Strategies for Managing AHF Today and in the Future

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Heart failure
theheart.org from WebMD
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Treatment of AHF: Pulmonary Congestion

General nonspecific Recommendations

Recommendations*

Patients with pulmonary congestion/edema without shock

IV loop diuretic [Class I, Level B]

High-flow oxygen [Class I, Level C]

Thromboembolism prophylaxis (e.g. with LMWH) [Class I, Level A]

Noninvasive ventilation (eg, CPAP) should be considered in dyspneic patients with pulmonary edema and decreased respiratory rate. Not recommended in patients with systolic BP < 85 mm Hg [Class IIa, Level B]

An IV opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory status should be monitored. [Class IIa, Level C]

**Please consult published guidelines for specific recommendations.*

AHF = acute heart failure; BP = blood pressure; CPAP = continuous positive airway pressure; IV = intravenous; LMWH = low-molecular-weight heparin

Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Treatment of AHF: Pulmonary Congestion

… are stronger than those on specific drugs?

Recommendations*

IV nitrates should be considered in patients with pulmonary congestion/edema and a systolic BP > 110 mm Hg who do not have severe aortic or mitral stenosis [Class IIa, Level B]

IV sodium nitroprusside may be considered in patients with pulmonary congestion/edema and a systolic BP > 110 mm Hg who do not have severe aortic or mitral stenosis [Class IIb, Level B]

Inotropic agents are NOT recommended unless the patient is hypotensive (systolic BP < 85 mm Hg), hypoperfused, or shocked. [Class III, Level C]

**Please consult published guidelines for specific recommendations.*

Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Strategies for Managing AHF Today and in the Future

- Right endpoint
- Intelligent novel mechanisms of action
- Safety

European Medicines Agency Criteria

4.1 Primary Endpoints

4.1.1 Mortality

The preferred primary endpoint is all-cause mortality. As the treatment for AHF is often short-term administration of the investigational agent (drug), these would either be:

- In-hospital mortality during the index admission
- Mortality at 30 days

4.1.2 Short-term outcomes (symptoms)

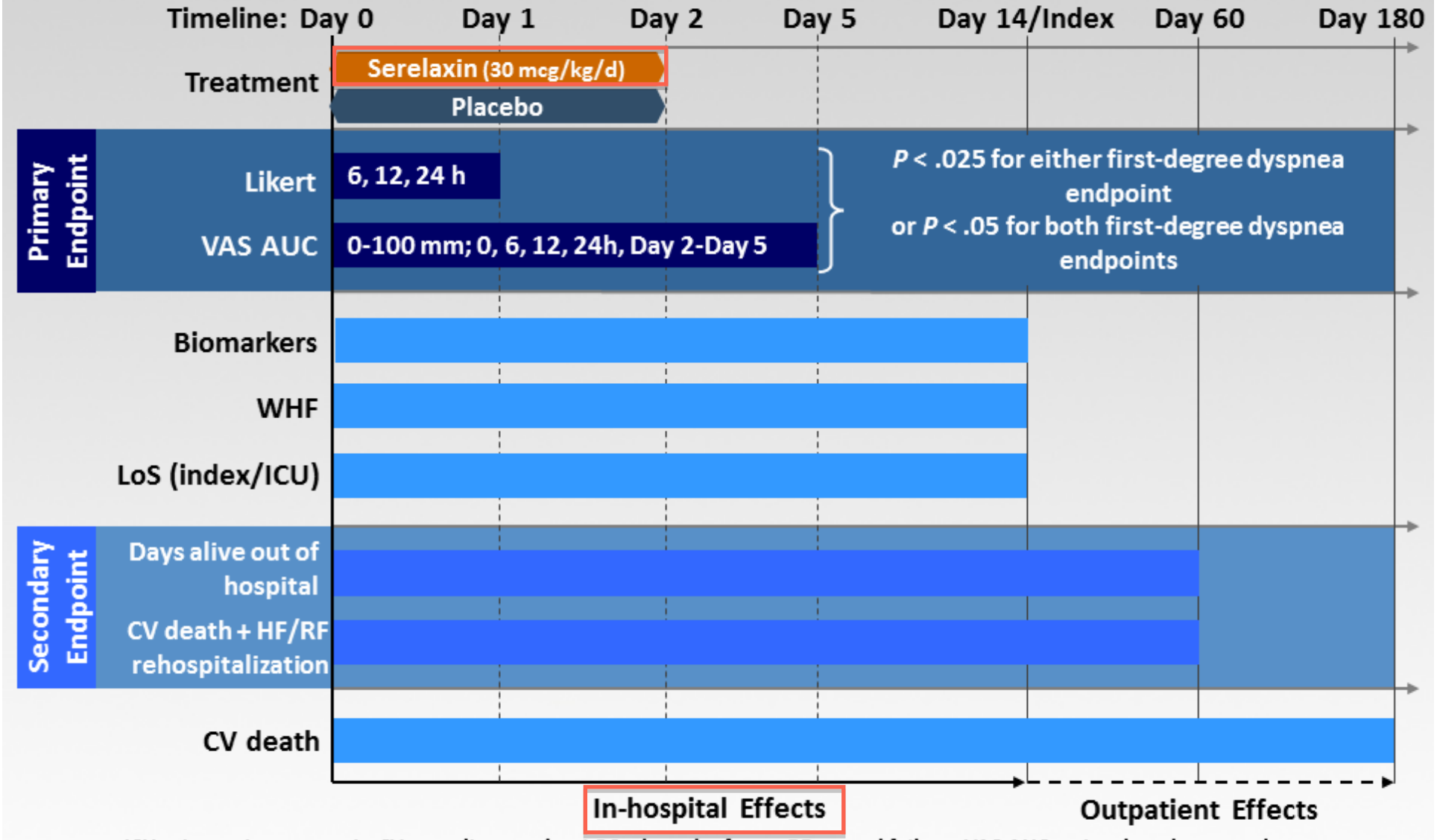
4.1.2.1 Dyspnea

4.1.2.2 Other symptoms/signs

4.1.3 Coprimary endpoints or composite endpoints

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133497.pdf

Key Efficacy Measures



ICU = intensive care unit; CV = cardiovascular; LOS = length of stay; RF = renal failure; VAS AUC = visual analogue scale area under the curve; WHF = worsening heart failure

Heart failure

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

theheart.org from WebMD

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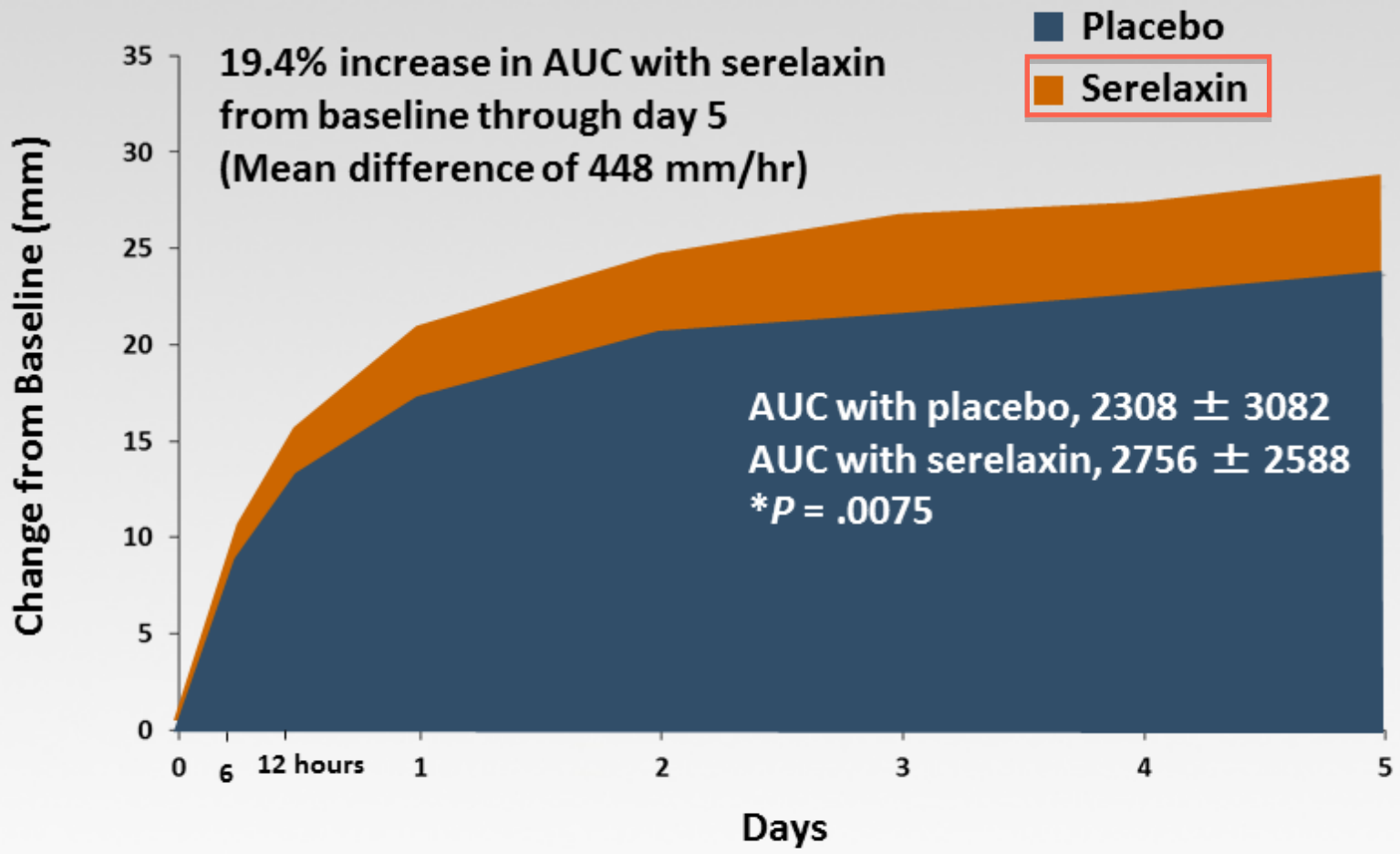
First-Degree Endpoint: Dyspnea Relief (VAS AUC)



Heart failure

From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

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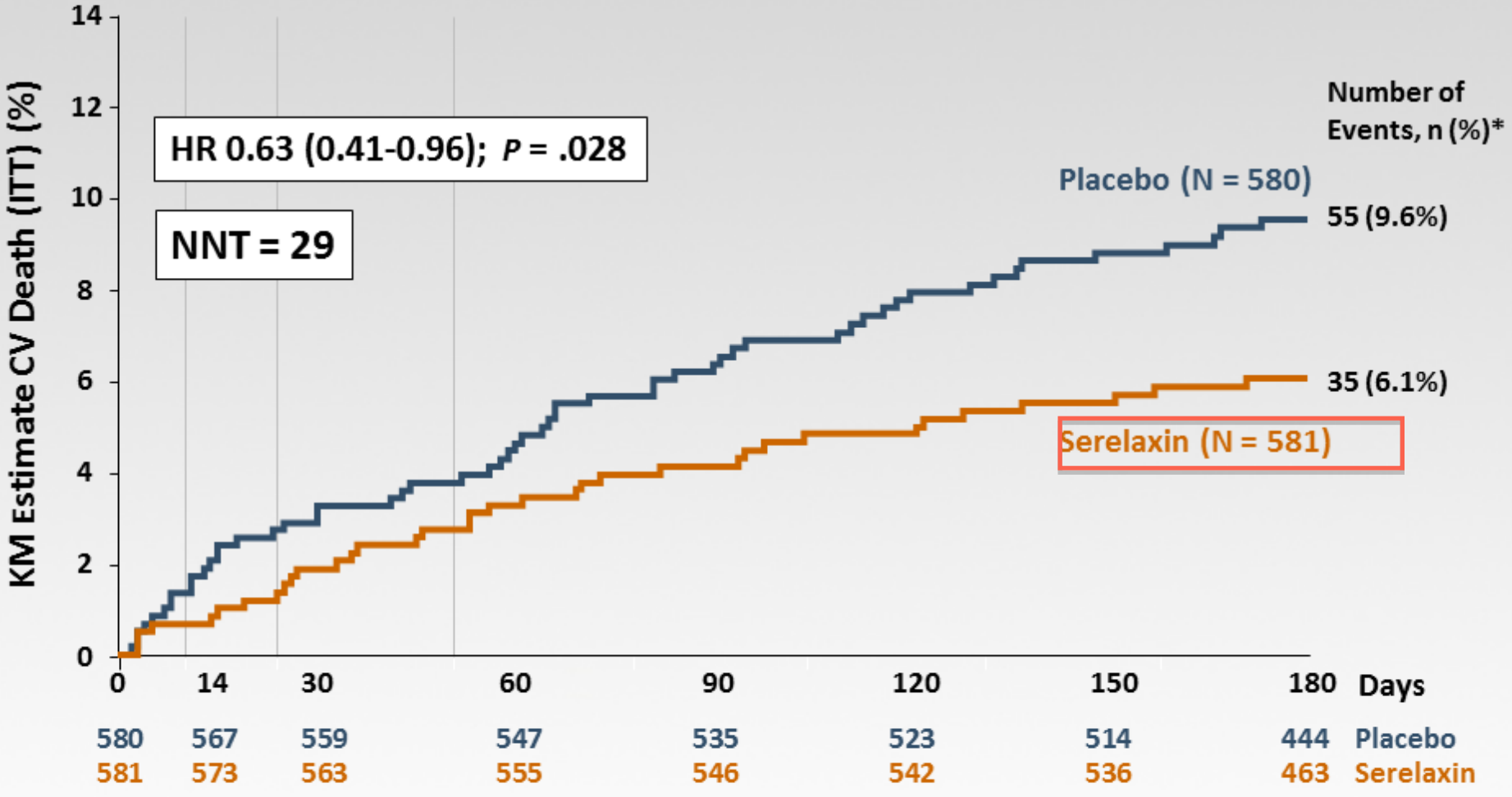
CV Death Through Day 180



ITT = intent to treat; NNT = number need to treat

Heart failure

From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

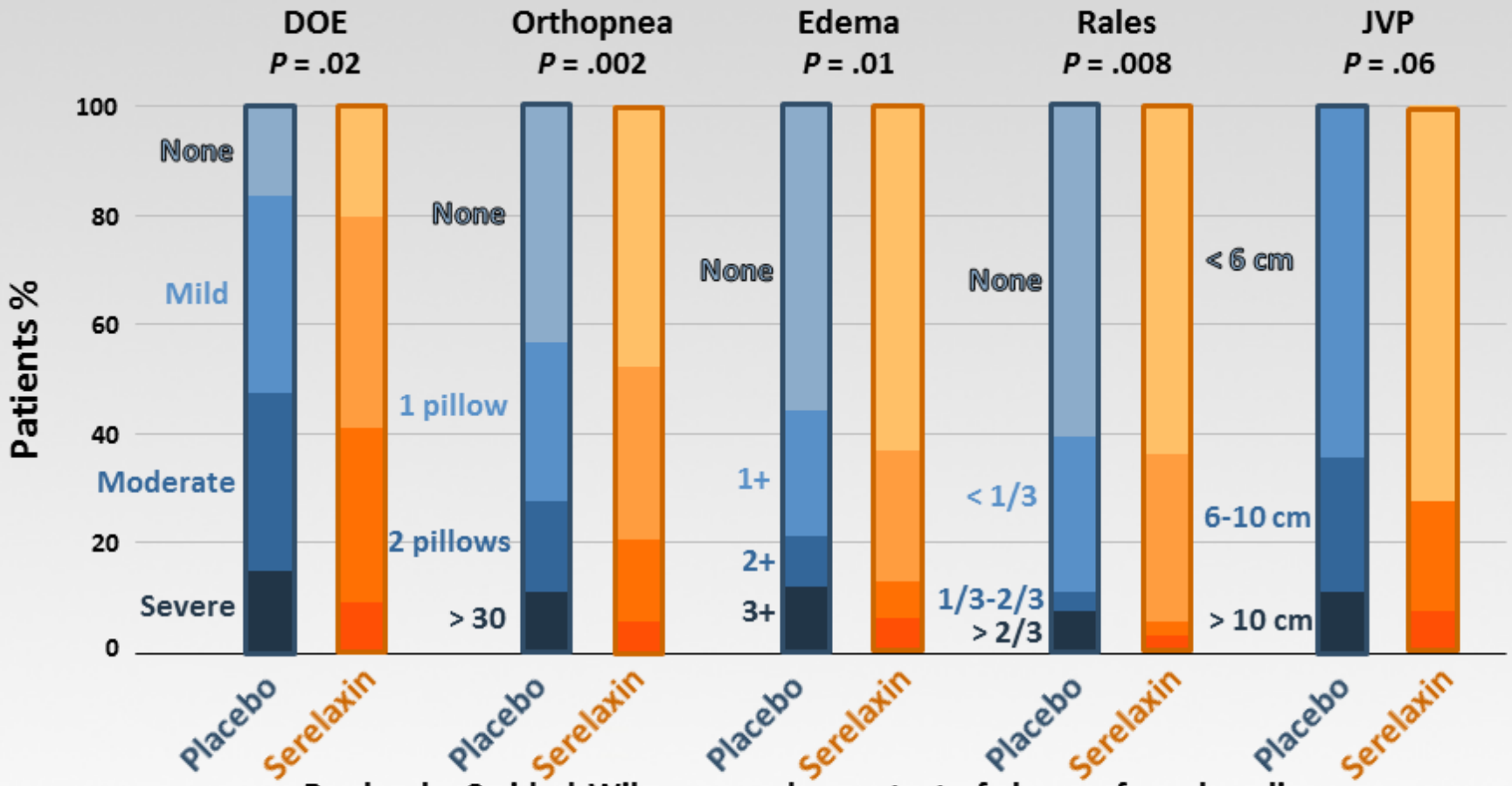
European Medicines Agency Criteria

4.2 Secondary Endpoints

- 4.2.1 Cardiac and noncardiac deaths
- 4.2.2 Hospitalization
- 4.2.3 Days alive and out of hospital
- 4.2.4 Recurrent ischemic events
- 4.2.5 Hemodynamic measurements
- **4.2.6 Changes in signs of congestion**
- 4.2.7 Other objective measurements
- 4.2.8 Quality of life /global clinical status
- 4.2.9 BNP and NT-pro-BNP
- 4.2.10 Indices of renal function

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133497.pdf

Signs and Symptoms of Congestion



DOE = dyspnea on exertion; JVP = jugular venous pressure

Heart failure

From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

theheart.org from WebMD

Medscape EDUCATION

European Medicines Agency Criteria

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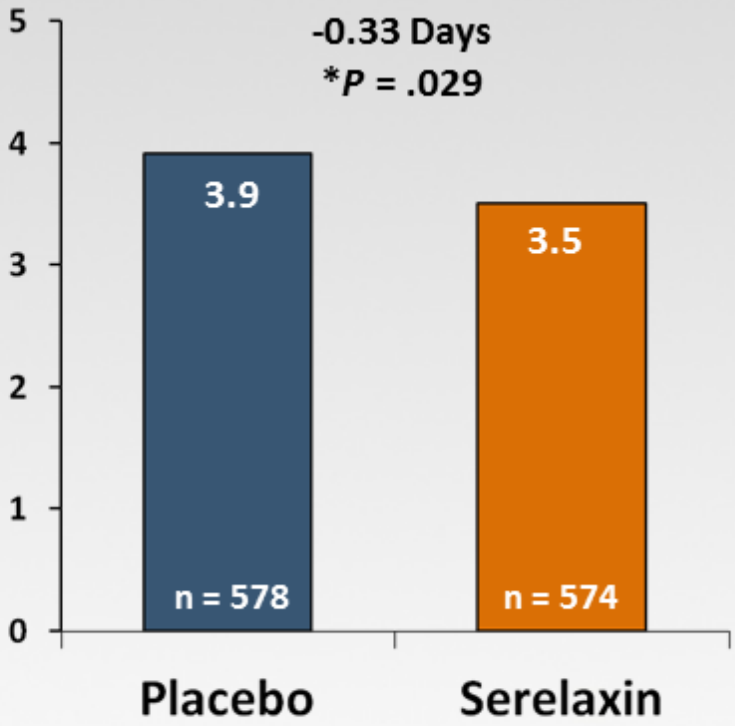
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133497.pdf

Index Hospitalization LOS

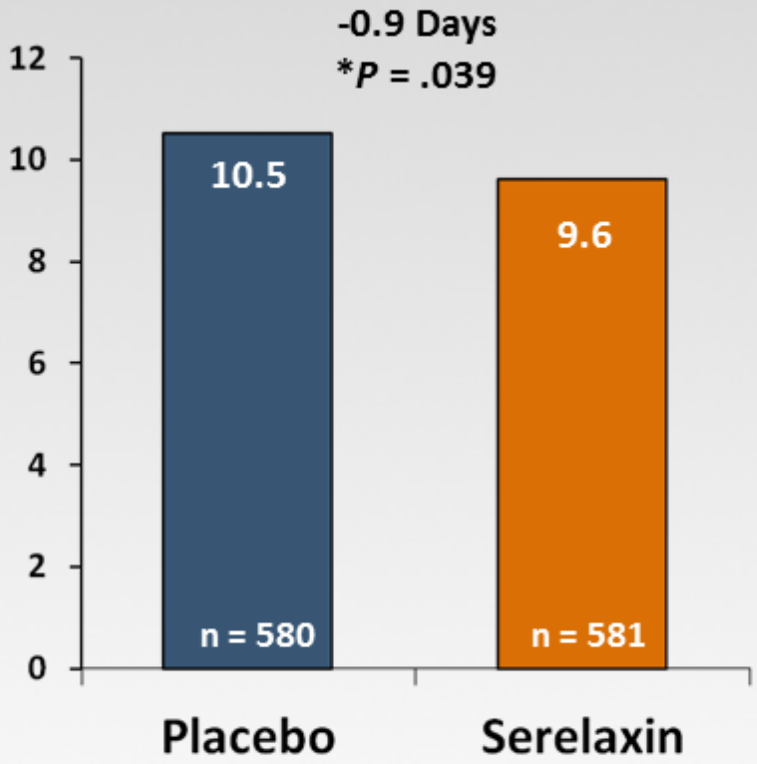
Duration of ICU/CCU Care (Days)



*P value by 2-sided Wilcoxon rank sum test

CCU = critical care unit

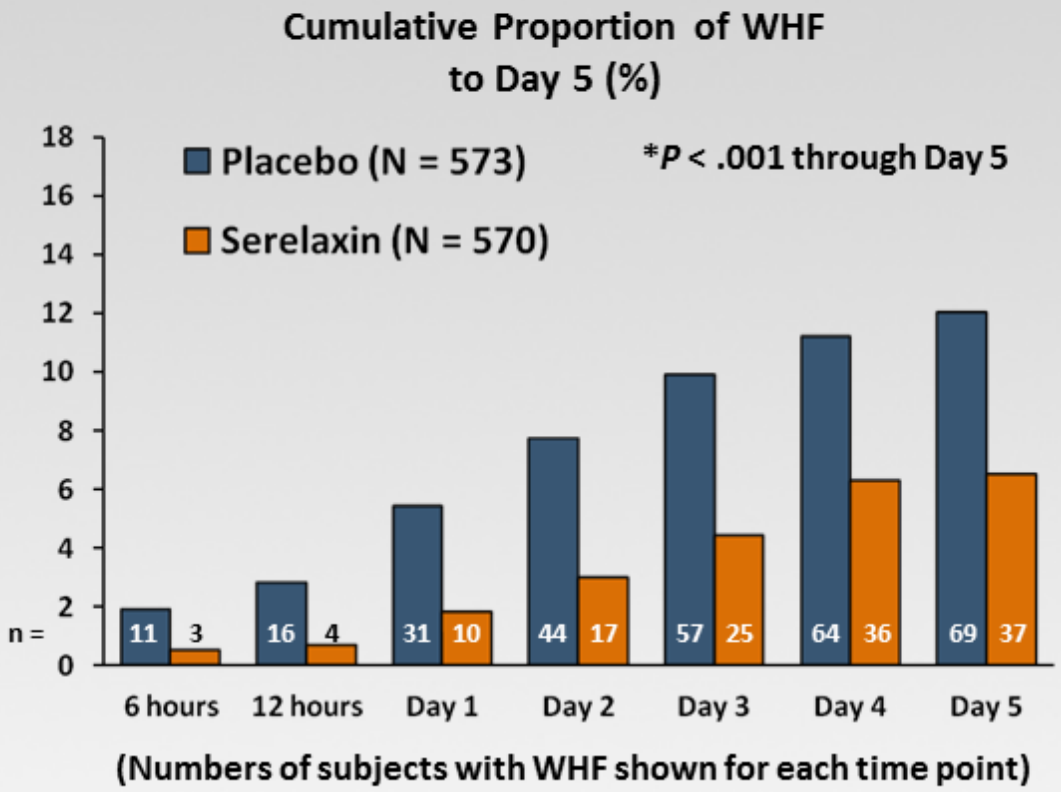
Index Hospitalization LOS (Days)

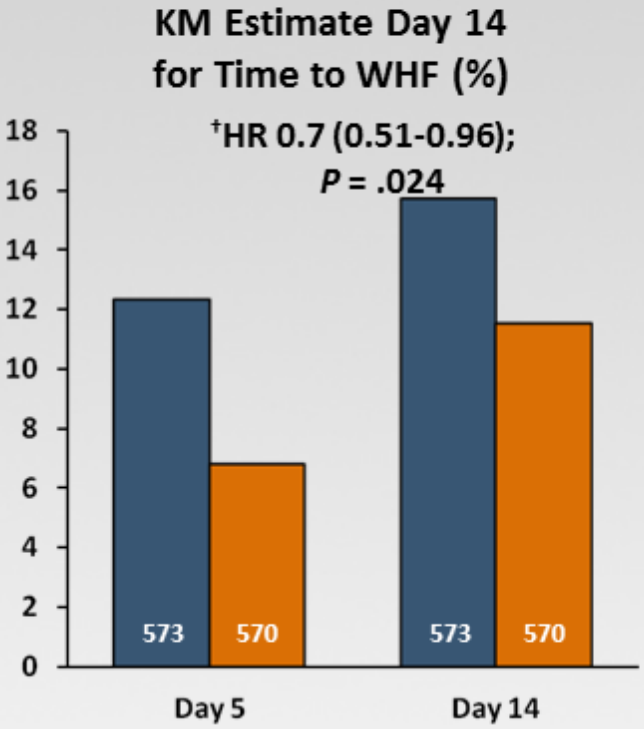


Patients still in the hospital at day 60 are censored at day 60. Patients who died in-hospital are imputed as the maximum +1 day..

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Worsening of Heart Failure





WHF was defined as 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

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

European Medicines Agency Criteria

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- **4.2.9 BNP and NT-pro-BNP**
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http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133497.pdf

Biomarkers

Criteria		Placebo	Serelaxin
NT-pro-BNP (≥ 30% decrease at day 2)	Yes	315 (58.0%)	371 (69.0%)*
	No	228 (42.0%)	167 (31.0%)
Creatinine (≥ 0.3 mg/dL increase at day 2)	Yes	108 (19.8%)	59 (10.9%)†
	No	437 (80.2%)	482 (89.1%)
Troponin T (≥ 20% increase at day 2)	Yes	145 (27.2%)	86 (16.5%)†
	No	389 (72.8%)	436 (83.5%)
ALT (Change at day 2)	mg/dL	-2.3	-6.4‡

*P = .0002
†P < .0001
‡P < .0010

ALT = alanine transaminase

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

European Medicines Agency Criteria

4.1 Primary Endpoints

4.1.1 Mortality

The prefered primary endpoint is all-cause mortality. As the treatment for AHF is often short-term administration of the investigational agent (drug), these would either be:

- **In-hospital mortality during the index admission**
- **Mortality at 30 days**

4.1.2 Short-term outcomes (symptoms)

4.1.2.1 Dyspnea
4.1.2.2 Other symptoms/signs

4.1.3 Coprimary endpoints or composite endpoints

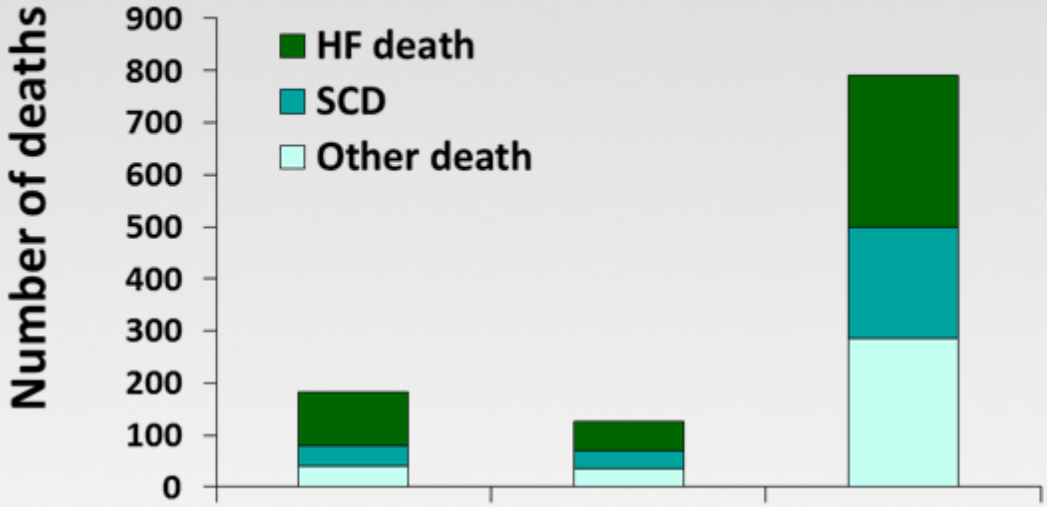
Where are the problems in AHF?

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133497.pdf

EVEREST Trial: Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction:

Different Causes of Death! What Is the Target?

Timing of primary modes of death



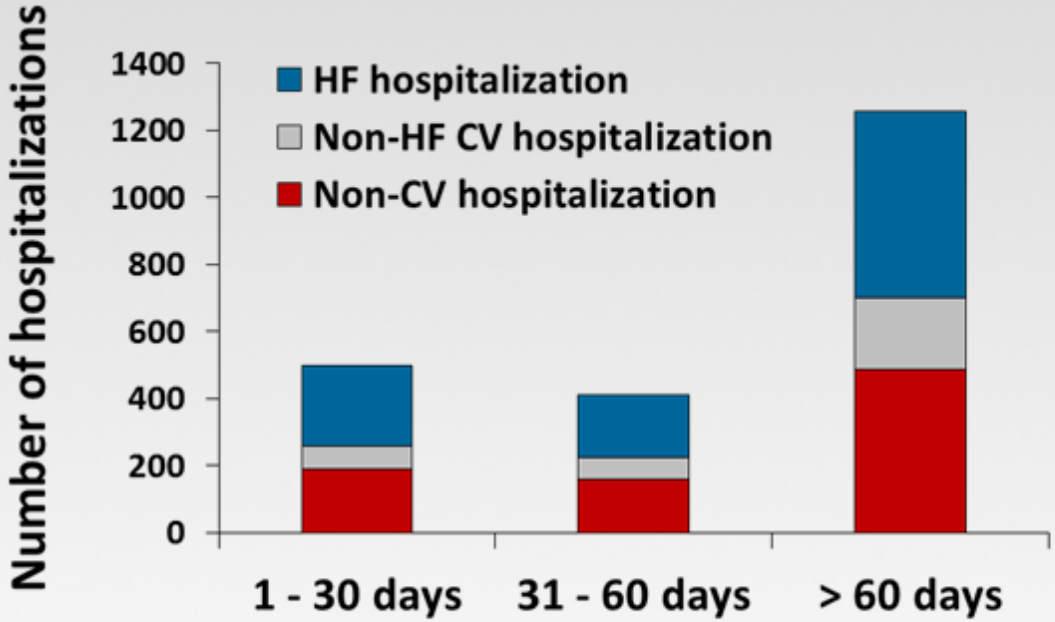
	1 - 30 days	31 - 60 days	> 60 days
HF death	102 (23.0%)	52 (11.7%)	289 (65.2%)
SCD	41 (14.6%)	28 (10.0%)	212 (75.4%)
Other death	35 (9.8%)	32 (9.0%)	289 (81.2%)
Total	178 (16.5%)	112 (10.4%)	790 (73.1%)

From O'Connor CM, et al. *Am Heart J.* 2010; 159:841-849.

EVEREST Trial: Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction:

Hospitalizations late

Timing of major causes of first hospitalization



	1 - 30 days	31 - 60 days	> 60 days
HF hospitalization	237 (24.1%)	191 (19.5%)	554 (56.4%)
Non-HF CV hospitalization	71 (19.5%)	74 (20.3%)	219 (60.2%)
Non-CV hospitalization	188 (23.1%)	148 (18.2%)	477 (58.7%)
Total	496 (23.0%)	413 (19.1%)	1250 (57.9%)

From O'Connor CM, et al. *Am Heart J.*2010;159:841-849.

Strategies for Managing AHF Today and in the Future

- Right endpoint
- **Intelligent novel mechanisms of action**
- Safety

Serelaxin Has Potential Multimechanistic Effects that May Address the Pathophysiology of AHF

1. ↓ Myocardial overload (preload and afterload)	• Cardiac vasodilation	– ↑ Endothelial nitric oxide – ↓ Systemic vascular resistance – ↑ Cardiac index
2. ↑ Cell preservation	• ↓ Cardiac inflammation	– ↓ Inflammatory cell infiltration – ↓ Oxidative stress
	• ↑ Kidney tissue healing	– ↑ Angiogenesis – ↑ Stem cell survival and coupling
	• ↑ Kidney cell survival	– ↓ Oxidative stress – ↓ Apoptosis – ↓ Ca^{2+} overload – ↓ Infarct size
3. ↓ Kidney remodeling	• ↓ Kidney remodeling	– ↓ CF-stimulated protein synthesis – ↑ ANP expression
	• ↓ Kidney fibrosis	– ↓ CF activation and proliferation – ↓ Collagen synthesis – ↑ Collagen breakdown

ANP = atrial natriuretic peptide

Adapted from Du XJ, et al. *Nat Rev Cardiol.* 2010;7(1):48-58.

Relaxin in AHF

Parameter	AHF
Cardiac output (L/min)	Decrease
Systemic vascular resistance (dyne-sec/cm^2)	Increase
Global arterial compliance (mL/mm Hg)	Decrease
Renal blood flow (mL/min/1.73 m^2)	Decrease
Creatinine clearance (mL/min/1.73 m^2)	Decrease

Relaxin in AHF

Parameter	AHF	Pregnancy
Cardiac output (L/min)	Decrease	20% Increase
Systemic vascular resistance (dyne-sec/cm^2)	Increase	30% Decrease
Global arterial compliance (mL/mm Hg)	Decrease	30 % Increase
Renal blood flow (mL/min/1.73 m^2)	Decrease	50%-85% Increase
Creatinine clearance (mL/min/1.73 m^2)	Decrease	40%-65% Increase

- Relaxin Reverse AHF Pathophysiology
- Safety Provided in Billions of Pregnant Women

Strategies for Managing AHF Today and in the Future

- Right endpoint
- Intelligent novel mechanisms of action
- **Safety**

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.
Nonserious AEs were collected through Day 5, SAEs through Day 14
AE = adverse event; d/c = discontinuation; SAE = serious adverse event

*P < 0.05

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Strategies for Managing AHF Today and in the Future

- Where are the gaps?
- Do we have to be pessimistic?

Randomized Controlled Trials in AHF

New treatments Refinements or data available

Drug, Mechanism, TRIAL	No.	Phase	Primary Endpoint
Omecamtiv mecarbil, myosin activator, ATOMIC-AHF	600	2	Relief of dyspnea
Ularitide, TRUE-AHF	2116	3	Hierarchical clinical composite
Dopamine vs nesiritide vs placebo, ROSE-AHF	360	4	72-hour diuresis, cystatin-c change
Metolazone + furosemide vs furosemide alone	160		Diuresis
Furosemide high- vs low-dose vs low-dose + dopamine, DAD-HF-2	450	4	1-year mortality or rehospitalization
Tolvaptan, TACTICS-HF	250	3	Dyspnea relief

Novel Drugs Involving Positive Inotropic Mechanism

Drug	Mechanism
Na+/K+ ATPase inhibitors • Istaroxime	Sarcolemmal Na+-K+ pump inhibition: cytosolic calcium increase SERCA2 stimulation
Myosin activators • Omecamtiv mecarbil	Myosin stimulation: ↑ ejection phase duration, no change in ejection rate or calcium
RyR stabilizers • JTV-519, S107	RyR2/calstabin 2 interaction, ↓SR calcium leakage
SERCA2a activators • SERCA2a adeno-associated viral vector,...	↑ uptake of cytosolic calcium into the SR during diastole: better relaxation and increased calcium release during systole
Metabolic modulators • Perhexiline • Trimetazidine • Ranolazine • GLP-1	Carnitine palmitoyl transferase 1 inhibition: myocardial substrate shift from FFAs to glucose; other mechanisms
Urocortin 2	Myocardial and vascular CRF2 receptors

Negative Recommendations Despite Heterogenous Mechanisms of Action

Strategies for Managing AHF Today and in the Future

Summary: Studies and drugs with…

- Right endpoint
- Intelligent novel mechanisms of action
- Safety

… will have a great chance to fill gaps in present guidelines

Acute Heart Failure: A Historical Perspective

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Heart failure
theheart.org from WebMD
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AHF vs CHF

- Rodney Dangerfield—"I get no respect."
- AHF has not gotten a lot of respect through the years.
- Much attention has been given to CHF.
- Many concepts have been transferred directly from CHF to AHF.

AHF = acute heart failure; CHF = chronic heart failure

AHF: The Scope of the Problem

- In the United States, > 1.1 million hospitalizations annually for heart failure (3 million overall), tripling in last 3 decades[a]
- In ESC countries, HF is the cause of 5% of acute hospital admissions, is present in 10% of patients in hospital beds, and accounts for 2% of national expenditure on health, mostly due to the cost of hospital admissions.[b]
- Leading reason for hospitalization in patients > 65 years of age[a]

ESC = European Society of Cardiology

a. Lloyd-Jones D, et al. *Circulation*. 2010;121(7):e46-e215.
b. Dickstein K, et al. *Eur Heart J*. 2008;29:2388-2442.

2012 AHA Heart Disease Statistics

Hospital discharges for heart failure

- Upward trend over last 3 decades
  - 1,094,000 first-listed discharges in 2009 (Source: NHDS/NCHS and NHLBI)
- Affects both men and women equivalently

Note: Hospital discharges include people discharged alive, dead and status unknown.

Roger VL, et al. *Circulation*. 2012;125(1):e2-e220.

AHF: The Scope of the Problem (cont)

In United States:

- **Over 6 million hospital days**
- **Postdischarge hospitalization (20%-30%) and mortality (10%-20%) within 3-6 months**

Lloyd-Jones D, et al. *Circulation.* 2010;121(7):e46-e215.

Rehospitalizations for Heart Failure

Conditions at Index Discharge	30-Day Rehospitalization Rate	Proportion of All Rehospitalizations	Reason for Rehospitalization			
			Most Frequent	Second Most Frequent	Third Most Frequent	Fourth Most Frequent
	Percent		Percent of All Rehospitalizations Within 30 Days After Index Discharge			
Medical						
All	21.0	77.6	Heart failure 8.6	Pneumonia 7.1	Psychoses 4.3	COPD 3.9
Heart failure	26.9	7.6	Heart failure 37.0	Pneumonia 5.1	Renal failure 3.9	Nutrition-related or metabolic issues 3.1
Pneumonia	20.1	6.3	Pneumonia 29.1	Heart failure 7.4	COPD 6.1	Septicemia 3.6
COPD	22.6	4.0	COPD 36.2	Pneumonia 11.4	Heart failure 5.7	Pulmonary edema 3.9
GI problems	19.2	3.1	GI problems 21.1	Nutrition-related or metabolic issues 4.9	Pneumonia 4.3	Heart failure 4.2
Surgical						
All	15.6	22.4	Heart failure 6.0	Pneumonia 4.5	GI problems 3.3	Septicemia 2.9
Cardiac stent placement	14.5	1.6	Cardiac stent 19.7	Circulatory diagnosis 8.5	Chest pain 6.1	Heart failure 5.7

Medicare claims data from 11,855,702 Medicare beneficiaries in 2003-2004

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal

Heart failure

Adapted from Jencks SF, et al. *N Engl J Med.* 2009;360(14):1418-1428.

theheart.org from WebMD

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EURObservational Research Programme: Heart Failure Pilot Survey (ESC-HF Pilot)

136 Participating Centers

5118 patients enrolled

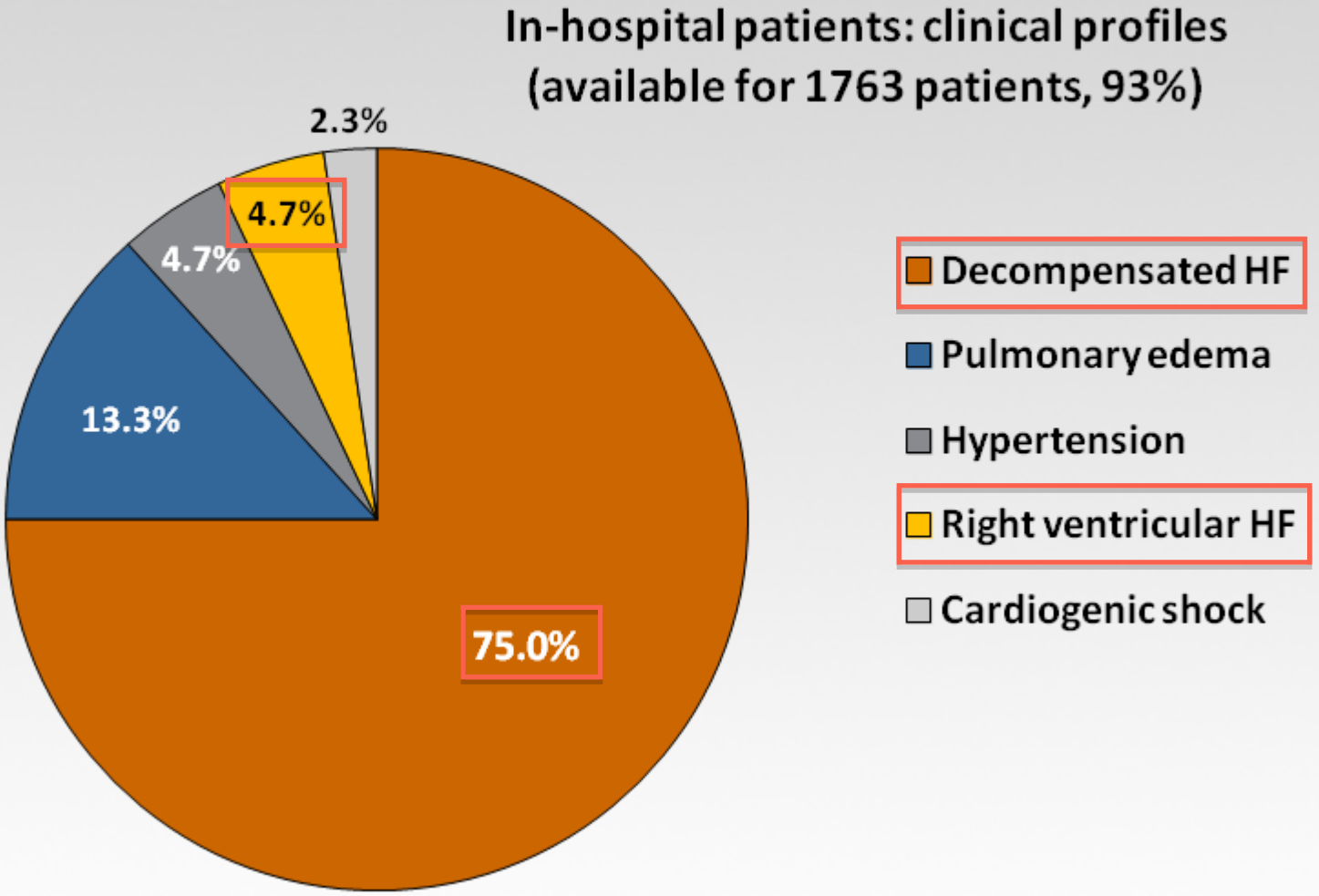
1892 (37%) in-hospital patients (AHF)

3226 (63%) outpatients with CHF

Region	AHF	CHF	Total
Northern 18 centers	140 (22%)	501 (78%)	641 (13%)
Eastern 36 centers	991 (73%)	363 (27%)	1354 (26%)
Western 32 centers	218 (39%)	337 (61%)	555 (11%)
Southern 50 centers	543 (21%)	2025 (79%)	2568 (50%)

Adapted from Maggioni AP, et al. *Eur J Heart Fail* 2010;12(10):1076-1084.

Clinical Profiles of AHF Patients: ESC-HF Pilot



Maggioni AP, *et al*. *Eur J Heart Fail*. 2010;12(10):1076-1084.

The Cost of Hospital Care of Patients with AHF

- In the United States, cost for hospital care of HF was $20.9 billion in 2010.
- Accounts for 60% of all expenditures on HF treatment

Lloyd-Jones D, et al. *Circulation.* 2010;121(7):e46-e215.

ADHERE Registry

- 187,565 patients
- Age: 75.1 (SD 13.9) years
- 51% female
- 76% history of heart failure
- 62% LVEF measured in hospital
- 57% LVEF < 40%
- Symptoms/signs:
  - 89% any dyspnea
  - 31% fatigue
  - 66% rales
  - 65% peripheral edema
  - 50% SBP > 140 mm Hg

Medical History

- CAD 57%
- MI 30%
- AF 31%
- DM 44%
- HTN 74%
- PVD 18%
- COPD/asthma 31%
- Renal insufficiency 30%
- Dyslipidemia 37%

AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PVD = peripheral vascular disease; SBP = systolic blood pressure; SD = standard deviation

Heart failure

ADHERE Core Module Q1 2006 Final Cumulative National Benchmark Report.

theheart.org from WebMD Medscape EDUCATION

Goals of Therapy for Patients with AHF

- Help patients feel better and live longer
  - Improve dyspnea or other symptoms
  - Relieve signs of congestion
  - Prevent worsening of HF
  - Decrease length of stay
  - Reduce rehospitalizations
  - Increase survival

AHF: A Historical Perspective

- AHF: The Extent of the Problem
- The Cost of AHF
- Goals of Treatment
- **Historical Solutions**

"Current" Therapeutic Mechanisms: Inotropes

- "Discovery" by William Withering reported in 1785[a]
  - Putative mechanism is inhibition of Na/K ATPase, increases intracellular Ca^{2+}
- Adrenal extracts with adrenaline first obtained by Polish physiologist Napoleon Cybulski in 1895.[b]
  - Receptor-based increases in intracellular Ca^{2+}

a. Krikler DM. *J Am Coll Cardiol.* 1985;5(Suppl A):3A-9A.
b. Pawlik W, et al. *J Physiol Pharmacol.* 2006;57(1):107-118.

"Current" Therapeutic Mechanisms: Vasodilators

- Nitroglycerin therapy first published as an option—"Nitroglycerin as a Remedy for Angina Pectoris," by William Murrell, MRCP—published in *The Lancet* in 1879

Murrell W. *Lancet*. 1879;113(2890):80-81.

Acute Heart Failure Management: Challenges and Future Therapies

Moderator

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Heart failure

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Heart Failure—Epidemiology

Prevalence

- > 2%-3% overall; 10%-20% at > 70 years[a]
- European Society of Cardiology countries: > 15 million patients with heart failure and increasing[a]

Burden

- Primary cause of 5% of hospital admissions[b]
- Present in 10% of hospitalized patients[b]
- 2% of national health expenditure (60%-70% of cost due to heart failure hospitalization)[b]
- 40% of patients admitted to hospital with heart failure are dead or readmitted within 1 year[b]

a. McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.
b. Dickstein K, et al. *Eur Heart J.* 2006;29:2388-2442.

Goals of Treatment in Acute Heart Failure

Immediate (ED/ICU/CCU)

- Treat symptoms and restore oxygenation
- Improve hemodynamics and organ perfusion
- Limit cardiac and renal damage
- Prevent thromboembolism
- Minimize ICU length of stay

Intermediate (in hospital)

- Stabilize patient and optimize treatment strategy
- Initiate and up-titrate appropriate pharmacologic therapy
- Consider device therapy in appropriate patients
- Identify etiology and relevant comorbidities

Pre-discharge and long-term management

- Plan follow-up strategy
- Enroll in disease management programs, educate and promote appropriate lifestyle changes
- Plan to up-titrate/optimize dose of disease-modifying drugs
- Ensure patient is assessed for appropriate device therapy
- Prevent early readmission
- Improve symptoms, quality of life, and survival

CCU = coronary care unit; ED = emergency department; ICU = intensive care unit

Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Limitations of Current Regimens for Management of Acute Heart Failure

- Relief of symptoms—treatments may have adverse effects
- Reassessment can take several days
- Able to "stabilize" the patient in a shorter period of time—newer medications and devices have helped
- Chronic heart failure patients who are *frequently* unstable and require frequent rehospitalizations continue to have poor outcomes.

PROTECT: Association Between Dyspnea Relief and Mortality

Variable	HR	95% CI	*P* Value
14-day mortality			
Dyspnea relief at days 2 and 3	0.34	0.18-0.62	< .0001
NYHA class before admission IV vs I/II/III	0.92	0.52-1.63	.780
Systolic blood pressure at screening, per 1 mm Hg increase	0.99	0.90-1.01	.426
Screening BNP > 750 or NT-proBNP > 3000 pg/mL	1.32	0.77-2.26	.306
Day 1 serum sodium, per 1 mEq/L increase	0.90	0.85-0.95	< .001
30-day mortality			
Dyspnea relief at days 2 and 3	0.42	0.26-0.67	< .0001
NYHA class before admission IV vs I/II/II	0.79	0.49-1.28	.332
Systolic blood pressure at screening, per 1 mm Hg increase	0.98	0.97-0.99	.004
Screening BNP > 750 or NT-proBNP > 3000 pg/mL	1.17	0.75-1.82	.492
Day 1 serum sodium, per 1 mEq/L increase	0.90	0.86-0.94	< .001

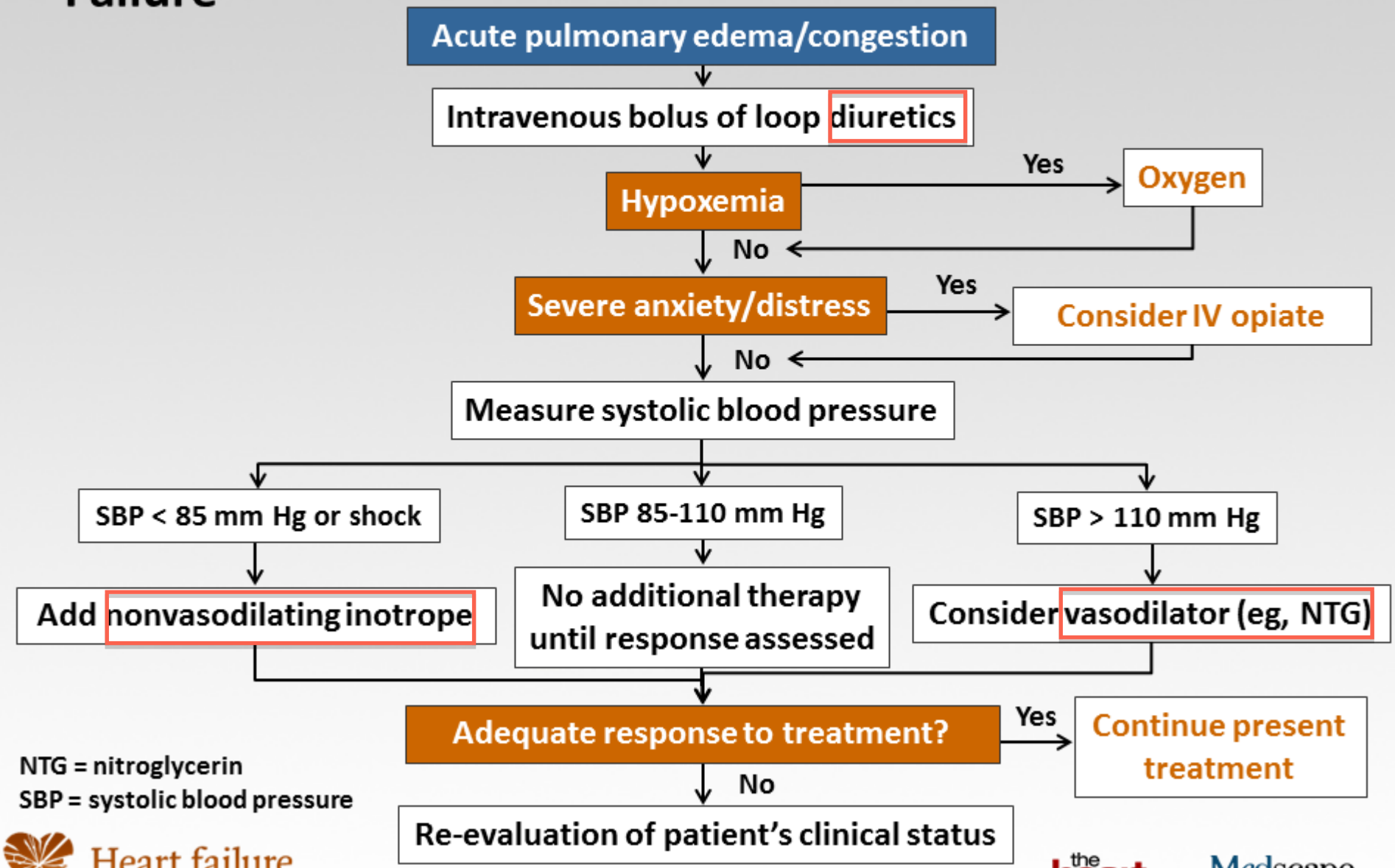
Adapted from Metra M, et al. *Eur Heart J.* 2011;32(12):1519-1534.

Phases of Acute Heart Failure Management

Phases	Goals
Initial or emergency department phase of management	• Treat life-threatening conditions • Establish the diagnosis • Determine the clinical profile • Identify and treat precipitant • Disposition
In-hospital phase	• Monitoring and reassessment • Assess right and left ventricular pressures • Assess and treat (in the right patient) other cardiac and noncardiac conditions • Assess for myocardial viability
Discharge phase	• Assess functional capacity • Re-evaluate exacerbating factors (eg, nonadherence, infection, anemia, arrhythmias, hypertension) and treat accordingly • Optimize pharmacologic therapy • Establish post-discharge planning

Adapted from Pang PS, et al. *Eur Heart J.* 2010;31(7):784-793.

Management of Acute Pulmonary Edema in Acute Heart Failure



NTG = nitroglycerin
SBP = systolic blood pressure

Heart failure

Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

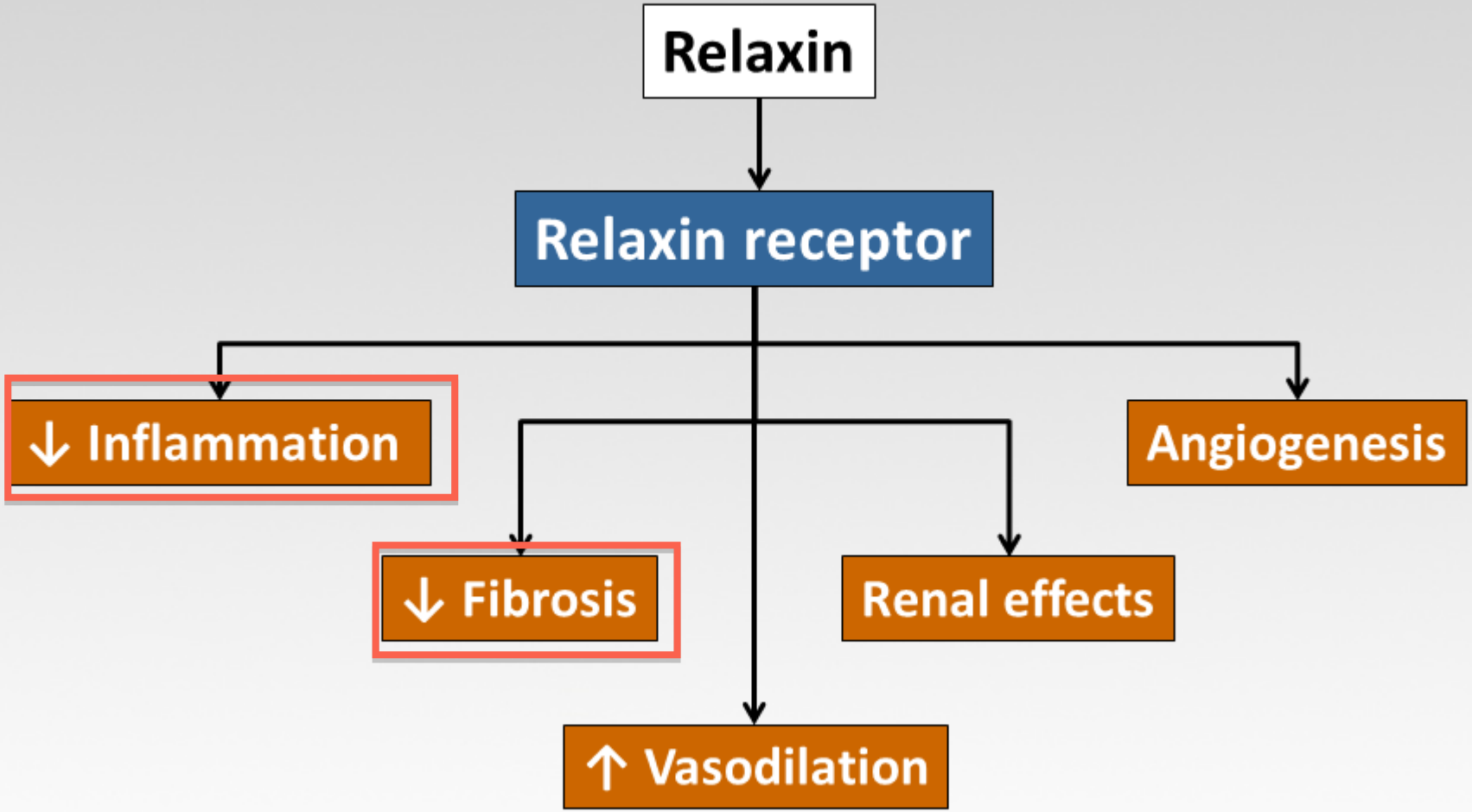
theheart.org from WebMD

Medscape EDUCATION

Questions to Ponder Regarding Failed Therapies in Acute Intervention

- Were they the wrong drugs?
- Were they favorable agents but not studied in the proper way?
- Should they have been starting sooner in the treatment regimen?
- Should we consider drugs that can be used in both acute and chronic phases of heart failure?

Relaxin—Mechanism of Action



Adapted from Teichman SI, et al. *Curr Heart Fail Rep.* 2010;7(2):75-82.

PRE-RELAX-AHF (Phase 2b) Results

		Relaxin (µg/kg/day)			
Short-term	**Placebo (n = 60)**	**10 (n = 40)**	**30 (n = 42)**	**100 (n = 37)**	**250 (n = 49)**
Proportion with moderately or markedly better dyspnea at 6 h, 12h, and 24h (Likert)	14 (23%)	11 (28%) *P* = .54	17 (40%) *P* = .044	5 (14%) *P* = .28	11 (22%) *P* = .86
Dyspnea AUC change from baseline to day 5 (VAS [mm x h])	1679 (2556)	2500 (2908) *P* = .15	2567 (2898) *P* = .11	2486 (2865) *P* = .16	2155 (2338) *P* = .31
Dyspnea AUC change from baseline to day 14 (VAS [mm x h])	4621 (9003)	6366 (10078) *P* = .37	8214 (8712) *P* = .053	8227 (9707) *P* = .064	6856 (7923) *P* = .16
Worsening heart failure through day 5 (%)	13 (21%)	8 (20%) *P* = .75	5 (12%) *P* = .29	5 (14%) *P* = .40	5 (10%) *P* = .15
Length of stay (days)	12.0 (7.3)	10.9 (8.5) *P* = .36	10.2 (6.1) *P* = .18	11.1 (6.6) *P* = .75	10.6 (6.6) *P* = .20
60 days					
Days alive out of hospital	44.2 (14.2)	47.0 (13.0) *P* = .40	47.9 (10.1) *P* = .16	48 (10.1) *P* = .40	47.6 (12.0) *P* = .048
KM cardiovascular death or readmission (HR, 95% CI)	17.2%	10.1% (0.55, 0.17-1.77) *P* = .32	2.6% (0.13, 0.02-1.03) *P* = .053	8.4% (0.46, 0.13-1.66) *P* = .23	6.2% (0.32, 0.09-1.17) *P* = .085
KM all-cause death or readmission (HR, 95% CI)	18.6%	12.5% (0.63, 0.22-1.81) *P* = .39	7.6% (0.36, 0.10-1.29) *P* = .12	10.9% (0.56, 0.18-1.76) *P* = .32	8.3% (0.41, 0.13-1.28) *P* = .12

AUC = area under the curve; KM = Kaplan-Meier estimates of event rate at specified time; HR = hazard ratio

Heart failure

Adapted from Teerlink JR, et al. *Lancet*. 2009;373(9673):1429-1439.

theheart.org from WebMD

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Emerging Therapies

Current and Investigational Pharmacologic Agents for the Treatment of Acute Heart Failure

	Current Agents	Emerging Agents
Congestion with normal to high SBP	a. Diuretics b. Vasodilators (high SBP) – Nitroglycerin – Nitroprusside – Nesiritide* c. ACE inhibitors (high SBP)	a. Vasopressin antagonists b. Adenosine antagonists (PROTECT Study) c. Endothelin antagonists d. Ularitide
Normal to low SBP† "Low" SBP with or without congestion	Levosimendan‡ a. Dobutamine b. Dopamine c. Milrinone d. Digoxin IV	a. Cardiac myosin activators b. Metabolic modulators (RELAX-ADF-1 Study) c. Istaroxime

*Approved by FDA.
†Should be avoided in SBP < 90 mm Hg.
‡Approved by EMA.

ACE = angiotensin-converting enzyme

Adapted from De Luca L, et al. *Eur J Heart Fail*. 2008;10(2):201-213.

Breaking Barriers in Acute Heart Failure Management: What Does the Future Hold?

Moderator

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Professor of Medicine, University of California, San Francisco
Director, Heart Failure Program & Echocardiography
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Heart failure

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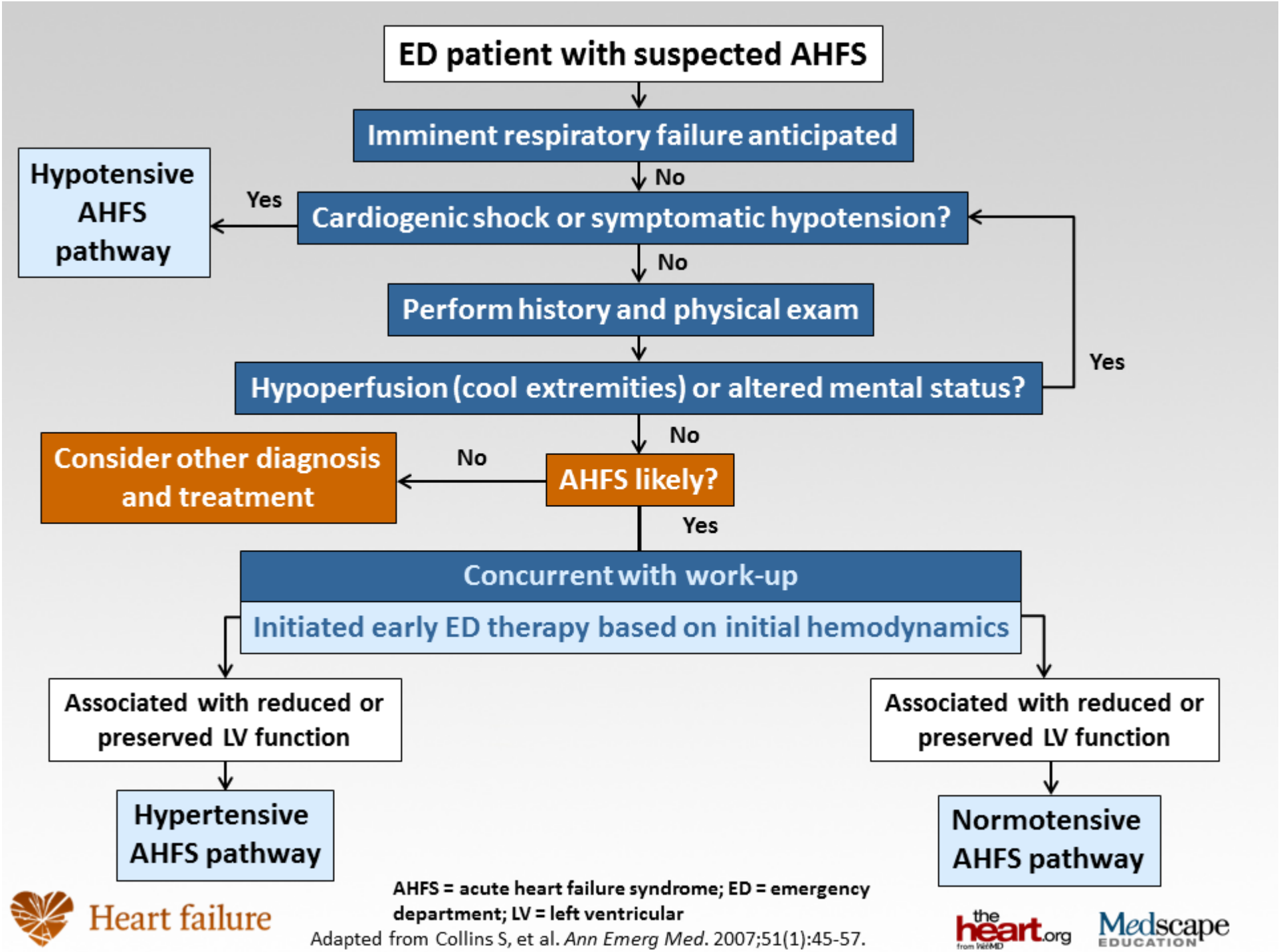

Heart failure

AHFS = acute heart failure syndrome; ED = emergency department; LV = left ventricular

Adapted from Collins S, et al. *Ann Emerg Med*. 2007;51(1):45-57.

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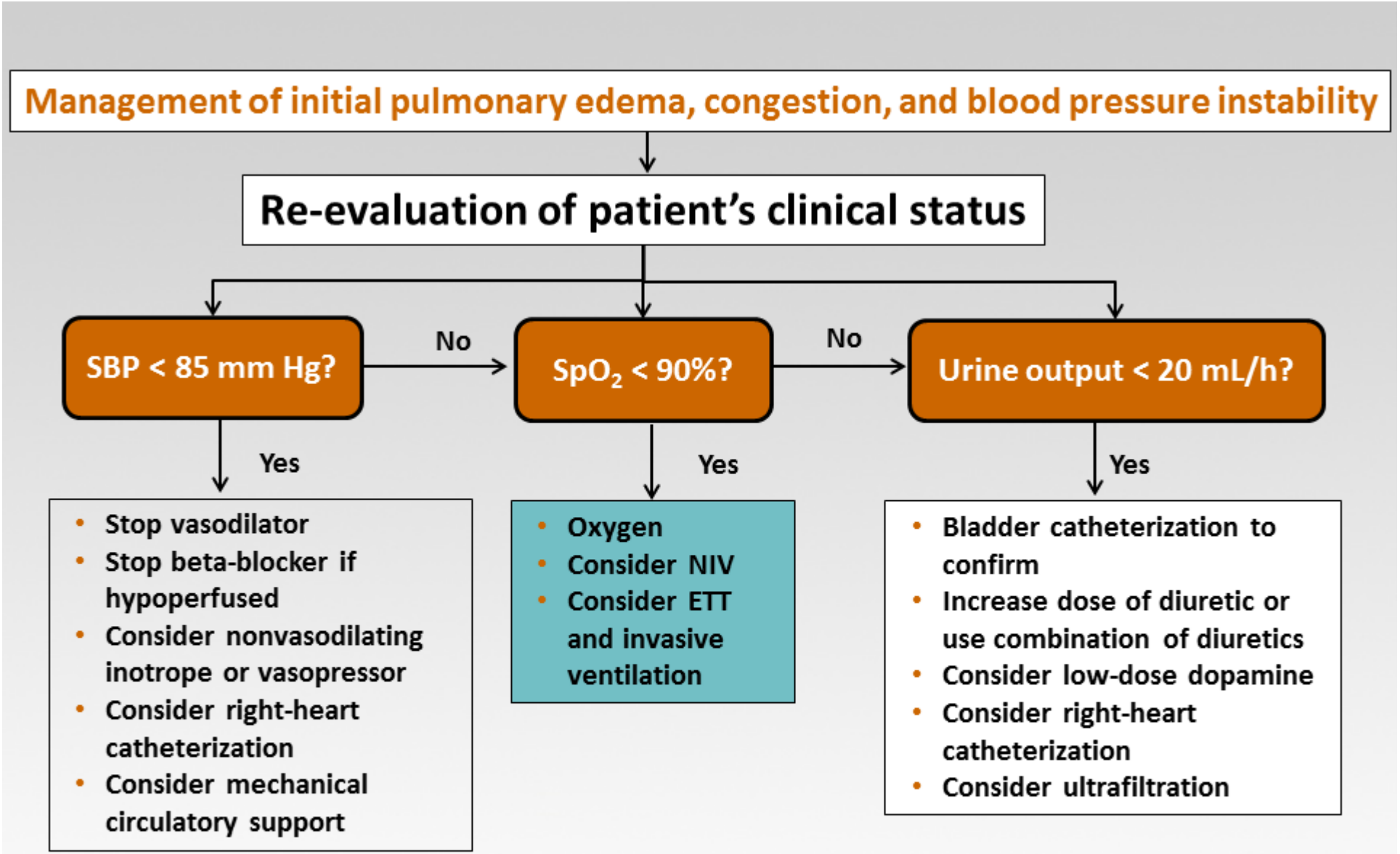

ETT = endotracheal tube; NIV = noninvasive ventilation; SBP = systolic blood pressure; SpO_2 = saturation of peripheral oxygen

Heart failure

Adapted from McMurray JJ, et al. *Eur J Heart Fail.* 2012;14(8):803-869.

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Heart Failure Management Based on Clinical Profiles

Clinical Presentation	Incidence	Targets and Therapies
Elevated BP (above 160 mm Hg)	~25%	Target: BP and volume management Therapy: vasodilators
Normal or moderately elevated BP	~50%	Target: volume management Therapy: loop diuretics ± vasodilators
Low BP (< 90 mm Hg)	< 8%	Target: cardiac output Therapy: inotropes with vasodilatory properties; consider digoxin ± vasopressor medications ± mechanical assist devices (eg, IABP)
Cardiogenic shock	< 1%	Target: improve cardiac pump function Therapy: inotropes ± vasoactive medications ± mechanical assist devices, corrective surgery
Flash pulmonary edema	3%	Target: BP, volume management Therapy: vasodilators, diuretics, invasive or NIV, morphine
ACS and AHFS	~25% of ACS have HF signs/symptoms	Target: coronary thrombosis, plaque stabilization, correction of ischemia Therapy: reperfusion (eg, PCI, lytics, nitrates, antiplatelet agents)
Isolated right HF from pulmonary HTN or intrinsic RV failure (eg, infarct) or valvular abnormalities	?	Target: PA pressure Therapy: nitrates, epoprostenol, phosphodiesterase inhibitors, endothelin-blocking agents, coronary reperfusion for RV infarcts, valve surgery
Post-cardiac surgery HF	?	Target: volume management, improve cardiac performance (output) Therapy: diuretic or fluid administration (directed by filling pressures and cardiac index), inotropic support, mechanical assistance (IABP, VAD)

ACS = acute coronary syndrome; HTN = hypertension; IABP = intra-aortic balloon pump; PA = pulmonary artery; PCI = percutaneous coronary intervention; RV = right ventricular; VAD = ventricular assist device

Heart failure

Adapted from Gheorghiade M, et al. *J Am Clin Cardiol*. 2009;53(7):557-573.

theheart.org from WebMD

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DOSE Trial: Mean Change in Serum Creatinine Level

	Change in Creatinine (mg/dL)	*P* Value
Bolus	0.05	.45
Continuous	0.07	
Low dose	0.04	.21
High dose	0.08	

The mean change in the serum creatinine level over the course of the 72-hour study treatment period is shown for the group that received boluses every 12 hours as compared with the group that received a continuous infusion and for the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose). To convert the values for creatinine to µmol/L, multiply by 88.4.

Felker GM, et al. *N Engl J Med.* 2011;364(9):797-805.

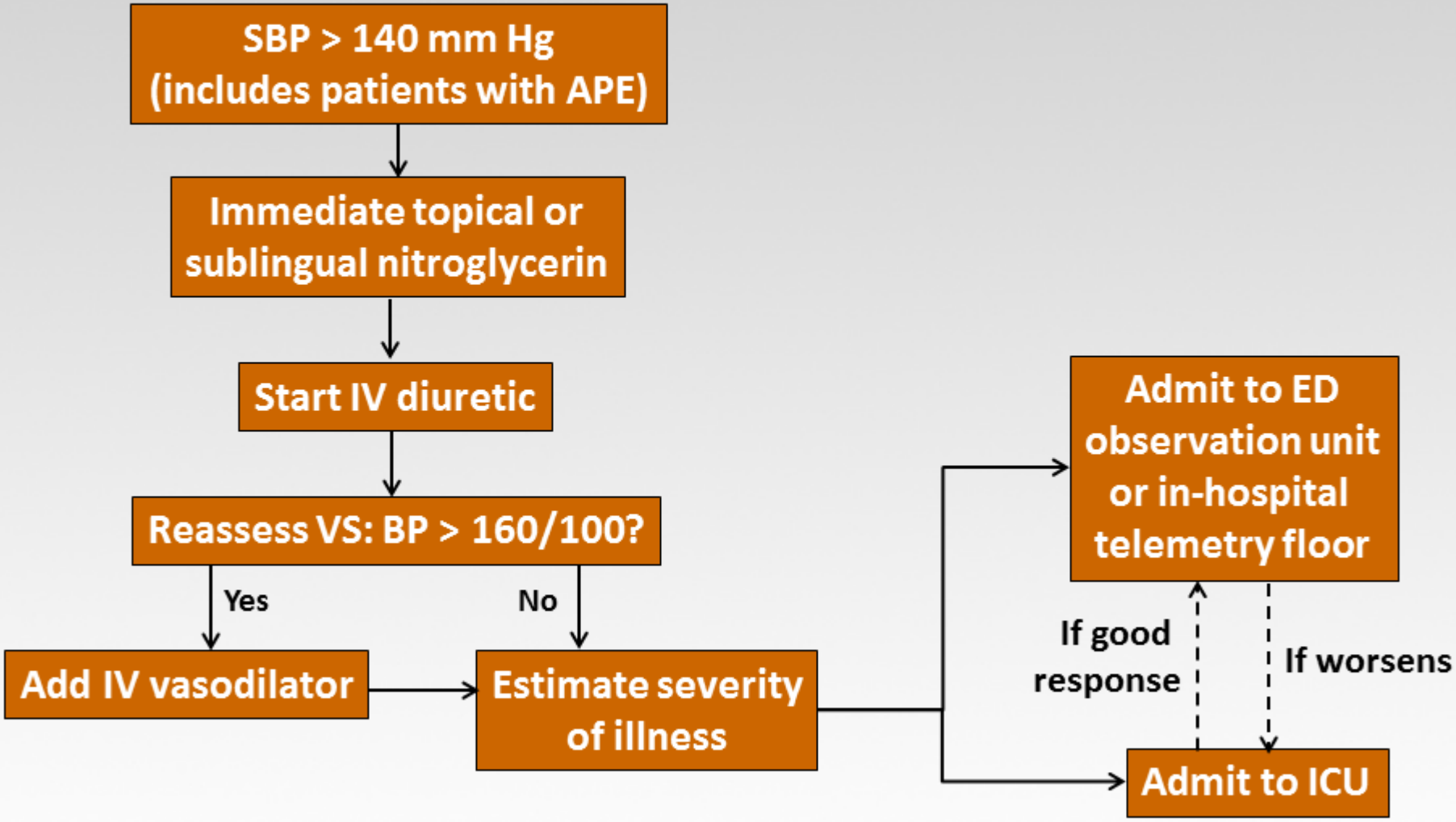
Initial Therapeutic Management for AHF

Target	Therapeutic Example	Side Effects
Alleviate congestion	IV furosemide	Electrolyte abnormalities
Reduce elevated LV filling pressures	IV nitrates	Hypotension, decreased coronary perfusion pressure
Poor cardiac performance	Inotropes	Hypotension, arrhythmias, myocardial damage, association with increased morbid events

IV = intravenous

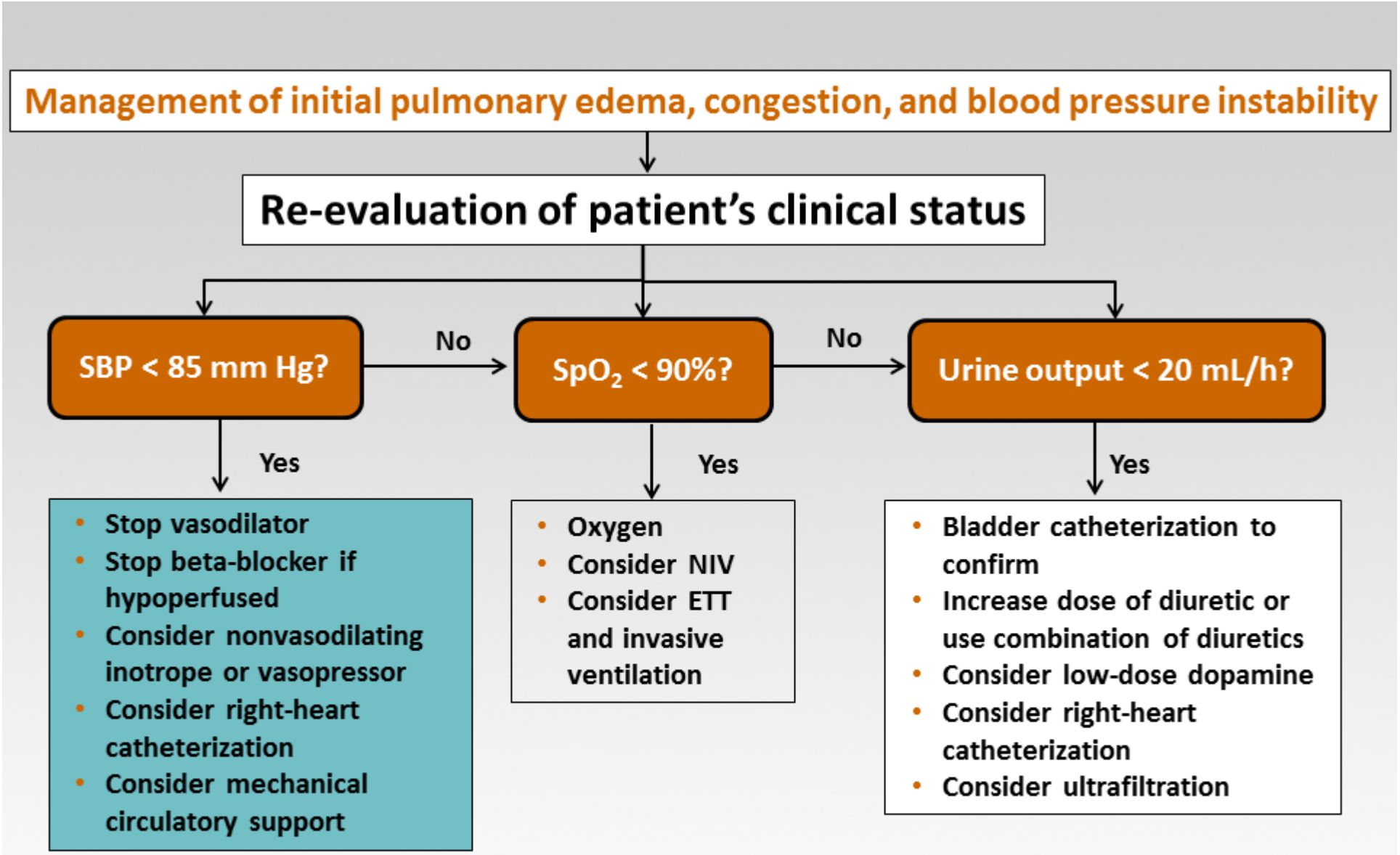
Adapted from Pang PS, et al. *Eur Heart J.* 2010;31(7):784-793.

Hypertensive AHFS



APE = acute pulmonary edema; ICU = intensive care unit; VS = vital signs

Adapted from Collins S, et al. *Ann Emerg Med*. 2007;51(1):45-57.



Heart failure

Adapted from McMurray JJ, et al. *Eur J Heart Fail.* 2012;14(8):803-869.

ESC Heart Failure Guidelines 2012—Use of Levosimendan in AHF

Recommendation

An IV infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effects of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. *See published guidelines for complete recommendation.*
[Class IIb, Level C]

Adapted from McMurray JJ, et al. *Eur Heart J*. 2012;33(14):1787-1847.

VERITAS Trial

	Day 7		Day 30	
	Tezosentan (n = 727)	Placebo (n = 708)	Tezosentan (n = 727)	Placebo (n = 708)
Death or Worsening Heart Failure		**No. (%)**		
Patients with an event*	191 (26.3)	187 (26.4)	232 (31.9)	235 (33.2)
Events†				
Death	11 (1.5)	8 (1.1)	28 (3.9)	34 (4.8)
Cardiogenic shock	3 (0.4)	5 (0.7)	2 (0.3)	4 (0.6)
Pulmonary edema	47 (6.5)	39 (5.5)	61 (8.4)	55 (7.8)
Other evidence of worsening heart failure	83 (11.4)	92 (13.0)	96 (13.2)	104 (14.7)
Treatment failure	47 (6.5)	43 (6.1)	42 (5.8)	37 (5.2)
Heart transplant	0	0	1 (0.1)	0
Lost to follow-up	0	0	2 (0.3)	1 (0.1)

*Comparison between treatment groups (Fisher exact test): *P* = .95 at day 7 and *P* = .61 at day 30

†Ranked by severity—*see publication for complete details*

McMurray JJ, et al. *JAMA.* 2009;298(17):2009-2019.

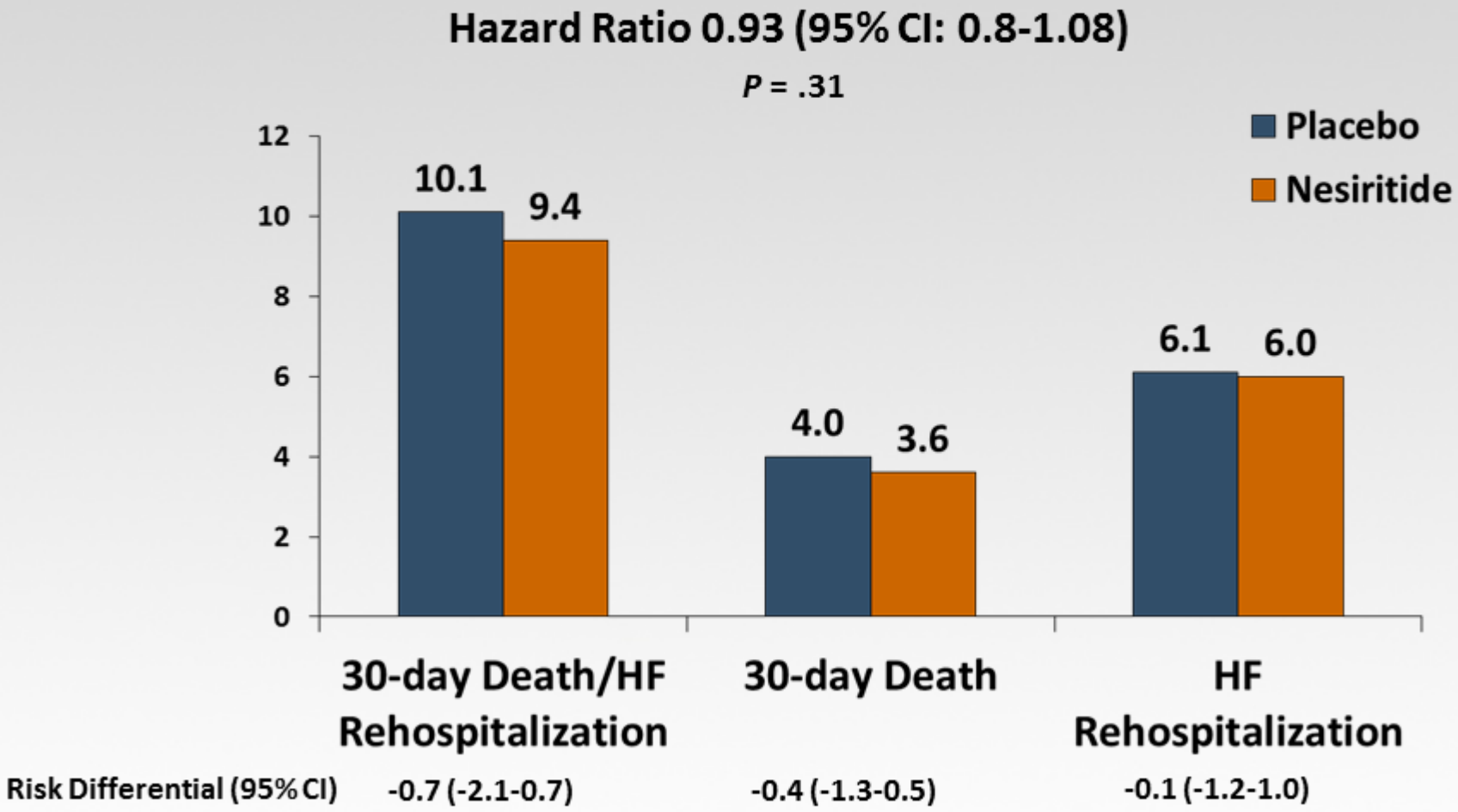
VMAC with Nesiritide

- Randomized controlled trial that compared the efficacy and safety of IV nesiritide, IV nitroglycerin, and placebo
- Assessed changes in PCWP and patient self-evaluation of dyspnea at 3 hours with assessment of secondary endpoints at 24 hours
- Results—significant reduction in mean PCWP with nesiritide vs nitroglycerin (P = .03) with continued benefit out to 24 hours but no significant difference in dyspnea between the drugs

PCWP = pulmonary capillary wedge pressure; VMAC = Vasodilation in the Management of Acute Congestive Heart Failure

VMAC Investigators. *JAMA.* 2002;287(12):1531-1540.

Coprimary Outcome: 30-Day All-Cause Mortality or HF Rehospitalization



Heart failure

From O'Connor CM, et al. *N Engl J Med*.2011;365(1):32-43.

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Pregnancy and the Heart

PARAMETER	PREGNANCY
Cardiac output (L/min)	20% increase
Systemic vascular resistance (dyne-sec/cm^2)	30% decrease
Global arterial compliance (mL/mm Hg)	30% increase
Renal blood flow (mL/min/1.73 m^2)	50%-85% increase
Creatinine clearance (mL/min/1.73 m^2)	40%-65% increase

- Relaxin has been shown to mediate these changes as well as to have anti-ischemic, anti-inflammatory, and antifibrotic effects.
- Relaxin is elevated through 9 months of pregnancy and mediates physiologic hemodynamic adjustments to the growing baby.
- Pharmacologic use of serelaxin may produce these beneficial effects in AHF.

Baylis C. *Am J Kidney Dis.* 1999;34(6):1142-1144.
Schrier RW, et al. *Am J Kidney Dis.* 1987;9(4):284-289.
Jeyabalan A, et al. *Adv Exp Med Biol.* 2007;612:65-87.
Teichman SL, et al. *Curr Heart Fail Rep.* 2010;7(2):75-82.
Helal I, et al. *Nat Rev Nephrol.* 2012;8(5):293-300.

Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Hospitalized for AHF
  - Dyspnea at rest or with minimal exertion
  - Pulmonary congestion on chest x-ray
  - BNP ≥ 350 pg/mL or NT-pro-BNP ≥ 1400 pg/mL
- Received ≥ 40 mg IV furosemide (or equivalent) at any time between admission to emergency services (either ambulance or hospital, including the ED) and the start of screening for the study
- SBP > 125 mm Hg
- Impaired renal function on admission (sMDRD eGFR 30-75 mL/min/1.73 m^2)
- Randomly assigned within 16 hours from presentation
- Age ≥ 18 years of age
- Body weight < 160 kg

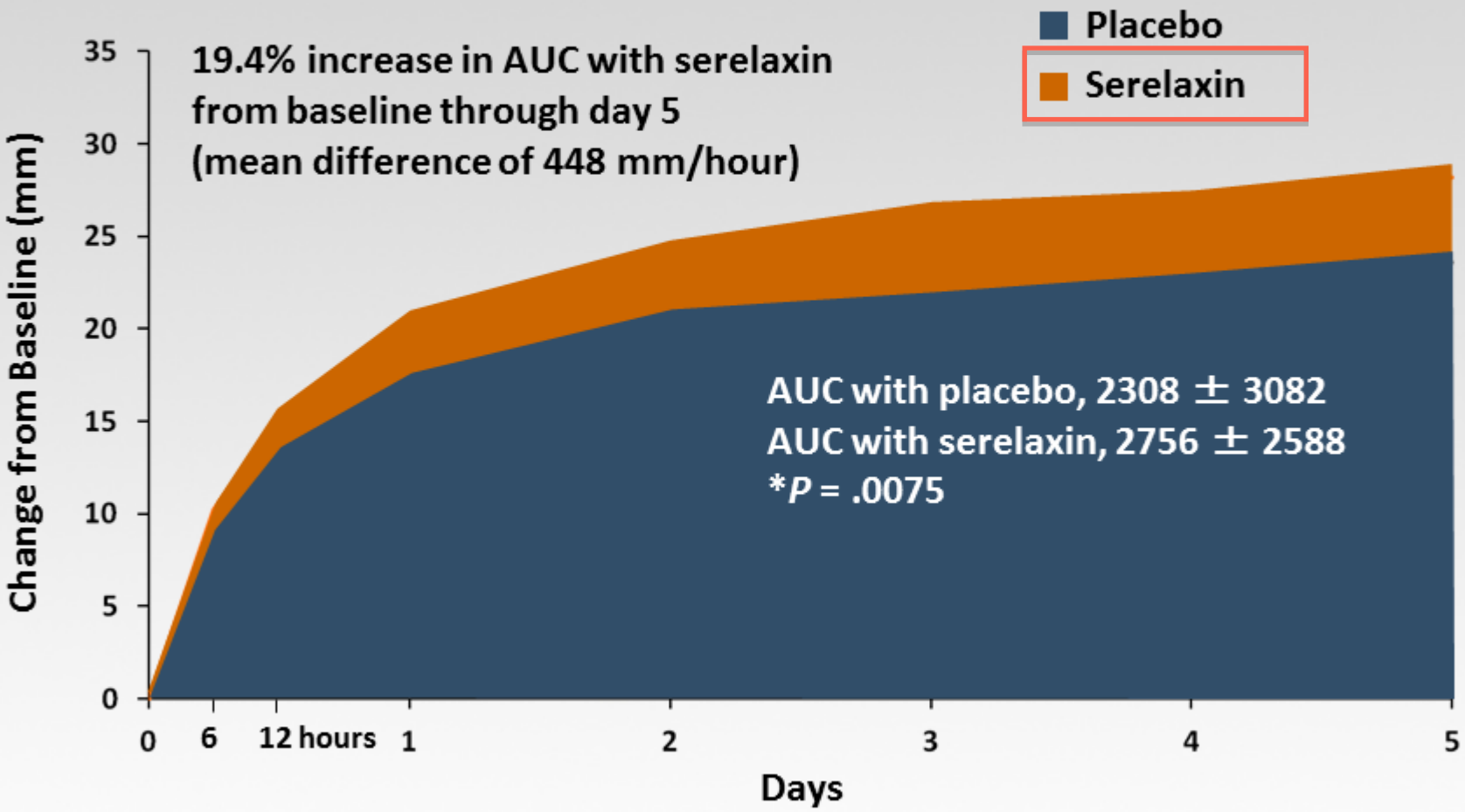
Key Exclusion Criteria

- Current or planned treatment with any IV therapies (ie, other vasodilators [nesiritide], positive inotropic agents, and vasopressors) or mechanical circulatory, renal, or ventilatory support, with the exception of IV furosemide (or equivalent) or of IV nitrates if patient has screening SBP > 150 mm Hg
- AHF and/or dyspnea from arrhythmias or noncardiac causes, such as lung disease, anemia, or severe obesity
- Infection or sepsis requiring IV antibiotics
- Pregnant or breastfeeding
- Stroke within 60 days; ACS within 45 days; major surgery within 30 days
- Presence of acute myocarditis, significant valvular heart disease, hypertrophic/restrictive/constrictive cardiomyopathy

BNP = brain natriuretic peptide;
eGFR = estimated glomerular filtration rate;
sMDRD = simplified modification of diet in renal disease

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

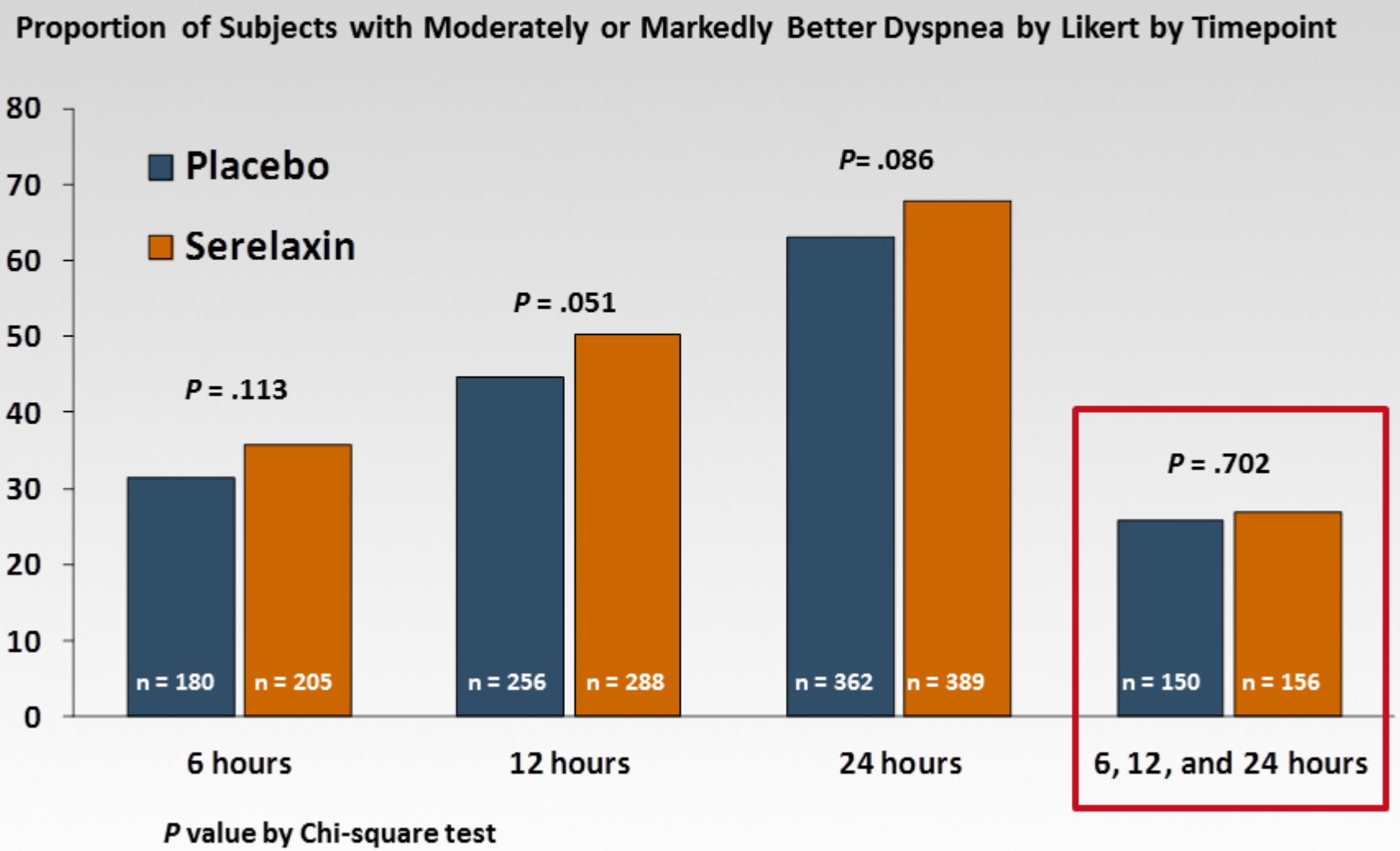
First-Degree Endpoint: Dyspnea Relief (VAS AUC)



AUC = area under the curve; VAS = visual analogue scale

From Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

First-Degree Endpoint: Dyspnea Relief (Likert)



Heart failure

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

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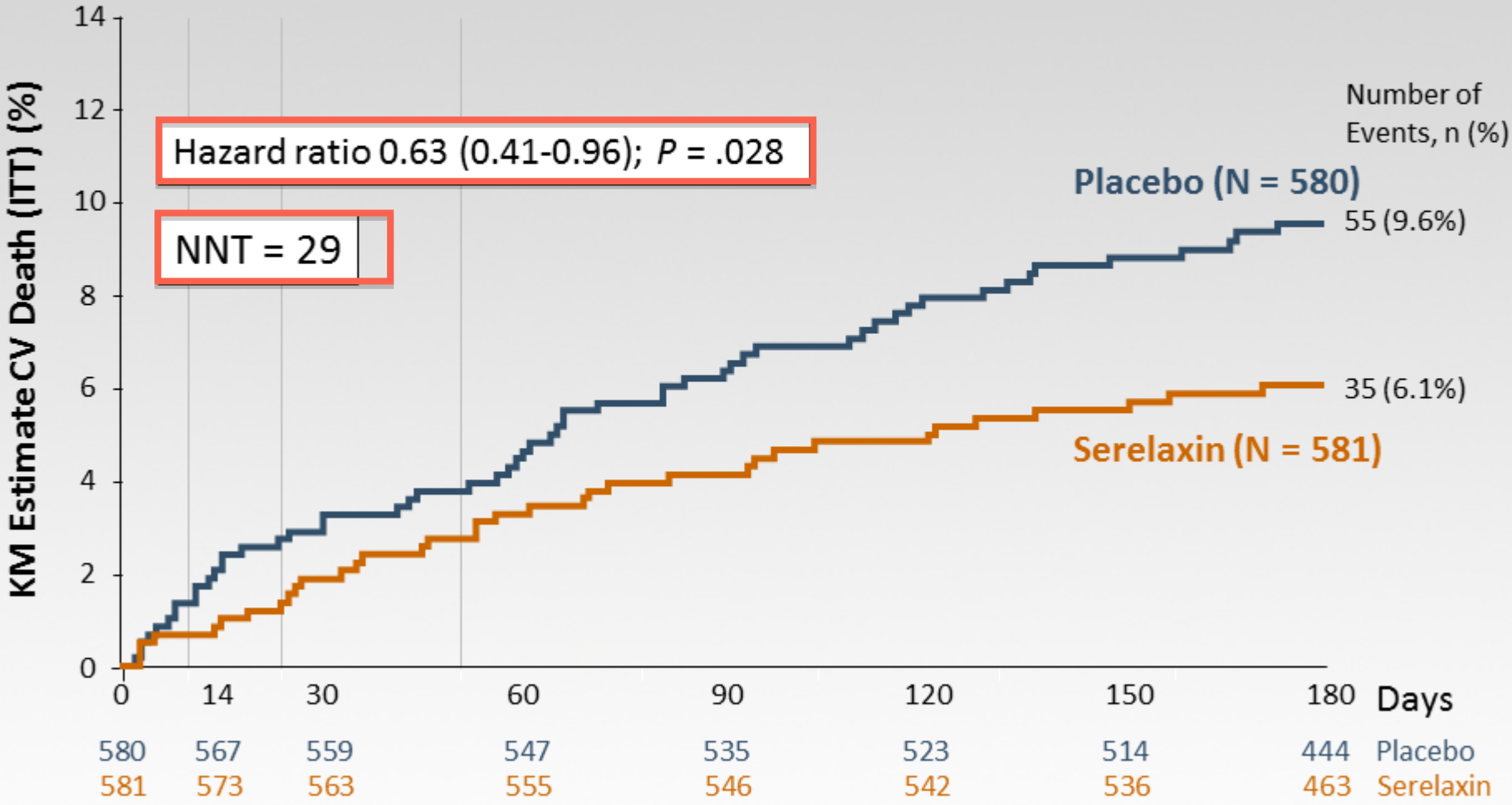
CV Death Through Day 180



CV = cardiovascular; ITT = intent to treat; KM = Kaplan-Meier; NNT = number needed to treat

Heart failure

From Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

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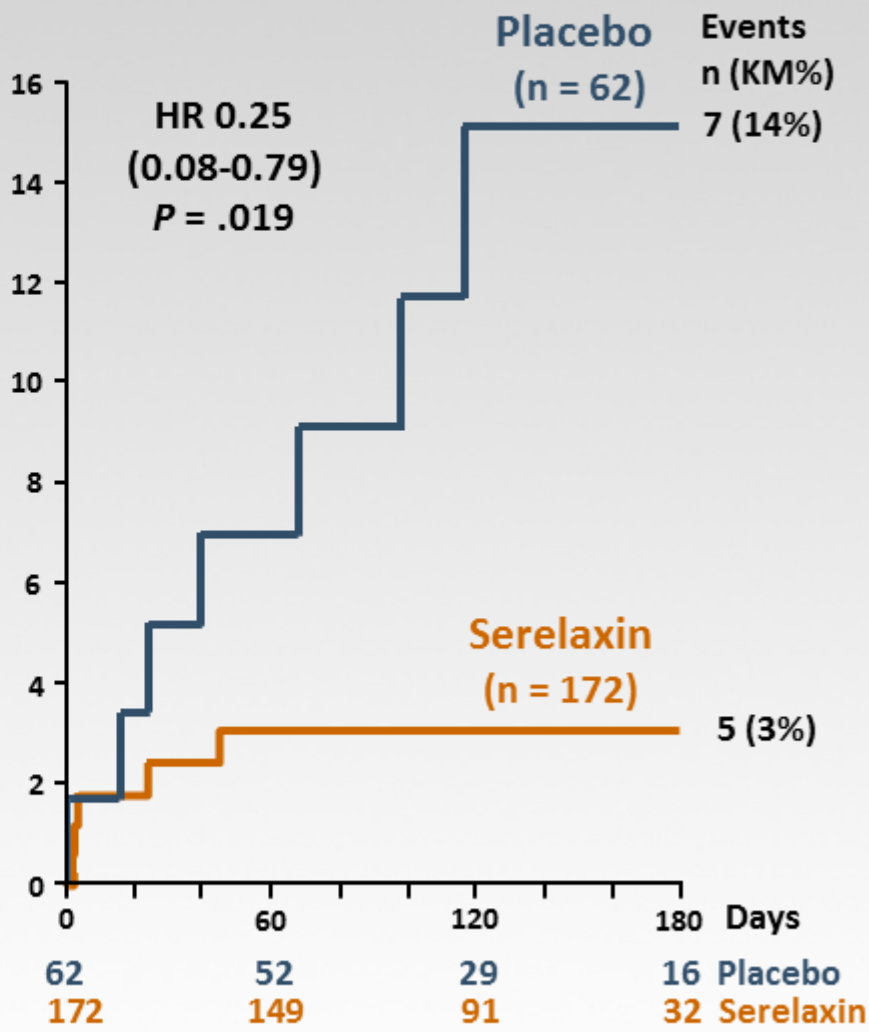
Pre-RELAX-AHF

- 234 patients, dose-finding phase 2 study
- Optimal dose across multiple clinical outcome domains was 30 mcg/kg/d
- Serelaxin had trends to:
  - Improved dyspnea relief
  - Decreased congestion
  - Reduced diuretic use
  - Less worsening of heart failure
  - Shorter length of hospital stay
  - Reduced days alive out of hospital
  - Improved CV and all-cause survival
- Safe and well tolerated without significant hypotension

HR = hazard ratio

CV Death (KM)



Teerlink JR, et al. *Lancet.* 2009;373(9673):1429-1439.

Biomarkers

Criteria		Placebo	Serelaxin
NT-pro-BNP (≥ 30% decrease at day 2)	Yes	315 (58.0%)	371 (69.0%)*
	No	228 (42.0%)	167 (31.0%)
Creatinine (≥ 0.3 mg/dL increase at day 2)	Yes	108 (19.8%)	59 (10.9%)†
	No	437 (80.2%)	482 (89.1%)
Troponin T (≥ 20% increase at day 2)	Yes	145 (27.2%)	86 (16.5%)†
	No	389 (72.8%)	436 (83.5%)
ALT (Change at day 2)	mg/dL	-2.3	-6.4‡

*P = .0002
†P < .0001
‡P < .0010

ALT = alanine transaminase

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

TRUE-AHF

- Phase 3 study with IV ularitide compared with placebo for 48 hours
- Primary endpoint—assessment of dyspnea relief at 6, 24, and 48 hours
- Primary safety endpoint—assessment of all-cause mortality and cardiovascular rehospitalization at 30 days

http://clinicaltrials.gov/ct2/show/NCT01661634

ATOMIC-AHF

- Omecamtiv mecarbil, a cardiac myosin activator IV infusion for 48 hours compared with placebo in patients with LV systolic dysfunction hospitalized for heart failure
- Designed to assess the tolerability and safety of 3 doses of omecamtiv mecarbil compared with placebo
- Evaluation of effects of 48 hours of treatment on dyspnea, changes in NT-pro-BNP, incidence of worsening heart failure, and short-term outcomes

http://clinicaltrials.gov/ct2/show/NCT01300013?term=ATOMIC-AHF&rank=1

AHF: Recommendations and Levels of Evidence

Group	Medication	Class Recommendation, Level of Evidence
Diuretics	IV loop diuretic	I, B
Vasodilators	Nitrates	IIa, B
	Sodium nitroprusside	IIb, B
Opiate	IV (ie, morphine)	IIa, C
Inotropics*	Dopamine	IIb, C
	Dobutamine	IIa, C

*Hypotension or cardiogenic shock; Recommendation is III, C if not present

McMurray JJ, et al. *Eur J Heart Fail*. 2012;14(8):803-869.

AHF Management: What's on the Horizon?

Marco Metra, MD

Professor of Cardiology
Director of the Institute of Cardiology

University of Brescia
Brescia, Italy

Randomized Controlled Trials with Pharmacologic Agents in AHF

Drug, Mechanism, TRIAL	No.	Phase	Primary Endpoint
Omecamtiv mecarbil, myosin activator, ATOMIC-AHF	600	2	Relief of dyspnea
Serelaxin	70	2	Hemodynamic response
Ularitide, TRUE-AHF	2116	3	Hierarchical clinical composite
Dopamine vs nesiritide vs placebo, ROSE-AHF	360	4	72-hour diuresis, cystatin-c change
Metolazone + furosemide vs furosemide alone	160		Diuresis
Furosemide high- vs low-dose vs low-dose + dopamine, DAD-HF-2	450	4	1-year mortality or rehospitalization
Tolvaptan, TACTICS-HF	250	3	Dyspnea relief

Inotropic Agents Under Investigation

Drug	Mechanism
Na+/K+ ATPase inhibitors • Istaroxime	Sarcolemmal Na+-K+ pump inhibition: cytosolic calcium increase SERCA2a stimulation
Myosin activators • Omecamtiv mecarbil	Myosin stimulation: ↑ ejection phase duration, no change in ejection rate or calcium
RyR stabilizers • JTV-519, S107	RyR2/calstabin 2 interaction, ↓SR calcium leakage
SERCA2a activators • SERCA2a adeno-associated viral vector,...	↑ uptake of cytosolic calcium into the SR during diastole: better relaxation and increased calcium release during systole
Metabolic modulators • Perhexiline • Trimetazidine • Ranolazine • GLP-1	Carnitine palmitoyl transferase 1 inhibition: myocardial substrate shift from FFAs to glucose; other mechanisms
Urocortin 2	Myocardial and vascular CRF2 receptors

FFA = free fatty acids; GLP = glucagon-like peptide; RyR = ryanodine receptor; SR = sarcoplasmic reticulum

Pregnancy and the Heart

PARAMETER	PREGNANCY
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Helal I, et al. *Nat Rev Nephrol.* 2012;8(5):293-300.

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 AHF.**
- **We hypothesized that serelaxin (30 mcg/kg/day IV) would improve dyspnea to a greater extent than placebo by one or both measures at 24 hours (Likert) and/or 5 days (VAS AUC), and improve other clinical outcomes.**

IV = intravenously; VAS AUC = visual analogue scale area under the curve

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Hospitalized for AHF
  - Dyspnea at rest or with minimal exertion
  - Pulmonary congestion on chest x-ray
  - BNP ≥ 350 pg/mL or NT-pro-BNP ≥ 1400 pg/mL
- Received ≥ 40 mg IV furosemide (or equivalent) at any time between admission to emergency services (either ambulance or hospital, including the ED) and the start of screening for the study
- SBP > 125 mm Hg
- Impaired renal function on admission (sMDRD eGFR 30-75 mL/min/1.73 m^2)
- Randomly assigned within 16 hours from presentation
- Age ≥ 18 years of age
- Body weight < 160 kg

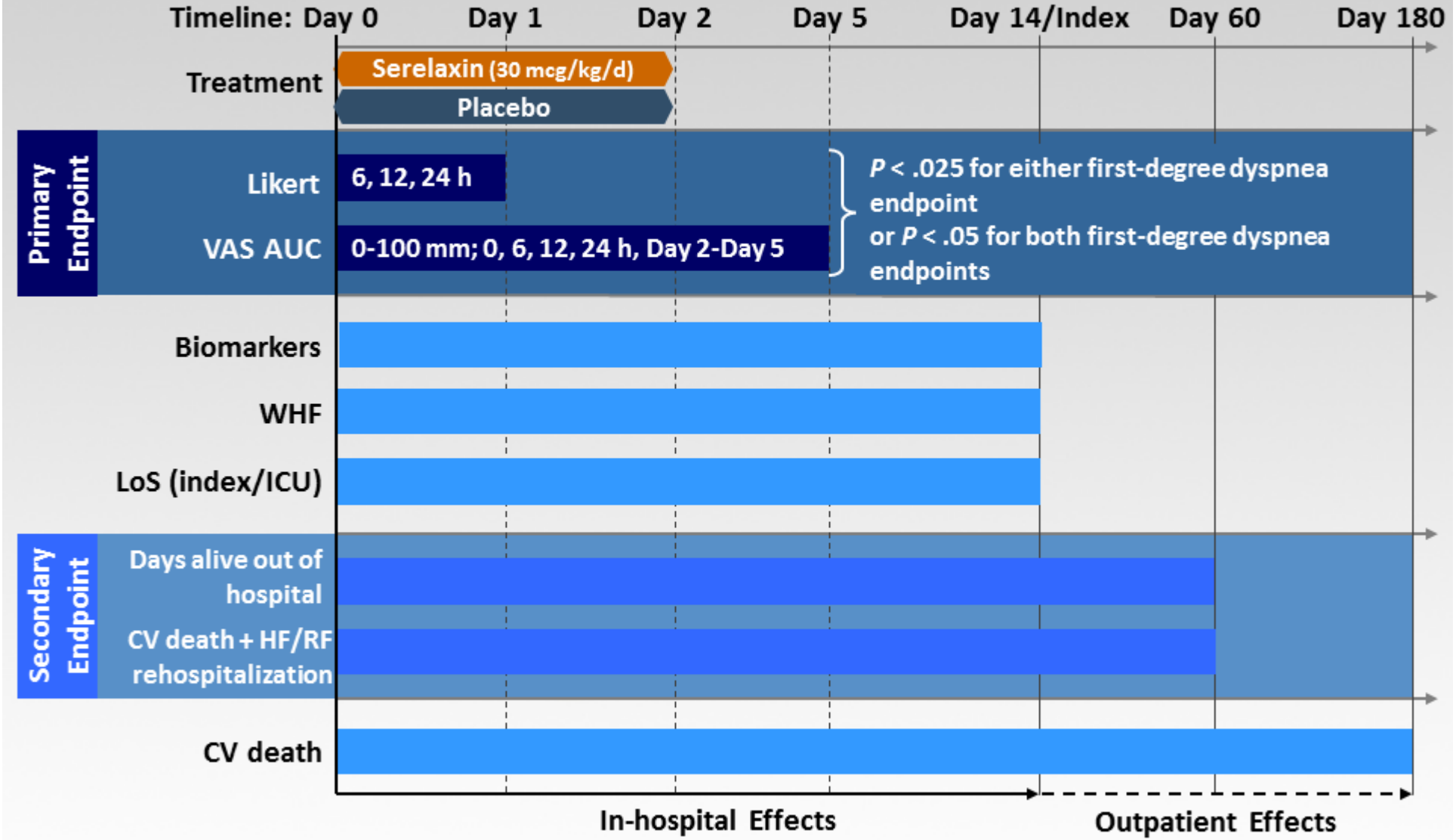
Key Exclusion Criteria

- Current or planned treatment with any IV therapies (ie, other vasodilators [nesiritide], positive inotropic agents, and vasopressors) or mechanical circulatory, renal, or ventilatory support, with the exception of IV furosemide (or equivalent), or of IV nitrates if patient has screening SBP > 150 mm Hg
- AHF and/or dyspnea from arrhythmias or noncardiac causes, such as lung disease, anemia, or severe obesity
- Infection or sepsis requiring IV antibiotics
- Pregnant or breastfeeding
- Stroke within 60 days; ACS within 45 days; major surgery within 30 days
- Presence of acute myocarditis, significant valvular heart disease, hypertrophic/restrictive/constrictive cardiomyopathy

ACS = acute coronary syndromes; BNP = brain natriuretic peptide;
ED = emergency department; eGFR = estimated glomerular filtration rate;
SBP = systolic blood pressure; sMDRD = simplified modification of diet in renal disease

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Key Efficacy Measures



ICU = intensive care unit; LoS = length of stay; RF = renal failure; WHF = worsening heart failure

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

Patient Population

Parameter		Placebo (N = 580)	Serelaxin (N = 581)
Age (years)	Mean	72.5	71.6
SBP at baseline (mm Hg)	Mean	142	142
Heart rate at baseline (beats/min)	Mean	80	79
Respiratory rate at baseline (breaths/min)	Mean	22	22
eGFR (MDRD; mL/min/1.73 m^2)	Mean	53.3	53.7
NT-pro-BNP (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

* *P* < .05

Heart failure

Adapted from Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

theheart.org from WebMD

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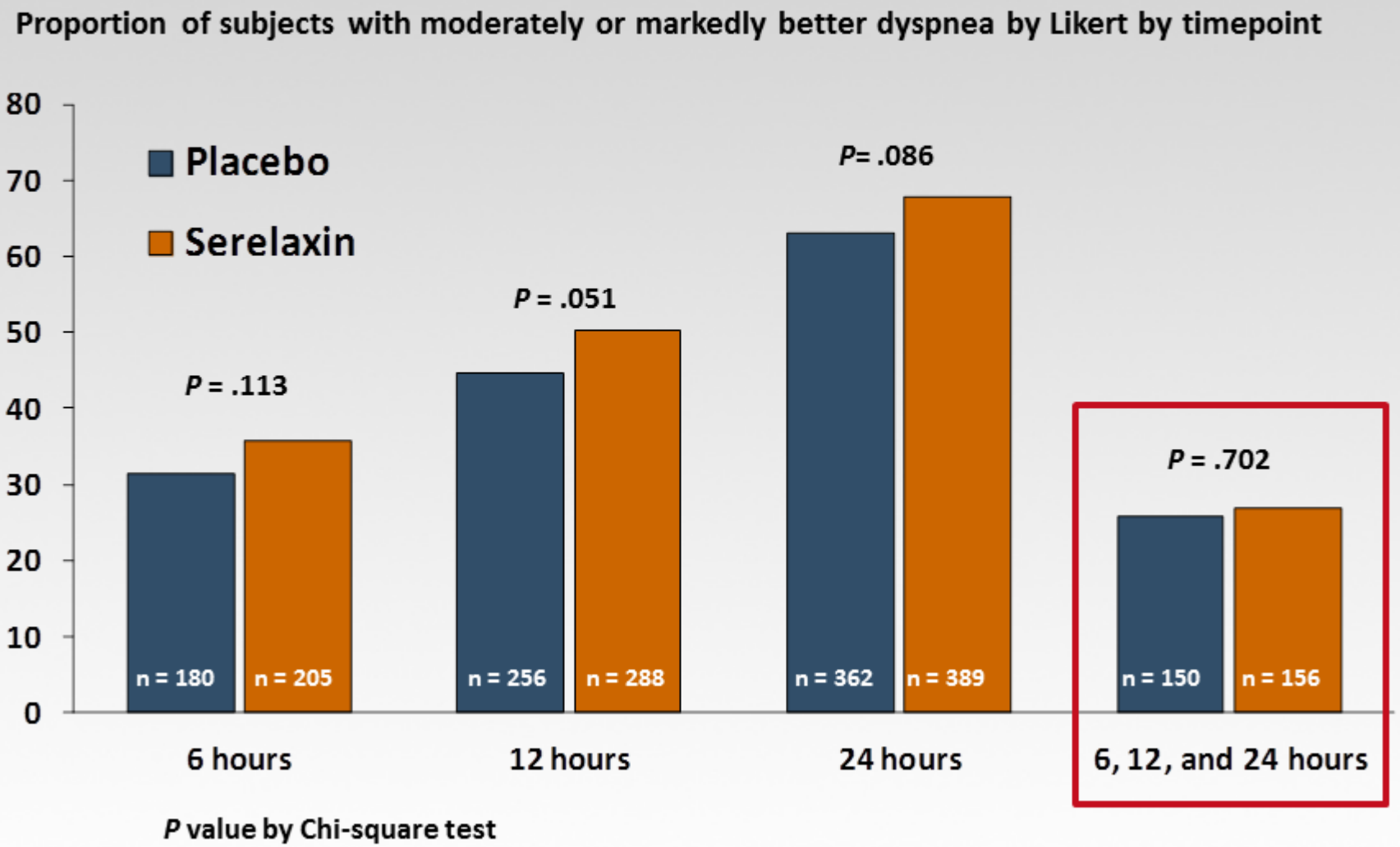
Patient Population (cont)

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 (hour)	Mean	7.9	7.8

ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blocker

Adapted from Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

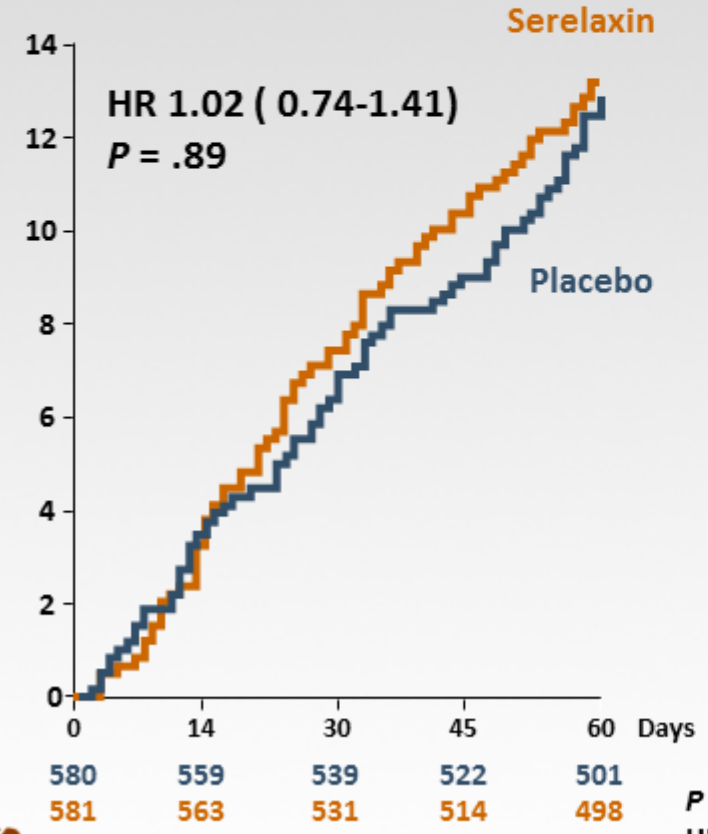
First-Degree Endpoint: Dyspnea Relief (Likert)



Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

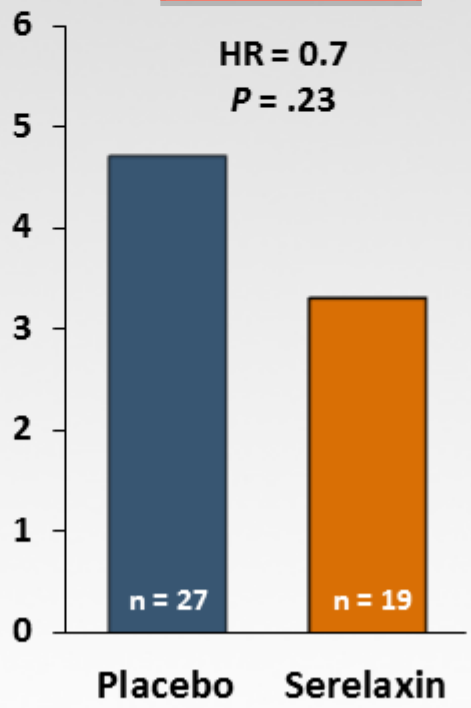
Second-Degree Endpoint: CV Death or HF/RF Rehospitalization Through Day 60

KM Estimate for Time to First CV Death or HF/RF Rehosp (%)

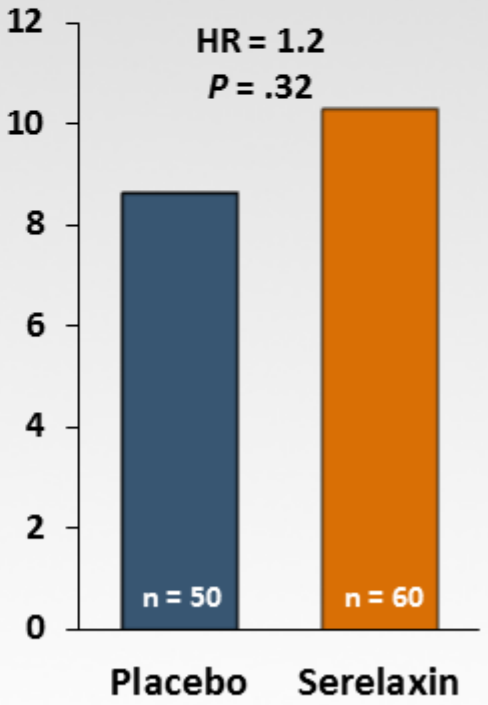


Composite Event Components (%)

CV Death: (% subjects)



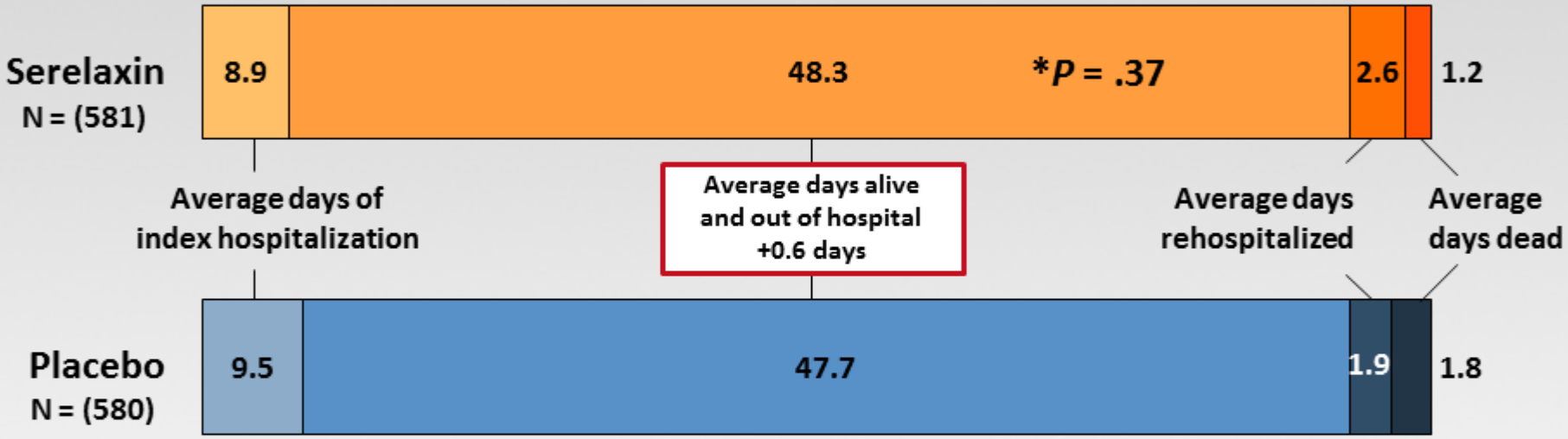
HF/RF Rehospitalization (% subjects)



P value by log rank test
HR estimate by Cox model

From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Second-Degree Endpoint: Days Alive and Out of Hospital Through Day 60

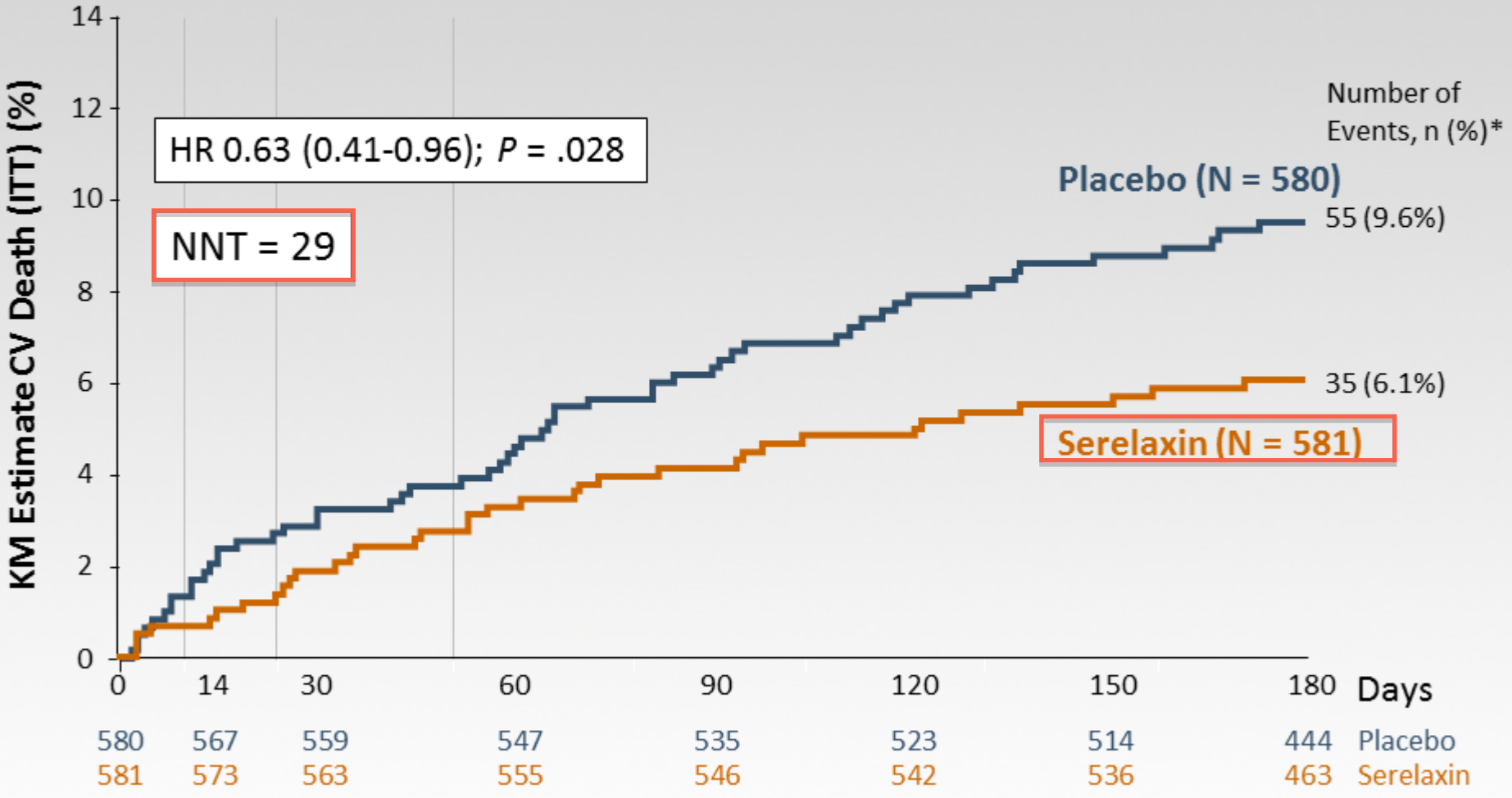


Days alive out of hospital = total follow-up time (Day 60) - days in hospital or dead

*P value by 2-sided Wilcoxon rank sum test

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

CV Death Through Day 180

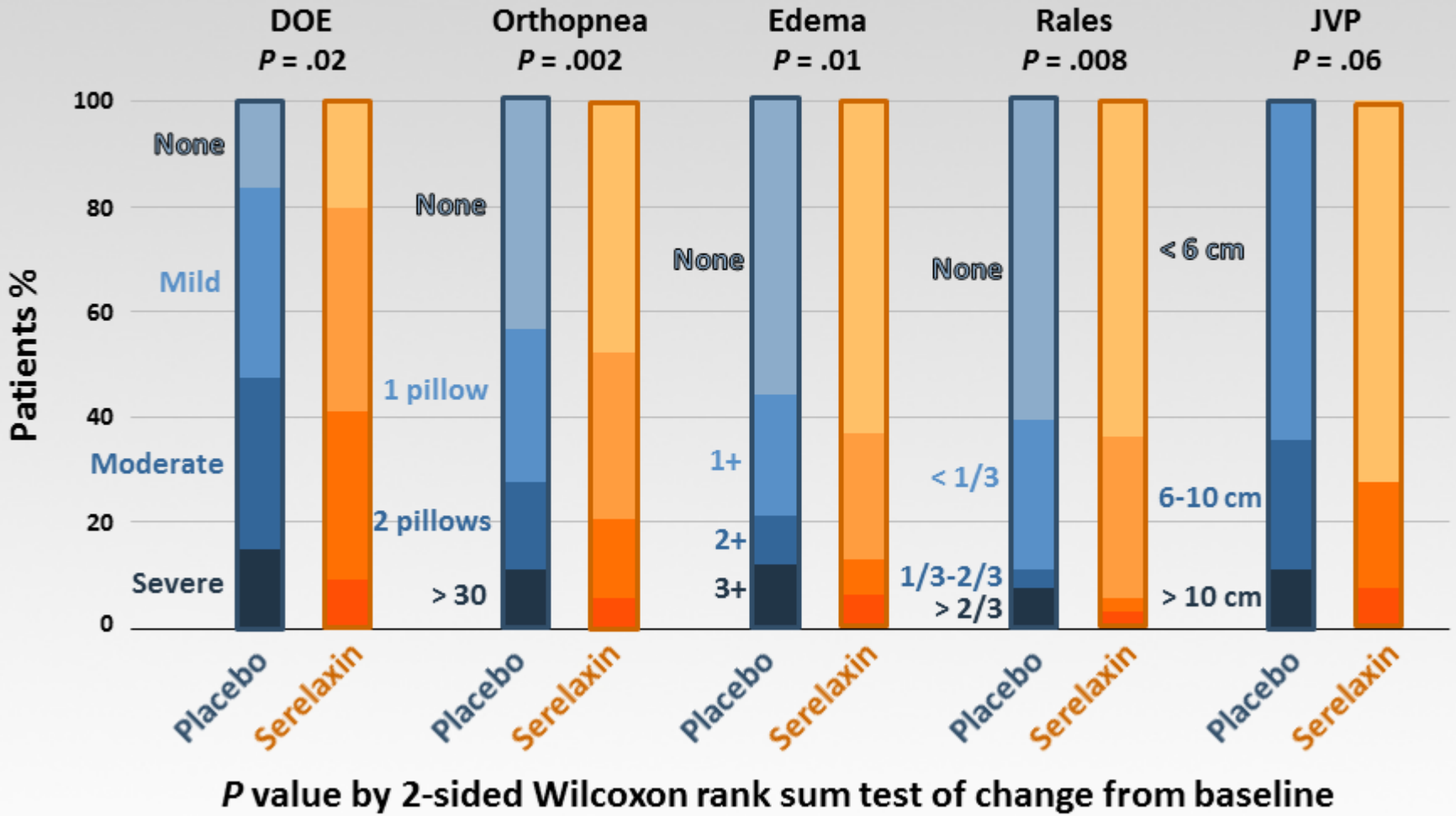


ITT = intent to treat; NNT = number need to treat

Heart failure

From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Signs and Symptoms of Congestion



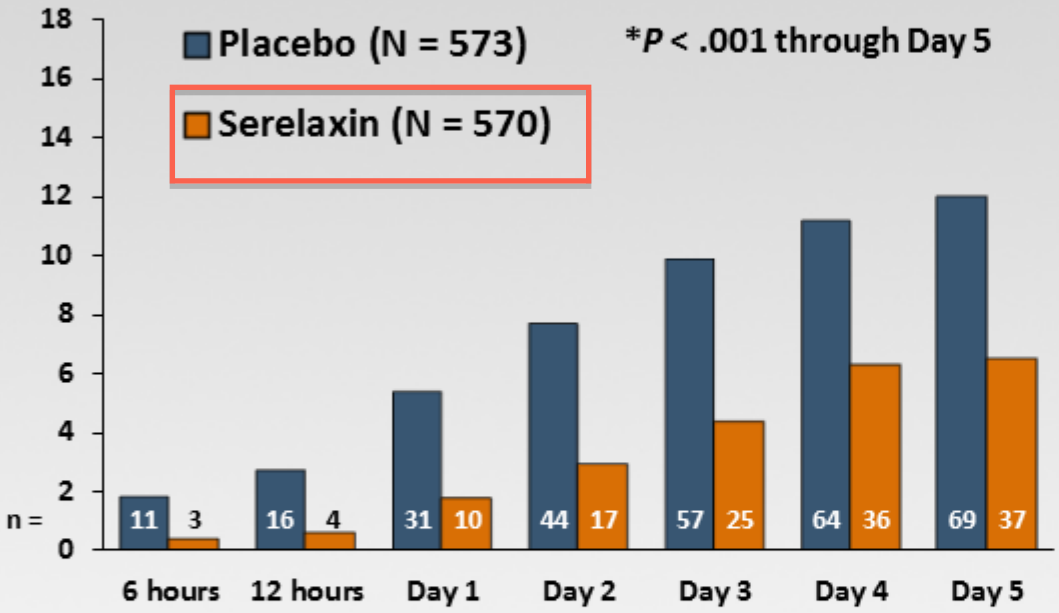
P value by 2-sided Wilcoxon rank sum test of change from baseline

DOE = dyspnea on exertion; JVP = jugular venous pressure

Heart failure From Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

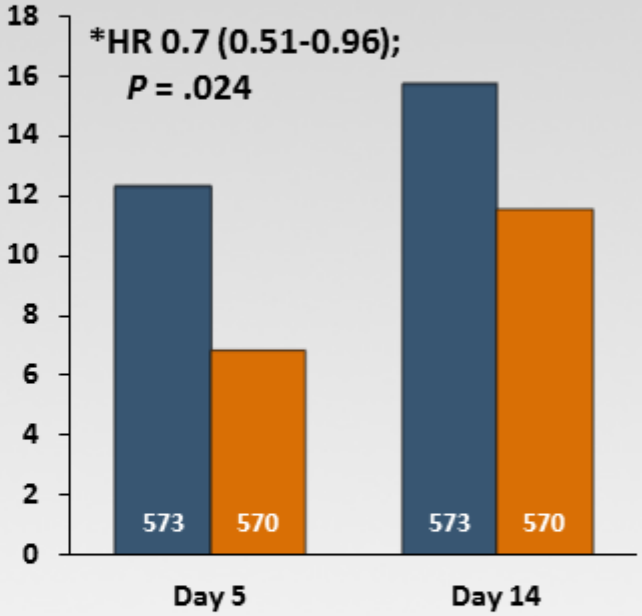
Worsening of Heart Failure

Cumulative Proportion of WHF to Day 5 (%)



(Numbers of subjects with WHF shown for each time point)

Kaplan-Meier Estimate Day 14 for Time to WHF (%)



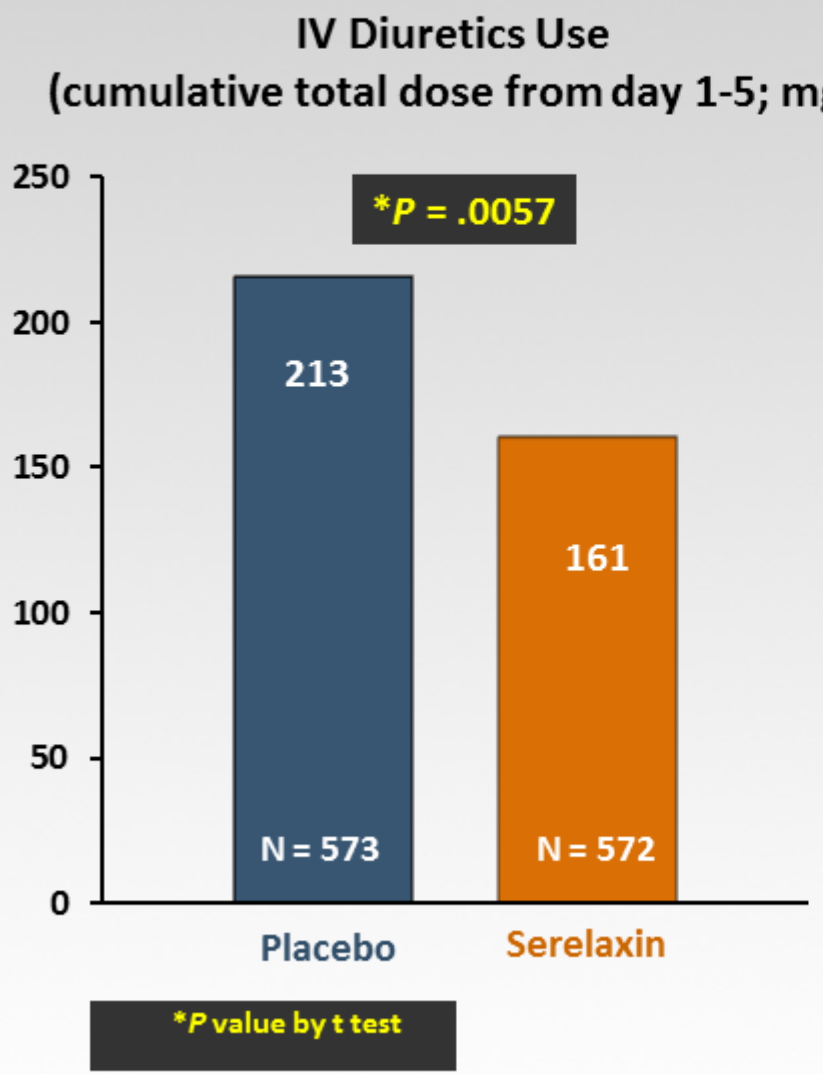
WHF was defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for heart failure or mechanical ventilatory or circulatory support.

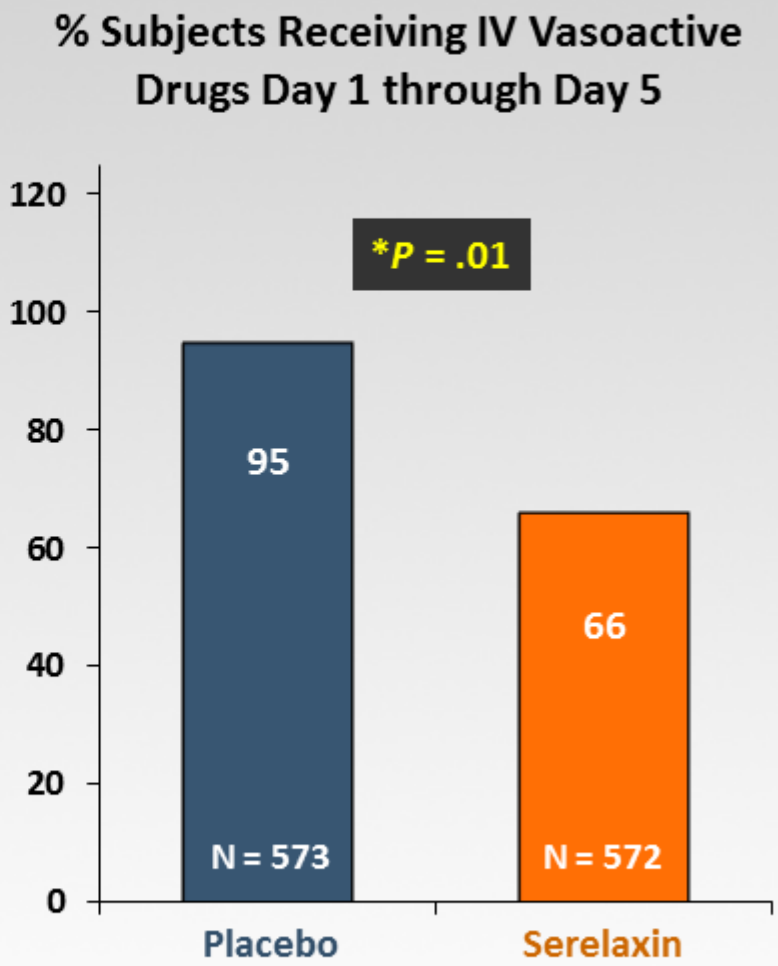
*P value by Wilcoxon test

*P value by log rank test for serelaxin vs placebo; HR estimate by Cox model, HR < 1.0 favors serelaxin

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

IV Medication Use

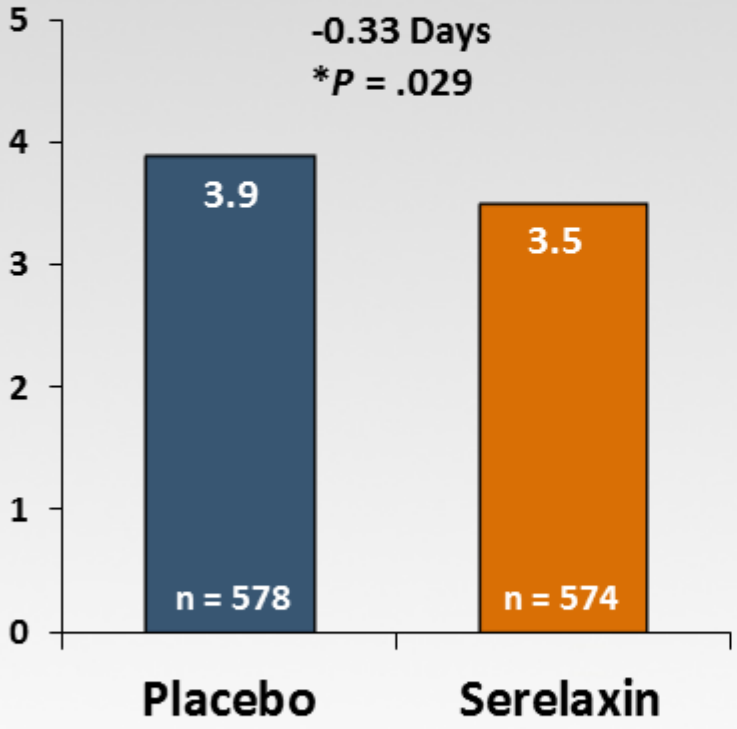




Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

Index Hospitalization LOS

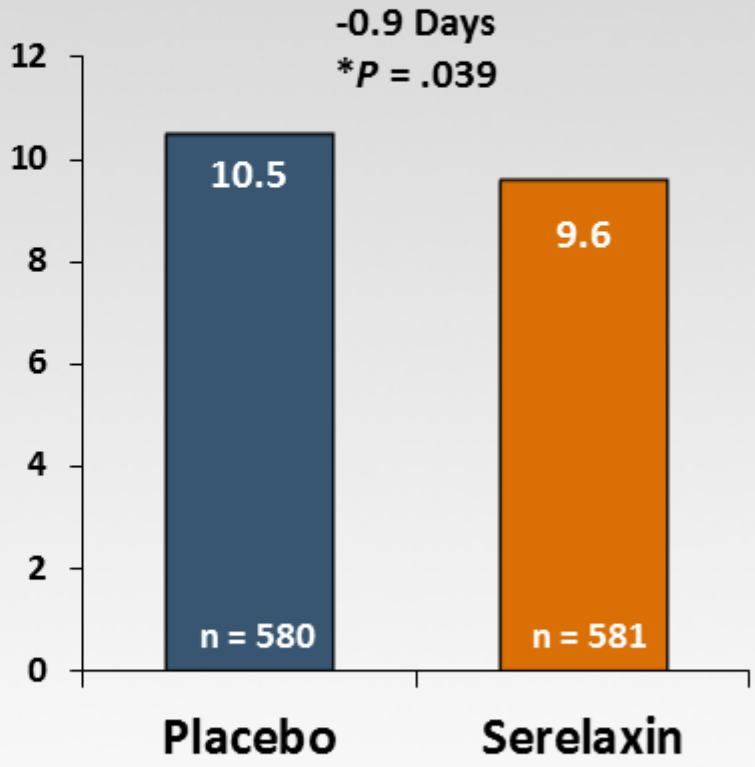
Duration of ICU/CCU Care (Days)



*P value by 2-sided Wilcoxon rank sum test

CCU = critical care unit

Index Hospitalization LOS (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.

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

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 discontinuation	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 discontinuation	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. Nonserious AEs were collected through Day 5, SAEs through Day 14.

*$P < .05$

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

Biomarkers

Criteria		Placebo	Serelaxin
NT-pro-BNP (≥ 30% decrease at day 2)	Yes	315 (58.0%)	371 (69.0%)*
	No	228 (42.0%)	167 (31.0%)
Creatinine (≥ 0.3 mg/dl increase at day 2)	Yes	108 (19.8%)	59 (10.9%)†
	No	437 (80.2%)	482 (89.1%)
Troponin T (≥ 20% increase at day 2)	Yes	145 (27.2%)	86 (16.5%)†
	No	389 (72.8%)	436 (83.5%)
ALT (Change at day 2)	mg/dL	-2.3	-6.4‡

*P = .0002
†P < .0001
‡P < .0010

ALT = alanine transaminase

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [Epub ahead of print]

Conclusions

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

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

…but had no effect on rehospitalizations.

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

Teerlink JR, et al. *Lancet*. 2012 Nov 6. [Epub ahead of print]

Publications

- "Serelaxin, recombinant human relaxin-2 for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial"—published online in *The Lancet,* Nov. 6, 2012
- "Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the RELAX-AHF development program: correlation with outcome" – *J Am Coll Cardiol.* 2012; in press

AHF Management in 2012: What's Missing Today?

Adriaan A. Voors, MD, PhD
Professor of Cardiology
University Medical Center Groningen
Groningen, The Netherlands

Heart failure
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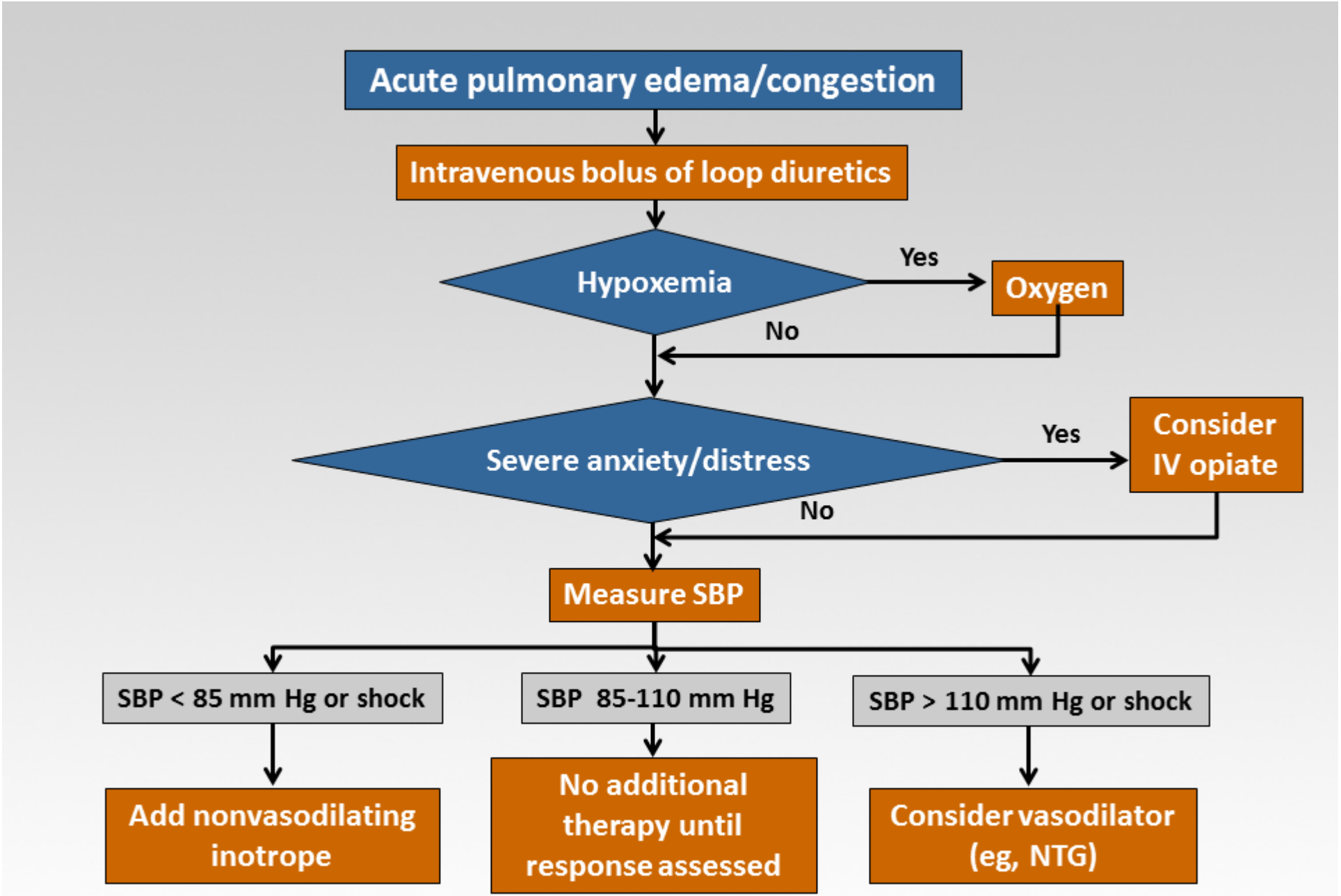
Chronic Systolic Heart Failure:

Recommendations and Levels of Evidence

Group	Class Recommendation, Level of Evidence
ACEis	I, A
ARBs (alternative for ACEis)	I, A
Beta-blockers	I, A
Aldosterone antagonists	I, A

ACEis = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers

McMurray JJ, et al. *Eur J Heart Fail.* 2012;14(8):803-869.



IV = intravenous; NTG = nitroglycerin; SBP = systolic blood pressure

Heart failure

Adapted from McMurray JJ, et al. *Eur J Heart Fail.* 2012;14(8):803-869.

AHF: Recommendations and Levels of Evidence

Group	Medication	Class Recommendation, Level of Evidence
Diuretics	Indication	I, B
Vasodilators	Nitrates	IIa, B
	Sodium nitroprusside	IIb, B
Morphine	Indication	IIa, C
Inotropics*	Dopamine	IIb, C
	Dobutamine	IIa, C

AHF = acute heart failure

*Hypotension or cardiogenic shock

McMurray JJ, et al. *Eur J Heart Fail*. 2012;14(8):803-869.

Other Treatment Options in AHF

1. PDE inhibitor: milrinone
2. Calcium sensitizer: levosimendan
3. AVP antagonist: tolvaptan
4. Adenosine A_1 receptor antagonist: rolofylline
5. Natriuretic peptide: nesiritide

AVP = arginine vasopressin; PDE = phosphodiesterase

Phosphodiesterase III Inhibitor: Milrinone

OPTIME-CHF: Acute on CHF; LVEF 23%

Events	Placebo (N = 472)	Milrinone (N = 477)	*P* Value
Days of hospital for CV causes < 60d	12.5 (mean)	12.3 (mean)	.71
During Hospitalization			
New AF	7 (1.5%)	22 (4.6%)	.004
VT/VF	7 (1.5%)	16 (3.4%)	.06
Sustained hypotension	15 (3.2%)	51 (10.7%)	< .001
Death	11 (2.3%)	18 (3.8%)	.19

AF = atrial fibrillation; CHF = chronic heart failure; CV = cardiovascular; LVEF = left ventricular ejection fraction; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; VF = ventricular fibrillation; VT = ventricular tachycardia

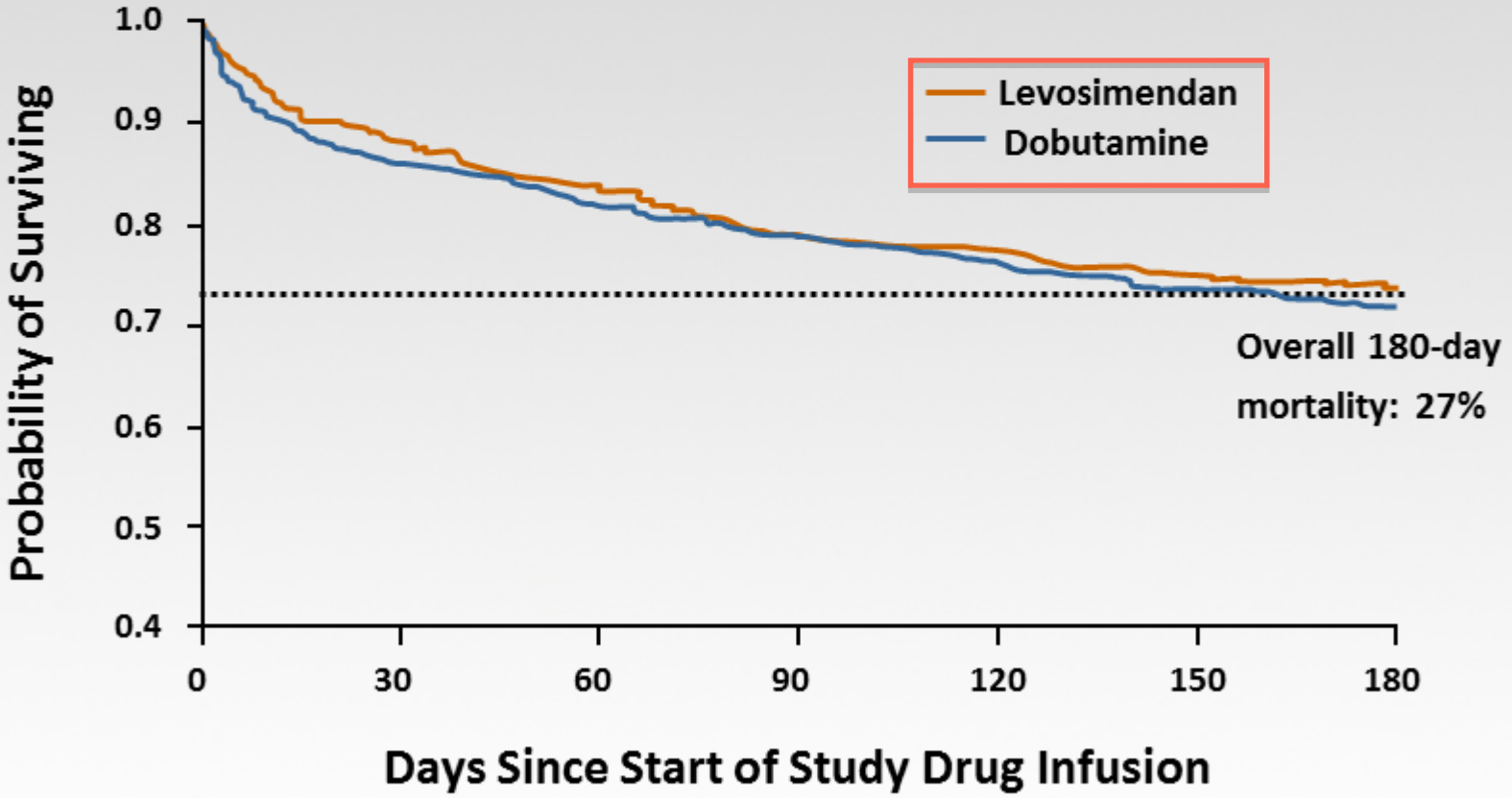
Cuffe MS, et al. *JAMA*. 2002;287(12):1541-1547.

Ca^{2+} Sensitizer: Levosimendan

- Ca^{2+} sensitization: inotropic action
- Smooth muscle K^{+} channel opening: vasodilation

Ca^{2+} Sensitizer: Levosimendan (cont)

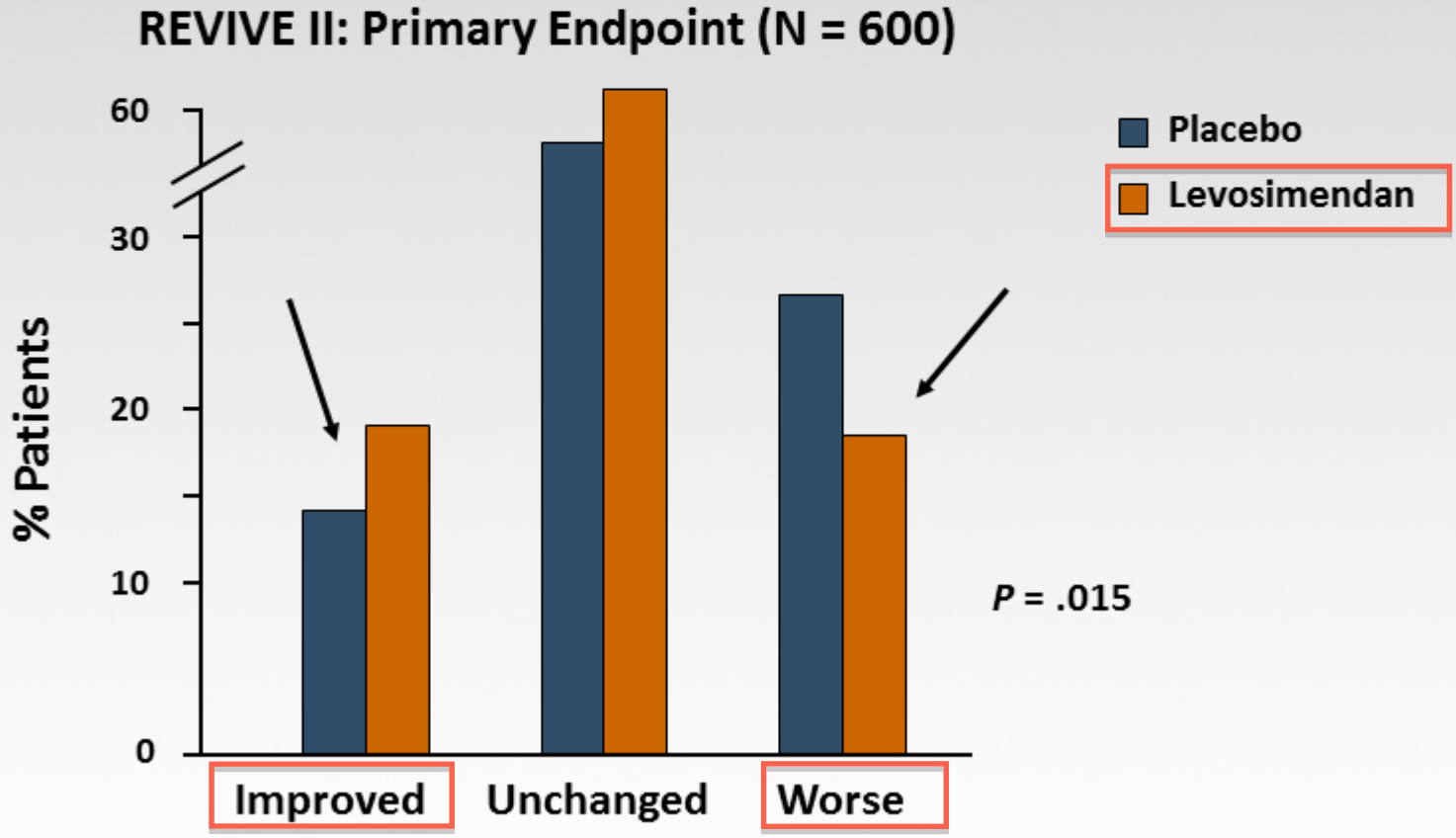
SURVIVE: The Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support trial



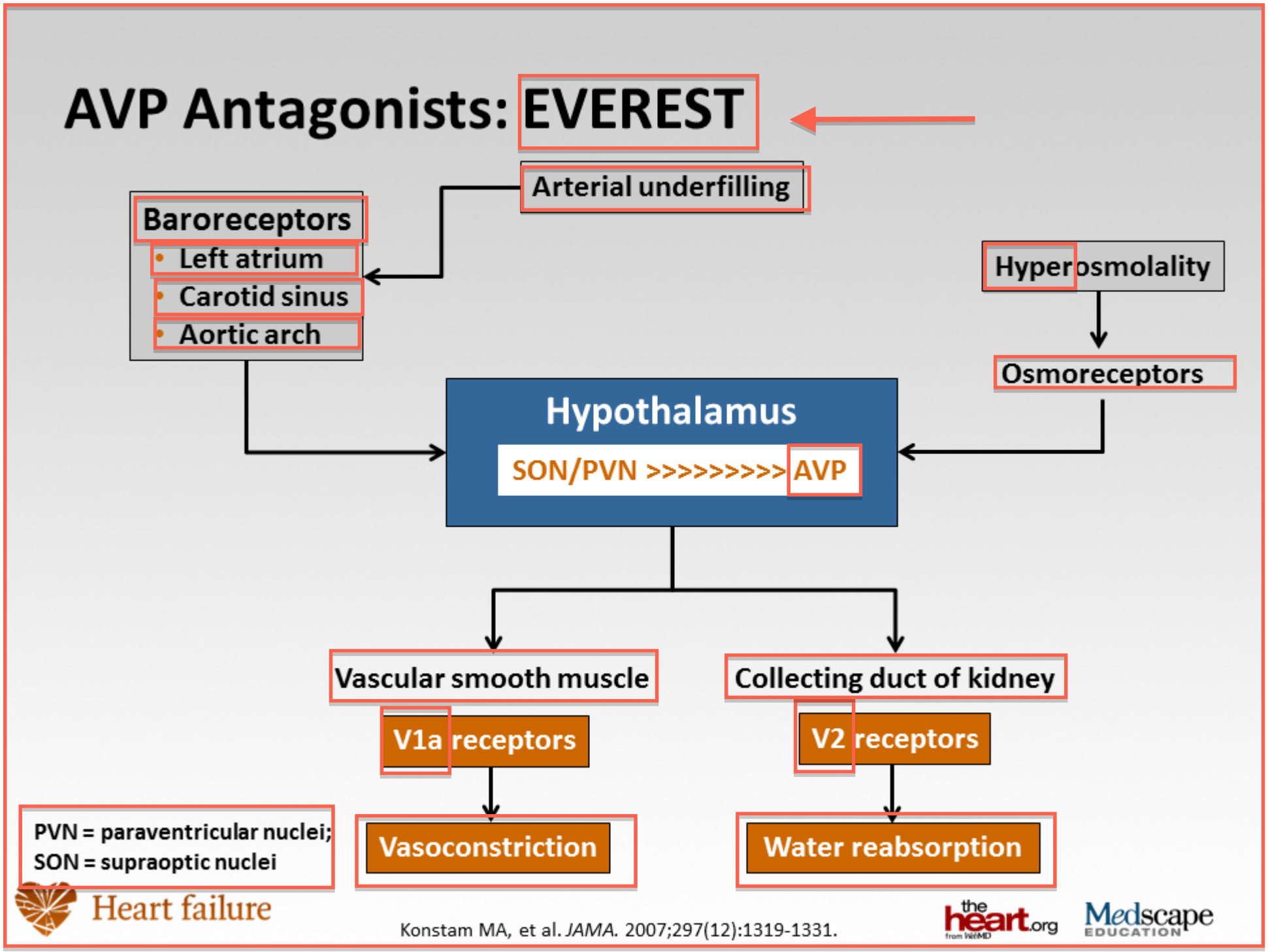
From Mebazaa A, et al. *JAMA*. 2007;297(17):1883-1891.

Ca^{2+} Sensitizer: Levosimendan (cont)

REVIVE: The Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Trial—AHA 2005

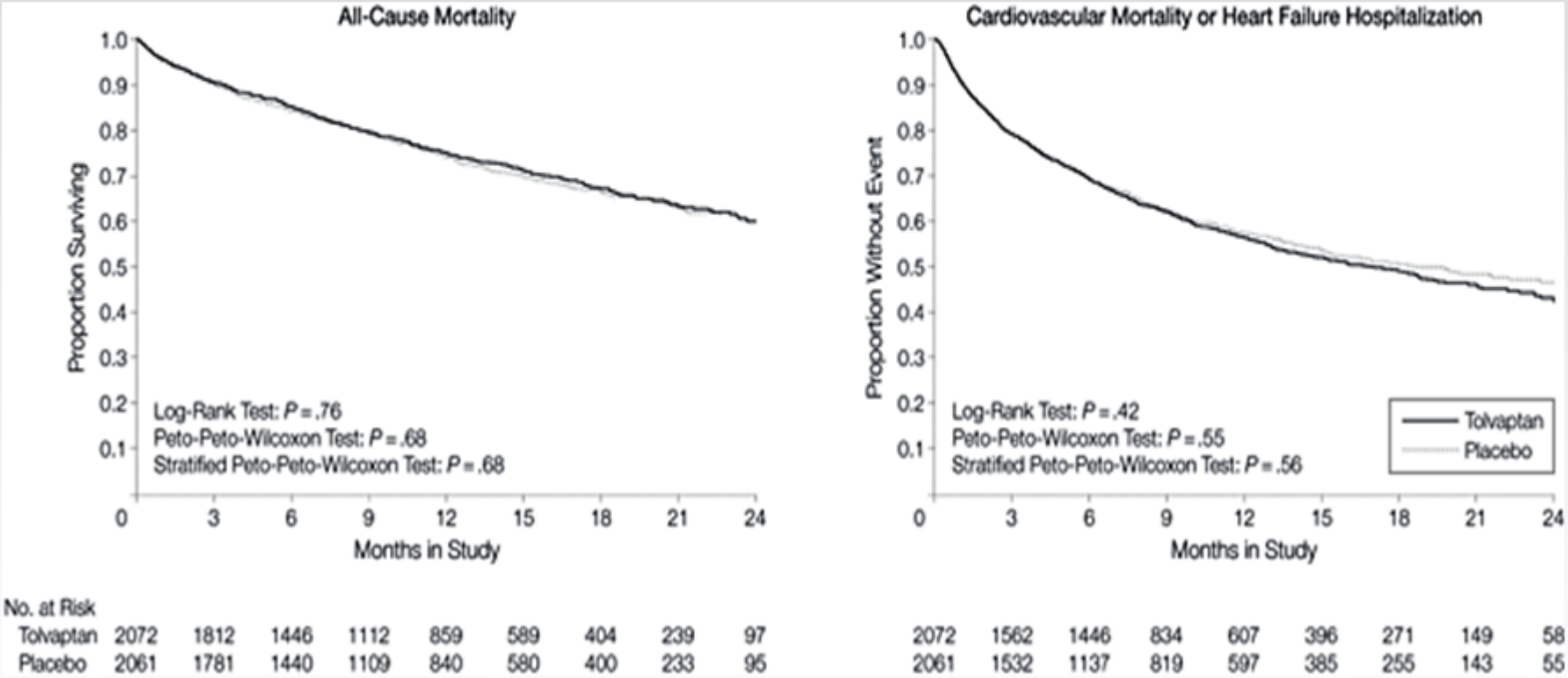


Packer M. AHA 2005. Late Breaking Clinical Trials II.


AVP Antagonists: EVEREST
Arterial underfilling
Baroreceptors
Left atrium
Carotid sinus
Aortic arch
Hyperosmolality
Osmoreceptors
Hypothalamus
SON/PVN >>>>>>>>> AVP
Vascular smooth muscle
V1a receptors
Vasoconstriction
Collecting duct of kidney
V2 receptors
Water reabsorption
PVN = paraventricular nuclei;
SON = supraoptic nuclei
Heart failure
Konstam MA, et al. JAMA. 2007;297(12):1319-1331.
theheart.org
Medscape EDUCATION

EVEREST: Primary Endpoint

- Tolvaptan 30 mg/day: death or CV death/HF hospitalizations
- N = 4133; < 48h AHF; LVEF ≤ 40% (28%); mean 10-month follow-up



Heart failure

From Konstam M, et al. *JAMA.* 2007;297(12):1319-1331.

theheart.org from WebMD

Medscape EDUCATION

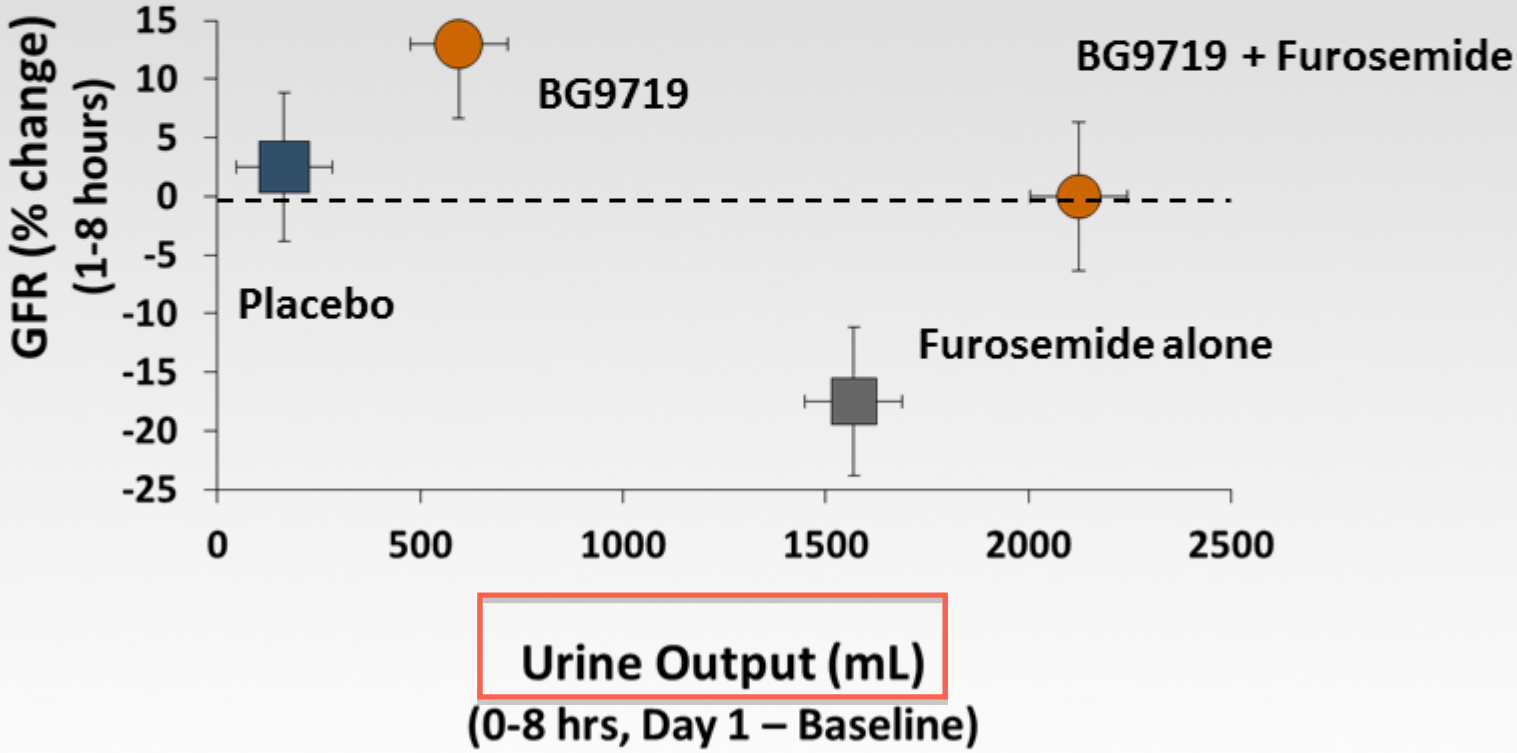
Adenosine A_1 Antagonist Mechanism of Action

- Inhibits sodium reabsorption in the proximal tubule → enhances diuresis
- Blocks adenosine-mediated vasoconstriction of afferent arteriole → maintains GFR

GFR = glomerular filtration rate

Adenosine A_1 Antagonist

BG9719 improves GFR and/or normalizes diuretic mediated decline in GFR.

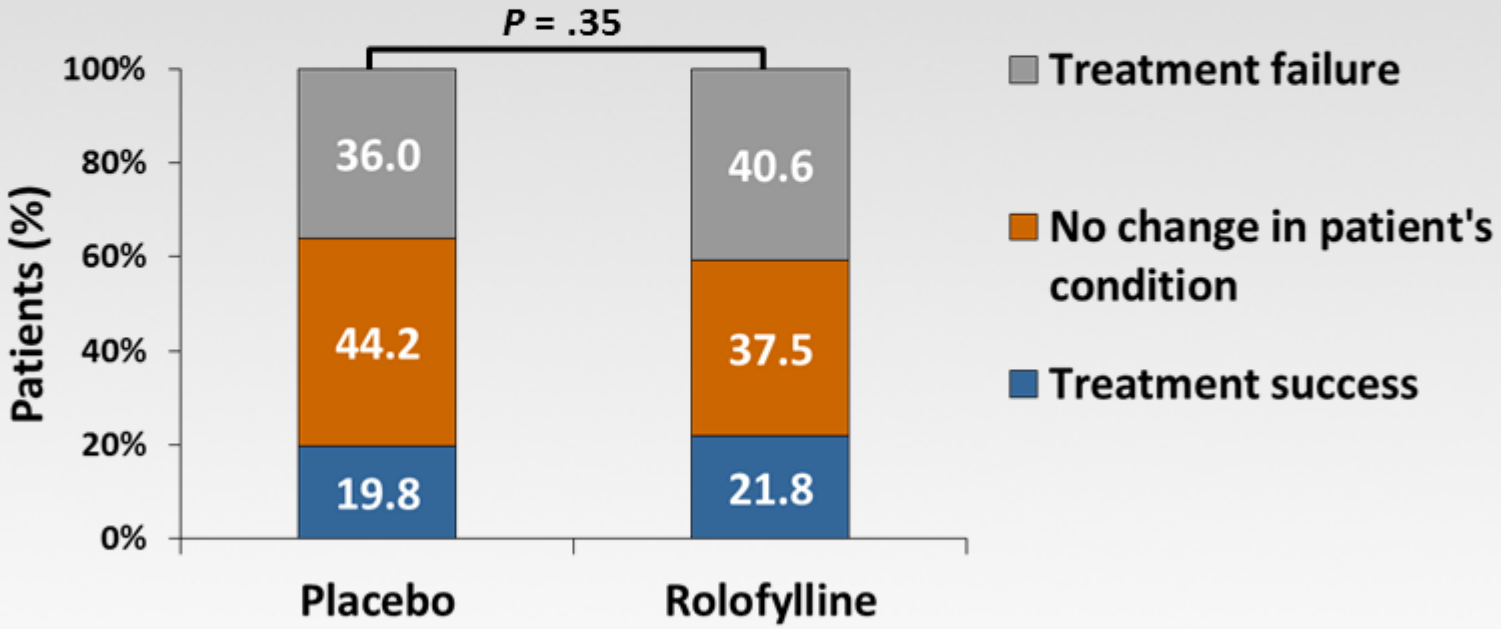


From Gottlieb SS, et al. *Circulation.* 2002;105(11):1348-1353.

PROTECT: Primary Endpoint

2033 patients with AHF and renal dysfunction within 24 hours randomly assigned to rolofylline 30 mg or placebo

Odds ratio for rolofylline, 0.92 (95% CI, 0.78-1.09)

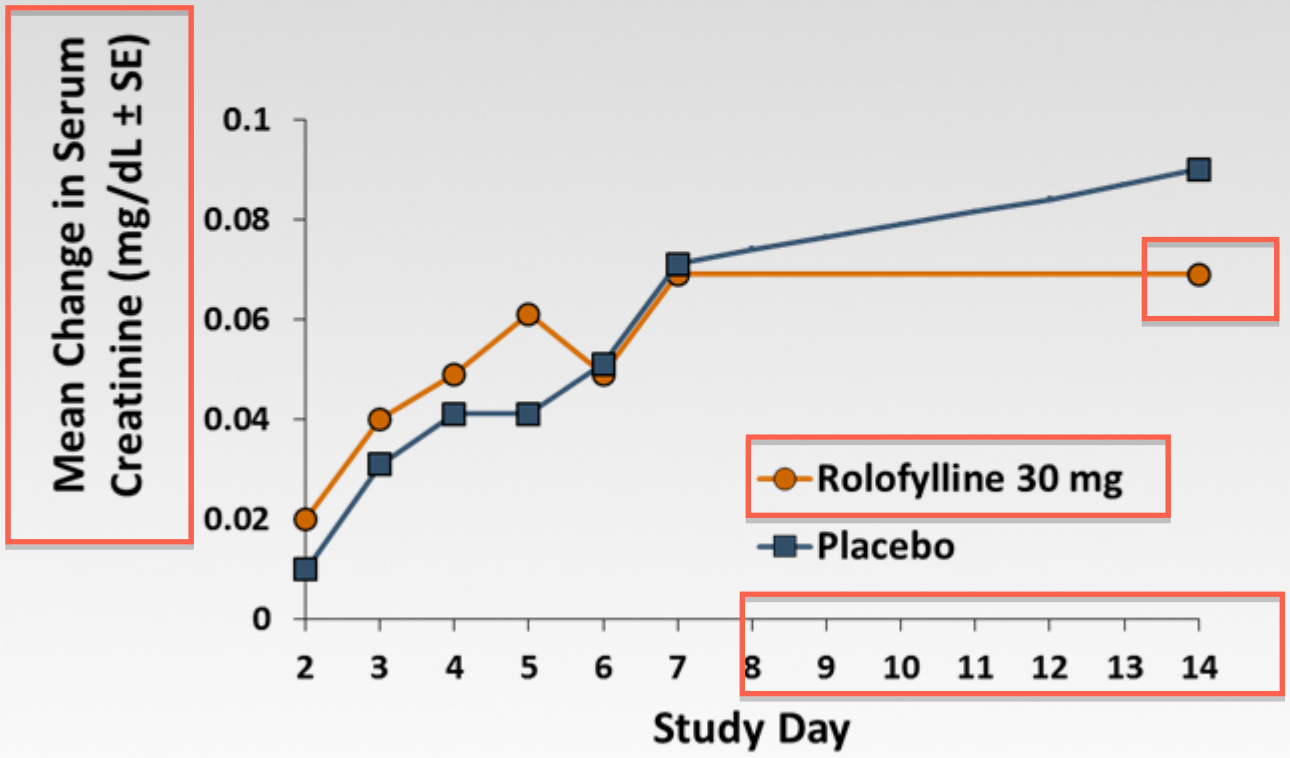


Distribution of the primary composite endpoint in the rolofylline and placebo groups

CI = confidence interval

From Massie BM, et al. *N Engl J Med.* 2010;363(15):1419-1428.

Adenosine A_1 Receptor Antagonist (Rolofylline): Effects on Renal Function in Patient with Heart Failure



From Voors AA, et al. *J Am Coll Cardiol*. 2011;57(19):1899-1907.

Recombinant BNP: Nesiritide

Mechanism: venous, arterial, coronary vasodilatation ↓pre- and afterload; ↑ CO; ↓ symptoms and ↑ natriuresis in AHF; not proarrythmic

Study	Nesiritide Therapy No. of Deaths/Total	Control Therapy No. of Patients (%)	Risk Ratio (95% CI)	*P* Value
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

BNP = B-type natriuretic peptide; CO = cardiac output; ND = not determined;
NSGET = Nesiritide Study Group Efficacy Trial; PROACTION = Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated in Outpatients with Natrecor; VMAC = Vasodilation in the Management of Acute Congestive Heart Failure

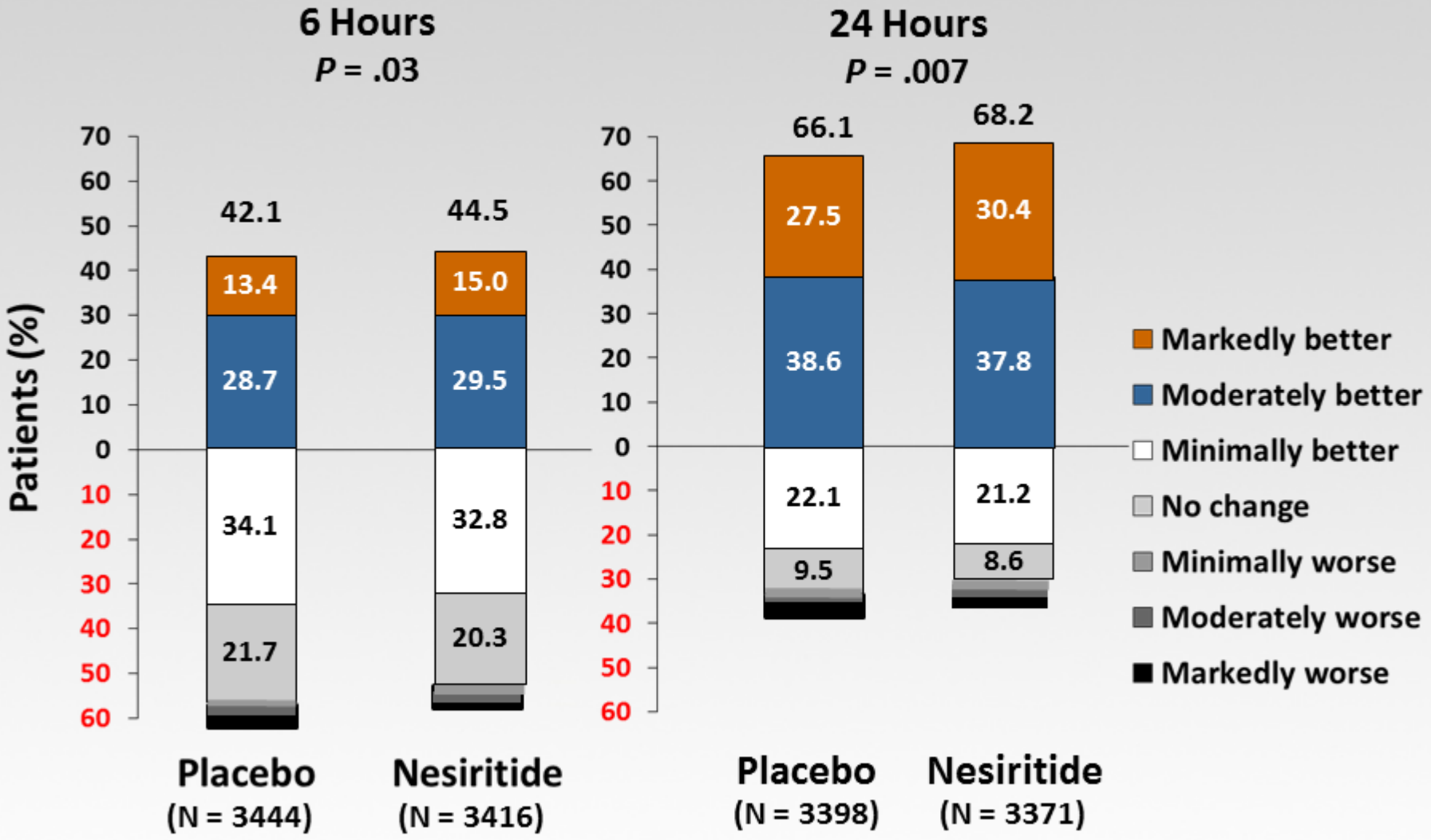
Sackner-Bernstein, JD, et al. *JAMA*.2005;293(15):1900-1905.

ASCEND-HF

- 7141 AHF patients within 24 hours randomly assigned to IV nesiritide or placebo
- Coprimary endpoint: change in dyspnea at 6 and 24 hours as measured by 7-point Likert scale and HF hospitalization or death within 30 days

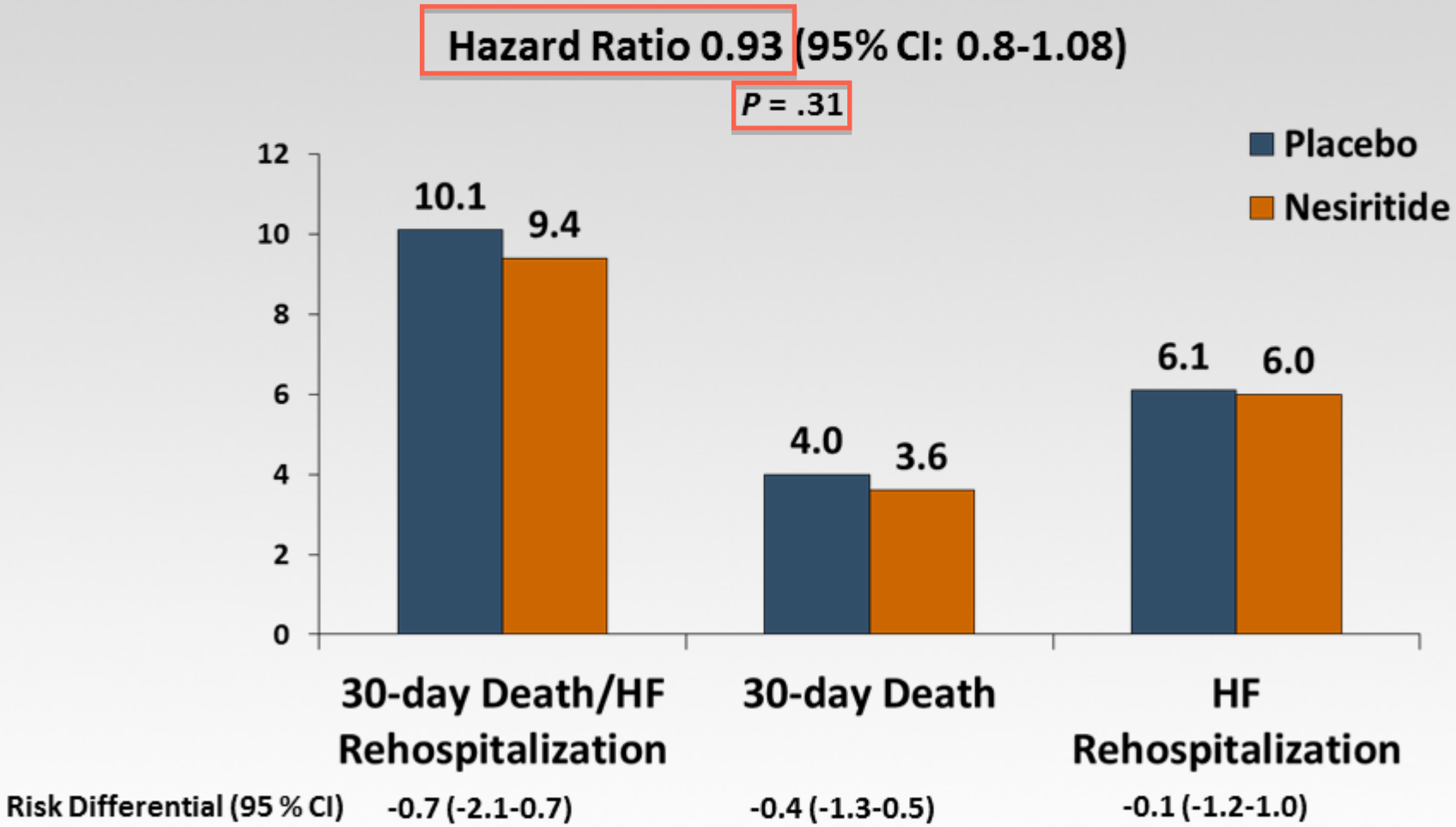
O'Connor CM, et al. *N Engl J Med*.2011;365(1):32-43.

Self-Assessed Change in Dyspnea at 6 and 24 Hours



From O'Connor CM, et al. *N Engl J Med*.2011;365(1):32-43.

Coprimary Outcome: 30-Day All-Cause Mortality or HF Rehospitalization



From O'Connor CM, et al. *N Engl J Med*.2011;365(1):32-43.

RCTs in AHF Not Successful

1. PDE inhibitor: milrinone; OPTIME-CHF[a]
2. Endothelin antagonist: tezosentan; VERITAS[b]
3. Ca sensitizer: levosimendan; SURVIVE/REVIVE[c]
4. AVP antagonist: tolvaptan; EVEREST[d]
5. Adenosine A_1 receptor antagonist: rolofylline; PROTECT[e]
6. Natriuretic peptide: nesiritide; ASCEND-HF[f]

a. Cuffe SM, et al. *JAMA*. 2002;287(12):1541-1547.
b. Milo-Cotter O, et al. *Cardiology*. 2011;119(2):96-105.
c. Mebazaa A, et al. *JAMA*. 2007;297(17):1883-1891.
d. Konstam MA, et al. *JAMA*. 2007;297(12):1319-1331.
e. Massie BM, et al. *N Engl J Med*. 2010;363(15):1419-1428.
f. O'Connor CM, et al. *N Engl J Med*. 2011;365(1):32-43.

Why Do Drugs for Heart Failure Fail?

1. Wrong drugs?
2. Wrong endpoints? Dyspnea? Composite endpoints? Clinical outcome?
3. Wrong design (eg, blood pressure, time of initiation of therapy, etc.)?

Voors AA, et al. *Eur J Heart Fail*. 2012;14(9):955-956.