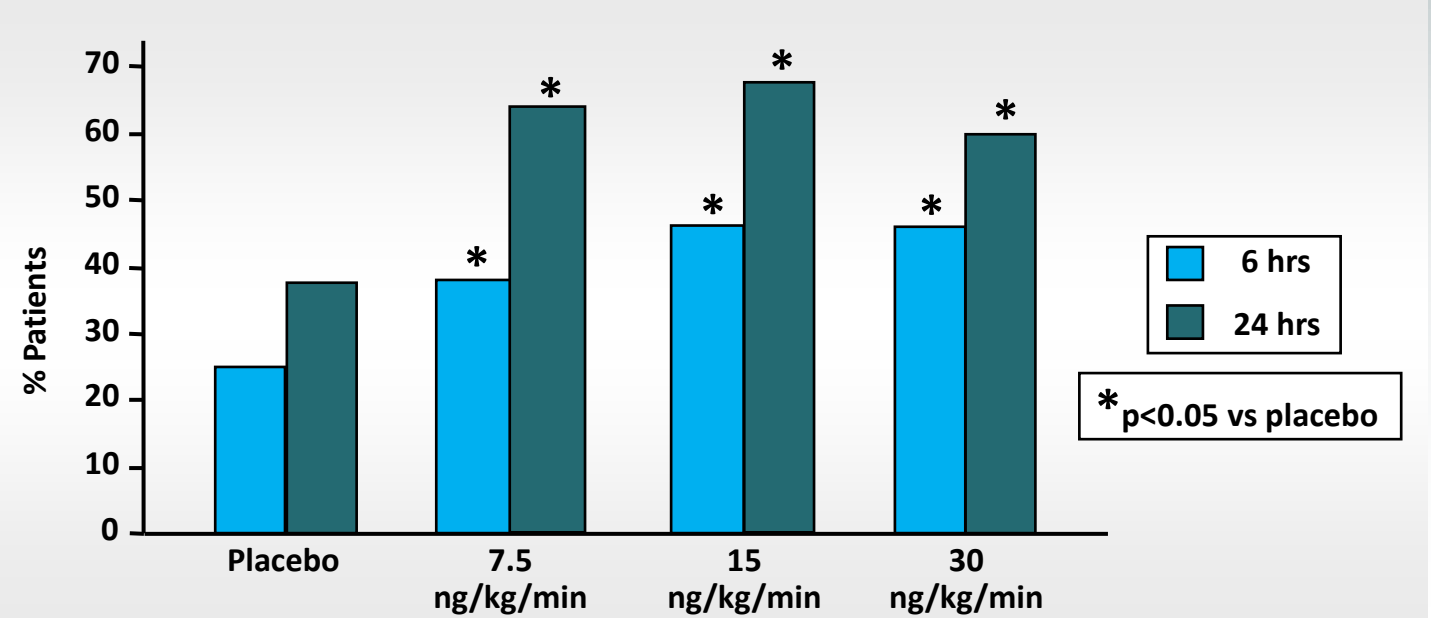


Source: multiple studies

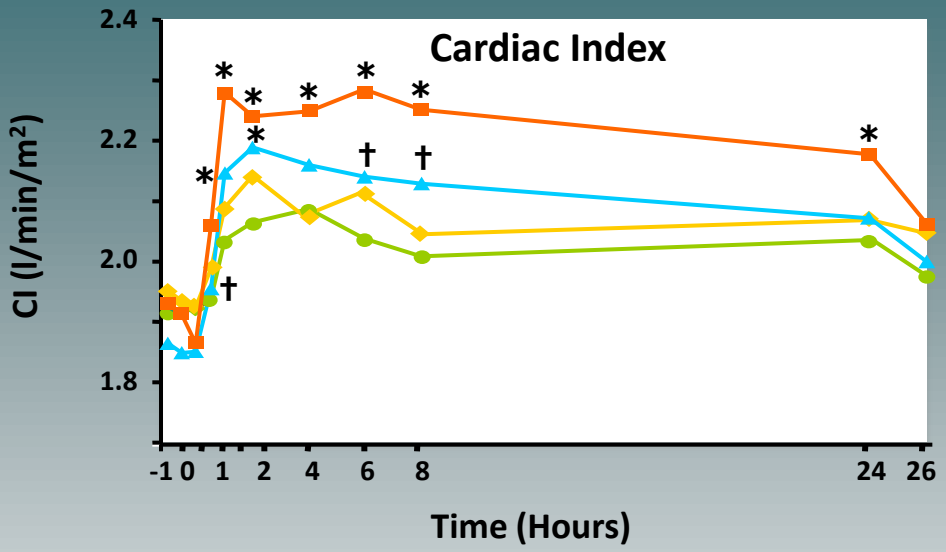
Treatment Responders (> 5mmHg PCWP decrease)

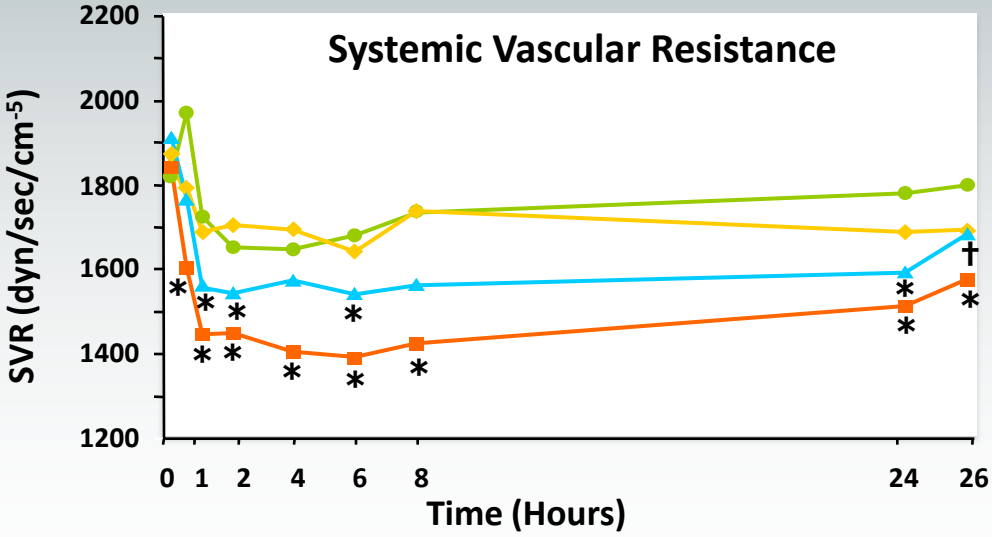


Patient-assessed dyspnea: Moderately or markedly better



Ularitide Improves Cardiac Index and SVR



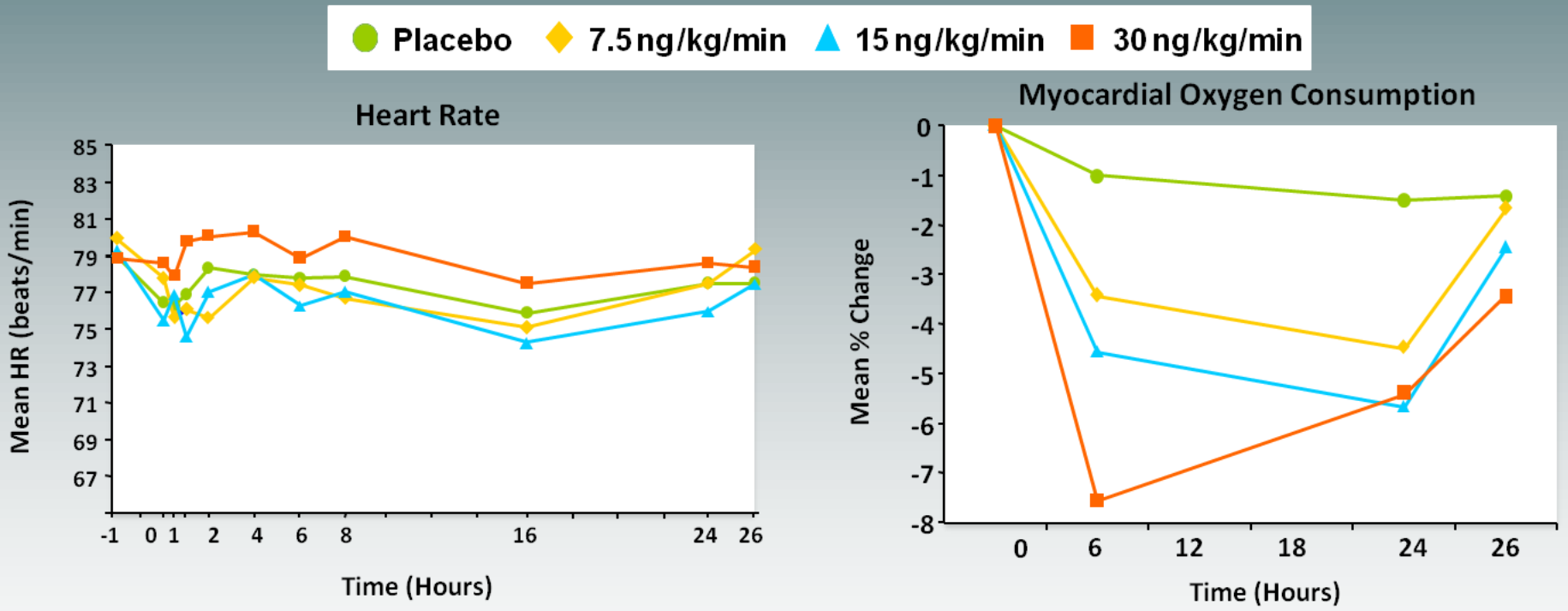


* p<0.01 vs Placebo

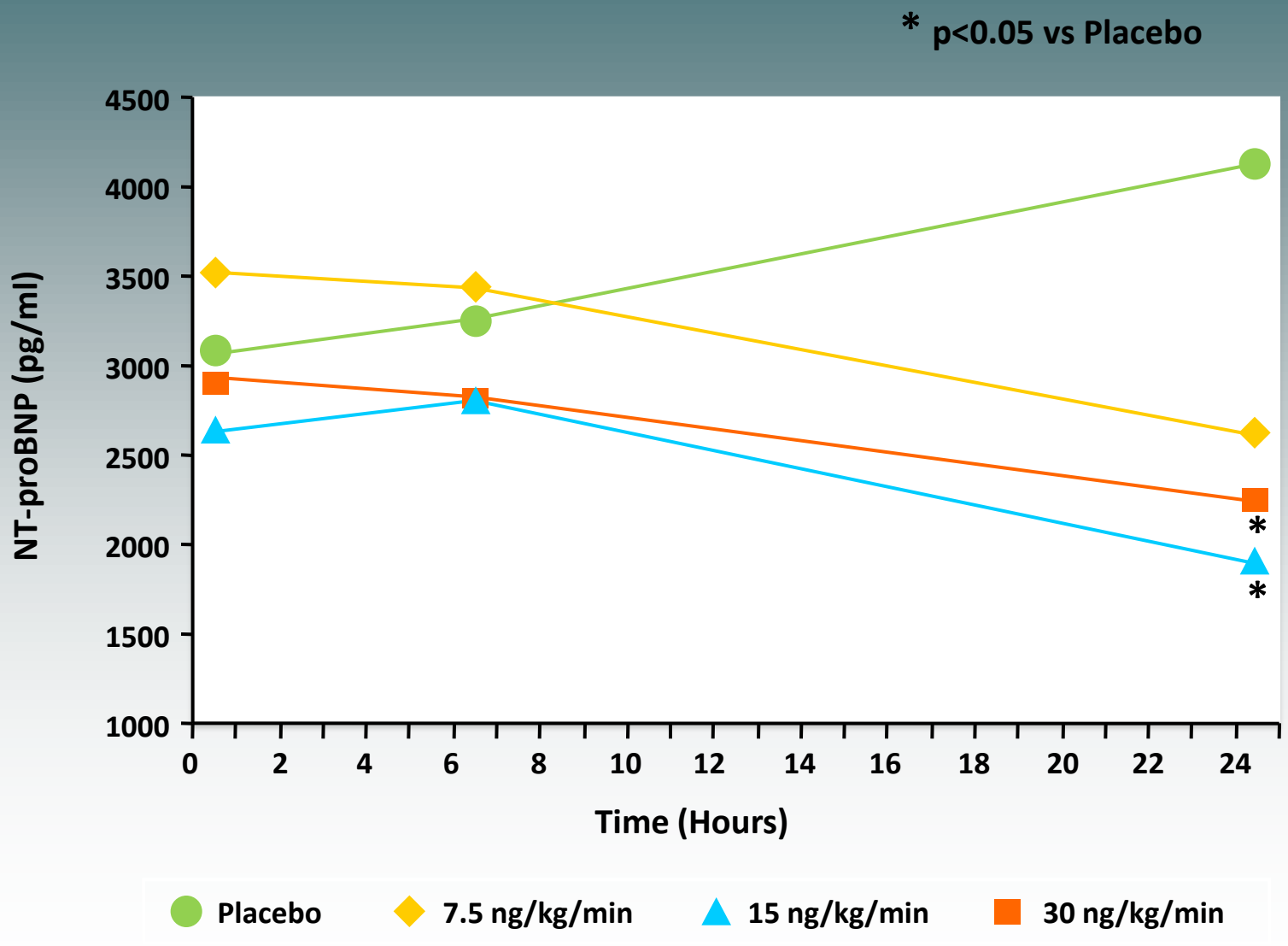
† p<0.05 vs Placebo

Placebo 7.5 ng/kg/min 15 ng/kg/min 30 ng/kg/min

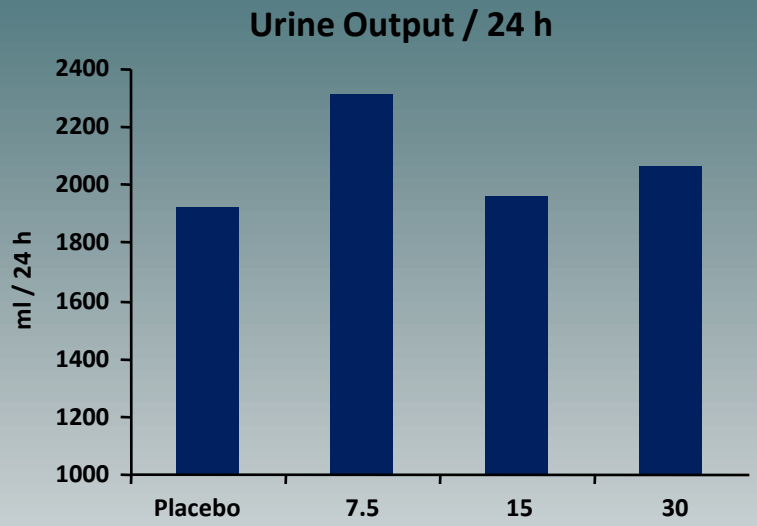
Effects of Ularitide on heart rate and myocardial O_2 consumption

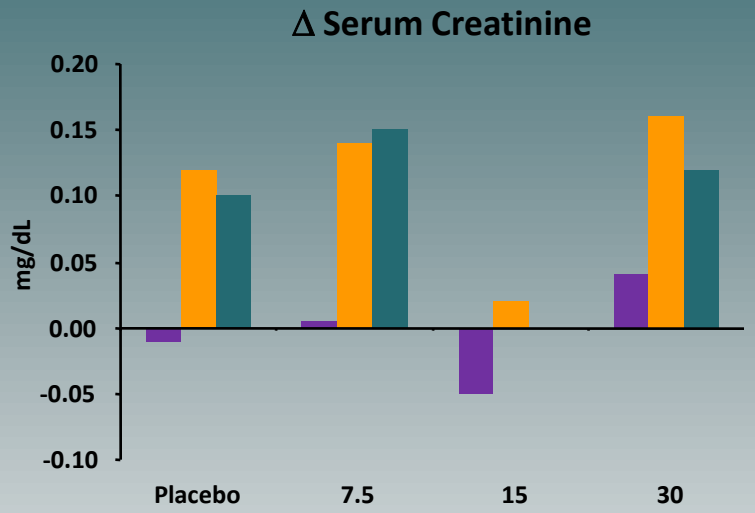


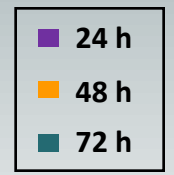
Ularitide Reduces NT-pro BNP Levels

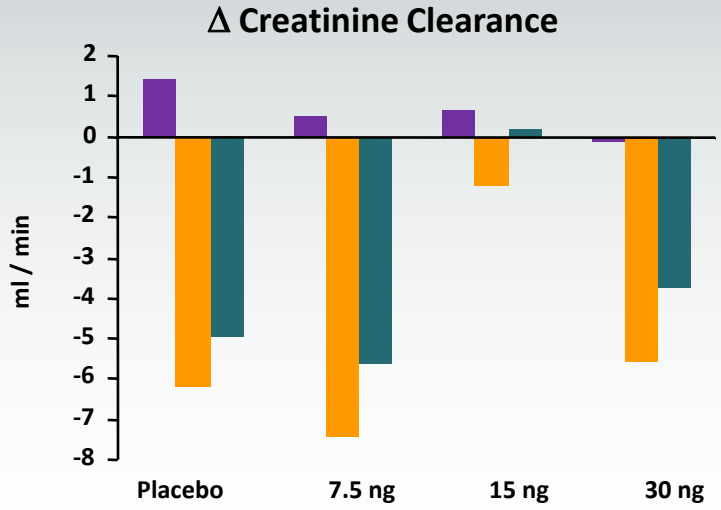


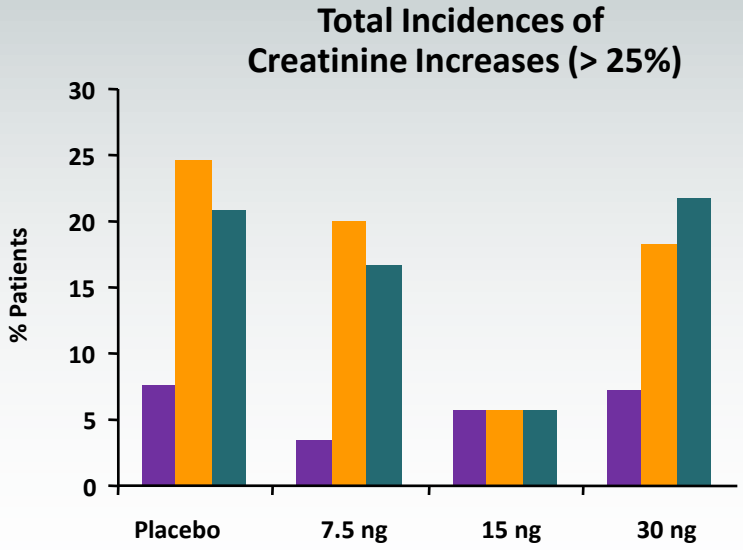
Ularitide does not worsen renal function through 72 hours







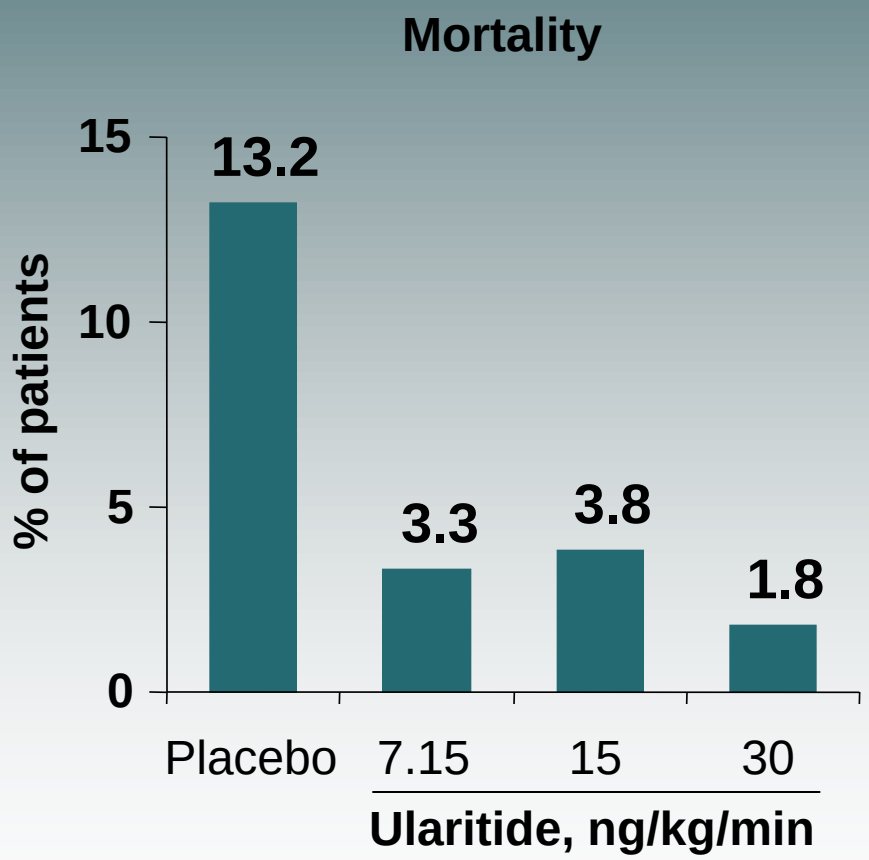


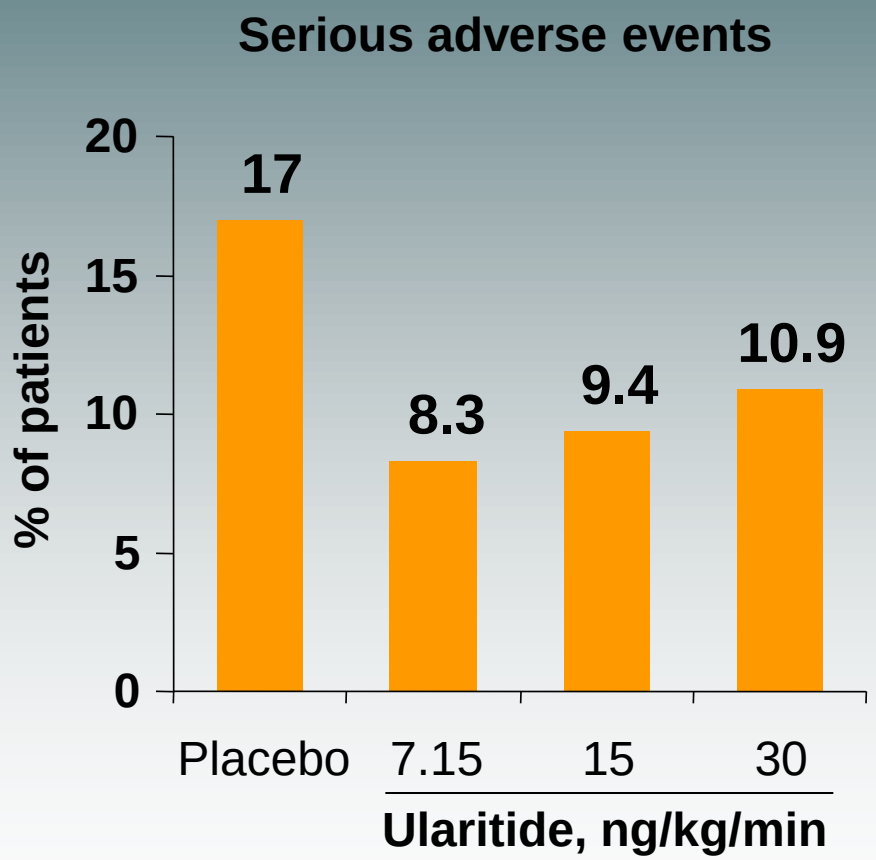


SIRIUS II – safety

	Placebo (n=53)	7.5 ng/kg/min (n=60)	15 ng/kg/min (n=53)	30 ng/kg/min (n=55)
Hypotensions During Infusion n (%)	1 (1.9)	5 (8.3)	6 (11.3)	9 (16.4)
Serious Adverse Events (day 1-30) n (%)	9 (17)	5 (8.3)	5 (9.4)	6 (10.9)
30-day Mortality n (%)	7 (13.2)	2 (3.3)	2 (3.8)	1 (1.8)

Outcomes in SIRIUS-II





TRUE-AHF

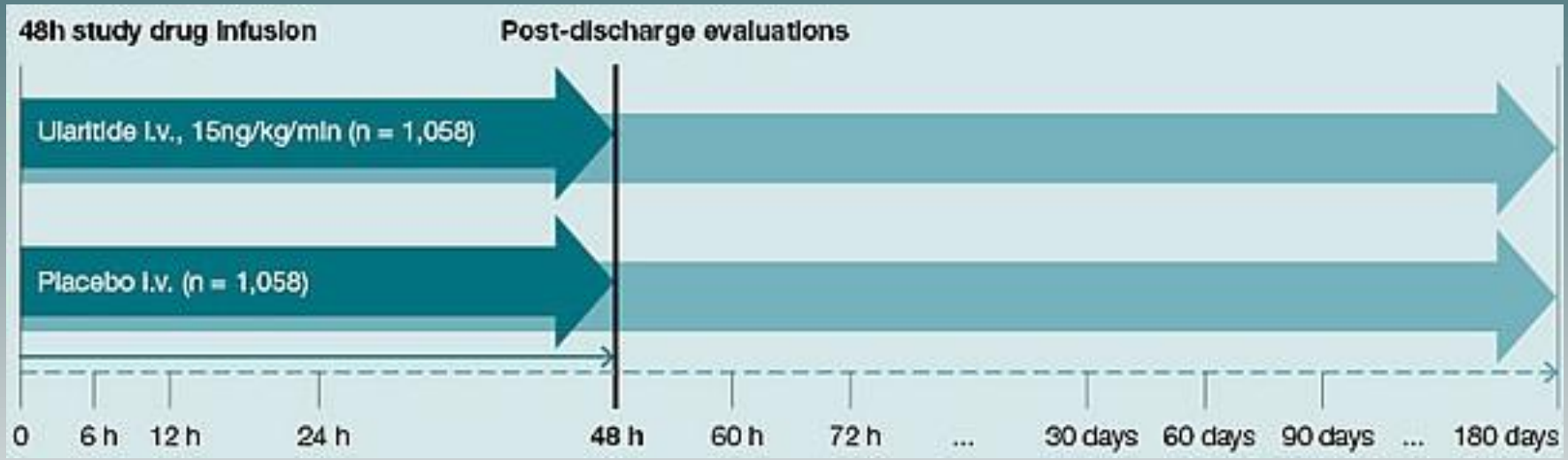
TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure

The **first-ever acute heart failure** (AHF) **Phase III** trial to be **specifically designed to assess the effect of early treatment on cardiovascular mortality as a co-primary endpoint**.

Study aim

- The goal of TRUE-AHF will be to evaluate the **efficacy and safety of ularitide** on **clinical status and mortality outcomes for the entire duration of the trial** in patients with AHF
- TRUE-AHF aims to build on the growing body of evidence to treat patients suffering from AHF as **early as possible**

Study design



- **Multicenter, randomized, double blind, placebo-controlled trial, to evaluate the efficacy and safety of intravenous (IV) ularitide in patients suffering from AHF**
- **Patient enrolment has started across approximately 190 centres in the US, Europe and Canada**
- **Minimum 2,152 patients with AHF will be randomised to receive placebo or ularitide for 48 hours in addition to standard care**
  - **The trial maybe enlarged in size after a planned interim analysis (up to 4,000 patients)**

Key efficacy measures

Primary Endpoint

A **composite score** that assesses the **symptoms and clinical course** of patients during the 48-hour infusion of ularitide

Cardiovascular mortality following randomisation for the **entire duration of the trial**

Secondary Endpoint

Changes in NT-pro BNP at 48 hours (vs. baseline)

All cause mortality and cardiovascular rehospitalisation at Day 90 after start of study drug infusion

Thank you

This satellite Symposium is sponsored by Cardiorentis at Cardiology Update 2013, Davos, Switzerland.

Cardiorentis is a private biopharmaceutical company, headquartered in Switzerland, dedicated to bringing novel therapies to the treatment of acute heart failure.

For more information, please contact: cardiorentis@toniclc.com

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