The new boy in town:

Serelaxin Therapy in Acute Heart Failure

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Disclosure

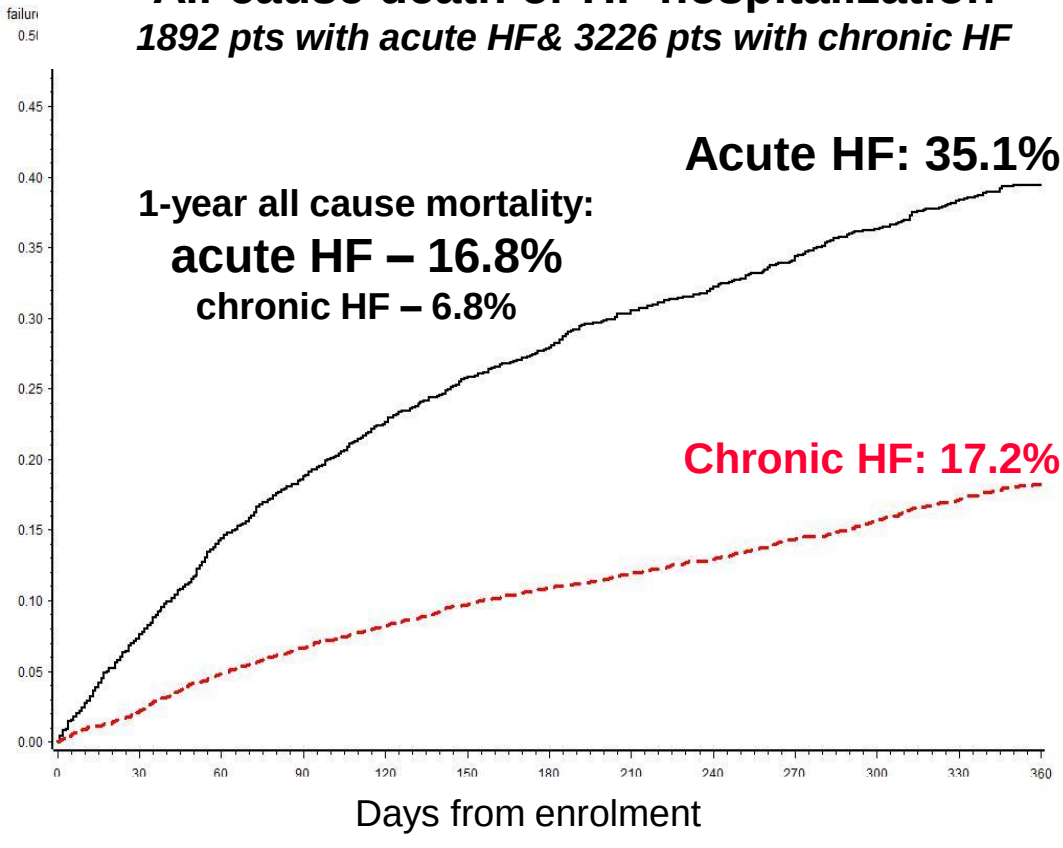
Consultancy fees and speaker’s honoraria from: Corthera, Novartis

Acute Heart Failure: landscape at the beginning of the 21st century

EURO*bservational* Research Program: The Heart Failure Pilot Survey

All-cause death or HF hospitalization

1892 pts with acute HF& 3226 pts with chronic HF



Cardiologist's summary:

„broadly speaking, the pharmacological armamentarium for AHFS – **loop diuretics, vasodilators and inotropes** – is largely ***unchanged from 1970s***…"

Felker GM et al., Circ Heart Fail 2010;3:314-25

Cardiologist's question:

Why all successful phase II studies are followed by failures in phase III trials ?

Do we need shift in a „AHF paradigm" ?

A. Maggioni ESC 2011

Long-term benefit from short-term intervention: ever possible ?

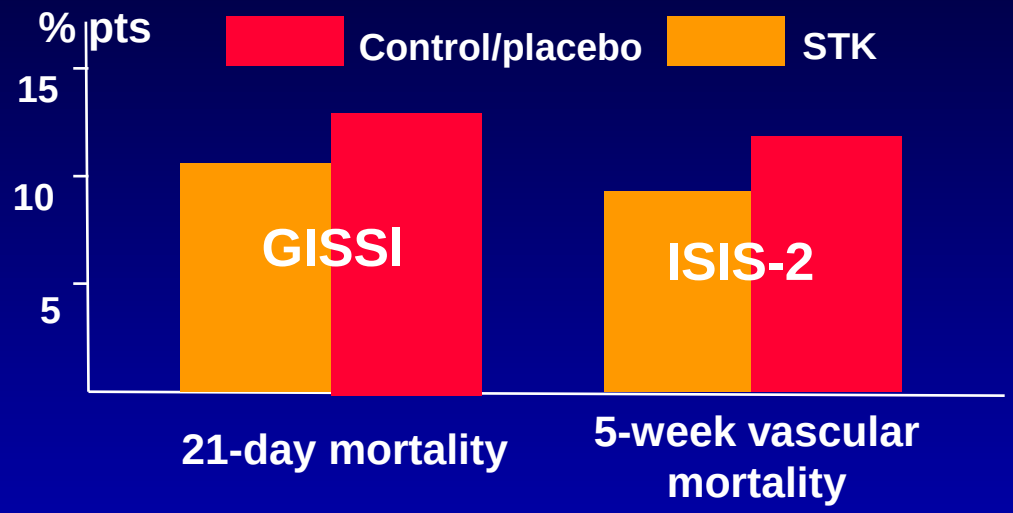
Initial, short-term therapies (hours-days)

Target	„Traditional" therapeutic approach	**Effects on long-term outcome**
Alleviate congestion	i.v. diuretics	**?** **May be detrimental**
Reduce ↑ LV filling pressure	i.v. nitrates	**?** **Potentially favourable**
Hypoperfusion Poor cardiac performance	i.v. inotropes	**Detrimental**

Dissociation between symptomatic improvement & clinical stabilisation and better long-term outcome

Modified from Pang PS et al. Eur Heart J 2010;31:784-93

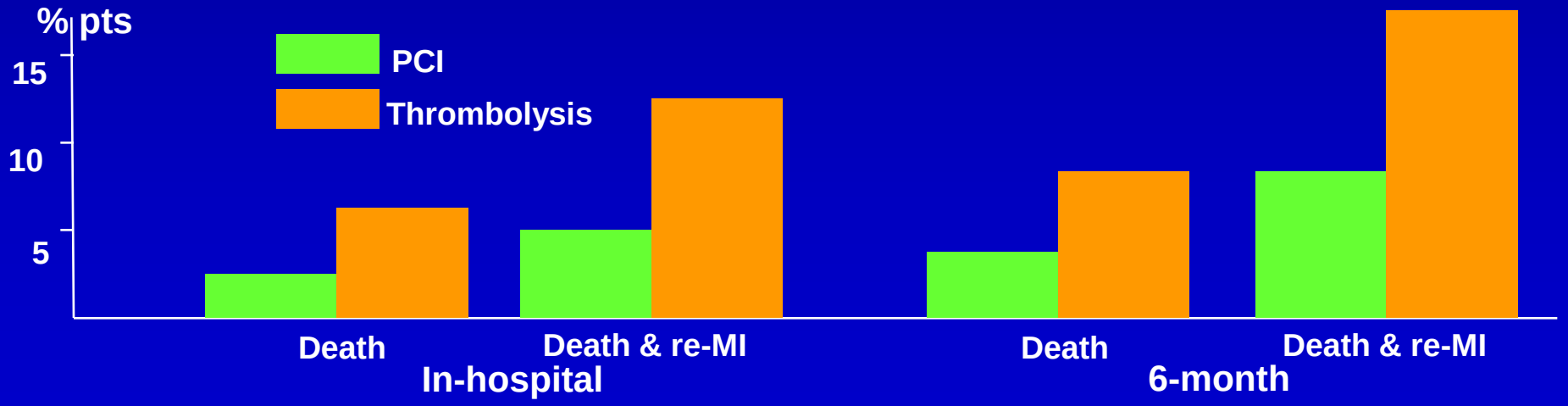
Lessons from ACS trials:
short-term intervention can result in long-term benefit



ISIS-2 follow-up

Period of follow up	No of deaths/ No of patients (% dead)		Death rate ratio (CI*)	Death rate ratio (CI*)
	Streptokinase infusion	Placebo infusion		
Subtotal: Days 0-35	796/8592 (9.3)	1045/8595 (12.2)		0.75 (0.69 to 0.83)
Day 36-year 1	475/7702 (6.2)	516/7460 (6.9)		0.89 (0.75 to 1.05)

Baigent C et al. BMJ 1998;316:1337-43



Grines CL et al. NEJM 1993;328:673-9

Need for paradigm shifting in acute heart failure:
short-term intervention and long-term goals (?)

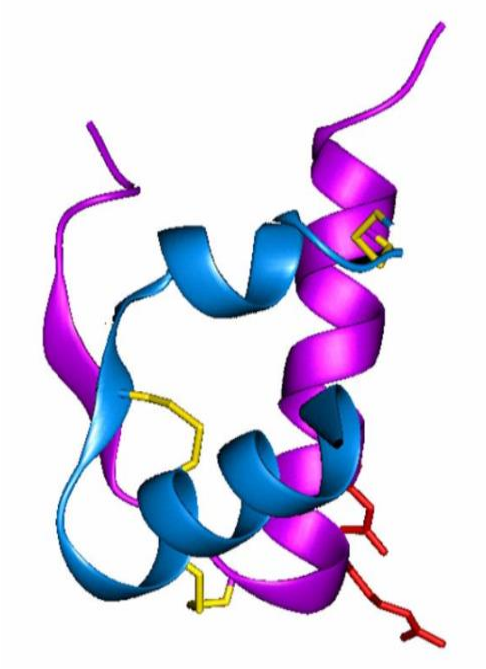
What is needed ?

- **Targeted-approach = characterizing patient' clinical profile**
  different pathophysiologies & therapies for different clinical profiles (?)

- **An ideal drug / intervention**
  symptomatic improvement, „end-organ" protection,
  improvement in neurohumoral and proinflammtory profile

- **Appropriate timing = early administration of therapy**
  „the earlier the better" (?)
  → **prevention of tissue damage;**
  → **phase of severe symptoms;**
  → **early clinical stabilization & chance to introduce disease-modifying therapies**

Serelaxin is a recombinant form of human relaxin-2



Relaxin

- **Relaxin-2 is a naturally occurring peptide hormone which mediates systemic hemodynamic and renal adaptive changes during pregnancy**
- **Structure of human relaxin-2: 53 amino acids (2 chains connected by 2 disulphide bonds)**
- **Human relaxin-2 is one of seven peptides in the relaxin family of hormones**
- **Each of these seven peptides is structurally and functionally distinct**
- **Relaxin-2 mediates its effects via specific G-protein-coupled receptors: RXFP1 (LGR7) and RXFP2 (LGR8)**
- **Relaxin-2 receptors are localized in many blood vessels**

Teichman et al. Heart Fail Rev 2009;14:321–9; Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87
Kong et al. Moll Cell Endocrinol 2010;320:1–15

Human relaxin-2 contributes to renal and cardiovascular adaptive changes in pregnancy

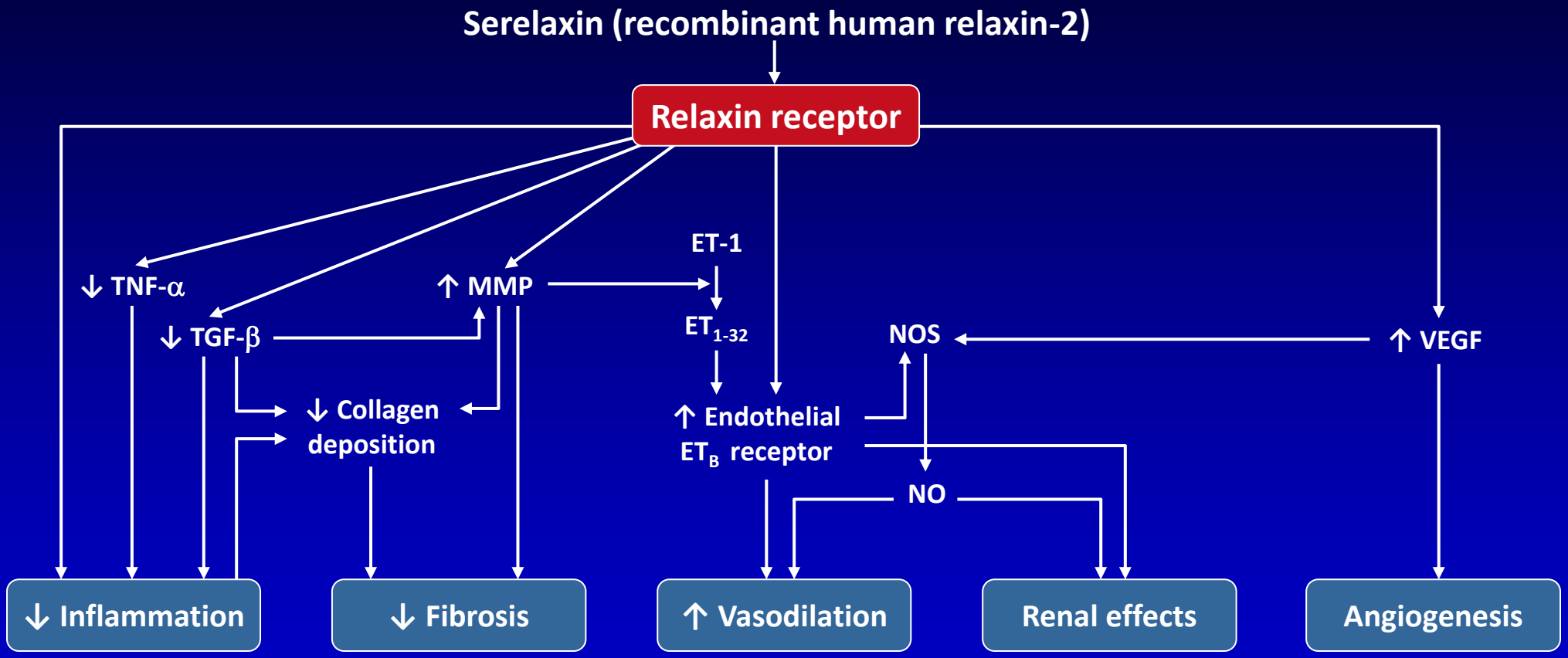
Parameter	Pregnancy
Cardiac output (L/min)	20% increase
Systemic vascular resistance (dyn.s.cm^2)	30% decrease
Global arterial compliance (mL/mmHg)	30% increase
Creatinine clearance (mL/min)	45% increase

- Levels are elevated in circulation in the first trimester of pregnancy and throughout 9 months

Teichman et al. Heart Fail Rev 2009;14:321–9; Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87; Sherwood. The Physiology of Reproduction. Acad Press 1994; 61–1009

Serelaxin Is NOT Just Another Vasodilator

Non-clinical and clinical evidence suggest that relaxin-2 may have additional effects



- The mechanism of action of relaxin/serelaxin involves upregulation of the endothelin type B (ET_B) receptor
- The ET_B receptor mediates: (1) increased systemic and renal vasodilation, (2) natriuresis, and (3) clearance of ET-1

ET_B receptor = endothelin receptor type B; ET-1= endothelin-1; MMP = matrix metalloproteinase; NO = nitric oxide; NOS = nitric oxide synthase; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

Teichman SL, et al. Curr Heart Fail Rep. 2010;7(2):75-82.

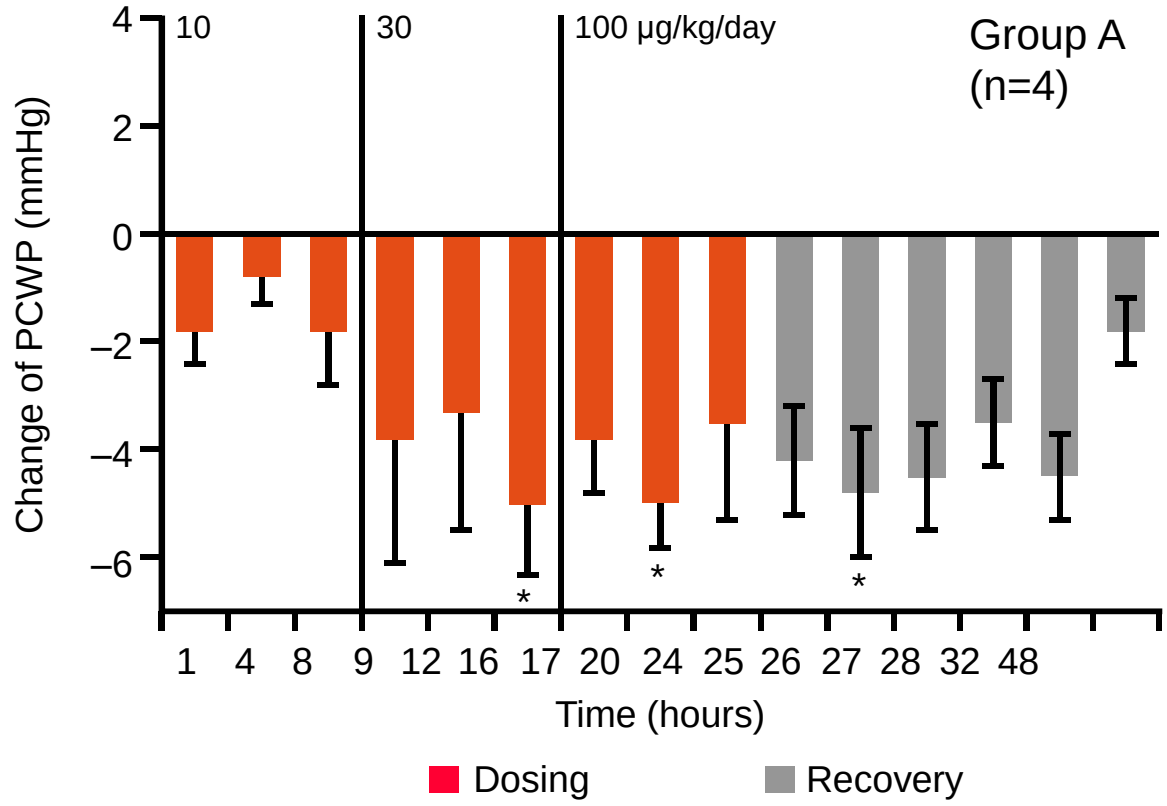
Serelaxin: proof of concept in heart failure

Reduction in left ventricular filling pressure

Open-label pilot study of serelaxin in 16 patients with stable chronic HF‡

Serelaxin:

- **reduced pulmonary capillary wedge pressure**
- **increased cardiac output**
- **improved renal function during infusion**
- **no abnormalities regarding vital signs, clinical status, electrocardiogram, serum chemistry, and hematology parameters, and no relevant adverse events at the doses tested (10–960 µg/kg/day)**

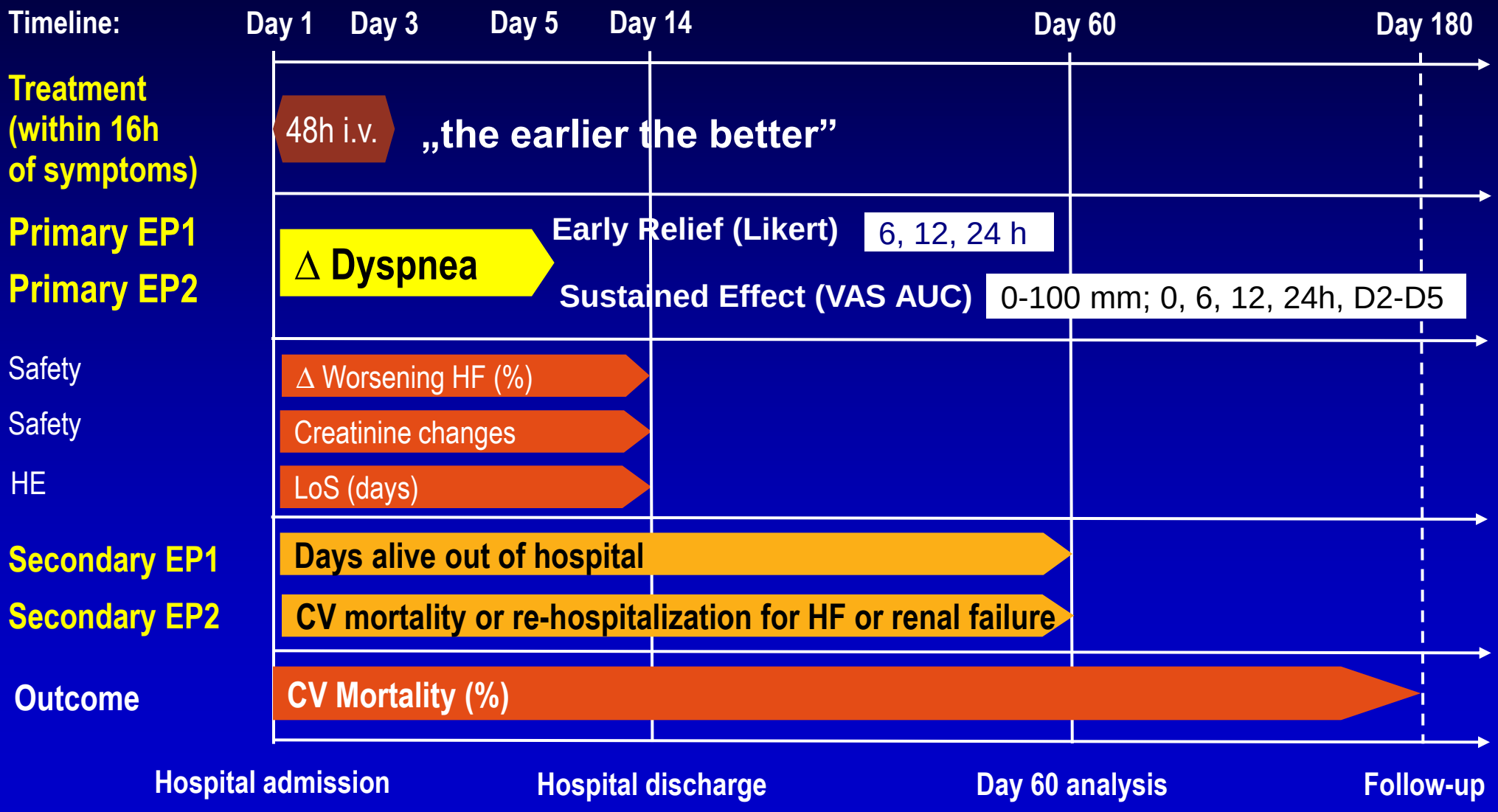


*p<0.05 vs. baseline

‡3 dose escalation cohorts: Group A (8-hour sequential i.v. infusions at 10, 30, 100 µg/kg/day); Group B (240, 480, 960 µg/kg/day); Group C (24-hour infusion at 960 µg/kg/day)

Dschietzig et al. J Card Failure 2009;15:182–90

Pre-RELAX-AHF and RELAX-AHF: clinical trials testing the efficacy of serelaxin in AHF

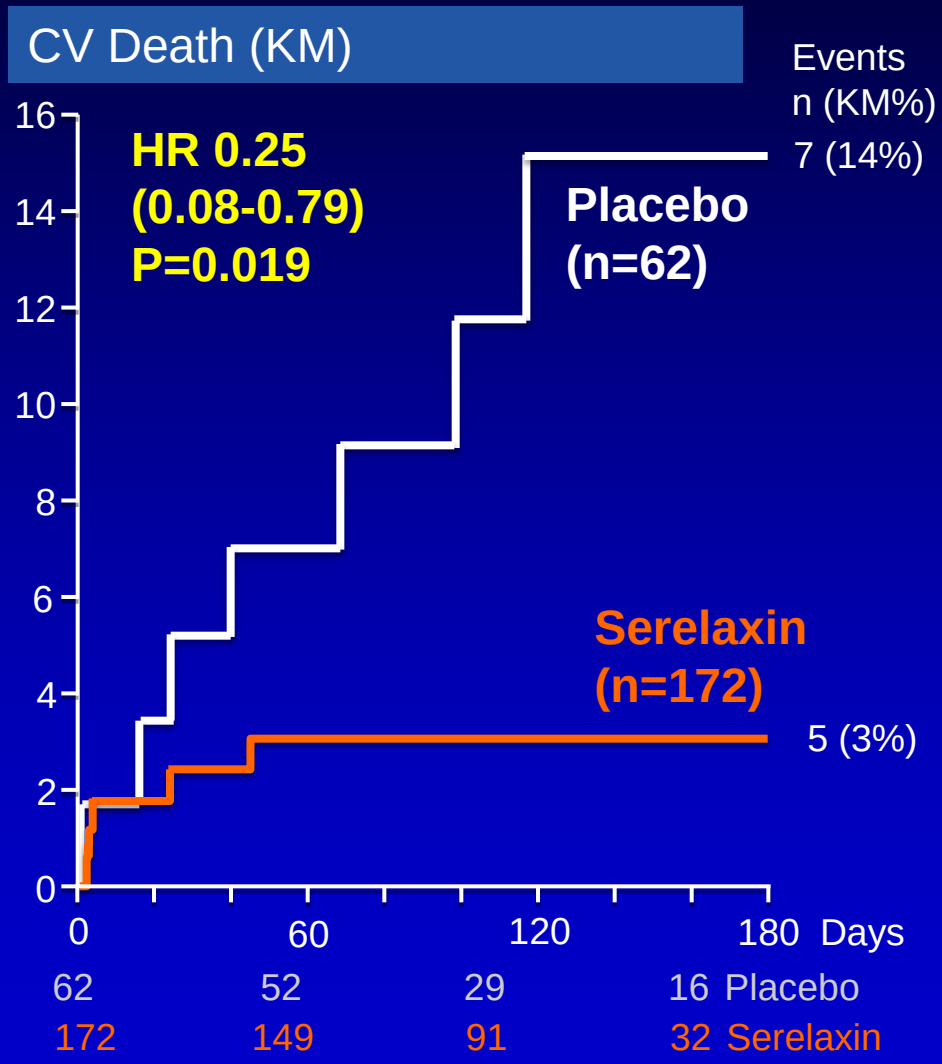


Teerlink et al. Lancet 2009;373:1429–39; Clinicaltrials.gov 2009 (NCT00520806)

Pre-RELAX-AHF

Teerlink JR, *et al. Lancet* 2009;373:1429-39.

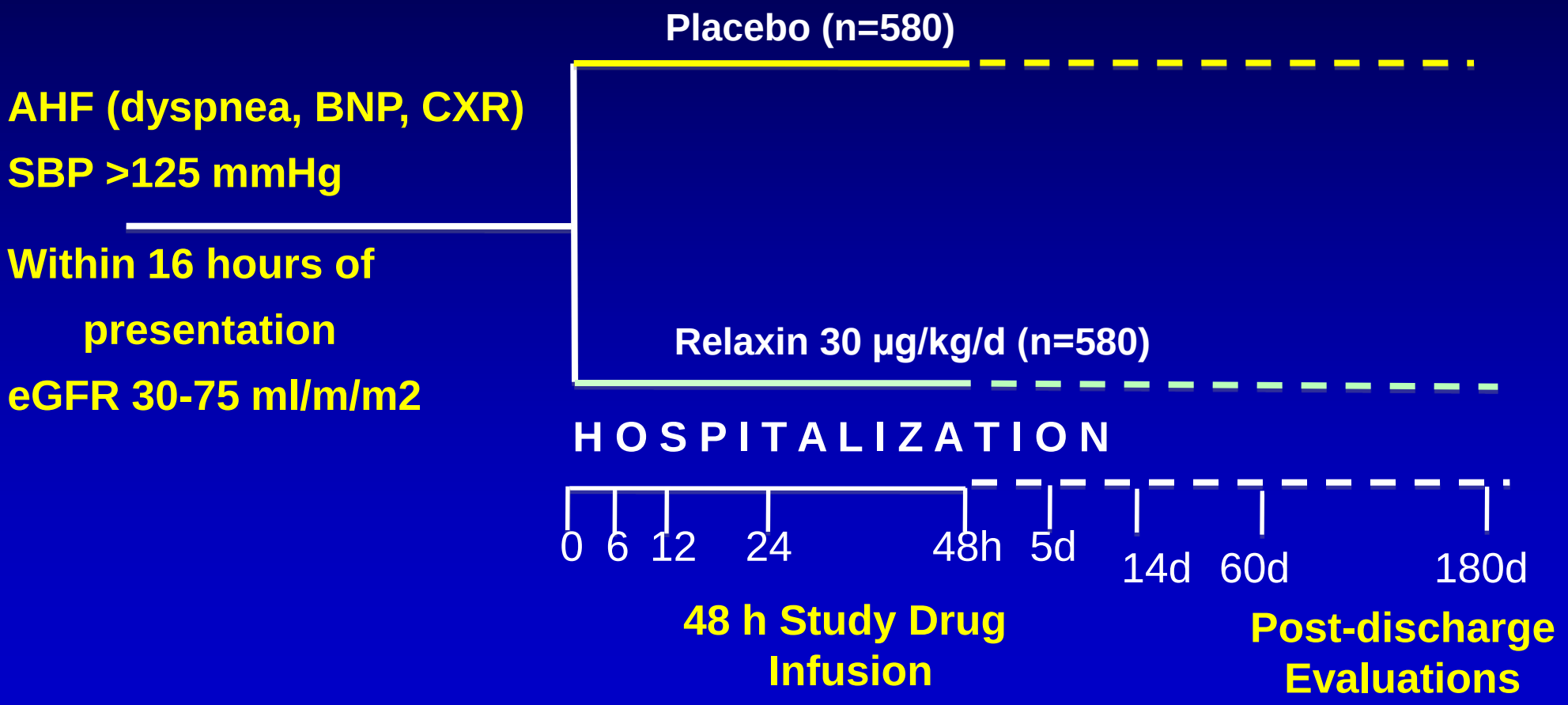
- 234 patient, dose-finding, Phase II study
- Optimal dose across multiple clinical outcome domains was 30 mcg/kg/d
- Serelaxin had <u>trends</u> to:
  - Improve dyspnea relief
  - Decrease congestion
  - Reduce diuretic use
  - Limit worsening of heart failure
  - Shorten length of stay
  - Increase days alive out of hospital
  - Improve cardiovascular and all-cause survival
- Safe and well-tolerated without significant hypotension



Teerlink J. LBCT Presentation, AHA 2012

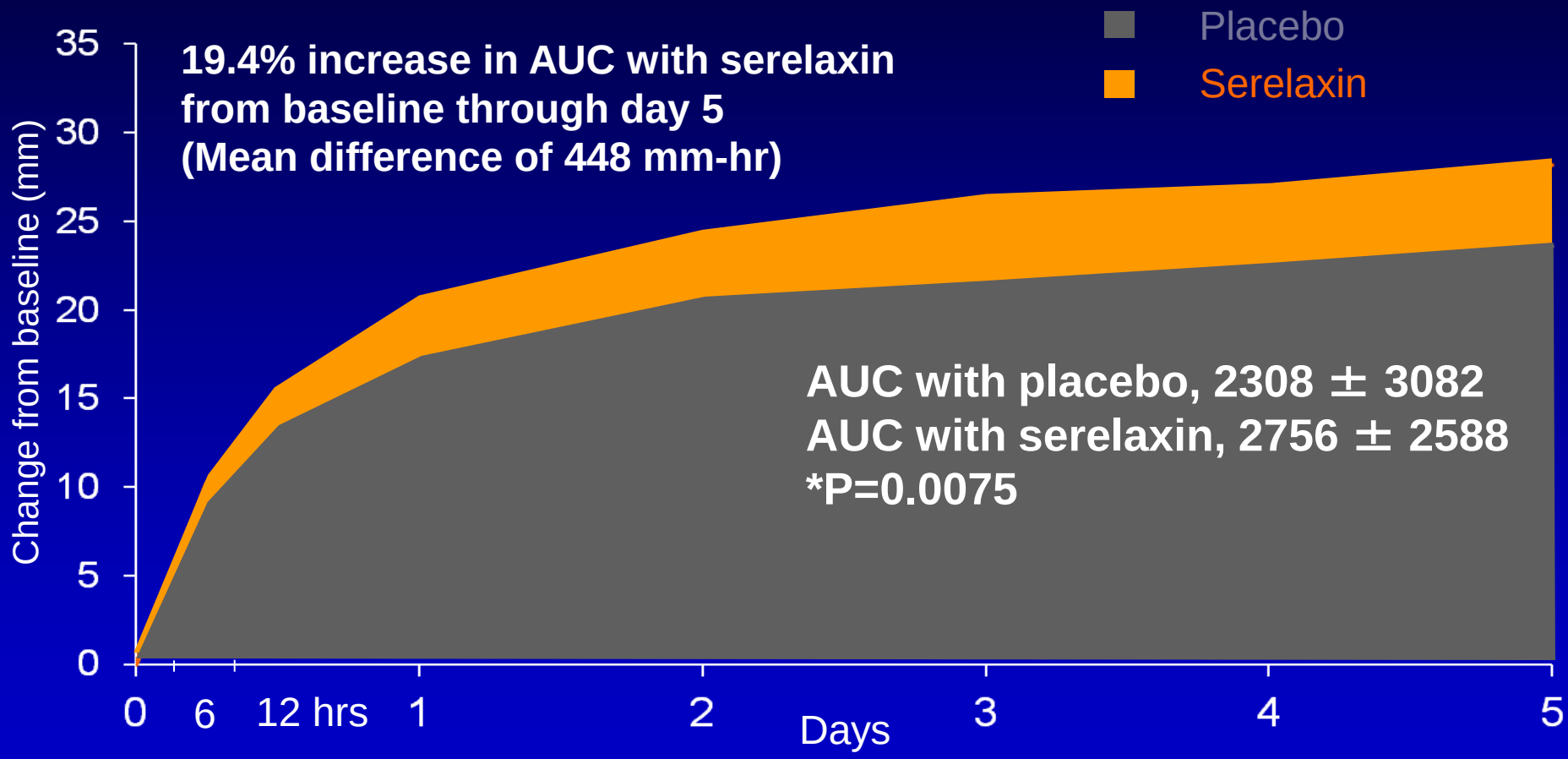
RELAX-AHF: Study Design

Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study



Ponikowski et al. Am Heart J 2012;163:149-155.e1

1˚ Endpoint: Dyspnea Relief (VAS AUC)



RELAX-AHF

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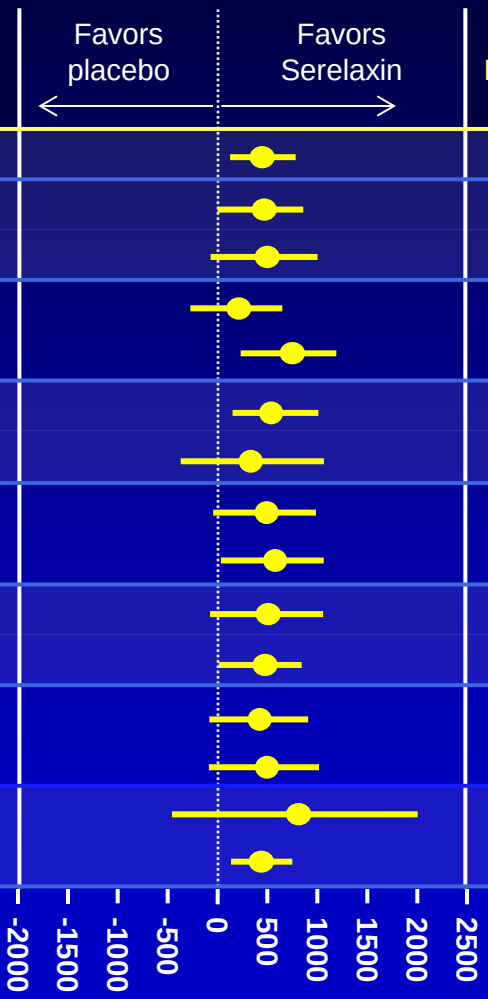
VAS Results Consistent across all Subgroups

Subgroup		Placebo N	Serelaxin N	LS mean difference Estimate (95%CI)	Interaction P value
Total population		580	581	448 (120, 775)	
Gender	Male	357	368	441 (26, 855)	0.92
	Female	223	213	474 (–61, 1009)	
Age	<75 years	296	315	192 (–260, 644)	0.11
	≥75 years	284	266	725 (249, 1202)	
eGFR	<60 mL/min	408	409	504 (113, 895)	0.55
	≥60 mL/min	160	155	280 (-350, 910)	
SBP	<140 mmHg	284	298	436 (–27, 899)	0.82
	≥140 mmHg	294	279	513 (47, 980)	
HF Past Year Hospitalization	Yes	180	214	488 (–75, 1051)	0.88
	No	400	367	433 (28, 838)	
LVEF	<40%	295	303	378 (–71, 828)	0.83
	≥40%	244	249	454 (–41, 949)	
IV nitrates at baseline	Yes	42	39	808 (–435, 2050)	0.56
	No	538	542	421 (81, 761)	

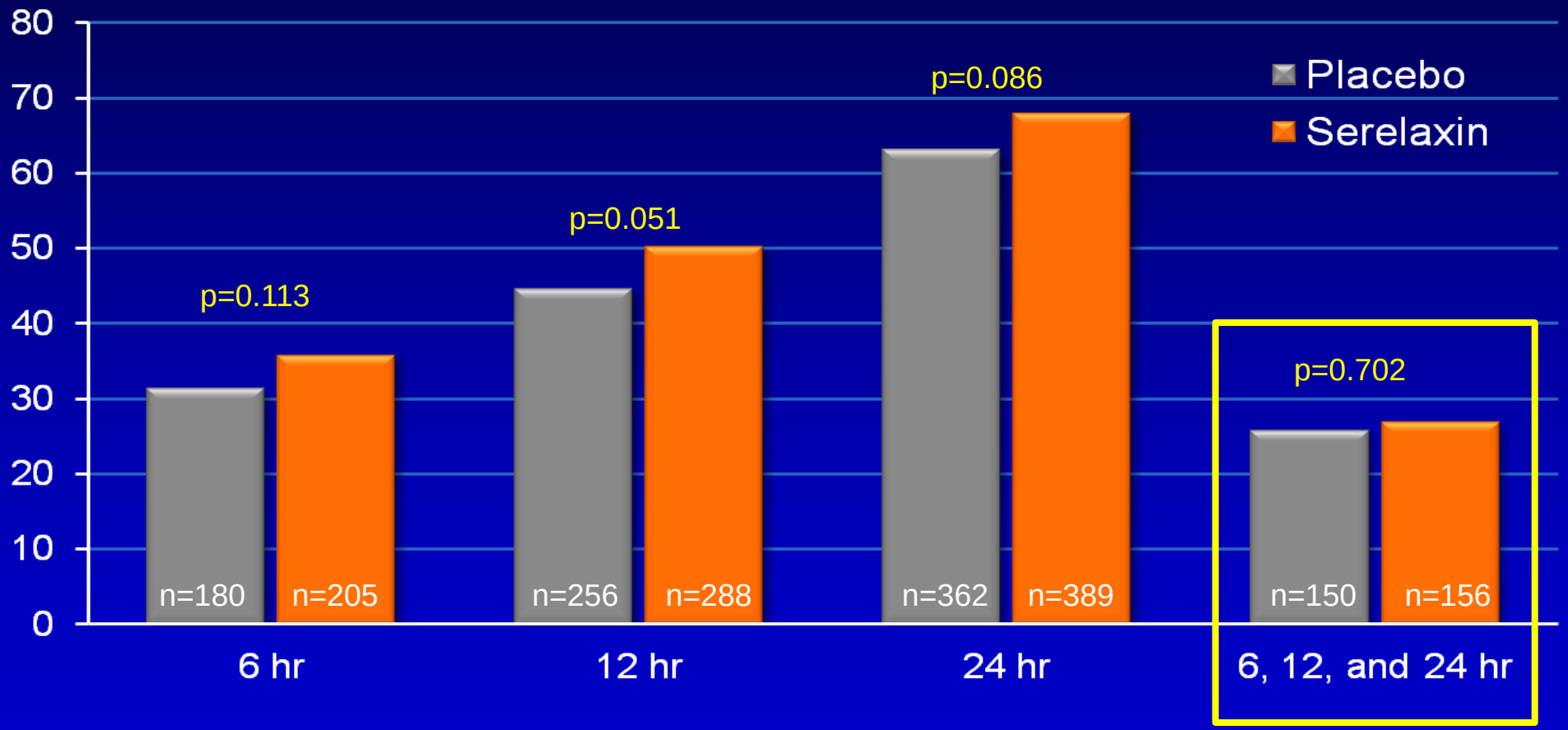


Metra et al., EHJ, 2013

AUC=area under the curve; HF=heart failure; LS=least squares; VAS=visual analogue scale;

1°Endpoint: Dyspnea Relief (Likert)

Proportion of subjects with moderately or markedly better dyspnea by Likert by time point

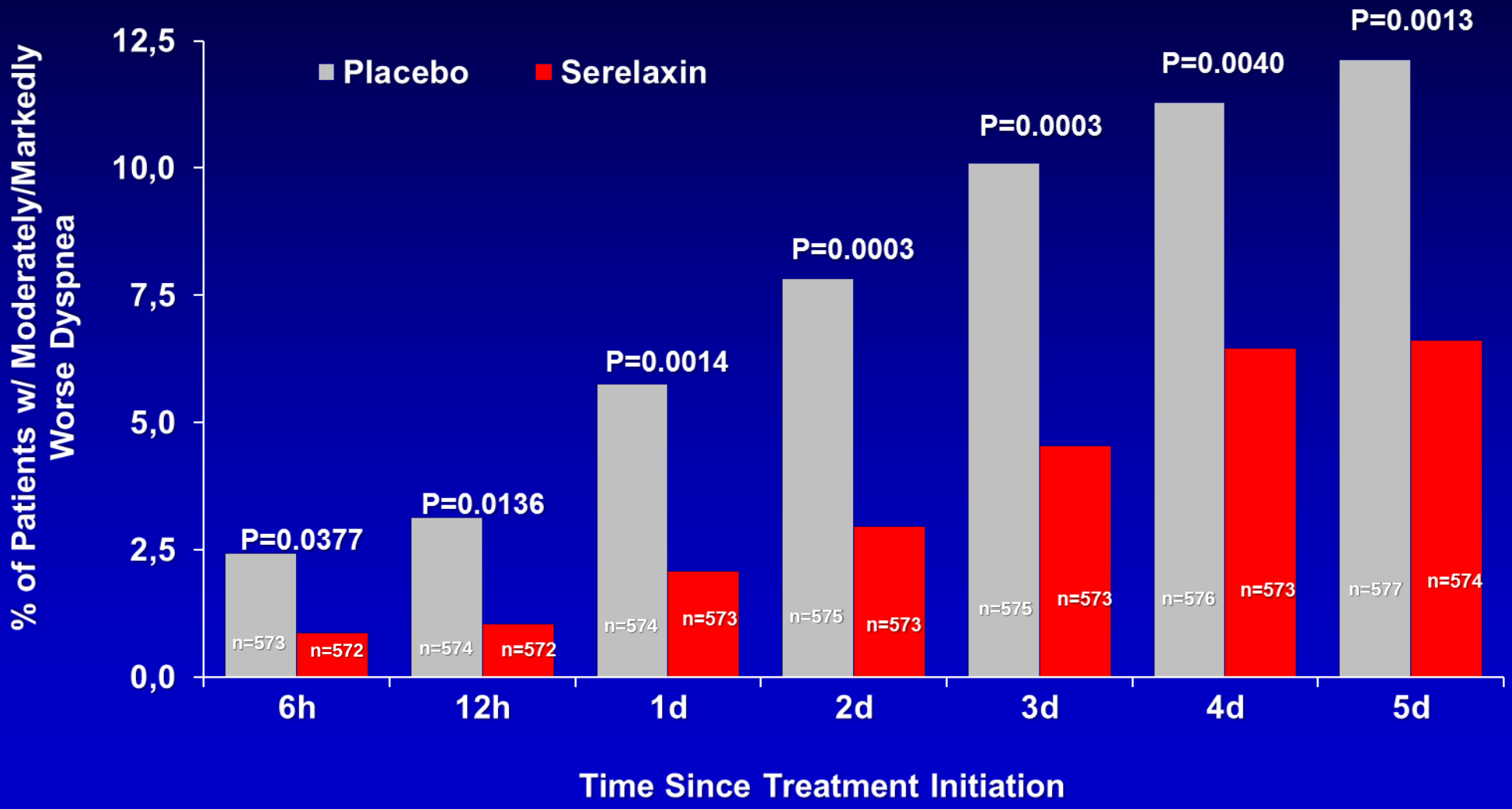


RELAX-AHF

Teerlink J. LBCT Presentation, AHA 2012

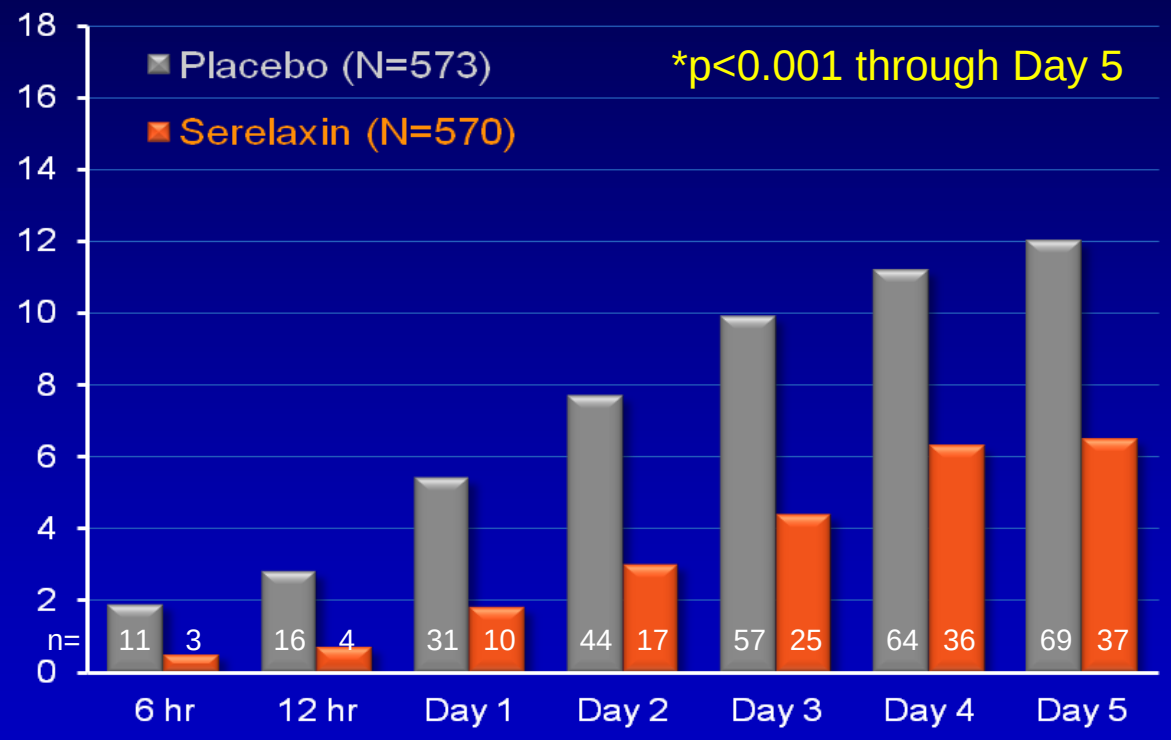
Moderately or Markedly Worsening of Dyspnea on the Likert Scale

Less worsening than placebo at all time points through Day 5

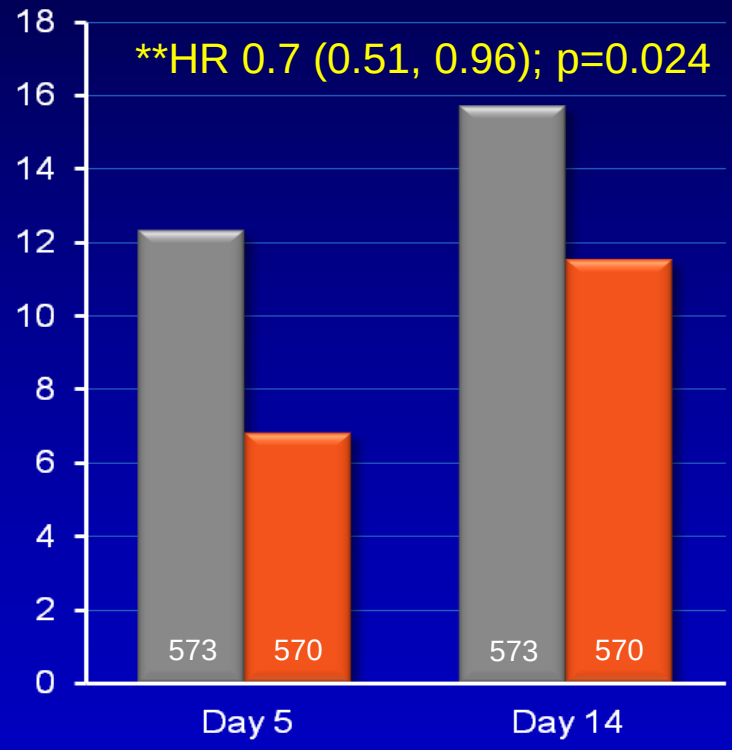


RELAX-AHF: Worsening of Heart Failure

Cumulative proportion of worsening heart failure to Day 5 (%)



Kaplan-Meier estimate for time to WHF (%)



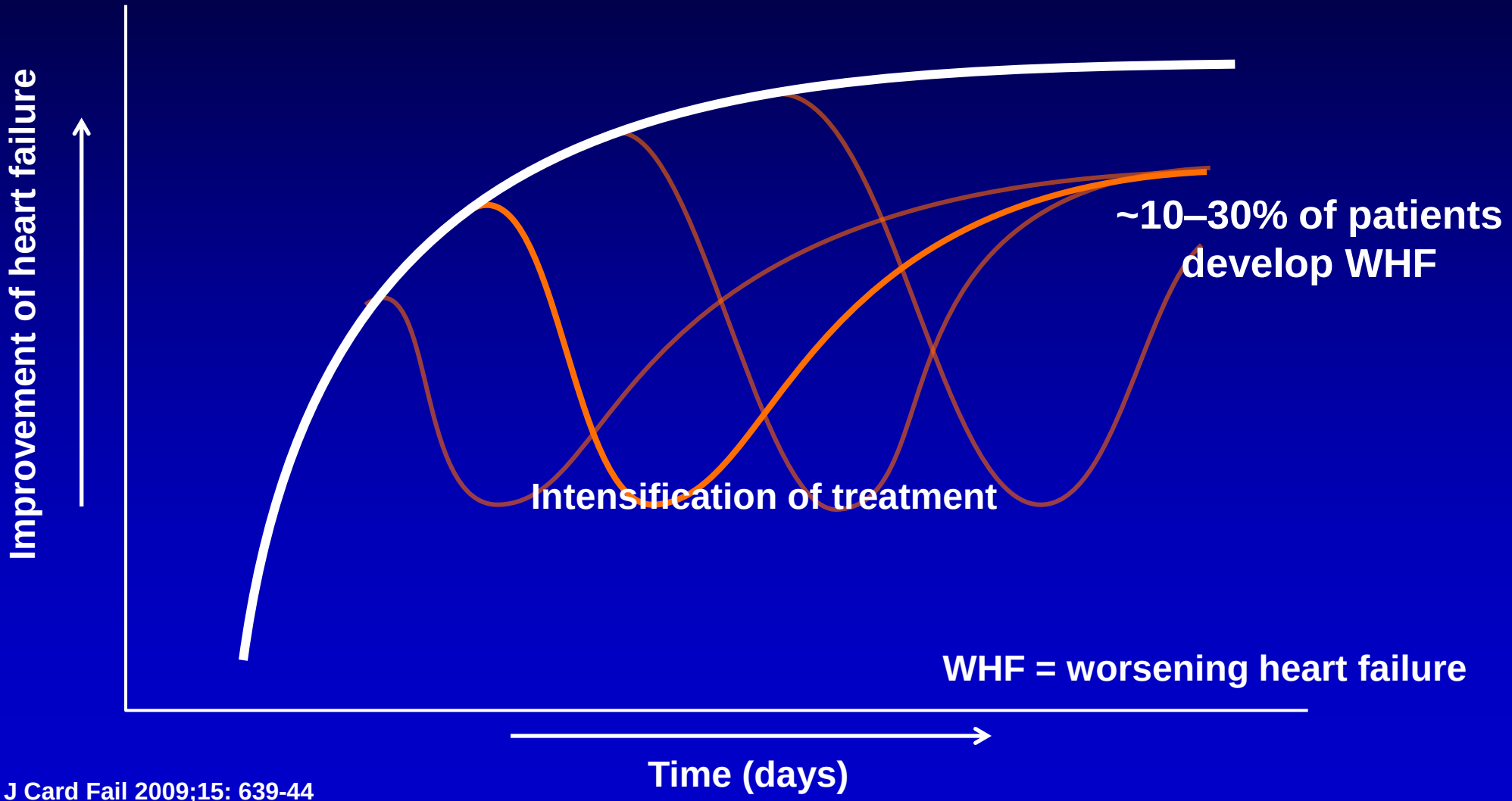
Worsening Heart Failure (WHF) - worsening signs and/or symptoms of HF that required an intensification of IV therapy for heart failure or mechanical ventilatory or circulatory support.

p value by Wilcoxon test **p value by log rank test for Serelaxin vs. Placebo; HR estimate by Cox model, HR<1.0 favors Serelaxin

RELAX-AHF

Teerlink J. LBCT Presentation, AHA 2012

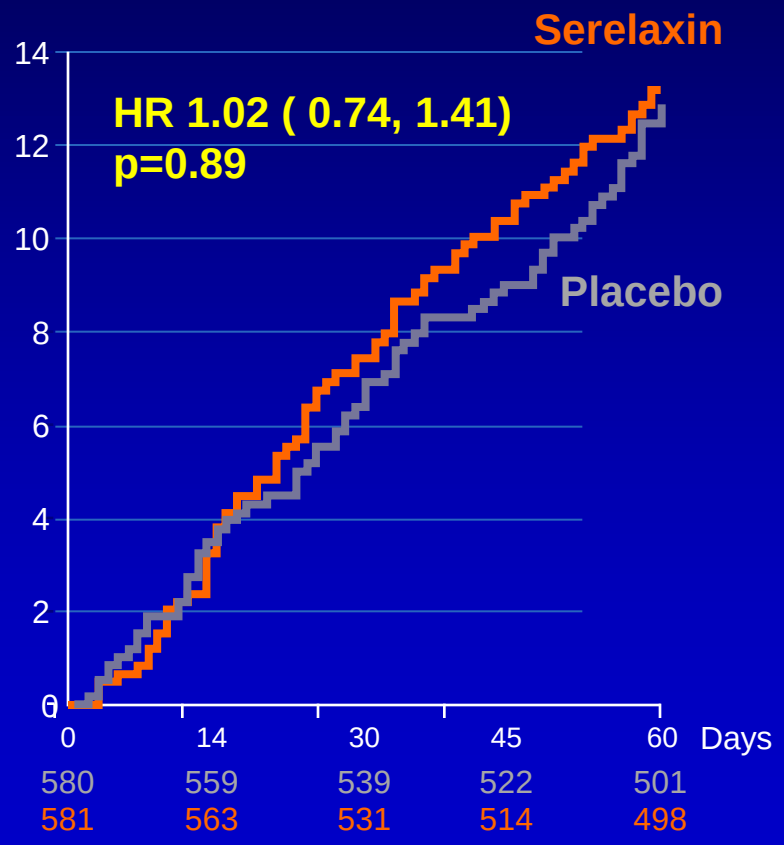
Variability in the clinical course of AHF: steady improvement vs. worsening



J Card Fail 2009;15: 639-44
Fundam Clin Pharmacol 2009;23:633-9 f

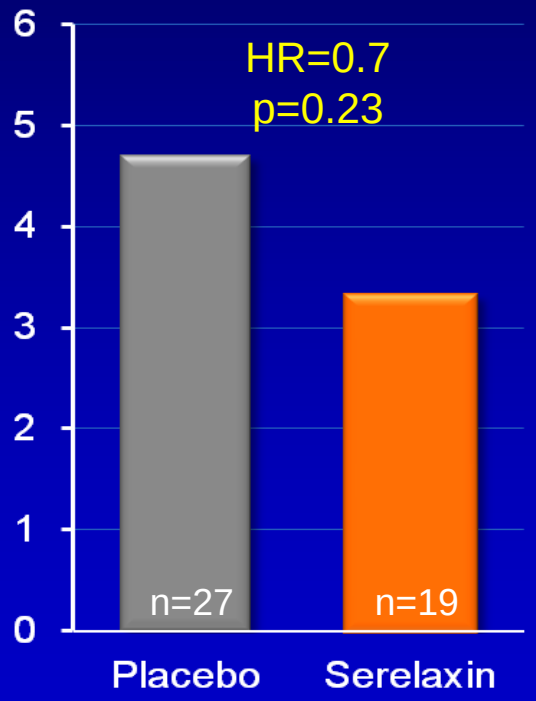
2°Endpoint: CV Death or Heart Failure / Renal Failure Re-hospitalization through Day 60

K-M estimate for time to first CV Death or HF/RF re-hosp (%)

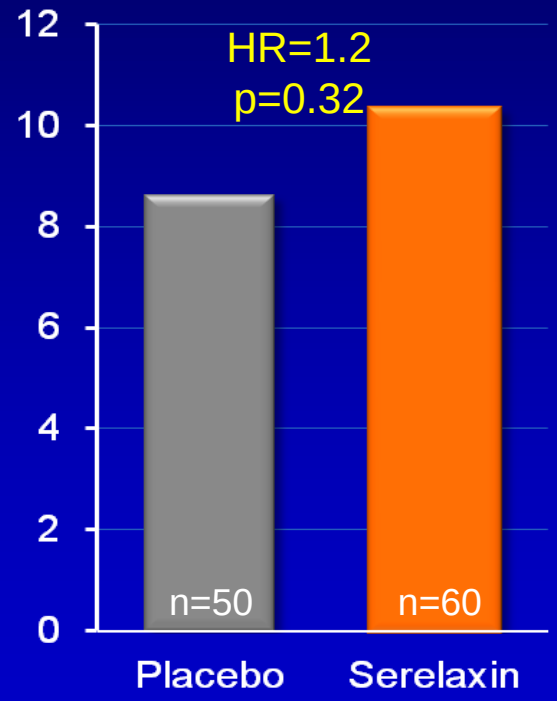


Composite event components (%)

CV death: (% subjects)



HF/RF re-hospitalization (% subjects)



RELAX-AHF

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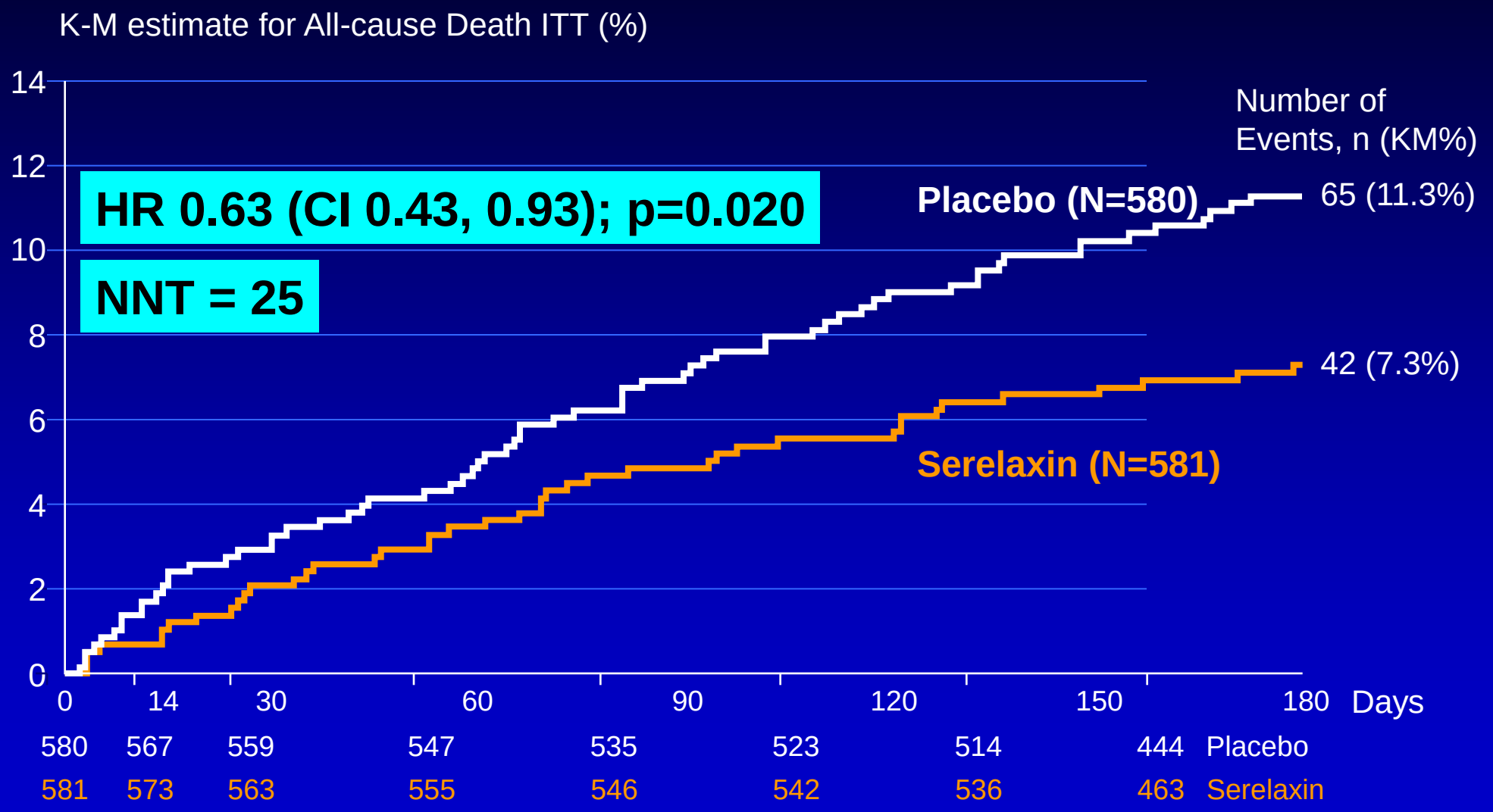
All-cause Death through Day 180



RELAX-AHF

Teerlink J. LBCT Presentation, AHA 2012

RELAX-AHF: Incidence of AEs/SAEs to Day 14

	Placebo (N=570) n (%)	Serelaxin (N=568) n (%)
Subjects with any AE	320 (56.1)	305 (53.7)
Subjects with any drug-related AE	**46 (8.1)**	**47 (8.3)**
Subjects with AE leading to study drug d/c	**22 (3.9)**	**26 (4.6)**
Hypotension-related AE (through day 5)	**25 (4.4)**	**28 (4.9)**
Renal Impairment-related AE (through day 5)	**49 (8.6)**	**26 (4.6)***
Subjects with any SAE	78 (13.7)	86 (15.1)
Subjects with any drug-related SAEs	**2 (0.4)**	**3 (0.5)**
Subjects with SAE leading to drug d/c	**3 (0.5)**	**5 (0.9)**
Serious AE with an outcome of death	**15 (2.6)**	**10 (1.8)**

The number of subjects with any AE includes all AEs and SAEs reported through Day 14.
Non-serious AEs were collected through Day 5, SAEs through Day 14

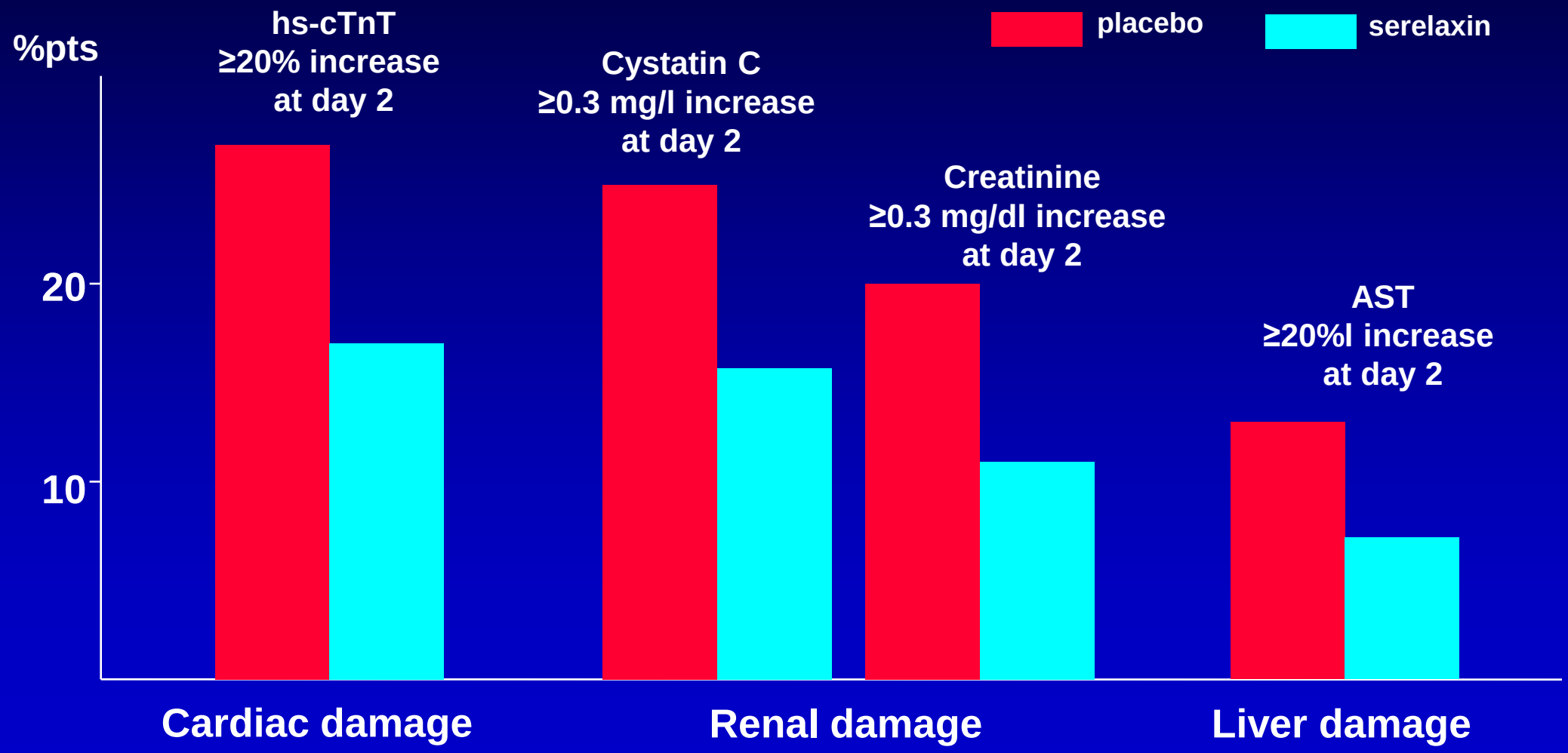
RELAX-AHF

Teerlink J. LBCT Presentation, AHA 2012

Mechamisms of Action of Serelaxin

- Beneficial effects of serelaxin in patients with AHF
  - Improvement in dypsnea
  - Improvement in signs and symptoms of heart failure
  - Preventing worsening heart failure
  - Reducing (CV) mortality
- How is serelaxin doing this?

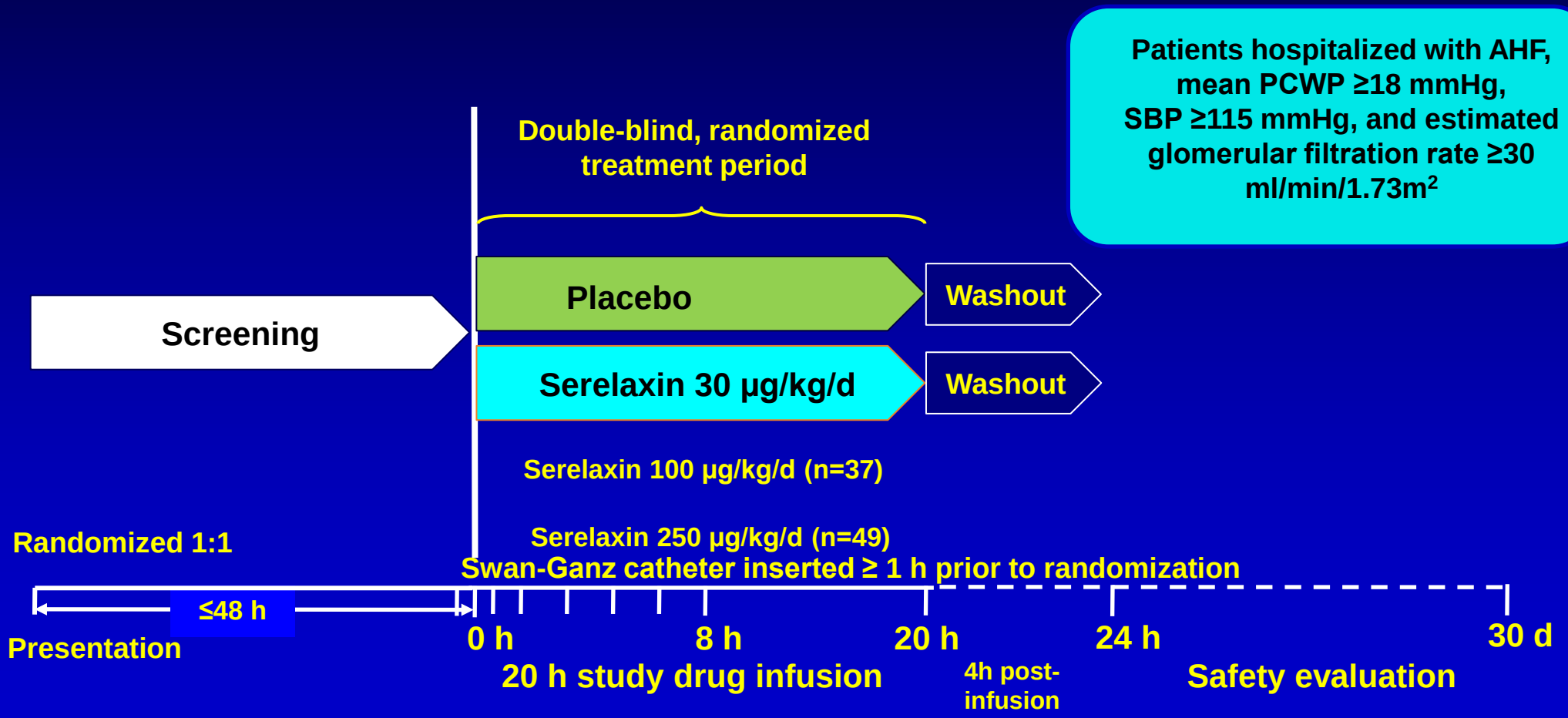
Changes from baseline in biomarkers related to organ damage in the RELAX-AHF study



Metra M et al. JACC 2013;61:196-206

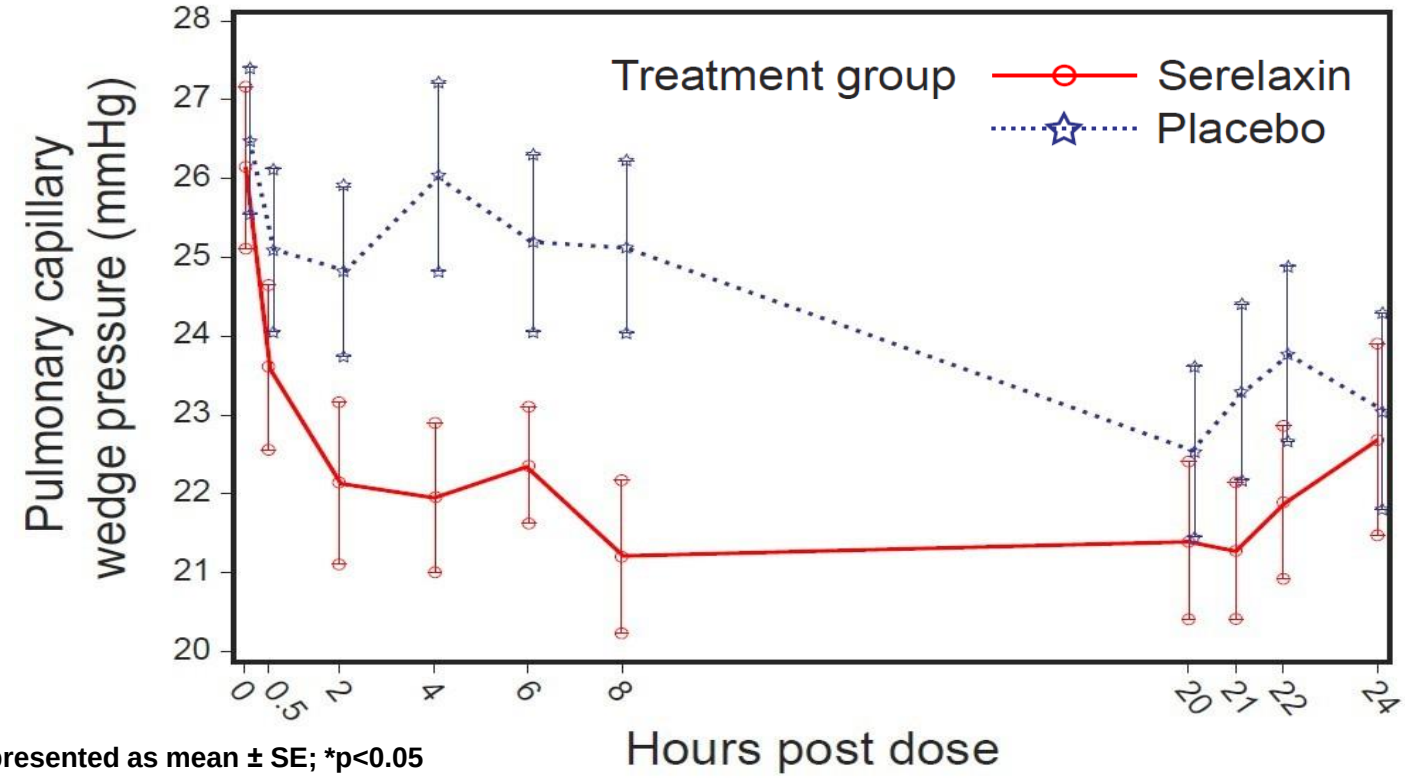
CRLX030A2201: Study objective and design

- Study objective: to evaluate the hemodynamic effects of serelaxin in 71 patients with AHF at a dose rate of 30 µg/kg/day



Ponikowski P et al. Eur Heart J 2013

Hemodynamic results: Change in PCWP



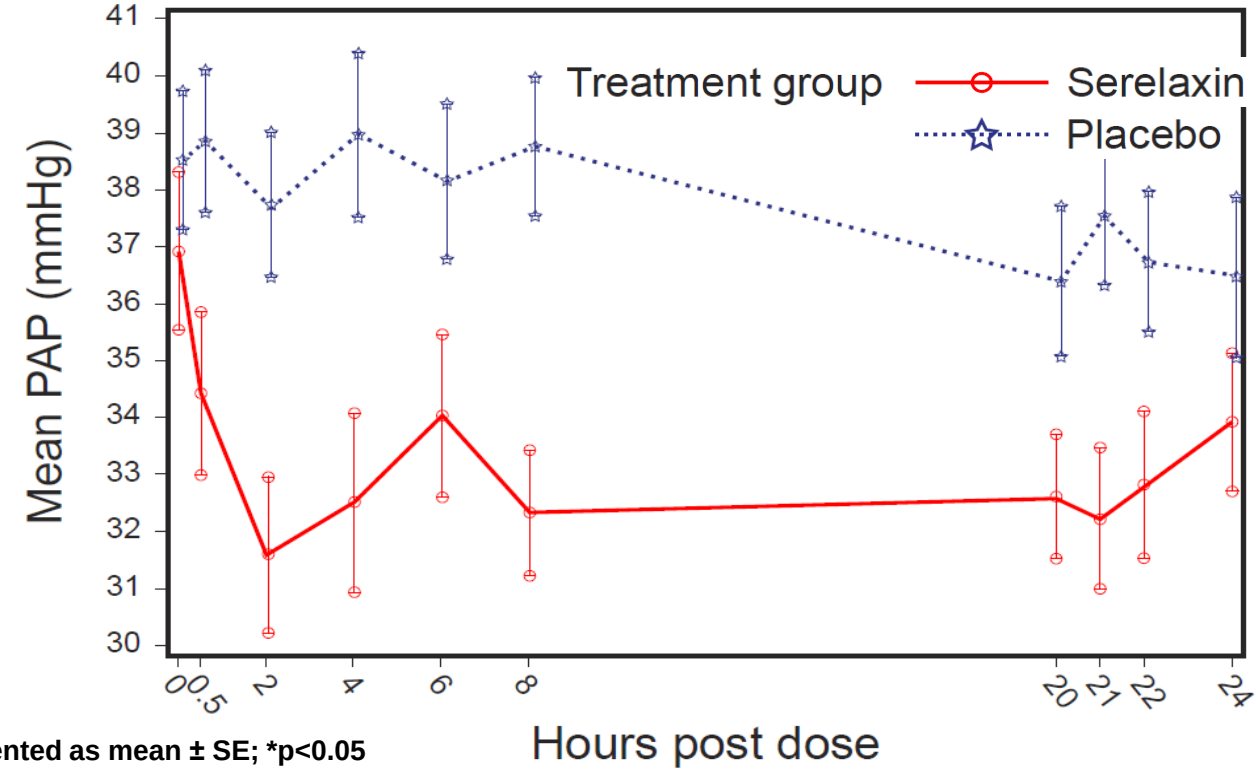
Data represented as mean ± SE; *p<0.05

Time-weighted average change from baseline	Serelaxin (n=32)	Placebo (n=31)	Treatment difference [95% confidence interval]	p-value
0-8 h	-3.79 (0.50)	-1.08 (0.51)	-2.70 [-4.10, -1.31]	0.0001
8-20 h	-4.90 (0.73)	-2.67 (0.74)	-2.24 [-4.28, -0.19]	0.0322
20-24 h	-4.41 (0.83)	-3.11 (0.85)	-1.30 [-3.63, 1.03]	0.27

PCWP, pulmonary capillary wedge pressure; SE, standard error. Data represented in mmHg as least squares mean (SE) change from baseline. Time-weighted average is based on area under the effect curve for the corresponding time interval

Ponikowski P et al. Eur Heart J 2013

Hemodynamic results: Change in mean PAP



Data represented as mean ± SE; *p<0.05

Time-weighted average change from baseline	Serelaxin (n=32)	Placebo (n=31)	Treatment difference [95% confidence interval]	p-value
0-8 h	-3.98 (0.65)	0.06 (0.66)	-4.04 [-5.86, -2.22]	<0.0001
8-20 h	-4.56 (0.88)	-0.80 (0.89)	-3.76 [-6.22, -1.29]	0.0028
20-24 h	-4.29 (0.96)	-1.67 (0.98)	-2.62 [-5.31, 0.07]	0.06

PAP, pulmonary arterial pressure; SE, standard error. Data represented in mmHg as least squares mean (SE) change from baseline. Time-weighted average is based on area under the effect curve for the corresponding time interval

Ponikowski P et al. Eur Heart J 2013

RELAX-AHF: Benefit-Risk Conclusion

Improvement in current clinical status	• Patient-reported dyspnea ↓ • Physician-assessed signs and symptoms of congestion • NT-pro-BNP ↓, PCWP ↓, troponin ↓ • Less diuretics required
Prevention of worsening clinical status	• Worsening HF ↓, NNT 15 by Day 5 • Length of hospital stay ↓ • Length of time in critical care unit ↓ • Less worsening renal function
Reduction in risk of death	• ↓ Cardiovascular mortality at Day 180 • ↓ All cause mortality at Day 180
Safety profile comparable to placebo	• BP decreases manageable • Strong evidence of no harm in AHF patients with high unmet medical need

Short-term relief, long-term goals – the cardiologist's perspective on a novel therapeutic approach to acute heart failure

Sunrise or sunset ?

„broadly speaking, the pharmacological armamentarium for AHFS – loop diuretics, vasodilators and inotropes – is largely unchanged from 1970s…"

Will it be changed after RELAX ?

HFA Congress 17-20 May 2014 – Athens

Will publish then:

International Consensus Document
on the Diagnosis & Treatment
of Acute Heart Failure

www.escardio.org