What serelaxin promises: the RELAX-AHF data

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Ideal properties for AHF therapy

1. Improve signs and symptoms (e.g. dyspnoea)
2. Improve haemodynamics without adversely effecting heart rate and blood pressure
3. Improve the neurohumoral profile
4. Do not cause myocardial and/or kidney damage
5. Be effective in the context of current evidence-based therapy such as ACE-I and beta-blockers
6. Demonstrate efficacy in both the acute and chronic setting
7. Be affordable
8. Reduce both in-hospital and post-discharge morbidity and mortality.

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

Current Paradigm of AHF Management: Goals of Treatment

- Treat symptoms
- Restore oxygenation
- Improve organ perfusion & haemodynamics
- Limit cardiac/renal damage
- Prevent thrombo-embolism
- Minimize ICU length of stay

Immediate (ED/ICU/CCU)

- Stabilise patient and optimise treatment strategy
- Initiate and up-titrate disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients
- Identify aetiology and relevant co-morbidities

Intermediate (in-hospital)

- Plan follow-up strategy
- Enrol in disease management programme, educate, initiate appropriate lifestyle adjustments
- Plan to up-titrate/optimize disease-modifying drugs
- Assess for appropriate device therapy
- Prevent early readmission
- Improve symptoms, quality of life and survival

Long-term and pre-discharge management

Phases in the AHF management

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012

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

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 & favourable long-term outcome

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

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

What is needed ?

- **Targeted-approach**
  specific types of AHF, different pathophysiologies & therapies(?)
- **End-organ protection**
- **Early administration of therapy**
  „the earlier the better" (?)

Linking short-term intervention with long-term benefit: what is needed ?

Targeted approach to limit phenotypic variability

Need to challenge „traditional" paradigm:

- AHF Syndrome(s) should not be viewed as a single disease entity, but rather as a multifaceted disorder with ***different clinical presentations***

Acute Heart Failure Syndromes: Scientific Statement from AHA; Circulation 2010;122:1975-96

„One size does not fit all"

- severe HTH,
- no history of HF
- pulmonary oedema
- normal LVEF
- „warm and wet"

- advanced HF
- INTERMACS: „frequent flyer"
- low LVEF
- low output state
- „cold and wet"

	Vascular (peripheral)	Cardiac (central)
Main mechanism of onset	↑ afterload	↓ contractility renal hypoperfusion
LVEF	Normal	Low
Main cause of symptoms	Fluid redistribution to the lungs	Fluid accumulation
Gain in body weight	No	Yes
Onset	Rapid (hours)	Gradual (days)
Main symptom	Dyspnea	Fatigue
Main sign(s)	Pulmonary congestion (rales, oedema)	Peripheral edema, jugular venous stasis, hepatomegaly
Systolic BP	Normal or high	Normal or low
LV filling pressure	High	May be reduced by low CO
Cardiac output	Normal or high	Low

Metra M et al. IJC 2010;175-9

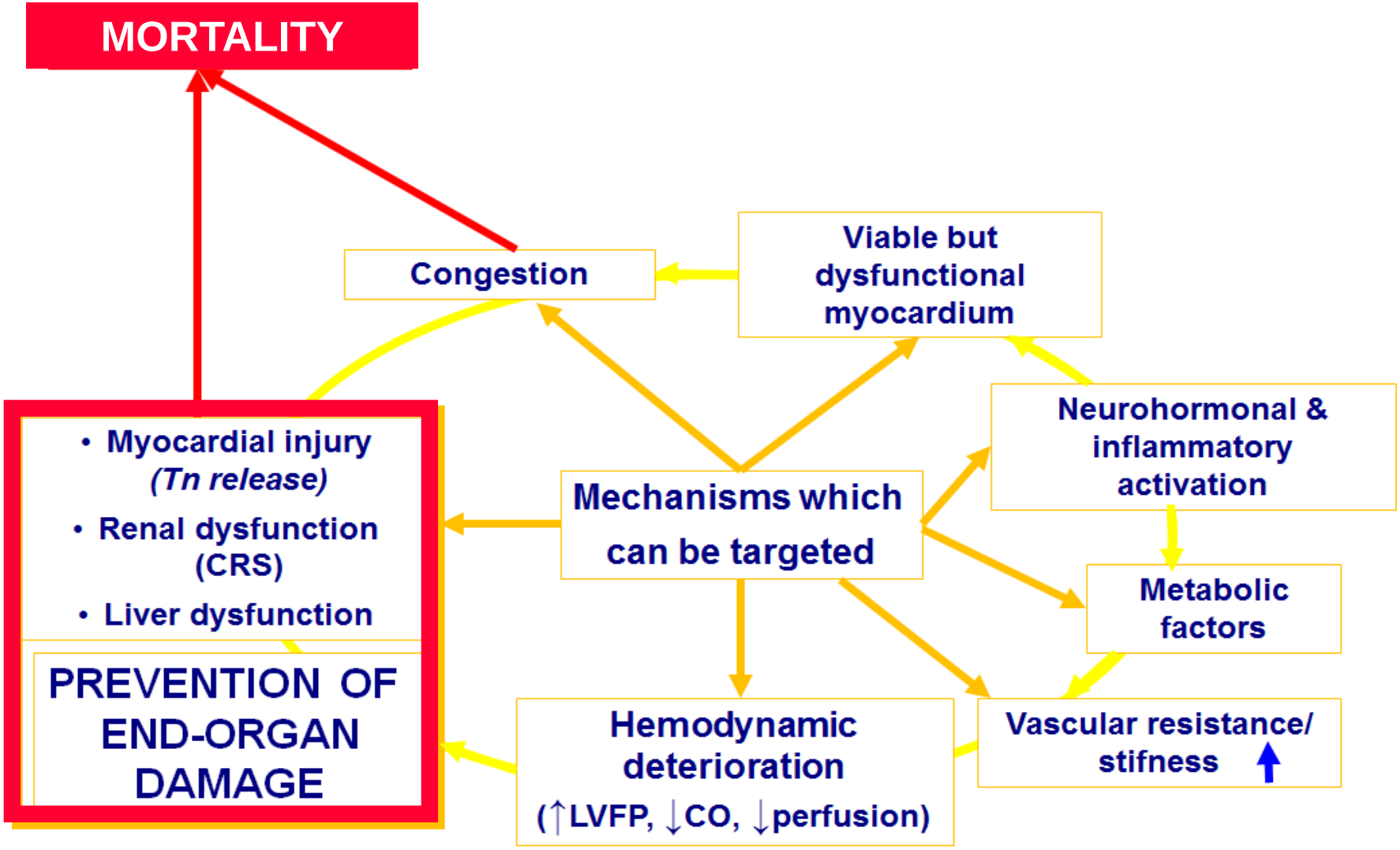
Need for paradigm shifting in acute heart failure:
short-term intervention and long-term goals (?)

What is needed ?

- **Targeted-approach**
  specific types of AHF, different pathophysiologies & therapies(?)
- **End-organ protection**
- **Early administration of therapy**
  „the earlier the better" (?)

Linking short-term intervention with long-term benefit: what is needed ?

Better understanding of Acute Heart Failure pathophysiology



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

What is needed ?

→ prevention of tissue / organ damage caused by hypoxia, acidosis, under-perfusion;

→ phase with severe symptoms (high chance to be effective);

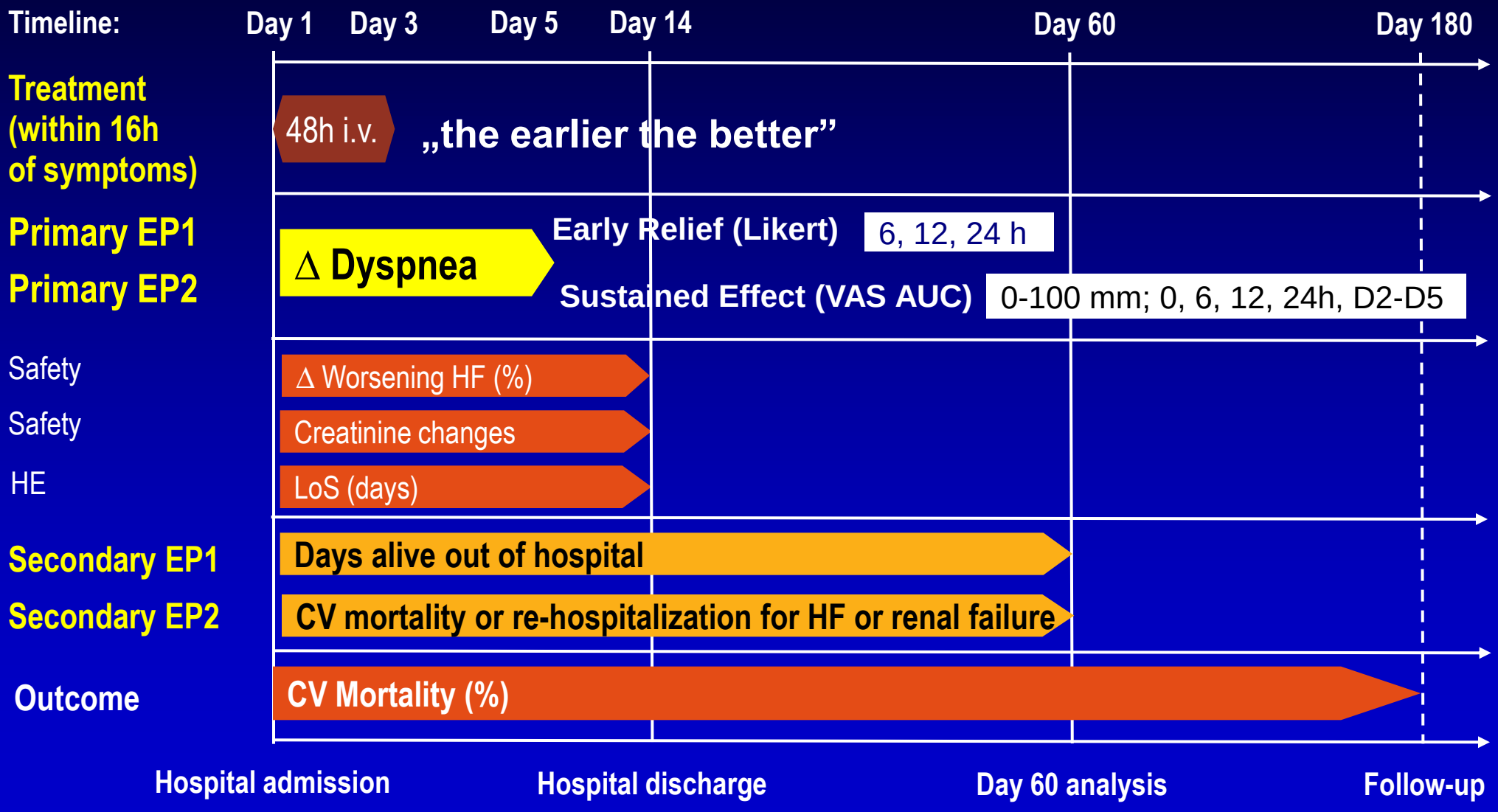
→ early clinical stabilization & chance to introduce other disease-modifying therapies;

→ no confounding effects of multiple concomitant therapies;

- **Early administration of therapy**

„the earlier the better" (?)

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

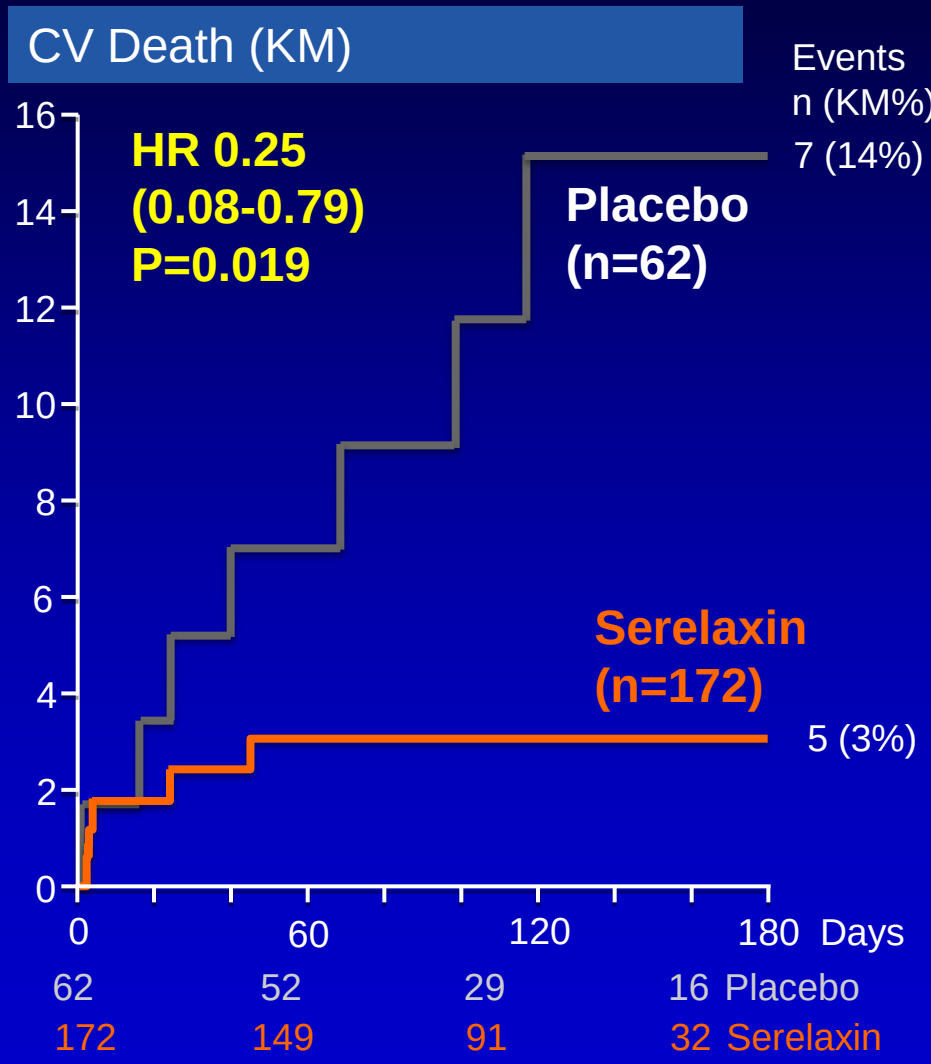


Teerlink et al. Lancet 2009;373:1429–39; Clinicaltrials.gov 2009 (NCT00520806)

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: Objectives and Hypothesis

- **Based upon the hypothesis-generating results of Pre-RELAX-AHF, the RELAX-AHF trial was designed to test the efficacy and safety of serelaxin in patients with acute heart failure.**
- **We hypothesized that serelaxin (30 mcg/kg/d iv) would improve dyspnea compared to placebo as measured at 24 hours (Likert) and/ or through 5 days (VAS AUC), and improve other clinical outcomes.**

Teerlink J. LBCT Presentation, AHA 2012

RELAX-AHF: Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Hospitalized for AHF
  - Dyspnea at rest or with minimal exertion
  - Pulmonary congestion on chest radiograph
  - BNP ≥350 pg/mL or NT-pro-BNP ≥1400 pg/mL
- Received ≥40 mg IV furo (or equivalent) at any time between admission to emergency services (ambulance or hospital) and the start of screening for the study
- Systolic blood pressure >125 mmHg
- Impaired renal function on admission (sMDRD eGFR 30-75 mL/min/1·73 m^2)
- Randomized within 16 hours from presentation
- Age ≥18 years of age
- Body weight <160 kg

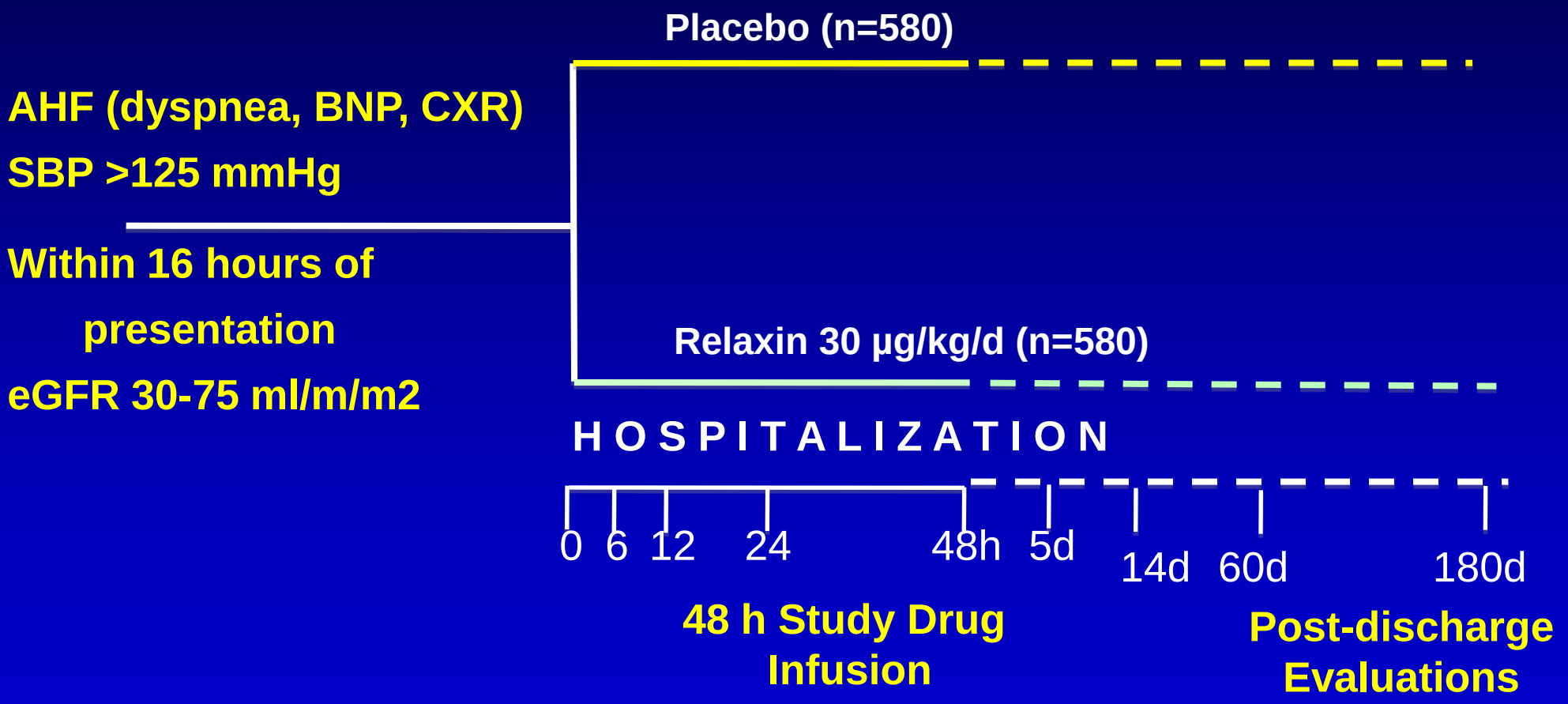
Key Exclusion Criteria

- Current / planned treatment with any IV therapies (other vasodilators, inotropes, vasopressors) or mechanical circulatory, renal, or ventilatory support; exception: IV furosemide (or equivalent), or IV nitrates (screening SBP >150 mmHg
- AHF and/or dyspnea from arrhythmias or non-cardiac causes, such as lung disease, anemia, or severe obesity
- Infection or sepsis requiring IV antibiotics
- Pregnant or breast-feeding
- Stroke within 60d; ACS within 45d; major surgery within 30d
- Presence of acute myocarditis, significant valvular heart disease, hypertrophic/ restrictive/ constrictive cardiomyopathy

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

RELAX-AHF: Patient population (1)

Parameter		Placebo (N=580)	Serelaxin (N=581)
Age (years)	Mean	72.5	71.6
Systolic BP at baseline (mmHg)	Mean	142	142
Heart Rate at Baseline (bpm)	Mean	80	79
Respiratory Rate at baseline (breaths/ min)	Mean	22	22
eGFR (MDRD; mL/min/1.73m^2)	Mean	53.3	53.7
NT-proBNP (ng/L)**	Geometric Mean	5003	5125
Most Recent Ejection Fraction	Mean	39	39
< 40%	%	55	55
NYHA Class III/IV (1 month prior to admission)	%	47/17	44/14
HF Hospitalization (in the past year)	%	31	37*
Troponin T (µg/L)**	Geometric Mean	0.036	0.034

** Core lab values

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RELAX-AHF: Patient population (2)

Parameter		Placebo (N=580)	Serelaxin (N=581)
Medical History			
Hypertension	%	88	85
Hyperlipidemia	%	54	52
Stroke or Other Cerebrovascular event	%	14	13
Atrial fibrillation/ atrial flutter at presentation	%	42	40
Diabetes Mellitus	%	47	48
Concomitant Heart Failure Meds at Baseline			
ACE inhibitors	%	55	54
ARB	%	17	15
Beta-blocker	%	70	67
Aldosterone antagonist	%	30	33
Digoxin	%	19	21
IV nitrates at randomization	%	7	7
Time from presentation to randomization (hr)	Mean	7.9	7.8

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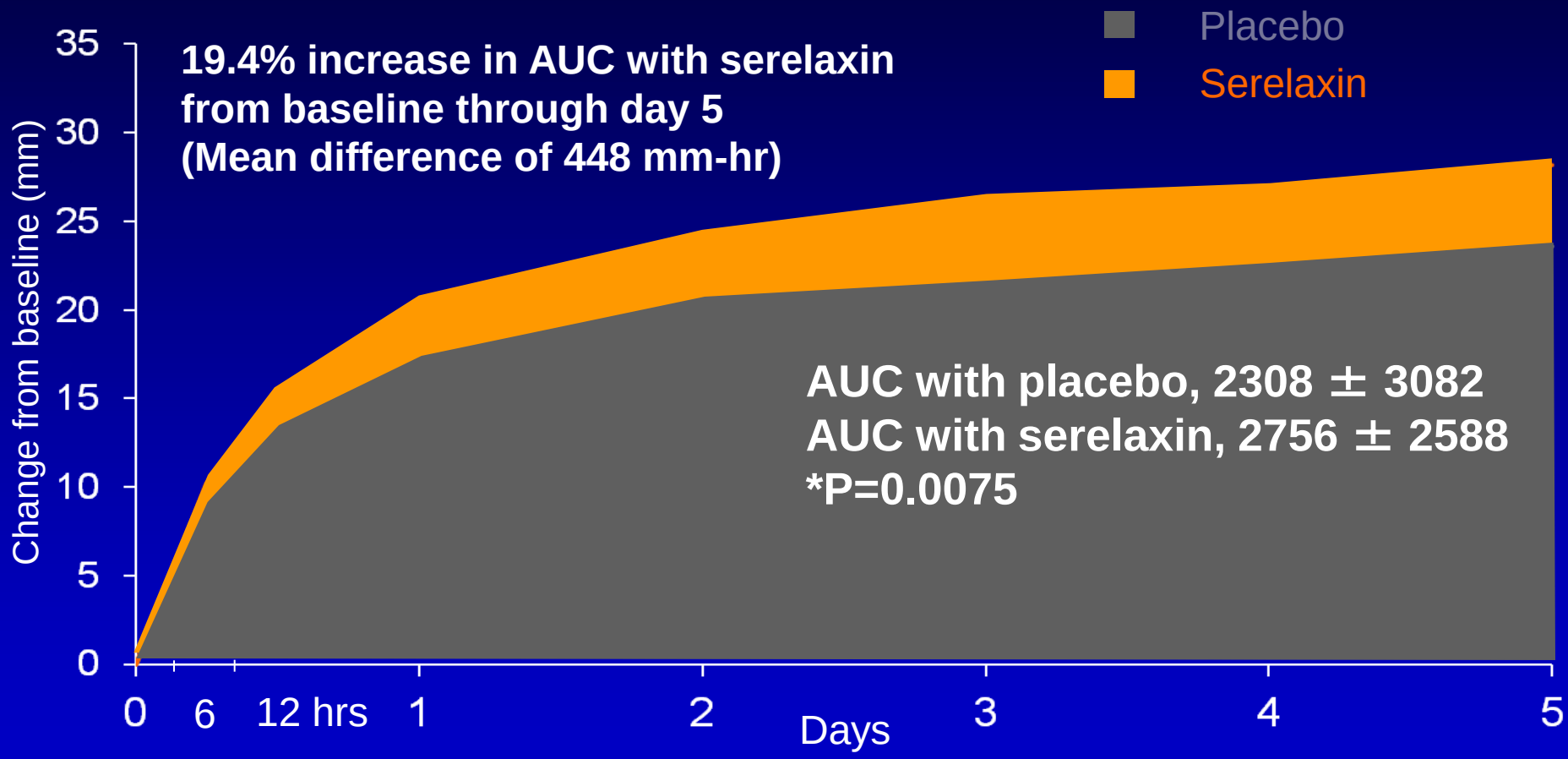
1˚ Endpoint: Dyspnea Relief (VAS AUC)



RELAX-AHF

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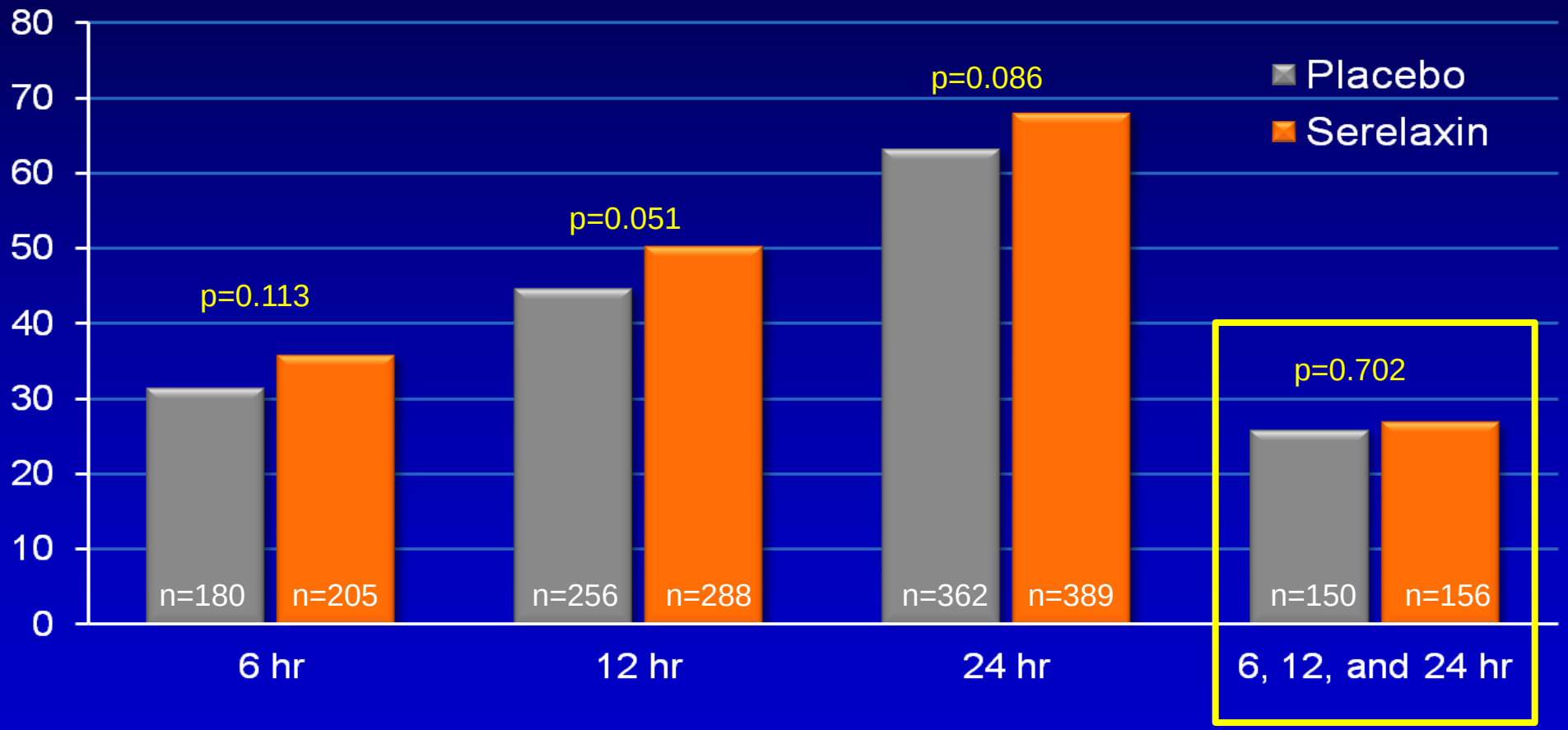
1°Endpoint: Dyspnea Relief (Likert)

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



RELAX-AHF

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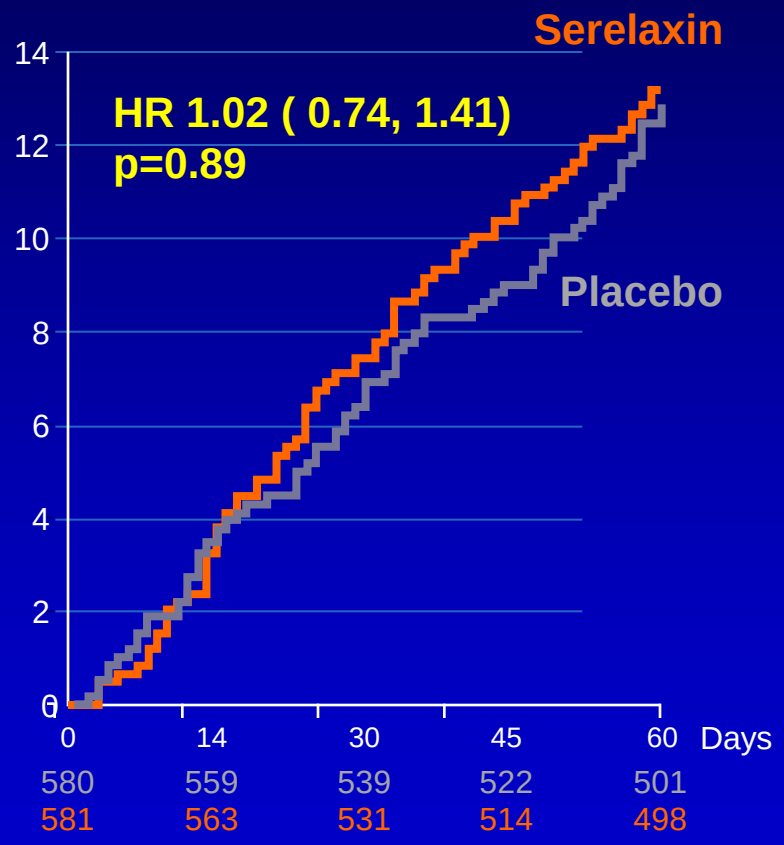
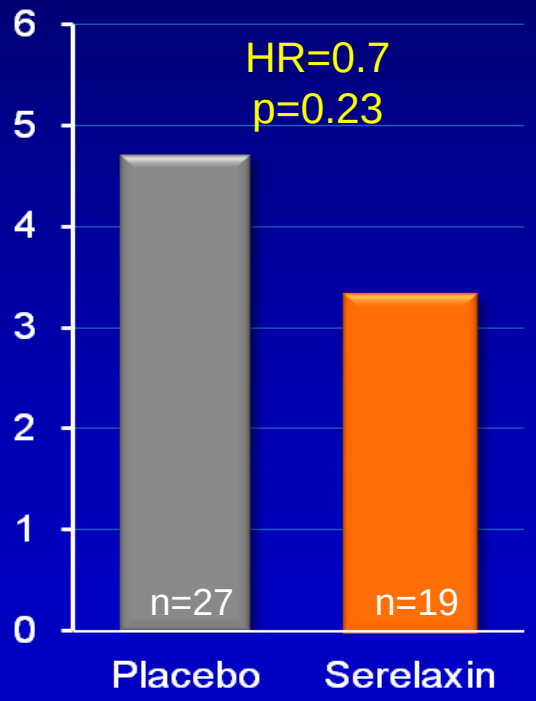
2°Endpoint: CV Death or Heart Failure / Renal Failure Re-hospitalization through Day 60

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

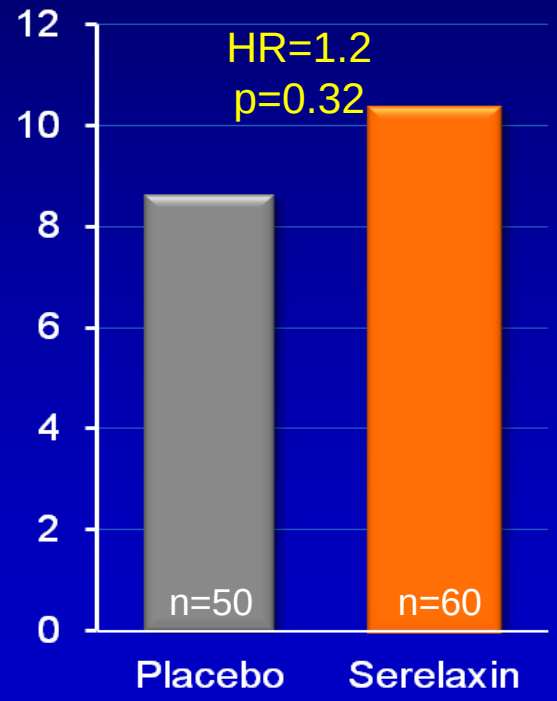


Composite event components (%)

CV death: (% subjects)



HF/RF re-hospitalization (% subjects)



RELAX-AHF

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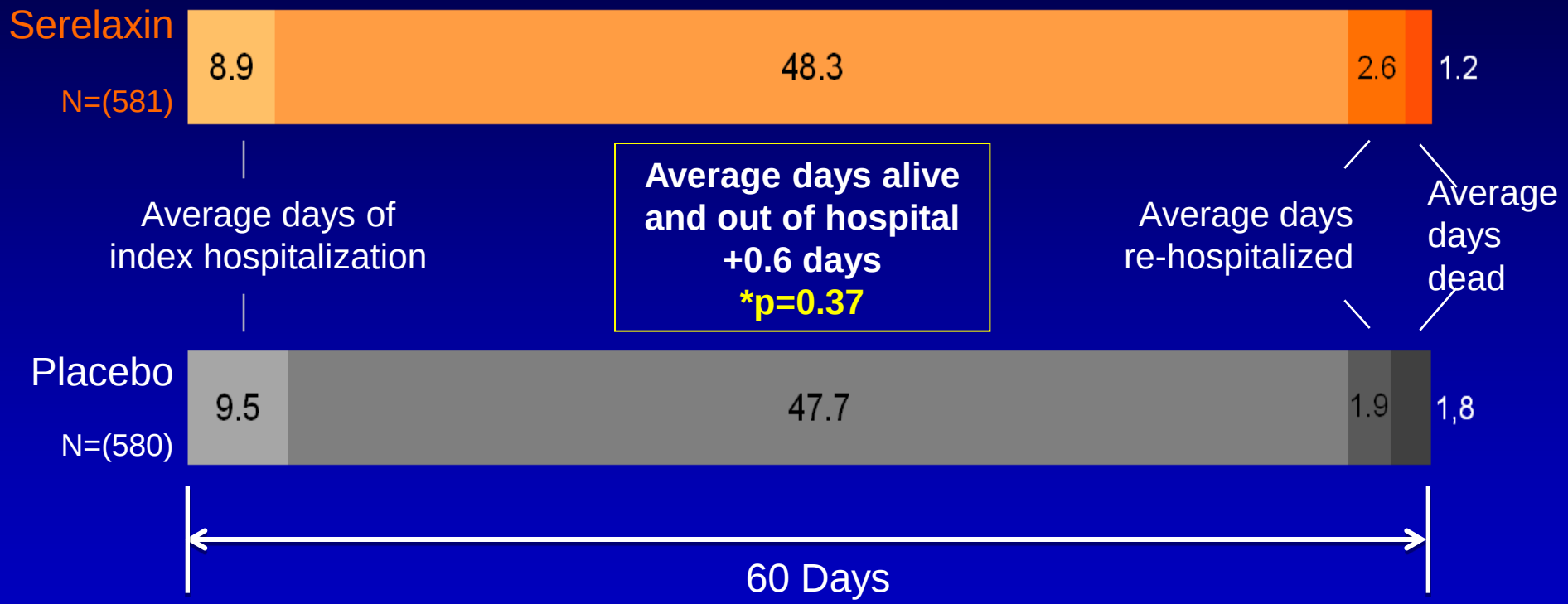
2°Endpoint: Days Alive and Out of Hospital through Day 60



Days Alive Out of Hospital = total follow-up time (D60) - days in hospital or dead
*p value by 2-sided Wilcoxon rank sum test

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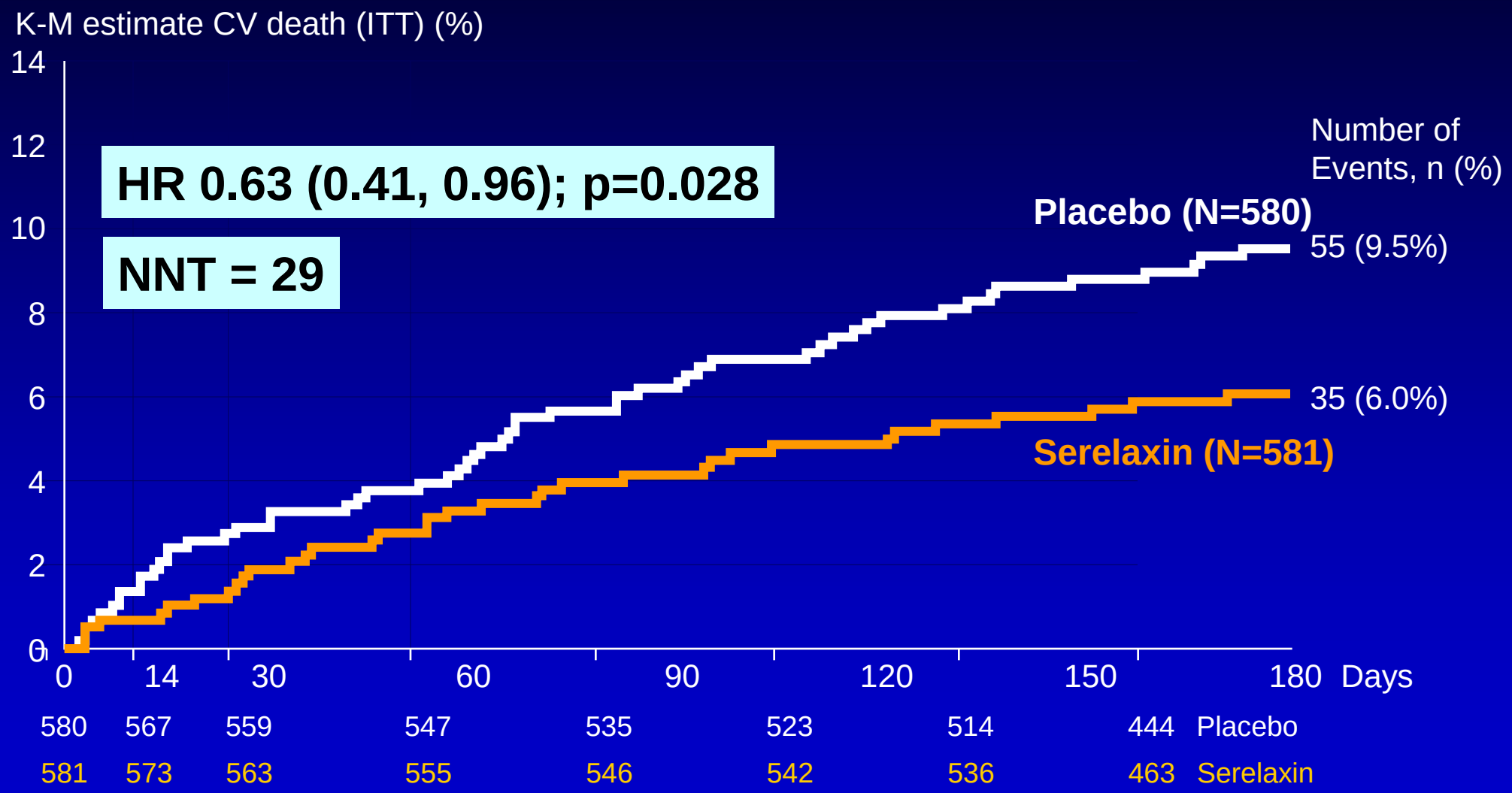
RELAX-AHF

CV Death through Day 180



RELAX-AHF

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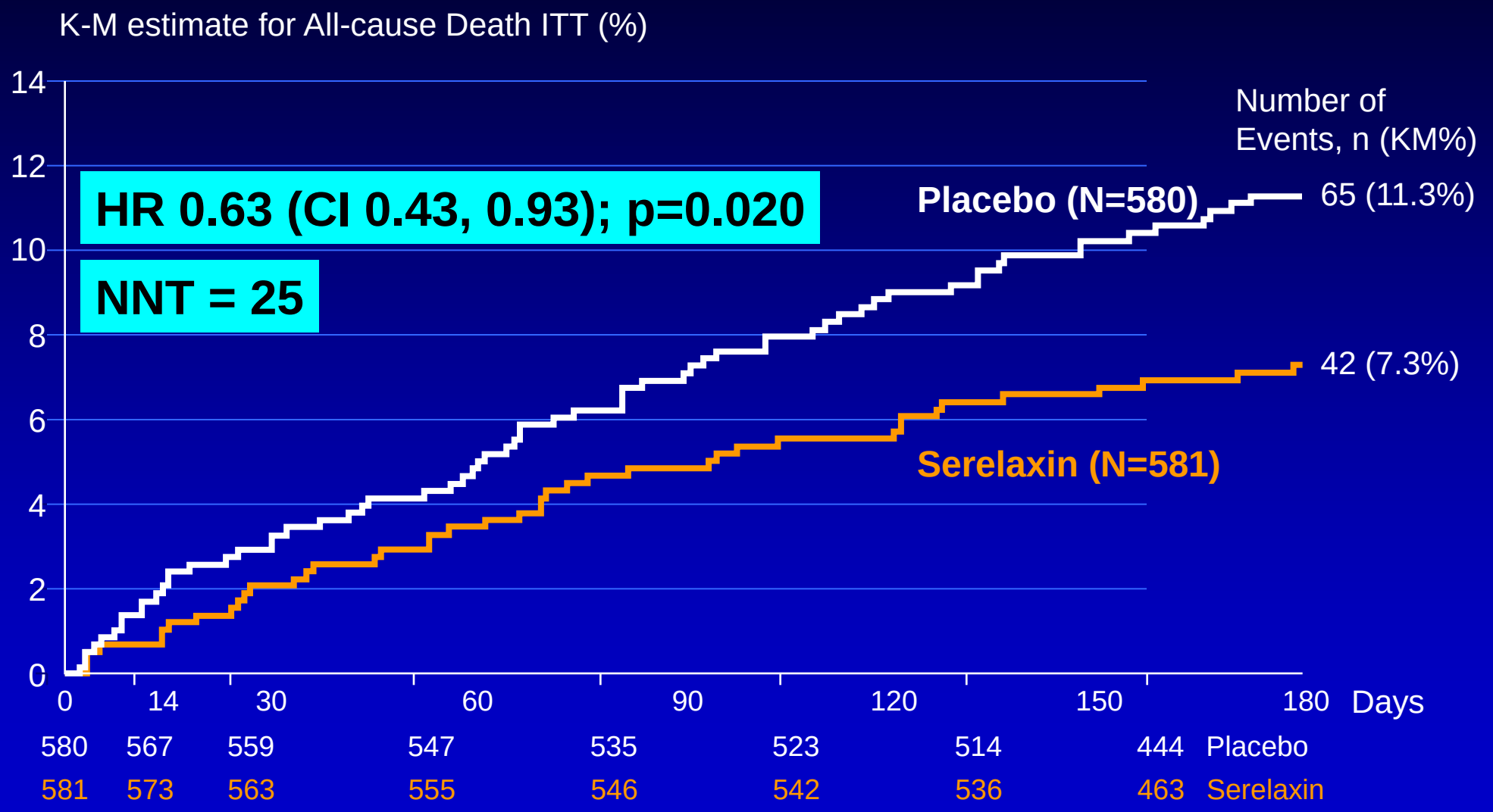
All-cause Death through Day 180



RELAX-AHF

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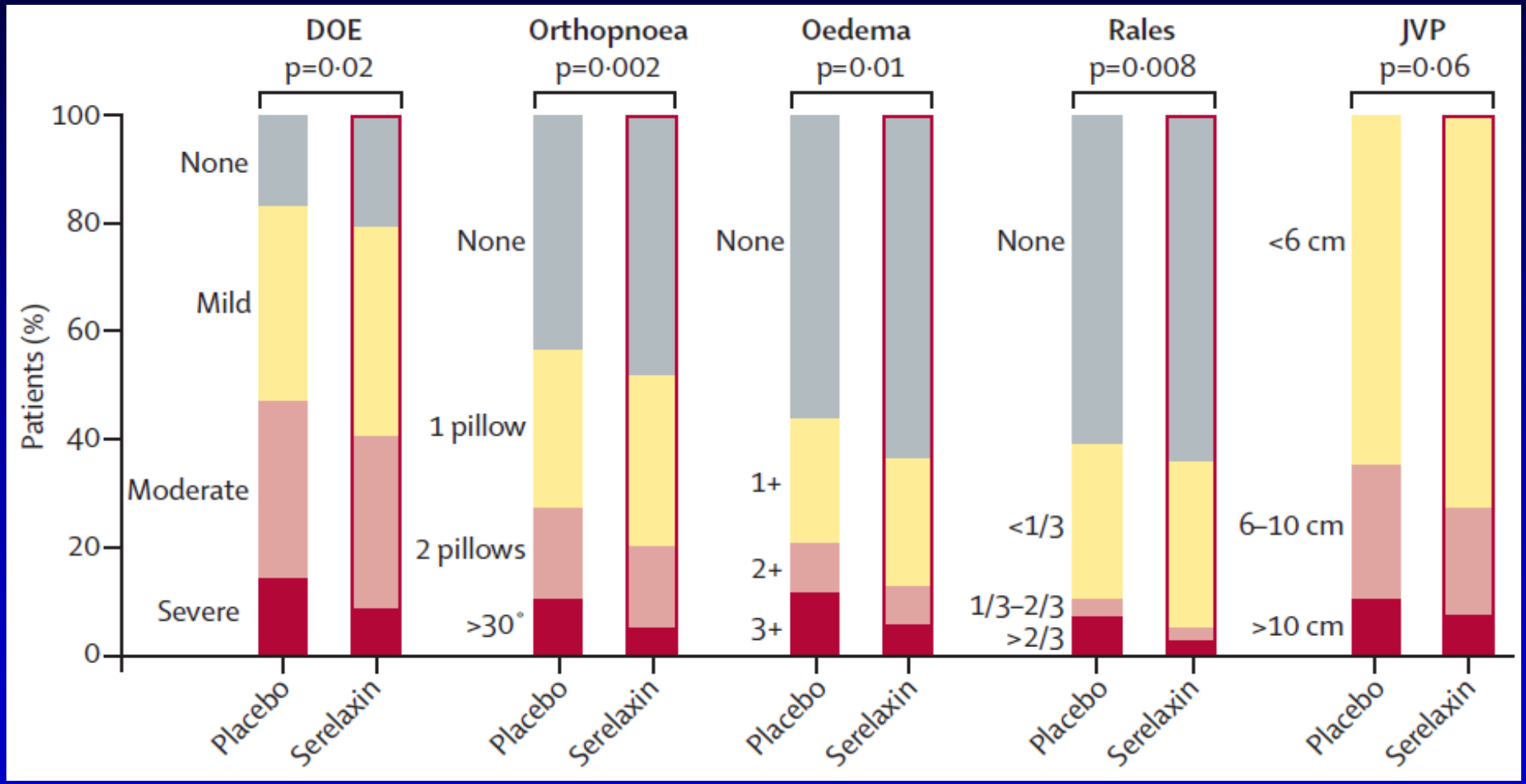
RELAX-AHF: Signs and Symptoms of Congestion

Signs and Symptoms of Congestion at Day 2



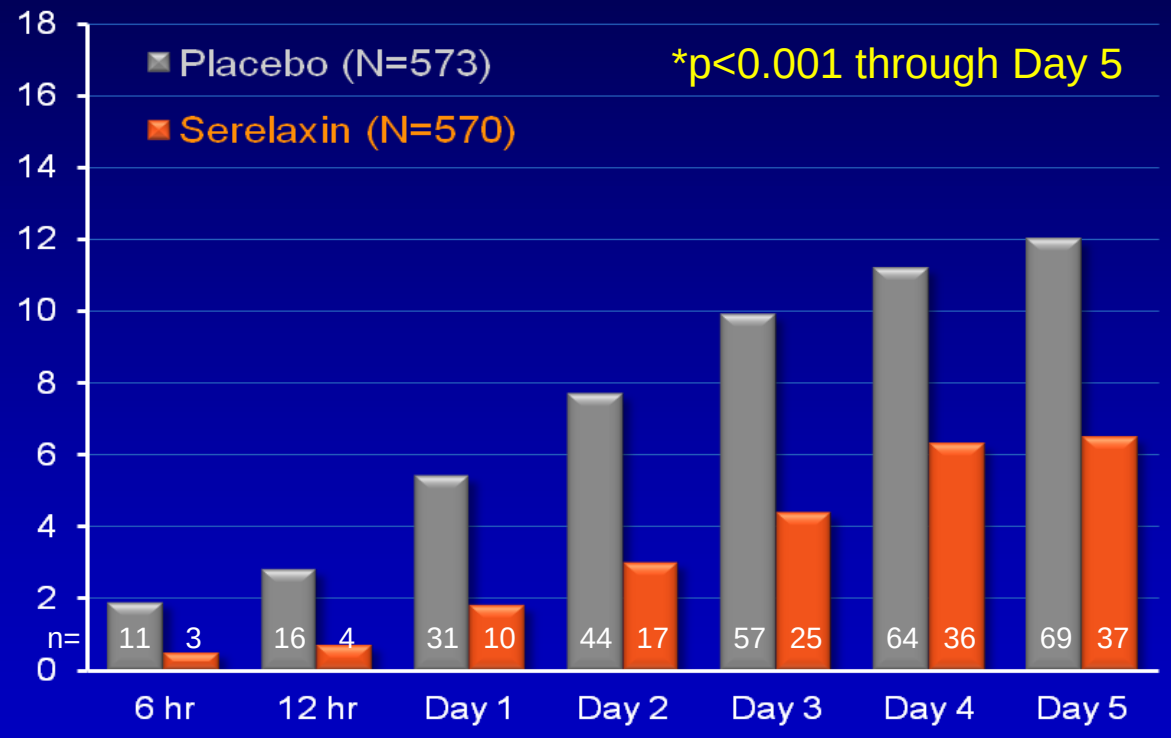
p value by 2-sided Wilcoxon rank sum test of change from baseline

Teerlink J et al. Lancet 2013; 381: 29–39

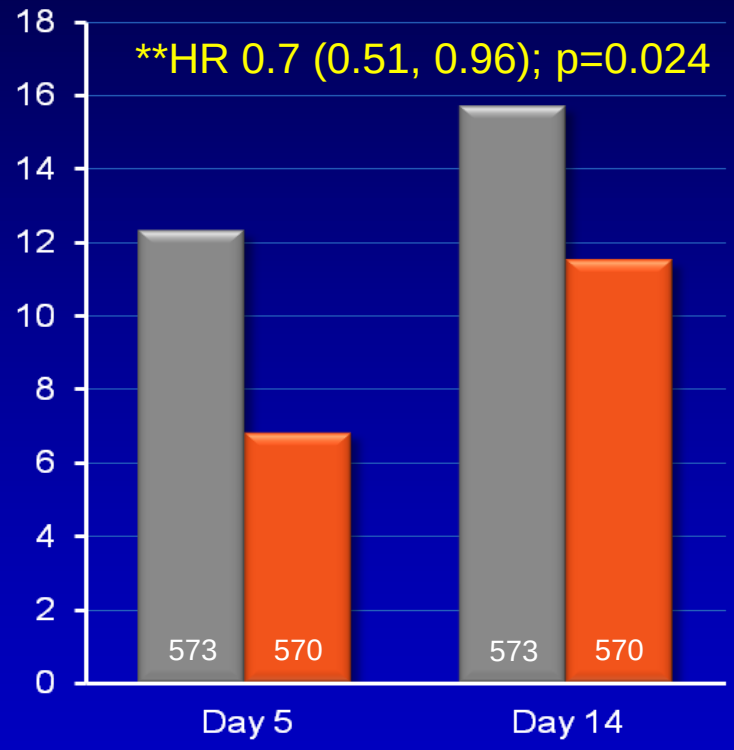
RELAX-AHF

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

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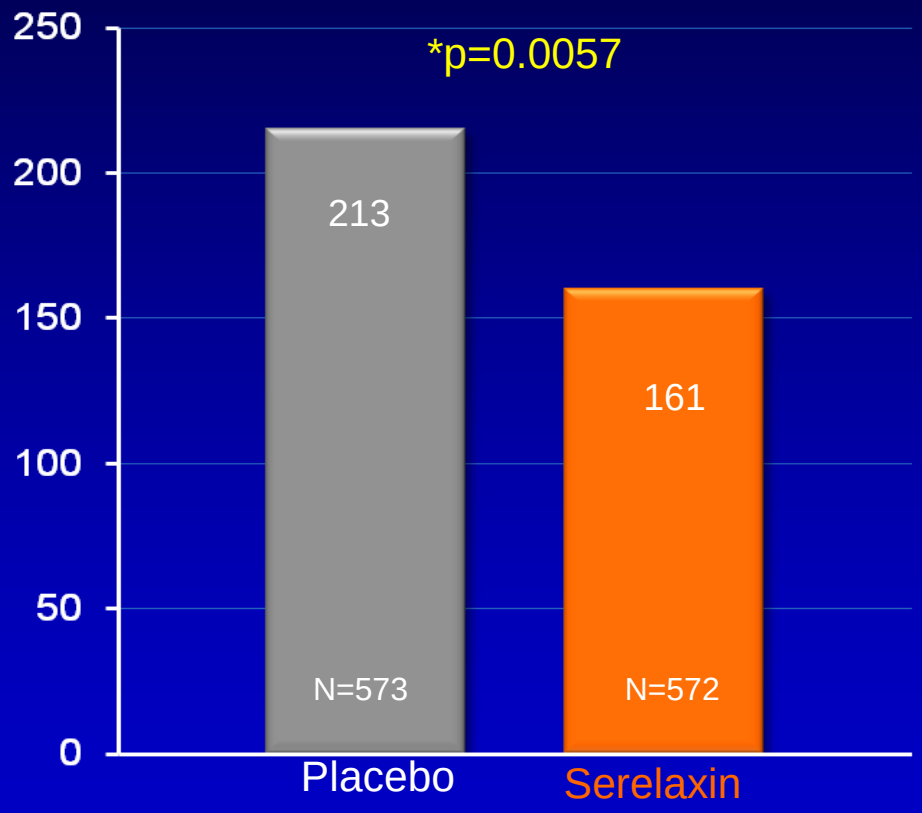
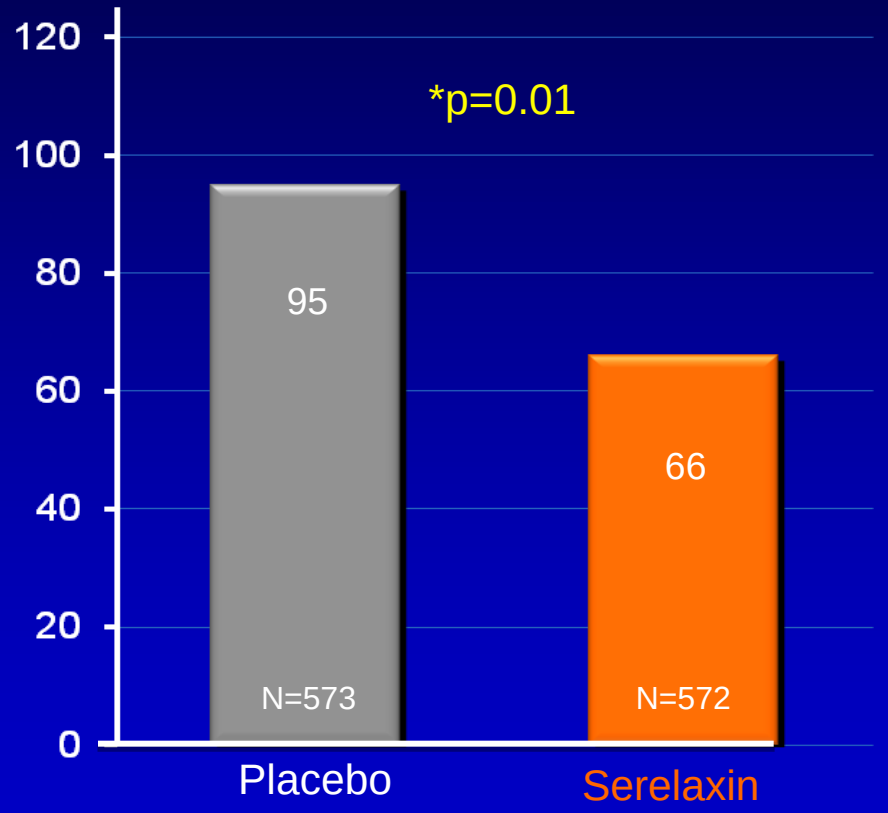
RELAX-AHF: Intravenous Medication Use

IV diuretics use (cumulative total dose from day 1-5; mg)



% Subjects Receiving IV Vasoactive Drugs Day 1 through Day 5



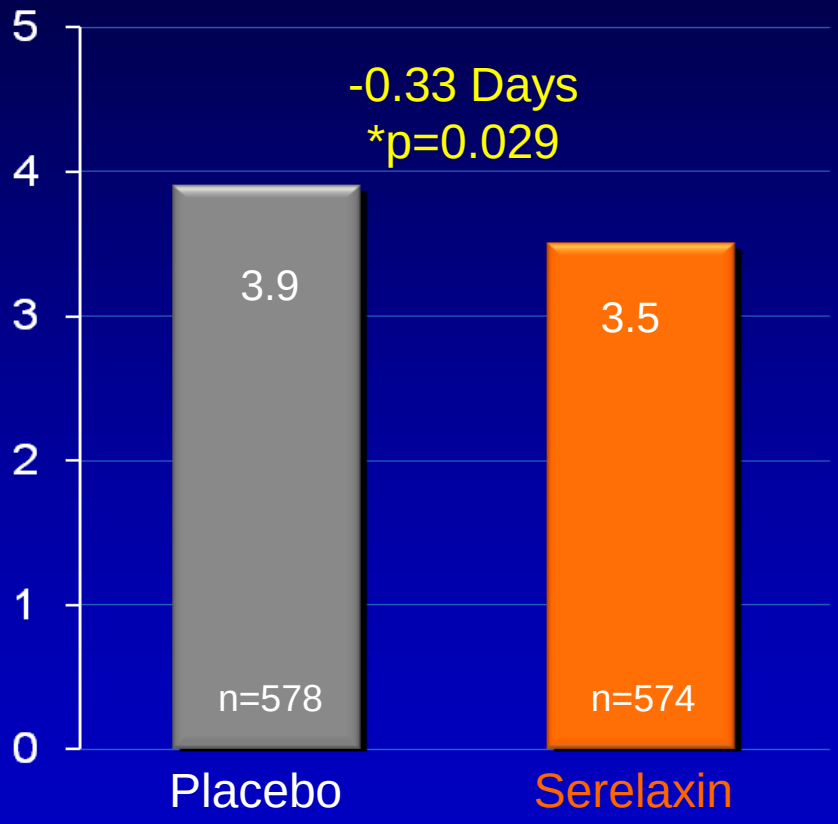
*p value by t test

Teerlink J. LBCT Presentation, AHA 2012

RELAX-AHF

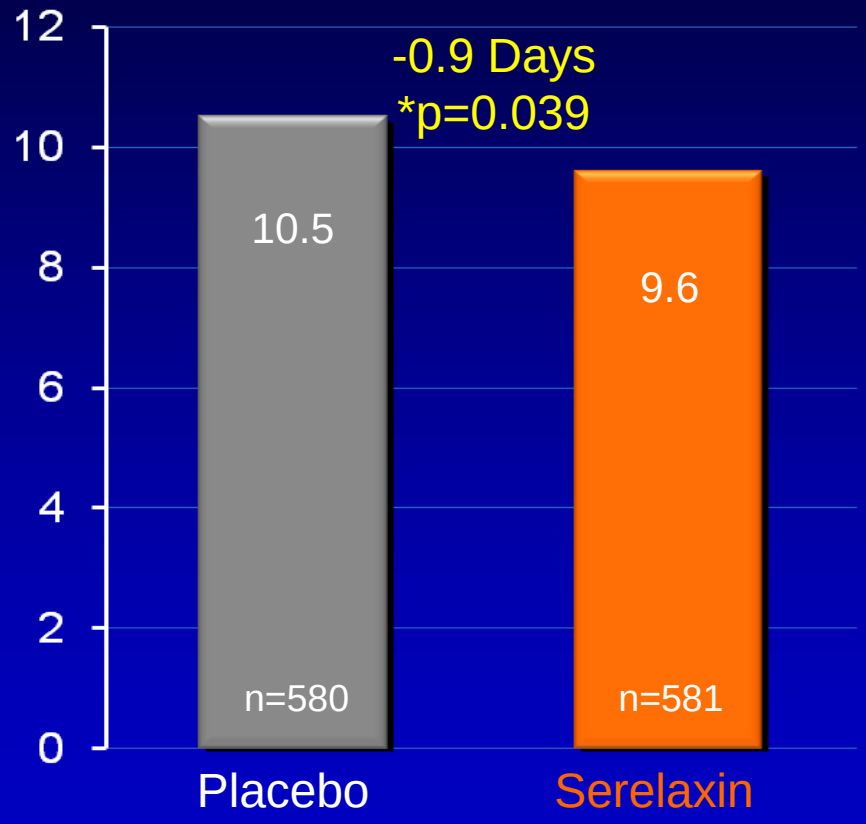
RELAX-AHF:Index Hospitalization LOS

Duration of ICU/CCU Care (Days)



***p value by 2-sided Wilcoxon rank sum test**

Index Hospitalization Length of Stay (Days)



Patients still in the hospital at Day 60 are censored at Day 60. Patients who died in-hospital are imputed as the maximum +1 day.

RELAX-AHF

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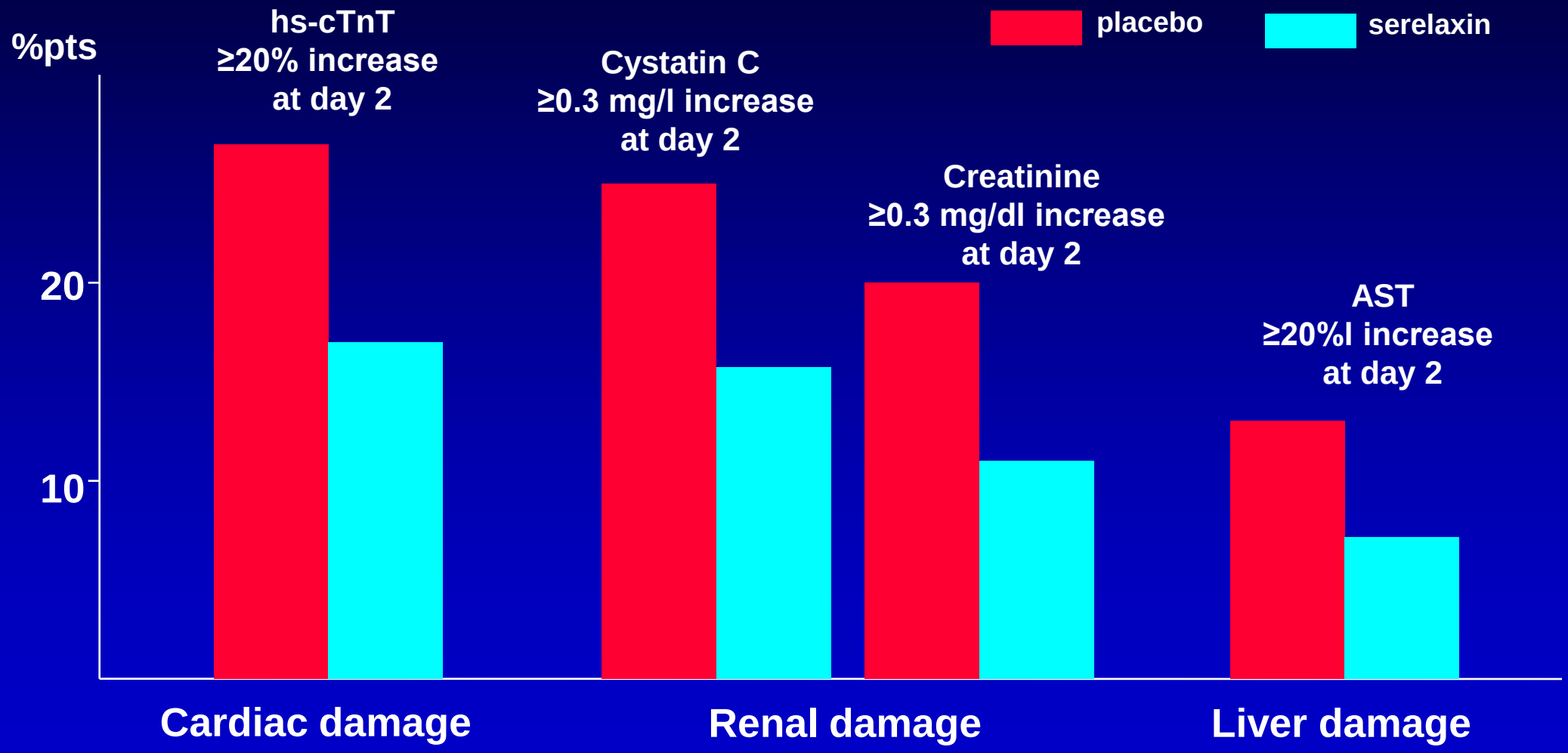
Changes from baseline in biomarkers related to organ damage in the RELAX-AHF study



RELAX-AHF

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

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

Conclusions

In selected patients with AHF, early treatment with serelaxin for 48 h improved:

- **Dyspnea relief: VAS AUC**
- **In-hospital signs and symptoms of AHF**
- **In-hospital end organ dysfunction/ damage**
- **In-hospital worsening of heart failure**
- **180-day CV and all-cause mortality**

…but had no effect on rehospitalizations.

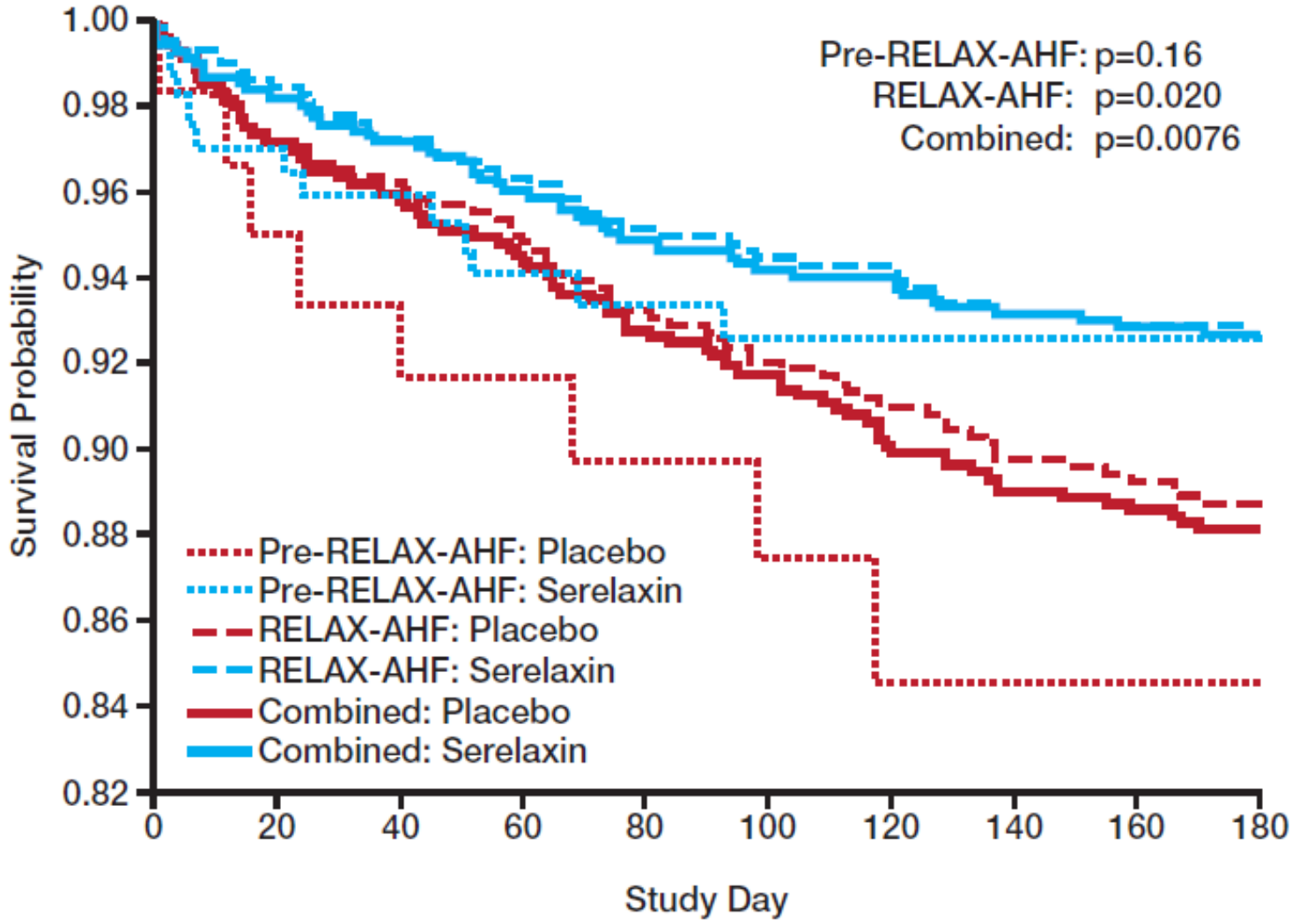
Patients had shorter hospital stay.

Serelaxin use in AHF was safe with few hypotensive events and adverse events similar to placebo

RELAX-AHF

Teerlink J. LBCT Presentation, AHA 2012

Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and Combined



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

RELAX-AHF: Study Organization

- Co-PIs: M Metra (IT), JR Teerlink (US)
- Executive Committee: G Cotter (US), BA Davison (US), GM Felker (US), G Filipatos (GR), BH Greenberg (US), P Ponikowski (PL), TM Severin (CH), SL Teichman (US), E Unemori (USA), AA Voors (NL).
- Steering Committee: KF Adams (US), M Dorobantu (RO), L Grinfeld (AR), G Jondeau (FR), A Marmor (IL), J Masip (ES), PS Pang (US), K Werdan (DE).
- DSMB: BM Massie-Chair (US), M Böhm (DE), E Davis (US), G Francis (US), S Goldstein (US).
- Sponsor: Corthera, Inc. (a Novartis affiliate company)
- Coordinating Center: Momentum Research, Inc.

RELAX-AHF Investigators

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France (21):	A Cohen-Solal; M Galinier; G Jondeau; R Isnard.
Germany (78):	H-G Olbrich; V Mitrovic; K Werdan; S Felix; T Heitzer; G Cieslinski; K Stangl.
Hungary (151):	J Tomcsányi; D Apró; K Tóth; A Vértes; G Lupkovics; Z László; A Cziraki.
Israel (210):	A Marmor; S Goland; A Katz; R Zimlichman; D Aronson; A Butnaru; M Omary; XA Piltz; D Zahger.
Italy (77):	M Metra; A Mortara; M Balbi; F Cosmi; S DiSomma; MC Brunazzi.
Netherlands (10):	AA Voors; PEF Bendermacher; G-J Milhous; PL van Haelst; P Dunselman.
Poland (258):	P Ponikowski; P Jankowski; A Wysokinski; M Dluzniewski; J Stepinska; W Tracz; M Krzeminska-Pakula; J Grzybowski; K Loboz-Grudzien.
Romania (153):	D-D Ionescu; CS Stamate; M Dorobantu; C Pop; A Matei; T Nanea; M Radoi; A Salajan.
Spain (18):	J Masip; D Pascual; MG Bueno; R Muñoz.
Us (114):	S Meymandi; P Levy; PS Pang; C Clark; G Fermann; KF Adams, Jr.; B Bozkurt; J Fulmer; D Mancini; T Vittorio; R Zolty; BH Greenberg; E Chung; V Florea; J Heilman III; A Storrow; MR Costanzo; G Lamas; M Greenspan; M Klapholz; J Martinez-Arraras; WF Peacock; N Saleh; R Small; JR Teerlink; B Trichon; D Wencker.

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…"

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

Will it be changed after RELAX-AHF ?