'Time to therapy' concept in AHF Syndromes – Treat early or die?

M. Birhan Yılmaz M.D, FESC
Professor of Medicine
Department of Cardiology
Cumhuriyet University
Sivas, TURKEY

- Time to therapy concept in CV disease
- Time concept in AHF: Overlooked data so far
- Recent data and paradigm shift

Disclosures: PI in Novartis and Cardiorentis studies

Time Dependency:
Understanding the Concept

Treat Early or Die

VENTRICULAR TACHYCARDIA
ACUTE MYOCARDIAL INFARCTION
CEREBROVASCULAR ACCIDENT
PNEUMONIA
HYPOGLYCEMIA
HYPOXIA

Think outside the box

- Where AHF stands with regard to time?
- *Any evidence???:*

Data derived from prospective randomized study versus registry

What am I supposed to measure?: «Dyspnea» and/or «outcome»

- Question: Is there an opportunity window for AHF just like other diseases?
- Answer: Probably yes…

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

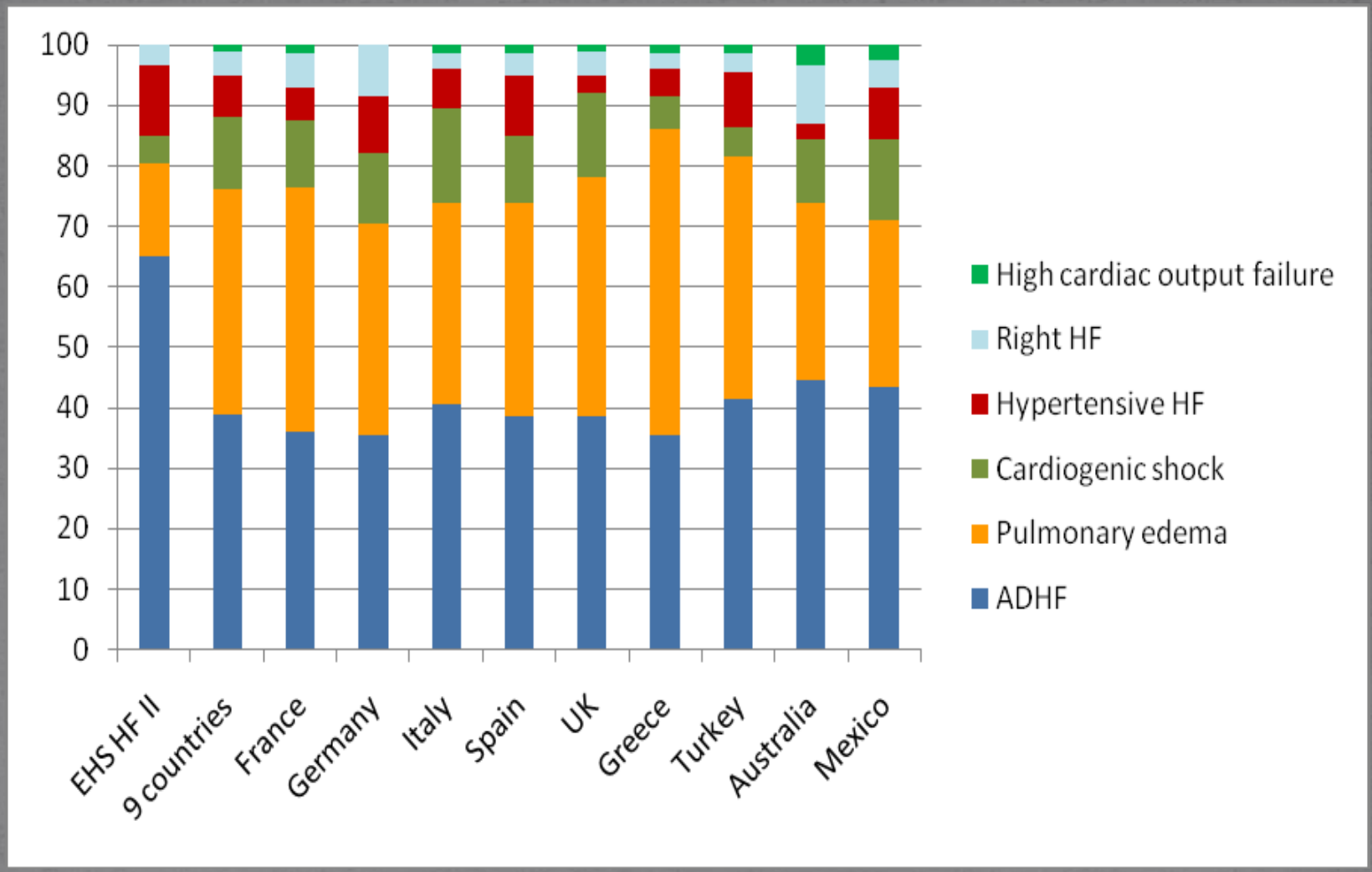
Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)

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

ORIGINAL

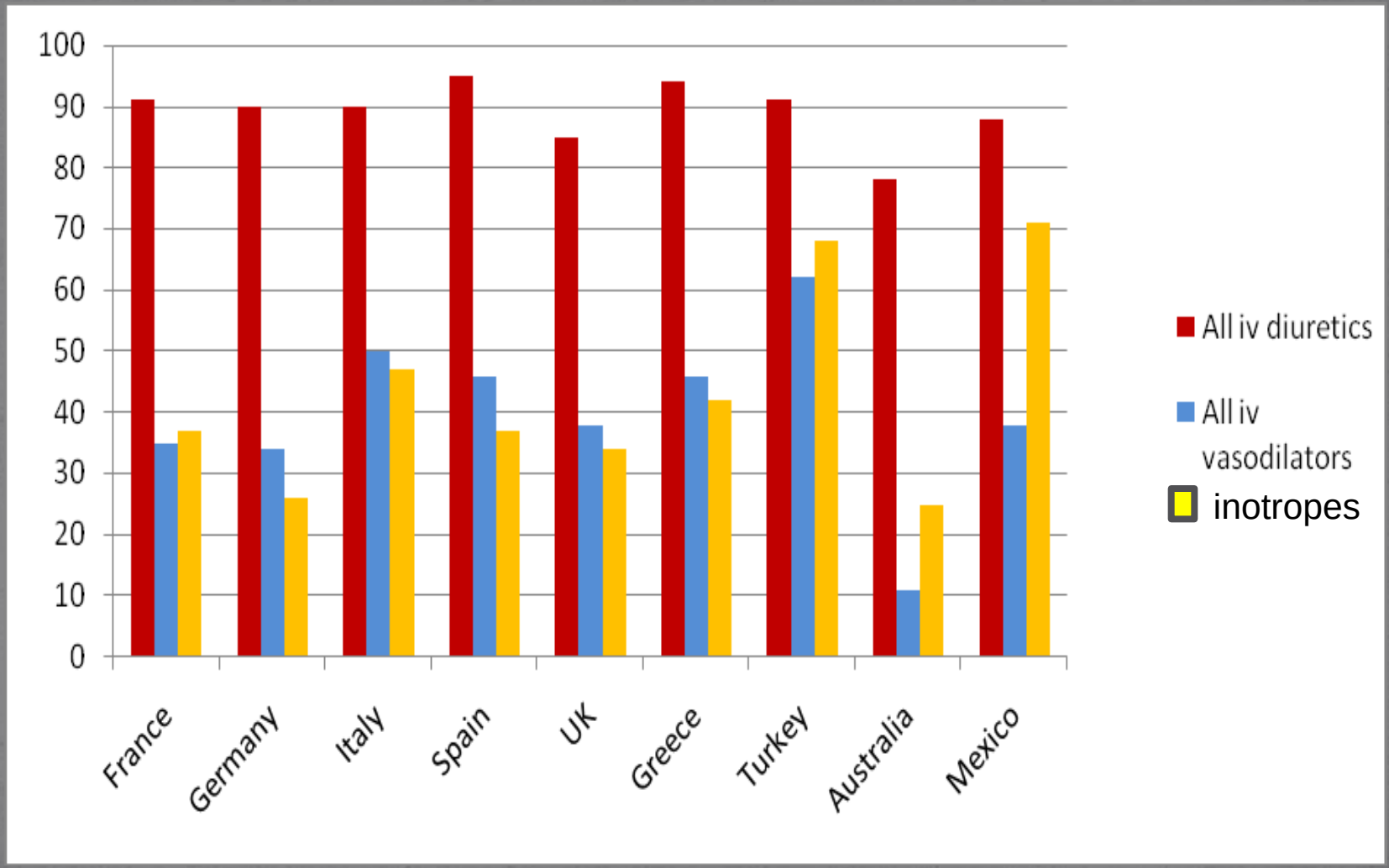
Alexandre Mebazaa
John Parissis
Raphael Porcher
Etienne Gayat
Maria Nikolaou
Fabio Vilas Boas
J. F. Delgado
Ferenc Follath

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

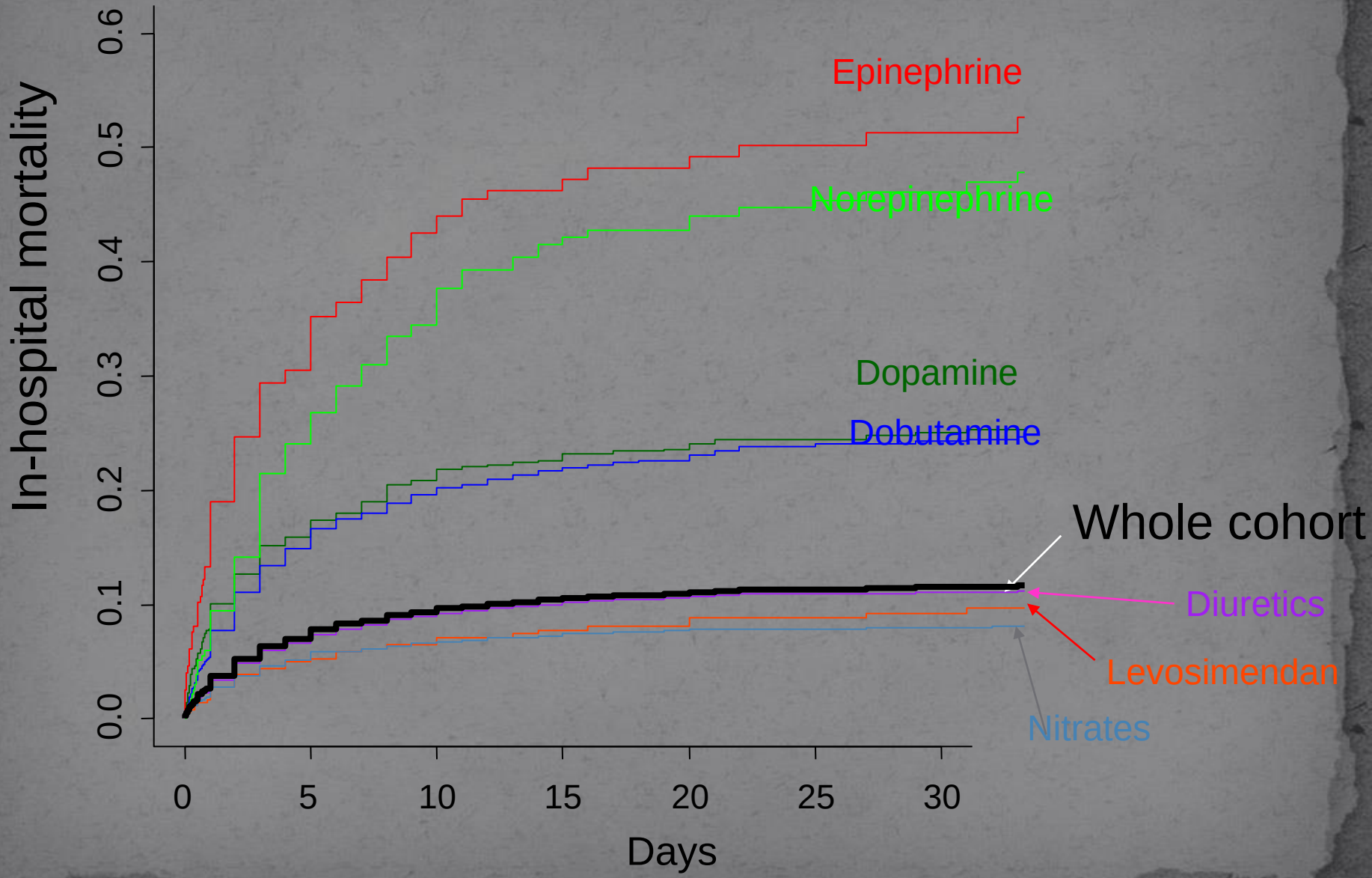


Mebazaa et al Intensive Care Medicine 2011

ALARM-HF: IV treatment at admission

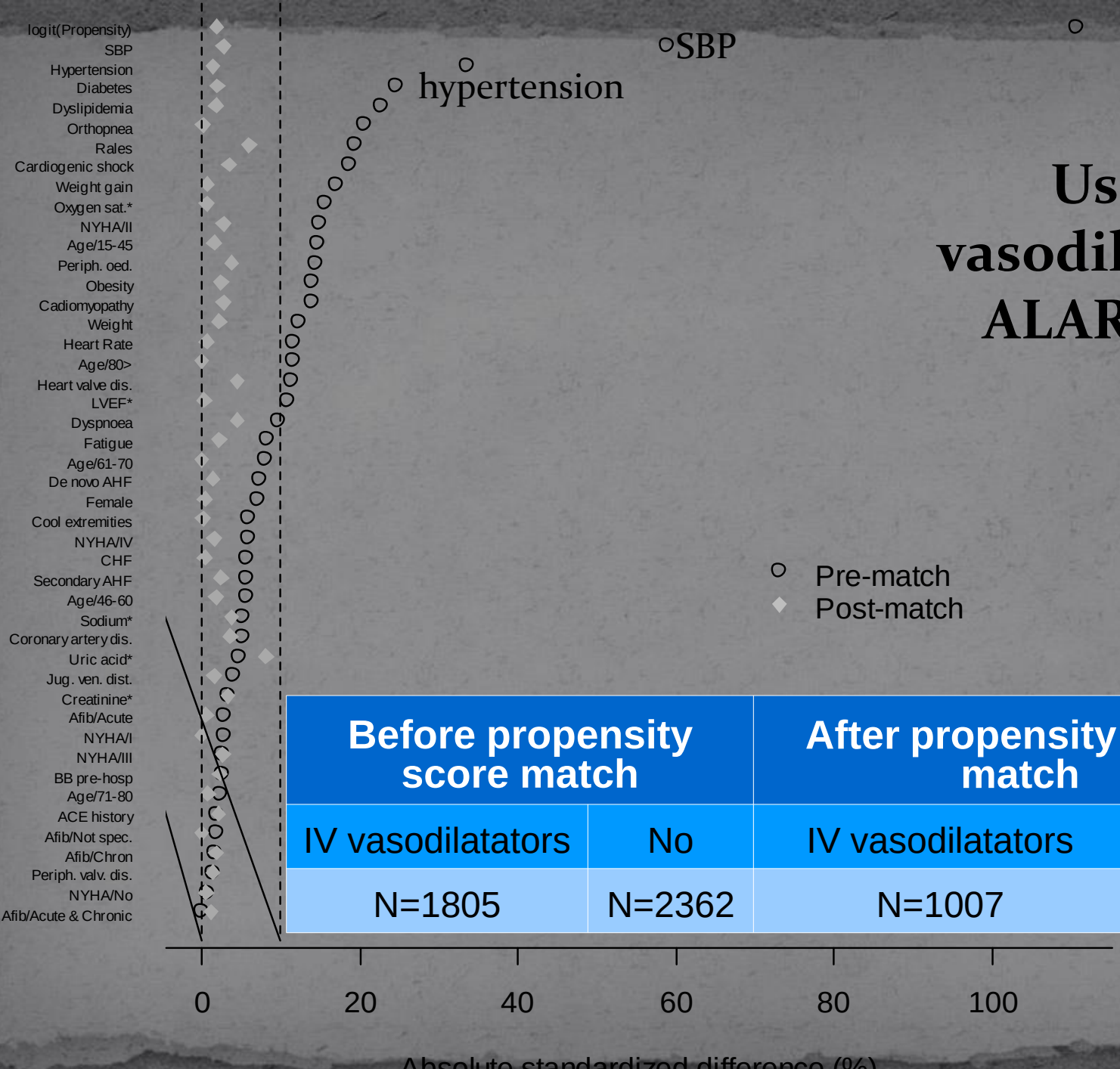


Mebazaa et al Intensive Care Medicine 2011



Mebazaa et al Intensive Care Medicine 2011

Use of vasodilators in ALARM-HF



Before propensity score match		After propensity score match	
IV vasodilatators	No	IV vasodilatators	No
N=1805	N=2362	N=1007	N=1007

Results from ALARM

- 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

Early Vasoactive Drugs Improve HF Outcomes

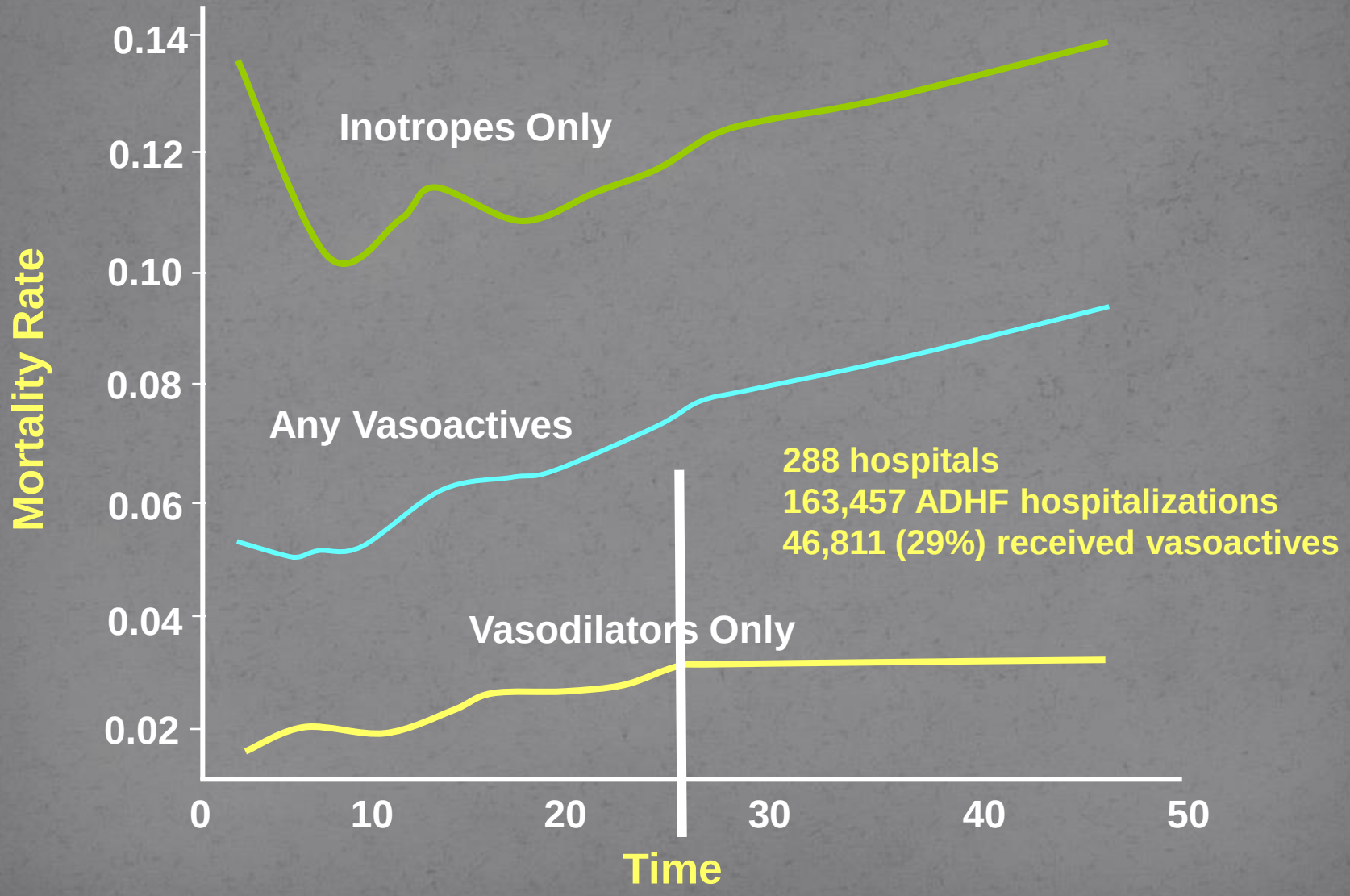
- **ADHERE Registry: N=35,700**
  - examined the relationship between vasoactive time and inpatient mortality within 48 hours of hospitalization.

- Early vasoactives defined as <6 hours
  - Early: 22,788 (63.8%) Late: 12,912 (36.2%)
- Median vasoactive time:
  - Early 1.7 hours Late 14.7 hours
- In-hospital mortality was lower in the early therapy group
  - (OR 0.87; 95% CI 0.79–0.96; P=.006)

- **The adjusted odds of death increased 6.8% for every 6 hours of treatment delay (95% CI 4.2–9.6; P<.0001)**

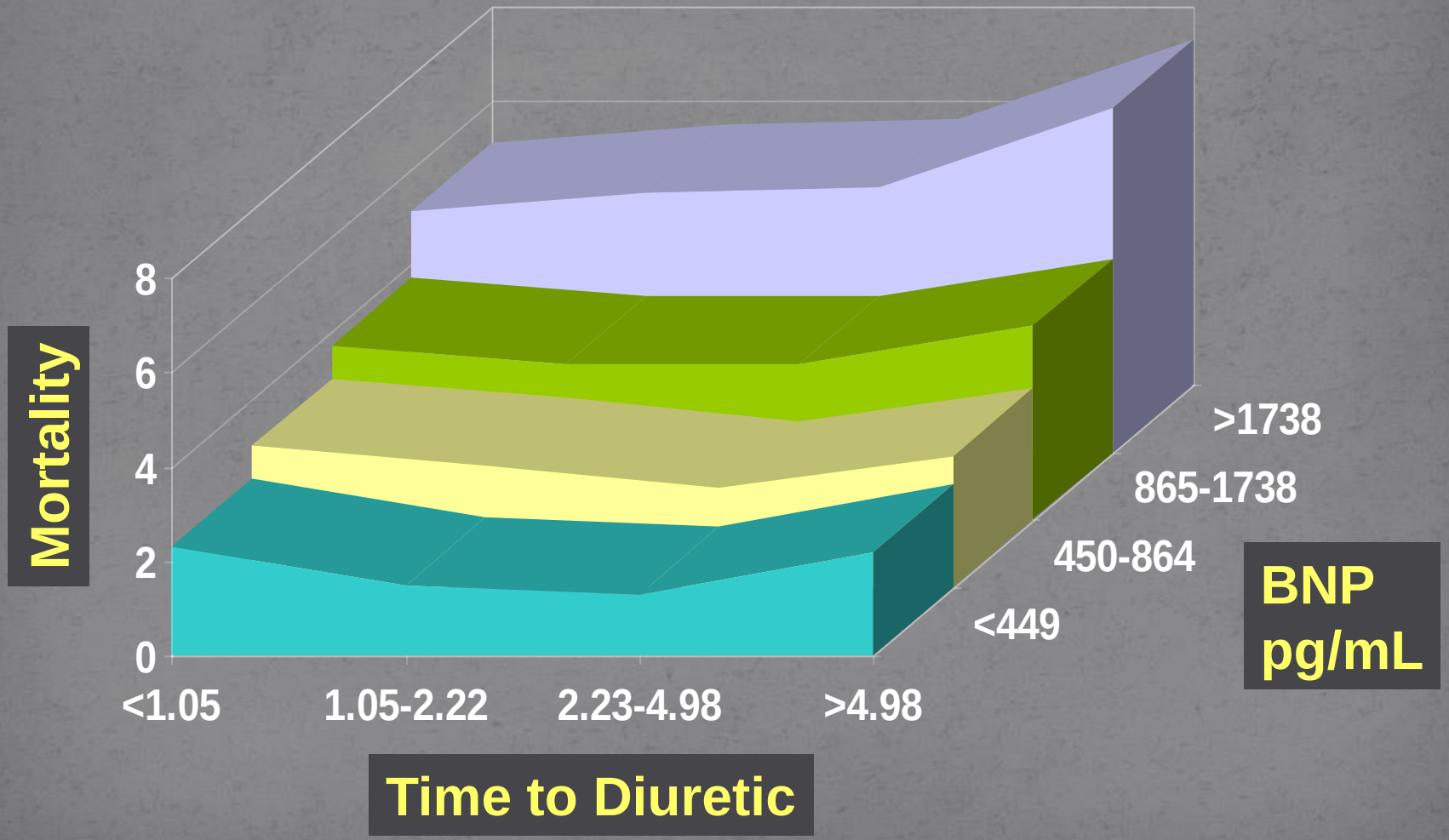
Peacock WF. Cong HF 2009;15(6):256-264.

Time to therapy versus mortality



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

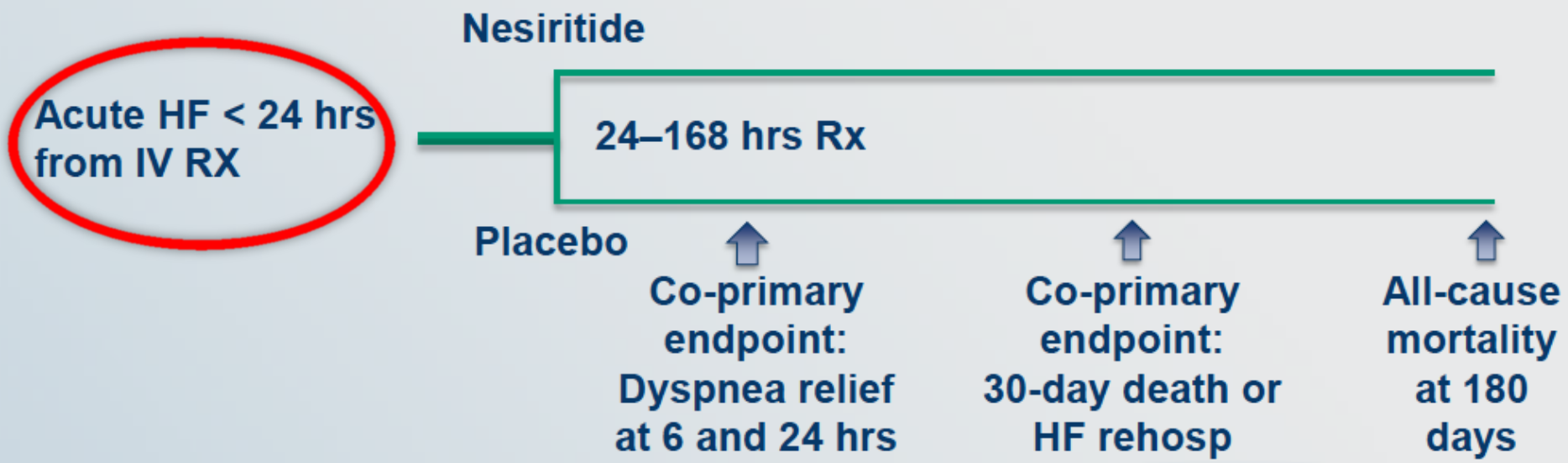
Mortality vs. Quartiles of Diuretic Time & BNP Level



Maisel AS, Peacock WF. JACC 2008; **52**(7) 534-540

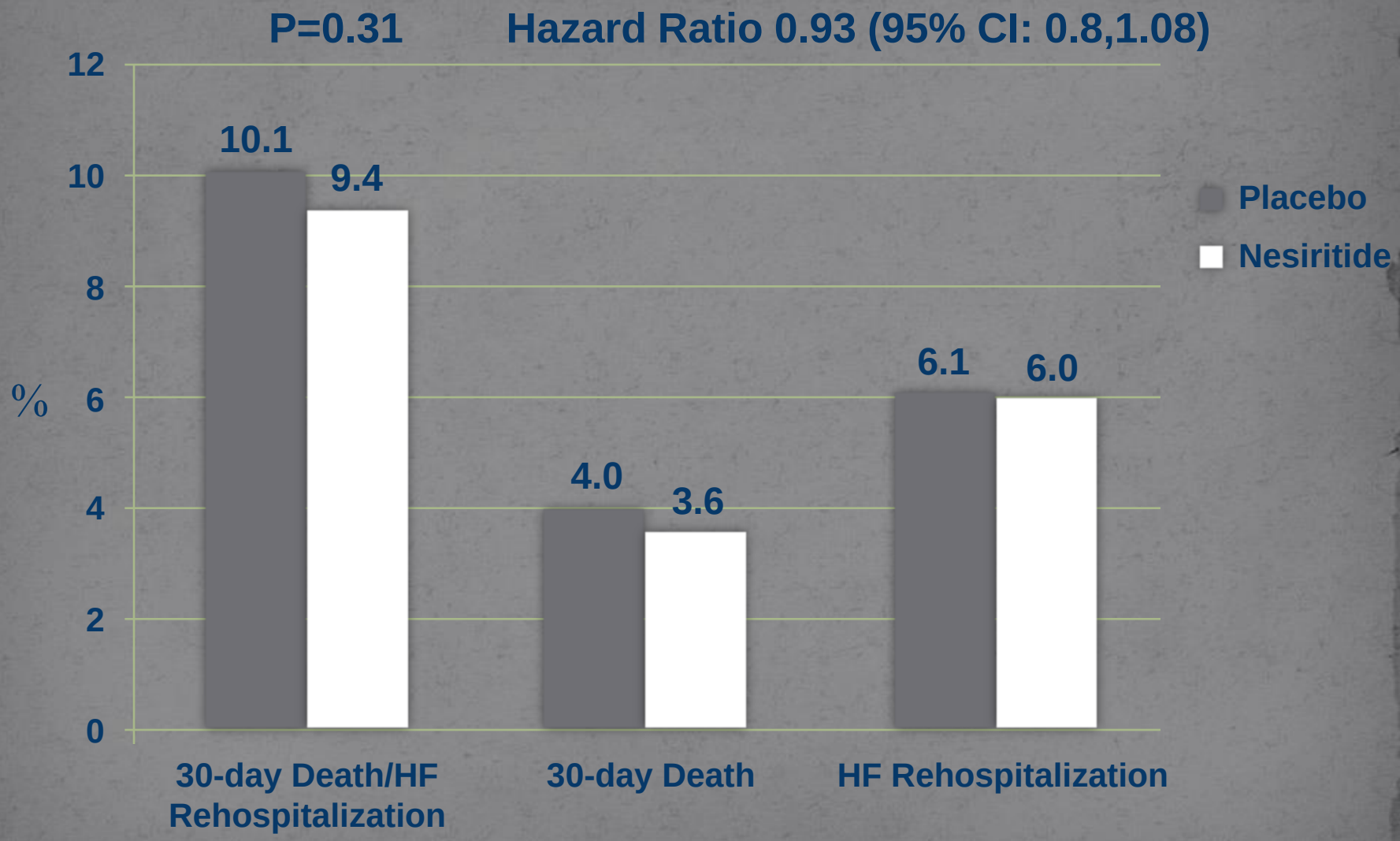
Study design and drug procedures

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



- Double – blind placebo controlled
- IV bolus (loading dose) of 2 µg/kg nesiritide or placebo
  - Investigator's discretion for bolus
  - Followed by continuous IV infusion of nesiritide 0.01 µg/kg/min or placebo *for up to 7 days*
- Usual care per investigators including diuretics and/or other therapies as needed
- Duration of treatment per investigator based on clinical improvement

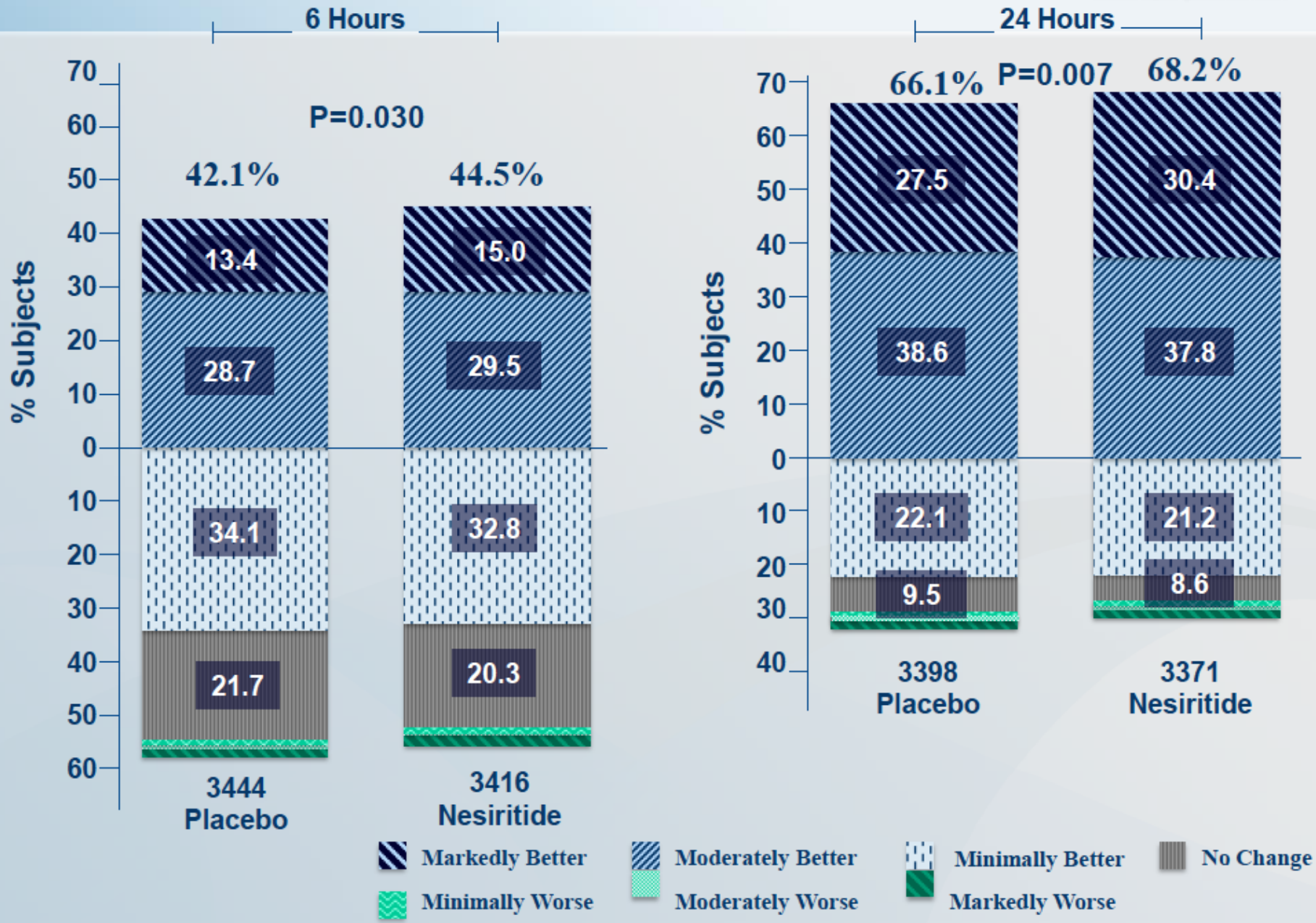
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization (n=6836)



O'Connor et al NEJM 2011

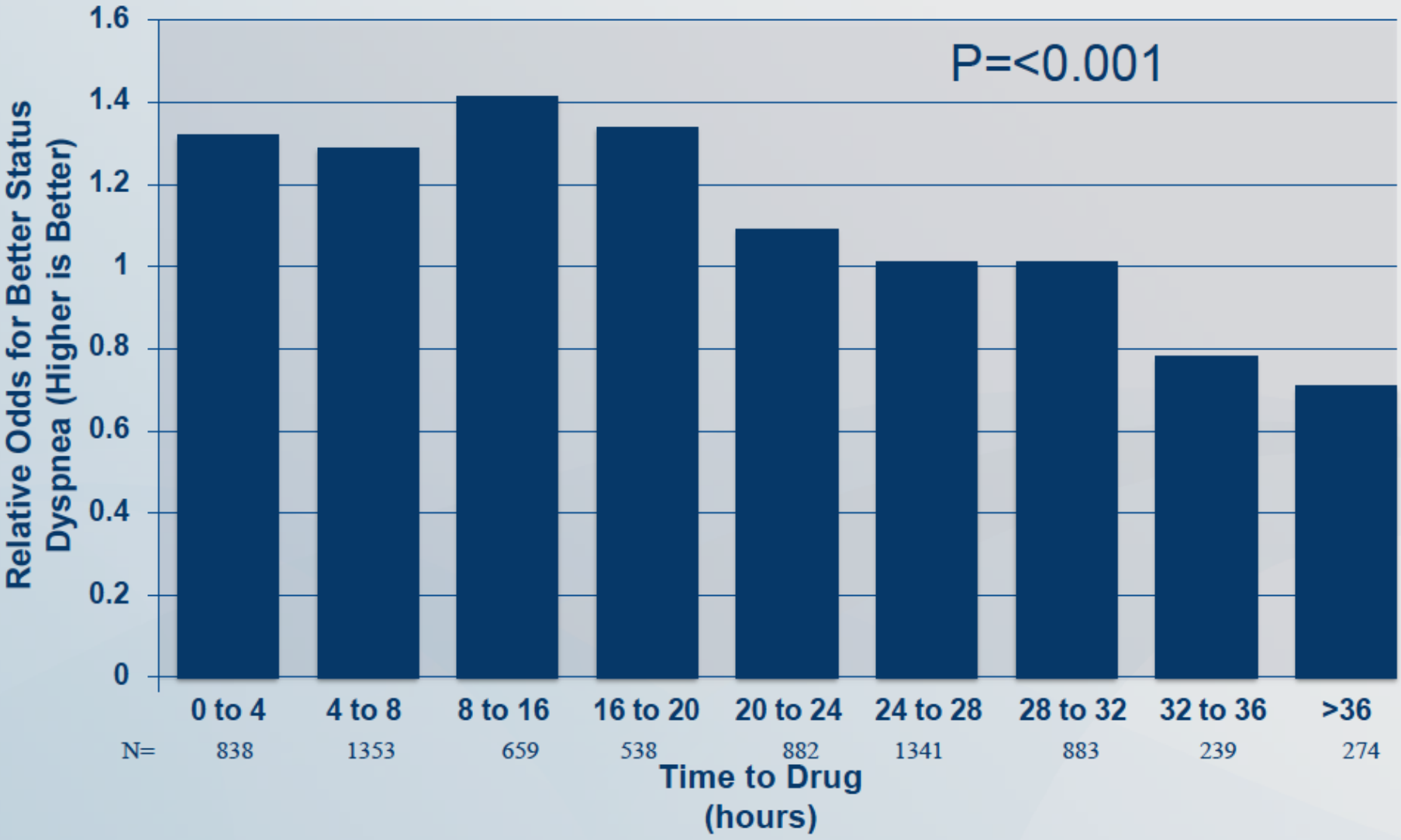
Co-Primary Endpoint: 6 and 24 hour dyspnea

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

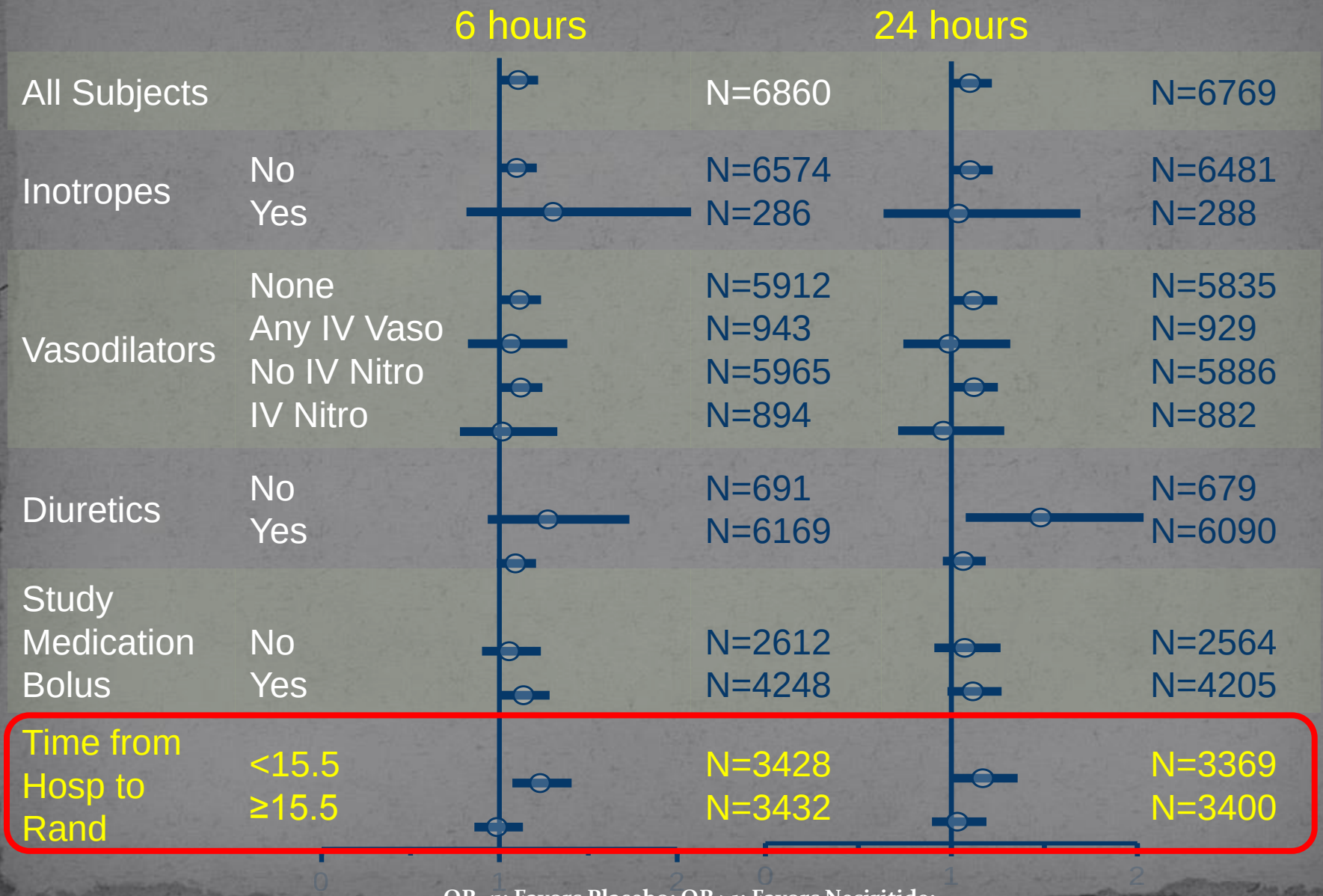


Overall effect of time from presentation to study drug on 6 hour dyspnea relief

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



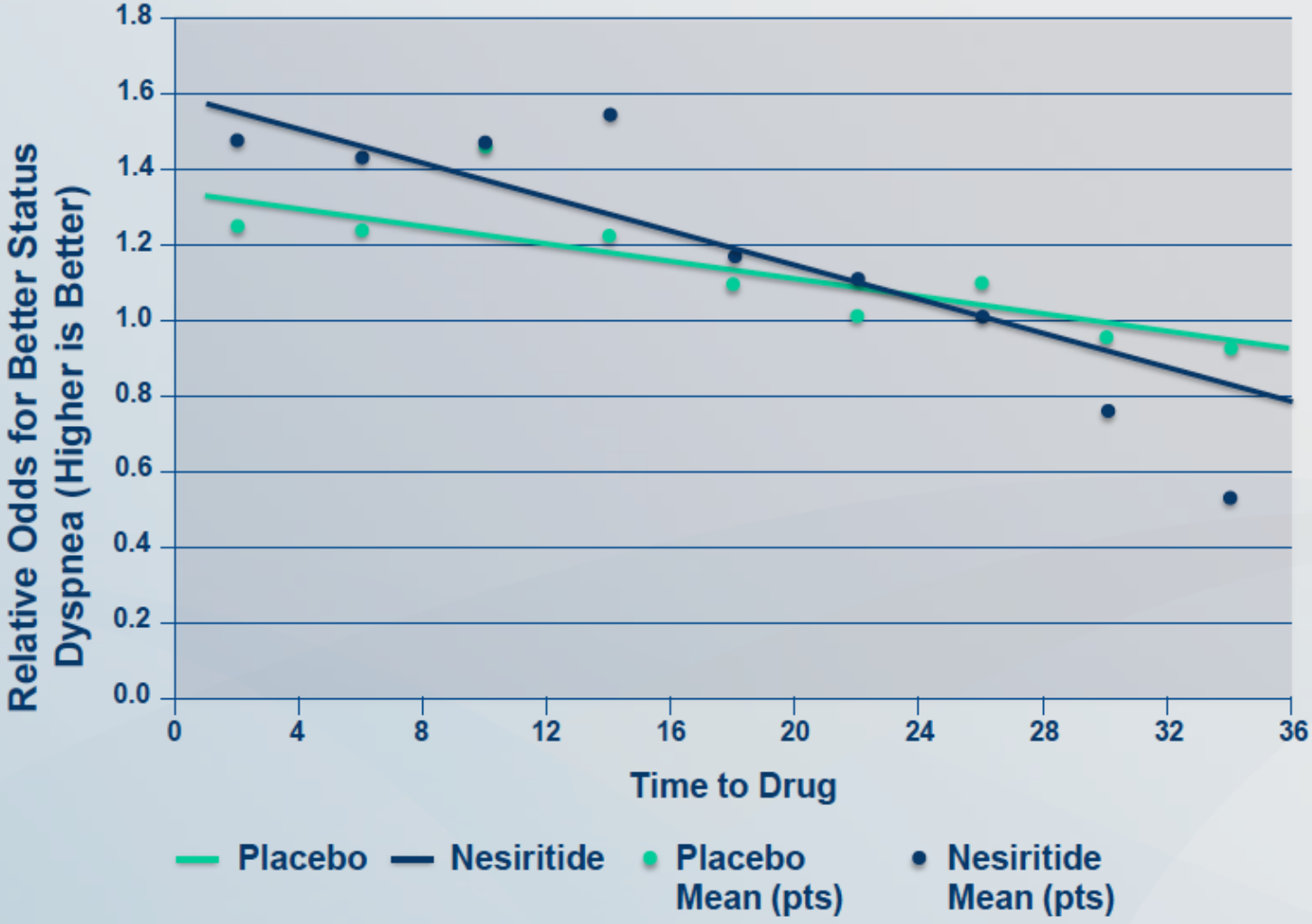
Dyspnea at 6 and 24 Hours
Odds for Marked-Moderate Improvement



OR <1: Favors Placebo; OR >1: Favors Nesiritide;
Odds Ratio of Markedly/Moderately vs. Other

Estimate of effect of nesiritide on 6 hour dyspnea relief based on time from presentation to study drug

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



Chi-square for treatment = 9.66 for 2 d.o.f., p = 0.0080

Think outside the box

- Treat at admission: Time to therapy (TtT concept)
  - *Including patients >12-24 hours of admission was wrong!*

Any effect of prehospital therapy?

Ann Emerg Med. 1992 Jun;21(6):669-74.

Effects of prehospital medications on mortality and length of stay in congestive heart failure.

Wuerz RC, Meador SA.

Division of Emergency Medicine, Milton S Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey.

Abstract

HYPOTHESIS: Prehospital medications for congestive heart failure should affect hospital outcomes (survival and length of stay).

STUDY DESIGN: In a retrospective case series, hospital outcomes were compared for patients treated with prehospital nitroglycerin, furosemide, and/or morphine (252) versus those given no medications (241).

SETTING: A rural/suburban emergency medical services system (population 140,000) served by three paramedic units.

PARTICIPANTS: Four hundred ninety-three consecutive cases of congestive heart failure or pulmonary edema were identified by hospital discharge diagnosis from a data base of 8,315 paramedic transports with known outcome.

INTERVENTIONS: Oxygen was given by protocol to 489 patients. Other medications were given by order of on-line physician medical command.

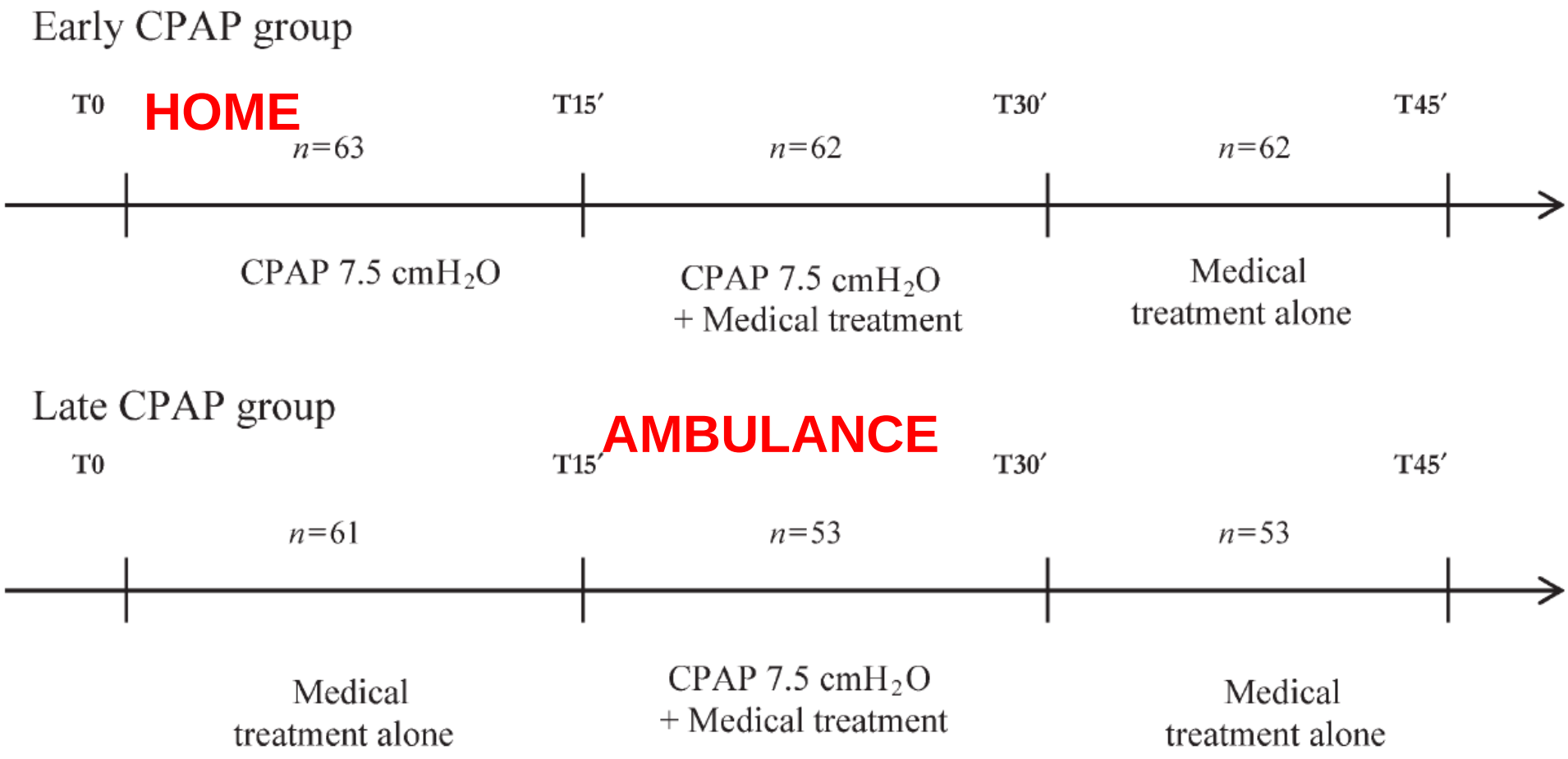
RESULTS: Overall mortality was 10.9% (54 of 493). Treated and untreated patients were comparable in age, sex, cardiac rhythms, prior use of cardiac medications, and response and scene times; mortality was reduced in treated versus untreated patients (odds ratio for improved survival, 2.51; 95% confidence interval, 1.37 to 4.55; P less than .01). Positive treatment effect was greatest for 58 nonhypotensive, critical patients (odds ratio for survival, 10.25; P less than .01). No single drug combination was unique in terms of treatment benefit. Patients treated in the field received medications 36 minutes earlier than patients first treated in the emergency department. No survival benefit was evidence for noncritical, nonhypotensive patients, and patients with final diagnoses of asthma, chronic obstructive pulmonary disease, pneumonia, or bronchitis had a higher than expected mortality if erroneously treated for congestive heart failure. Differences in hospital length of stay were not significant for any group.

CONCLUSION: Prehospital medications improve survival in congestive heart failure, especially in critical patients. More than one combination of medications seems effective, and early treatment is associated with improved survival. However, these medications appear to increase mortality in patients misdiagnosed in the field. Factors used in paramedica and medical command assessments require further study.

If treated,

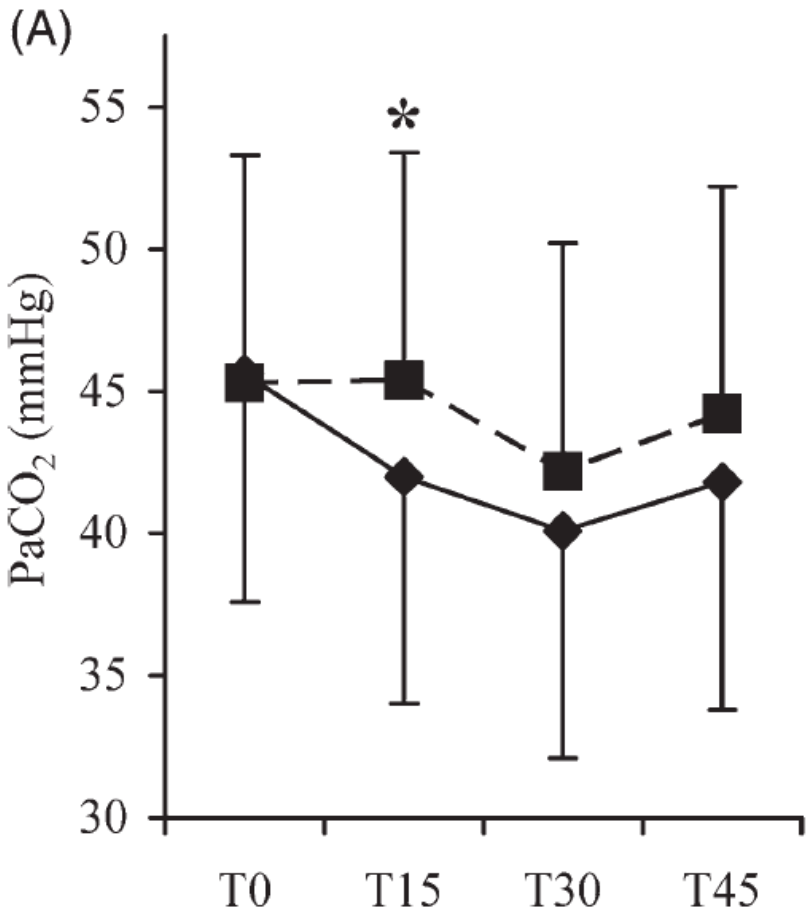
OR of survival 2.51 (1.37-4.55) p<0.01

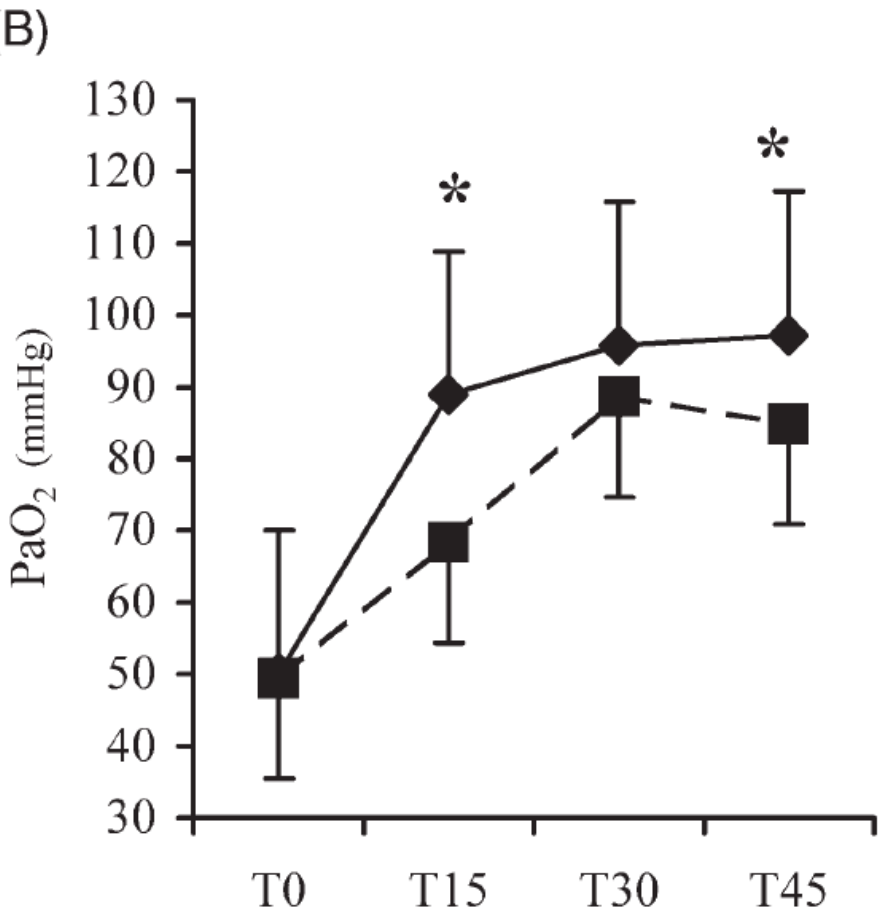
Early CPAP vs Late CPAP



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

Early CPAP vs Late CPAP





* p < 0,05

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

The earlier, the better

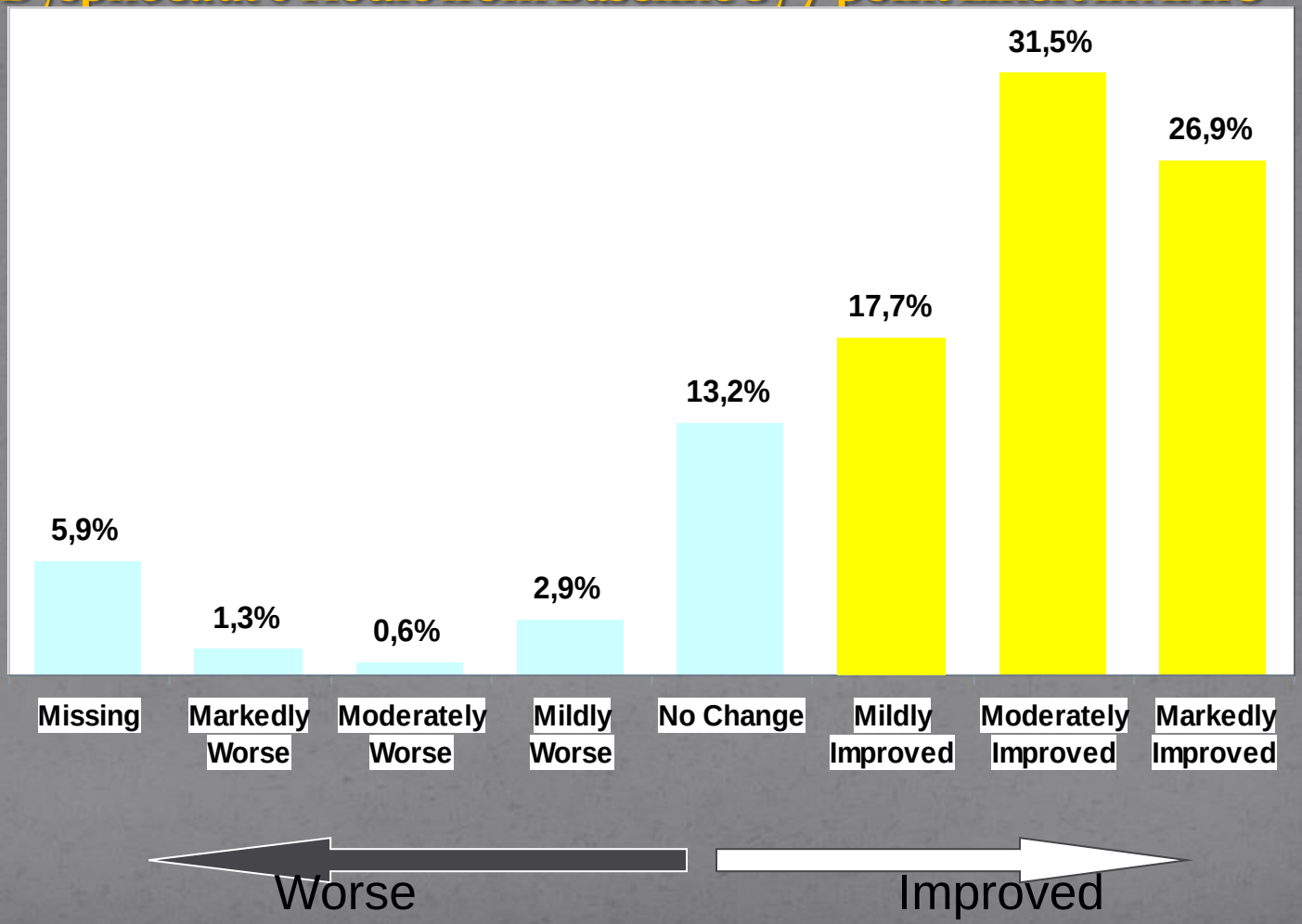
Eur Heart J. 2010 Apr;31(7):832-41. doi: 10.1093/eurheartj/ehp458. Epub 2009 Nov 11.

The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study.

Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, Andre S, Mark Courtney D, Hasa J, Spinar J, Masip J, Frank Peacock W, Sliwa K, Gayat E, Filippatos G, Cleland JG, Gheorghiade M.

Department of Anesthesiology and Critical Care Medicine, INSERM U942, University Paris Diderot, Paris, France.

Dyspnoea at 6 Hours from Baseline by 7-point Likert in AHFS



Mebazaa et al. Eur Heart J 2010;31(7):832-41

- Dyspnea is present in most patients at admission for AHF
- **Orthopnea** could help differentiating AHF from non-AHF
- Most of the patients have dyspnea that is improved within 6 hours
- **VAS** is an excellent tool to measure dyspnea

Mebazaa et al. Eur Heart J 2010;31(7):832-41

- IF dyspnea and «improvement in dyspnea» are the « optimal » or «must» inclusion criteria for trials
- Concerning clinical trials :
  - Who are the patients that are included in the trials and are still dyspneic after 24-48 hours ?
  - If dyspnea is so rapidly improved by conventional treatment, is there any room for « new » agents?

Any recent data?

Serelaxin, Recombinant Human Relaxin-2, For Treatment of Acute Heart Failure (RELAX-AHF): A Randomized, Placebo-controlled Trial

John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini,
Christoph Schumacher, Thomas M Severin, Marco Metra,
for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Lancet. 2013 Jan 5;381(9860):29-39.

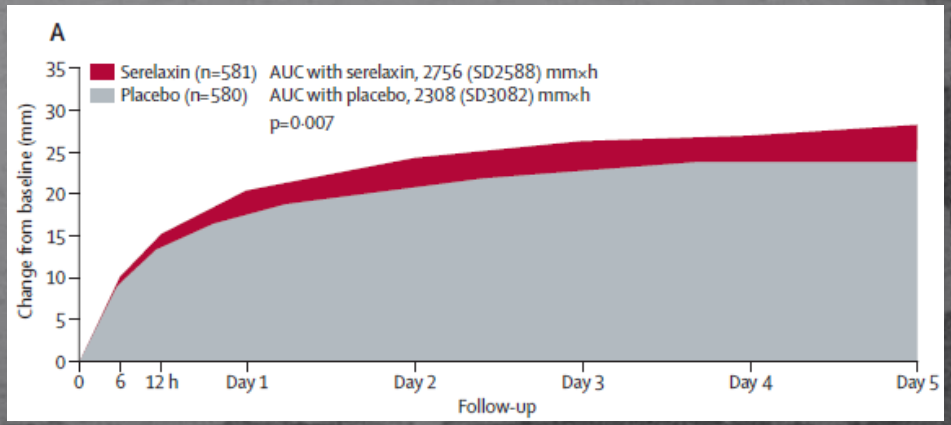
RELAX-AHF Methods

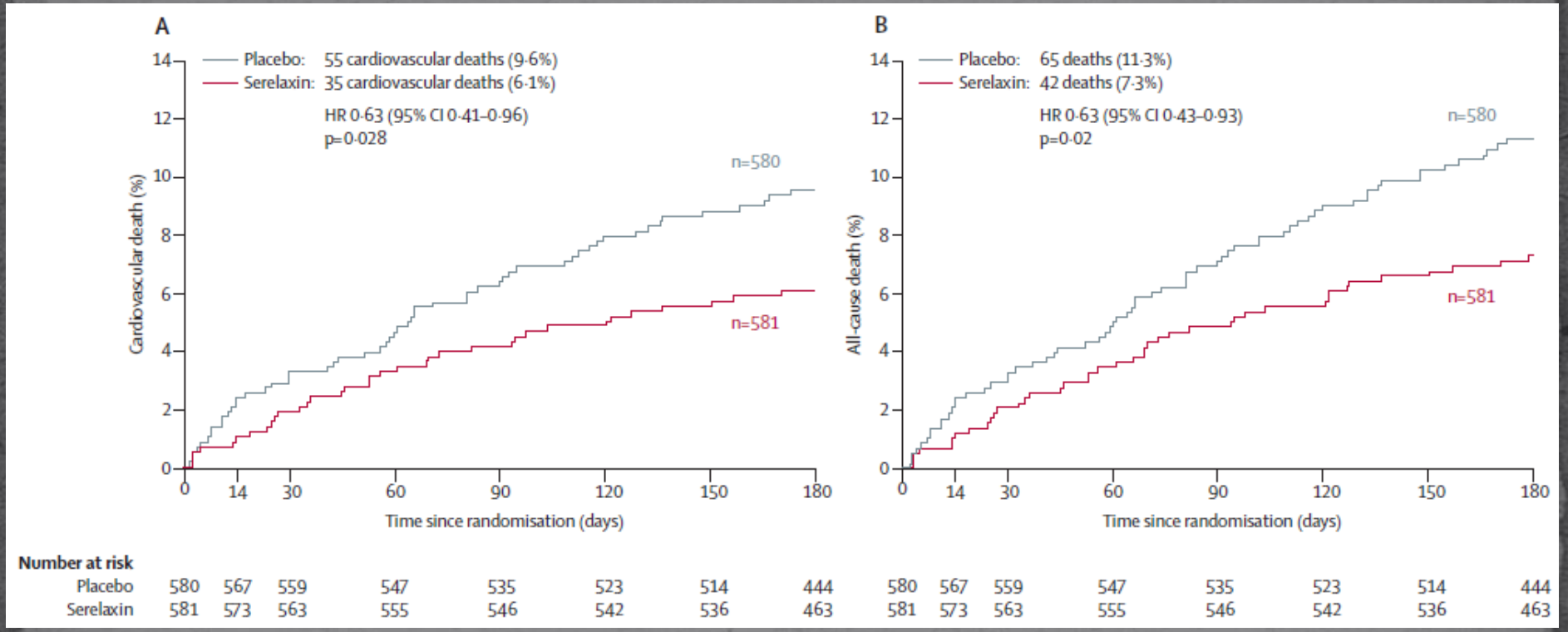
- International, double-blind, placebo-controlled trial
- Patients
  - Admitted to hospital for acute heart failure
  - Randomly assigned to standard care plus 48-h intravenous infusions of placebo or serelaxin (30 µg/kg per day) **within 16 h from presentation.**
  - Dyspnea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP,
    mild-to-moderate renal insufficiency, and systolic blood pressure greater than 125 mmHg.

Teerlink JR, Cotter G, Davidson BA et al. *Lancet*. Epub ahead of print. November 7, 2012.

	Placebo (n=580)	Serelaxin (n=581)
Age (years)	72·5 (10·8)	71·6 (11·7)
Men	357 (62%)	368 (63%)
White	552 (95%)	544 (94%)
Weight (kg)	82·8 (18·7)	81·9 (18·5)
Body-mass index (kg/m²)	29·5 (6·1)	29·1 (5·3)
Region*		
Eastern Europe	282 (49%)	280 (48%)
Western Europe	101 (17%)	103 (18%)
USA	55 (9%)	59 (10%)
Argentina	37 (6%)	34 (6%)
Israel	105 (18%)	105 (18%)
Systolic blood pressure (mm Hg)	142·1 (17·0)	142·2 (16·2)
Diastolic blood pressure (mm Hg)	81·7 (13·2)	82·2 (14·2)
Heart rate (beats per min)	80·4 (14·9)	78·9 (15·0)
Respiratory rate (breaths per min)	22·0 (4·6)	21·8 (4·6)
Time from presentation to randomisation (h)	7·9 (4·7)	7·8 (4·6)
Intravenous nitrates at randomisation	42 (7%)	39 (7%)

Primary endpoint by VAS was met
No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure




A
Placebo: 55 cardiovascular deaths (9·6%)
Serelaxin: 35 cardiovascular deaths (6·1%)
HR 0·63 (95% CI 0·41–0·96)
p=0·028
n=580
n=581
Cardiovascular death (%)
Time since randomisation (days)
B
Placebo: 65 deaths (11·3%)
Serelaxin: 42 deaths (7·3%)
HR 0·63 (95% CI 0·43–0·93)
p=0·02
n=580
n=581
All-cause death (%)
Time since randomisation (days)
Number at risk
Placebo 580 567 559 547 535 523 514 444 580 567 559 547 535 523 514 444
Serelaxin 581 573 563 555 546 542 536 463 581 573 563 555 546 542 536 463

- In RELAX-AHF, a 48-h infusion of serelaxin resulted in mild improvements in measures of dyspnoea, associated with significant reductions in early worsening heart failure events, signs and symptoms of congestion, initial length of hospital stay, and duration of intensive care.
- However, there was no improvement in readmission to hospital for heart failure or renal failure.
- A 37% reduction in cardiovascular and all-cause mortality was also noted in the serelaxin-treated patients.
- Serelaxin mildly reduced blood pressure, and was well tolerated with no notable difference in the overall adverse event profile and a lower rate of renal adverse events compared with placebo.

Clevidipine Improves Dyspnea in ED Acute Heart Failure: A Randomized, Open Label Study

Peacock WF, Baylor College of Medicine, Houston, TX

Chandra A, Kaiser Permanente, Sacramento, CA

Collins S, Vanderbilt University, Nashville, TN

Fonarow G, University of California LA, Los Angeles, CA

Garrison N, Drug Research & Analysis, Montgomery, AL

Mebazaa A, University Paris, Paris, France

Enrollment

TMC-CLV-08-01
PRONTO
A Safety and Efficacy Study of Blood Pressure Control in Acute Heart Failure – Pilot Study

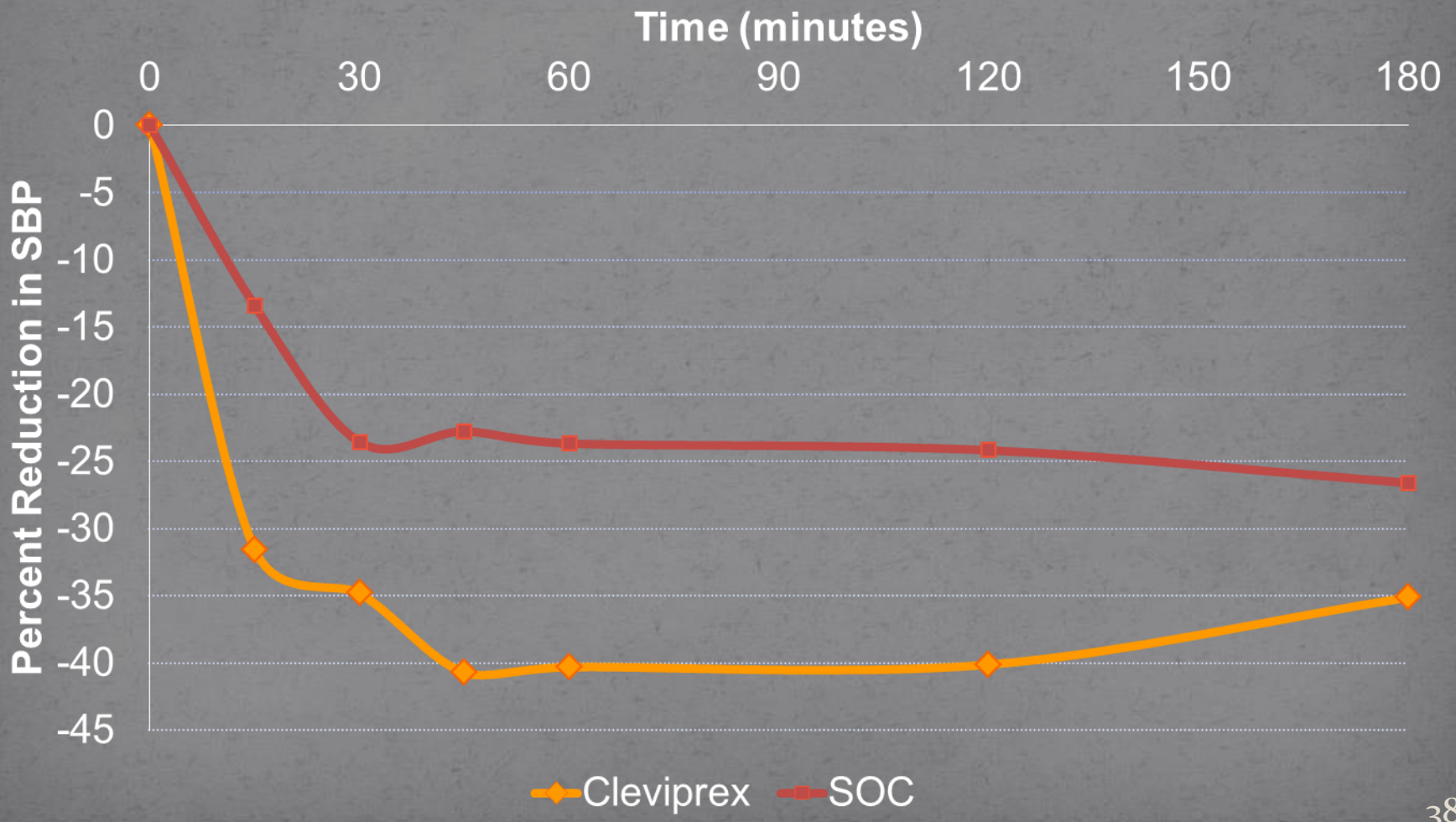
- Physicians generally specified target BP 15%-30% lower than the presentation SBP
- Most patients (86.8%) in the SOC group received
  - Nitroglycerin (56.6%)
  - Nicardipine (30.2%)
- 13.2% in the SOC group received
  - IV ISDN (4), hydralazine (1), diltiazem (1), SNP (1)

Median (IQR) Time To Treatment
(ER door to randomization)
CLV 2.8 hrs (2.2, 3.8)
SOC 2.6 hrs (1.8, 3.6)

Early BP Reduction

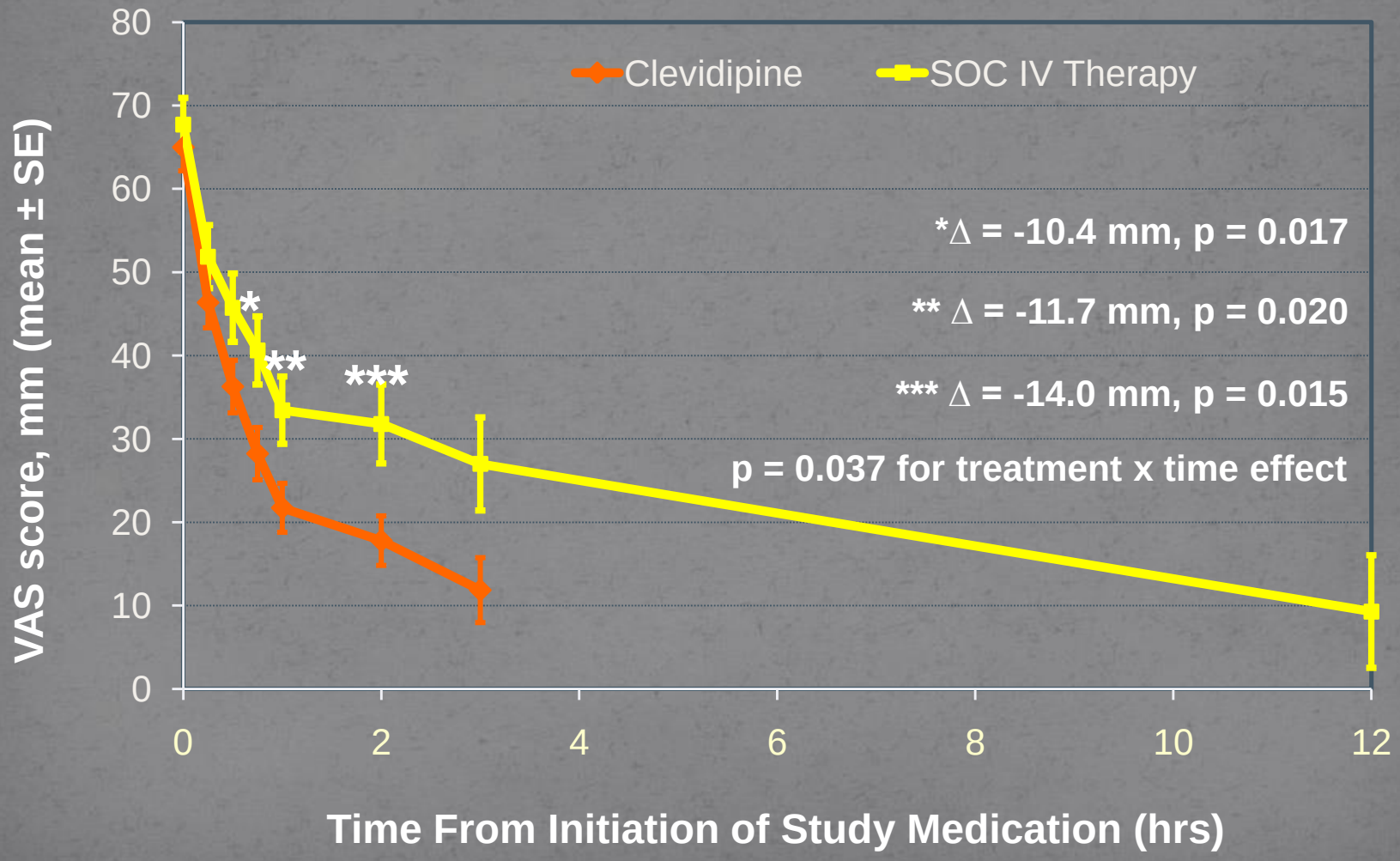
TMC-CLV-08-01
PRONTO
A Safety and Efficacy Study of Blood Pressure Control in Acute Heart Failure – Pilot Study

- Mean Change from Baseline in SBP (mITT)



SECONDARY ENDPOINT

VAS score over time (Confirmed AHF)



Is there a golden hour?

- **Probably yes….**

Suggested Guideline Statement

- All AHF patients should receive appropriate goal directed therapy as soon as possible, regardless of their location.
  - In hypertensive HF patients with significant dyspnoea, treatment with vasodilator therapy should not be delayed pending diagnostic testing.