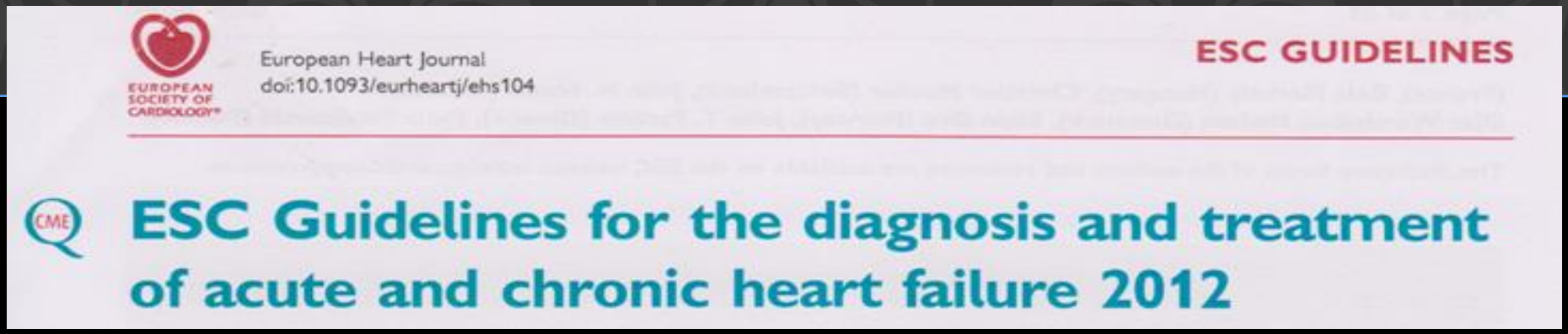
Management of acute heart failure: 2014
RELAXIN: A NEW HOPE ?

Susana Robalo Martins, MD, FESC
Cardiology Department, Hospital de Santa Maria
Centro Hospitalar Lisboa Norte, EPE
Faculdade de Medicina de Lisboa



- **The vague definition of Acute Heart Failure (AHF)…**

"AHF is the term used to describe the rapid onset of, or change in, symptoms and signs of HF.

It is a life-threatening condition that requires immediate medical attention and usually leads to urgent admission to hospital."

Acute Heart Failure - AHF –

AHF IS NOT A SINGLE DISEASE, BUT RATHER A HETEROGENEOUS FAMILY OF CLINICAL SYNDROMES, EACH WITH DISTINCT CLINICAL PRESENTATION, PROGNOSIS AND MANAGEMENT

HOSPITALIZATION FOR ACUTE HEART FAILURE (AHF) IS A SIGNIFICANT AND GROWING HEALTHCARE BURDEN

AHF is the most frequent cause of hospitalization in subjects >65 years[1]

Over 1 million hospitalizations with a primary diagnosis of HF occur each year in the USA[2] and Europe[5] alone

HF diagnosis at hospital discharge has tripled over the last three decades[2.] This trend will likely to continue due to an aging population, improved survival after MI, and better prevention of sudden cardiac death[2]

1. Tavazzi et al. Eur Heart J 2006;27:1207–15; 2. Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73; 3. Dickstein et al. Eur Heart J 2008; 29:2388–442; 4. Hunt et al. Am Coll Cardiol 2009;53:e1–90; 5. López-Sendón, Medicographia 2011;33:363-369

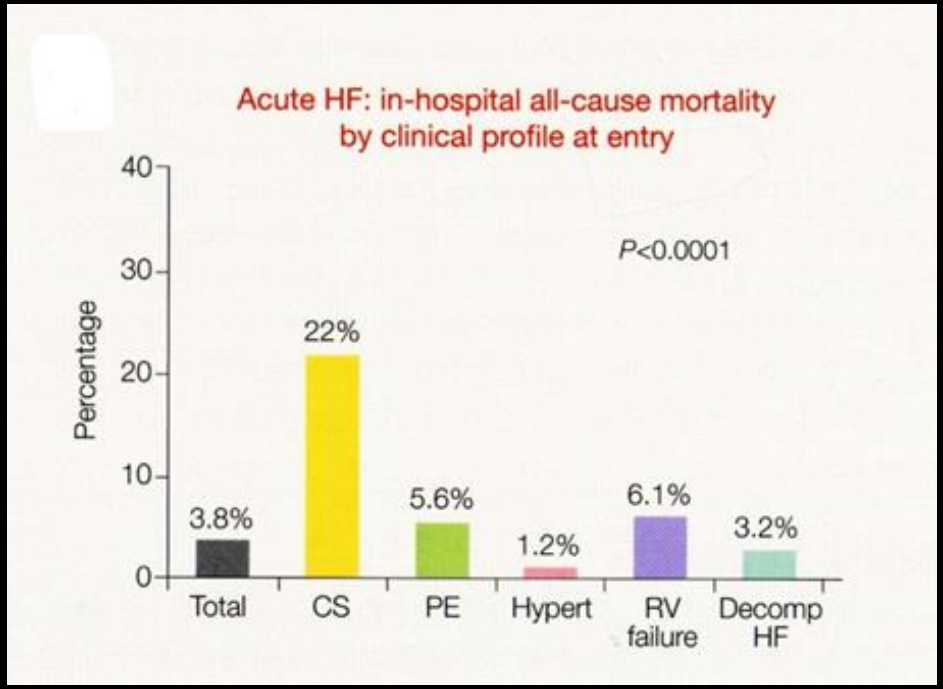
EUROObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot)

Eur J Heart Fail 2013; 15: 808-817

In-hospital mortality registries

Source	Patients	Age (years)	Hospital stay (days)	In-hospital mortality (%)
OPTIMIZE HF	5751	72	4	1.6
IMPACT-HF	567	71	8	2.8
ADHERE	65 000	72	4	4
Goldberg	2604	79	4	5.1
European HFS 2	3580	70	9	6.7
Italian AHFS	2807	73	9	7.3
FINN-AKVA	620	75	7	8
Rudiger	312	73	11.5	8
European HFS 1	11 327	71	11	8.4
EFFECT	4031	76	-	8.9
Argentina Reg	2974	65-70	7-9	4-12
EFICA	599	73	15	27/43 (4 weeks)

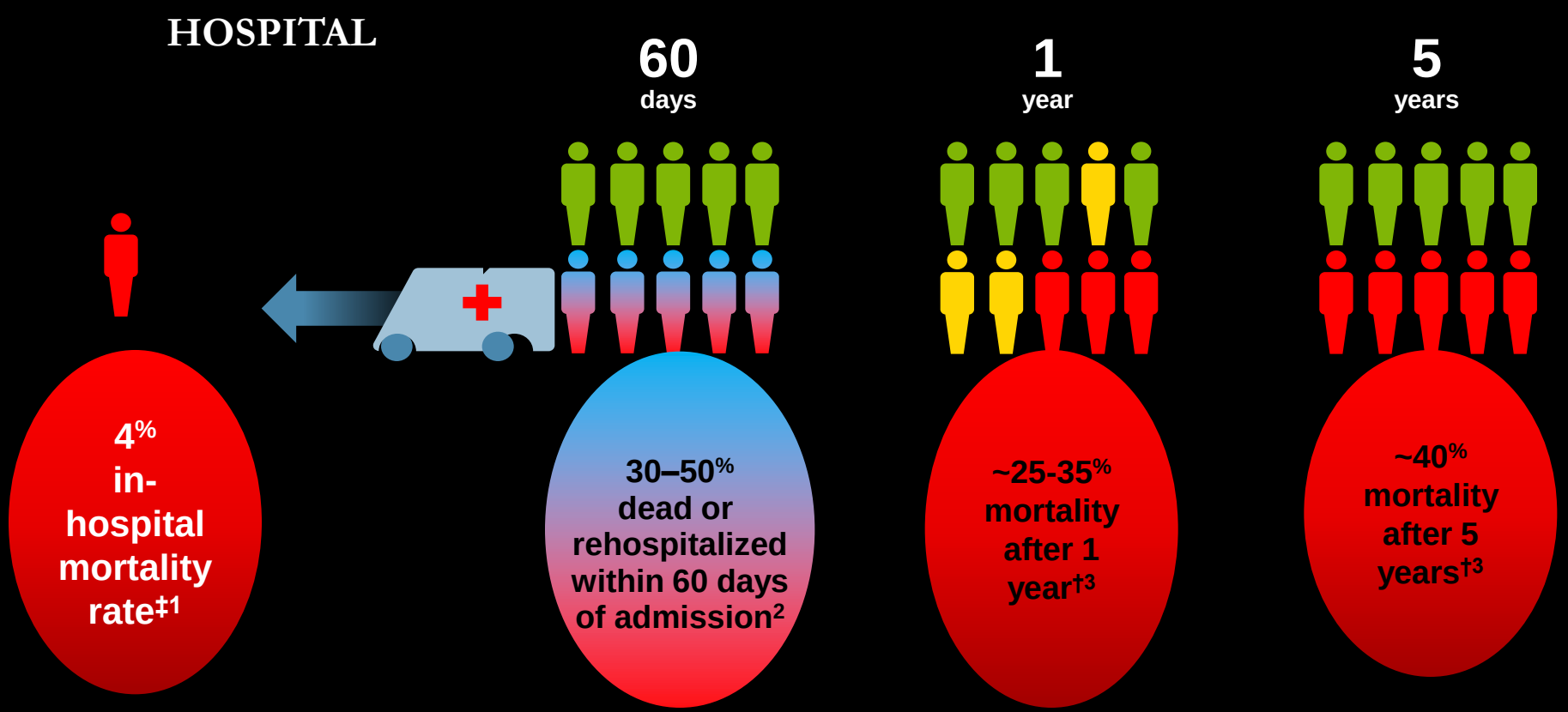
AHF - In-hospital mortality rates according to clinical profiles



93% of deaths could be explained by the presence of at least 1 of these RF:
<u>age, low SBP and reduced renal function</u>

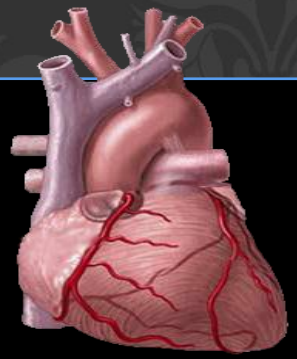
ACUTE HEART FAILURE IS ASSOCIATED WITH SIGNIFICANT MORBIDITY AND MORTALITY

Data from 105.388 US patients hospitalized for heart failure between 1997 and 2004 in the Acute Decompensated Heart Failure National Registry (ADHERE)

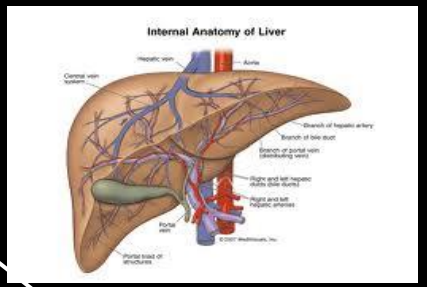


1, Adams et al. Am Heart J 2005; 149:209-16; 2. Dickstein et al. Eur Heart J 2008; 29:2388-442; 3.Harjola et al. Eur J Heart Fail 2010; 12:239-248; 4. Siirilä-Waris. Eur Heart J. 2006;27:3011-301; 5. Roger et al. Circulation 2012; 125;e2-220

THE PATHOPHYSIOLOGY OF ACUTE HEART FAILURE REMAINS POORLY UNDERSTOOD



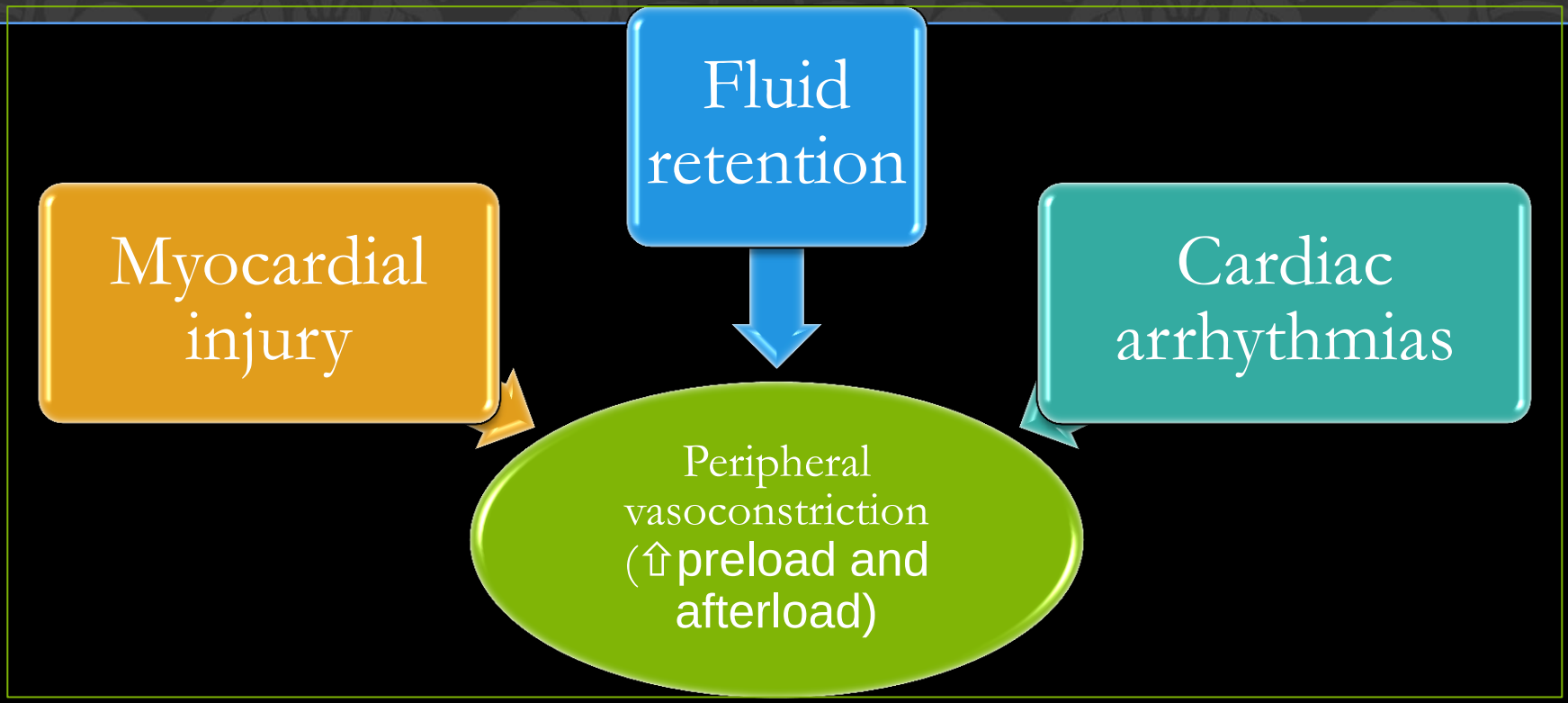
AHF involves a complex set of interactions between systems: heart, kidney, liver and peripheral vasculature



Future research is required to identify the exact mechanisms involved in the 'cross-talk' between systems, and the relative contribution of these mechanisms in the pathogenesis of acute HF**. This task is further complicated by the fact that the precise mechanisms implicated in connecting the heart, kidney, liver and peripheral vasculature, and their relative importance, may vary between patients.**

Felker et al. Circ Heart Fail 2010;3(2):314–25

CENTRAL ROLE OF VASOCONSTRICTION IN AHF



A large proportion of patients hospitalized for acute HF present with ⇧ blood pressure, which may be due to ⇧ vascular resistance/stiffness that can lead to reduced capacitance in large veins and ⇧ arterial resistance. In combination with cardiac dysfunction, ⇧preload and afterload can lead to redistribution of fluids to the lungs-

Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine

Mihai Gheorghiade[1], Ferenc Follath[2], Piotr Ponikowski[3], Jeffrey H. Barsuk[4], John E.A. Blair[5], John G. Cleland[6], Kenneth Dickstein[7,8], Mark H. Drazner[9], Gregg C. Fonarow[10], Tiny Jaarsma[11], Guillaume Jondeau[12], Jose Lopez Sendon[13], Alexander Mebazaa[14,15], Marco Metra[16], Markku Nieminen[17], Peter S. Pang[18], Petar Seferovic[19], Lynne W. Stevenson[20], Dirk J. van Veldhuisen[21], Faiez Zannad[22], Stefan D. Anker[22], Andrew Rhodes[23], John J.V. McMurray[24], and Gerasimos Filippatos[25]*

Patients with acute heart failure (AHF) require urgent in-hospital treatment for relief of symptoms. The main reason for hospitalization is congestion, rather than low cardiac output. Although congestion is associated with a poor prognosis, many patients are discharged with persistent signs and symptoms of congestion and/or a high left ventricular filling pressure. Available data suggest that a pre-discharge clinical assessment of congestion is often not performed, and even when it is performed, it is not done systematically because no method to assess congestion prior to discharge has been validated. Grading congestion would be helpful for initiating and following response to therapy. We have reviewed a variety of strategies to assess congestion which should be considered in the care of patients admitted with HF. We propose a combination of available measurements of congestion. Key elements in the measurement of congestion include bedside assessment, laboratory analysis, and dynamic manoeuvres. These strategies expand by suggesting a routine assessment of congestion and a pre-discharge scoring system. A point system is used to quantify the degree of congestion. This score offers a new instrument to direct both current and investigational therapies designed to optimize volume status during and after hospitalization. In conclusion, this document reviews the available methods of evaluating congestion, provides suggestions on how to properly perform these measurements, and proposes a method to quantify the amount of congestion present.

The main reason for hospitalization for acute heart failure is CONGESTION, rather than low cardiac output

Gheorghiade et al. Eur J Heart F 2010

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2010) **31**, 703–711
doi:10.1093/eurheartj/ehp507

CLINICAL RESEARCH
Heart failure/cardiomyopathy

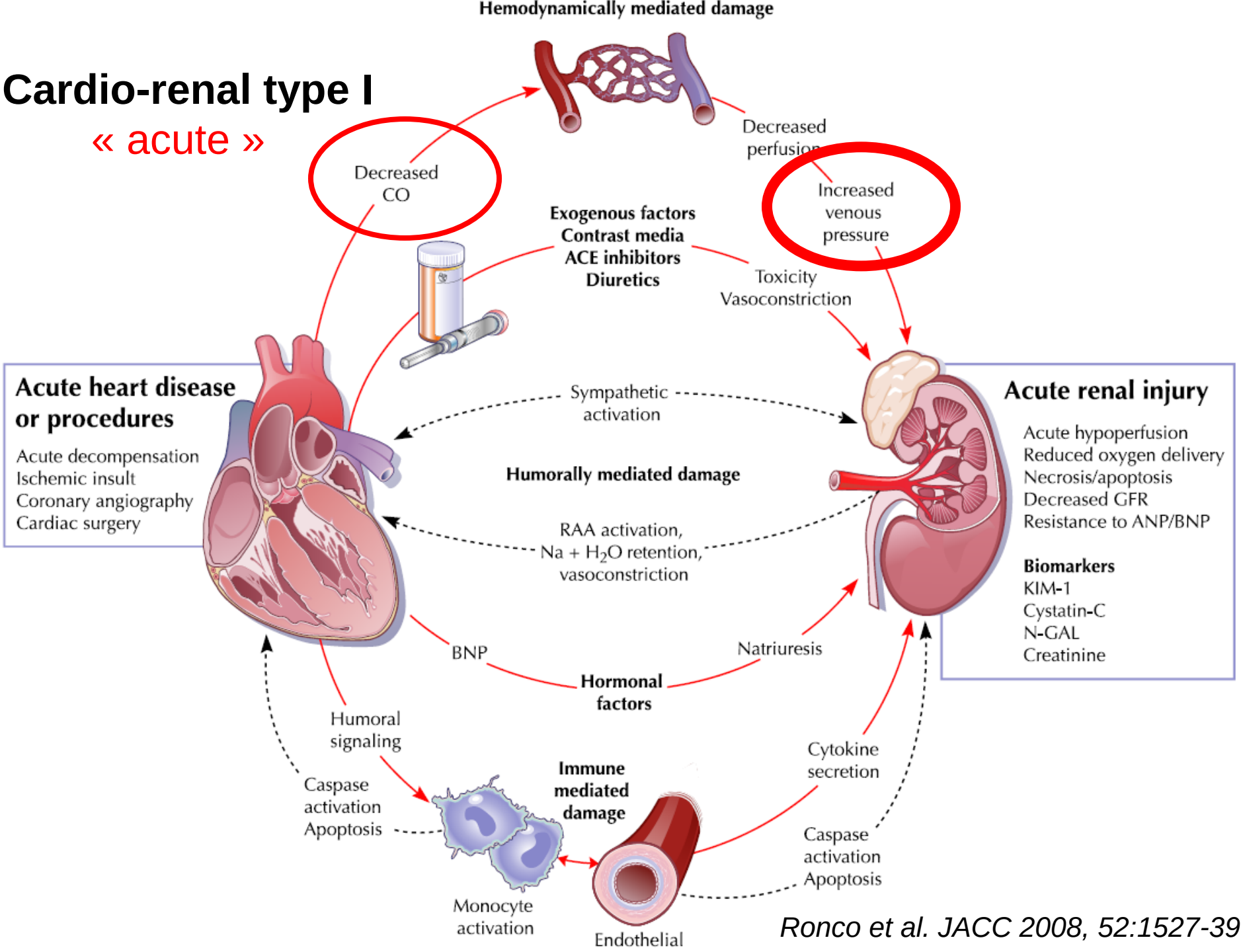
Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

Claudio Ronco[1,2*], Peter McCullough[3], Stefan D. Anker[4,5], Inder Anand[6], Nadia Aspromonte[7], Sean M. Bagshaw[8], Rinaldo Bellomo[9], Tomas Berl[10], Ilona Bobek[1], Dinna N. Cruz[1,2], Luciano Daliento[11], Andrew Davenport[12], Mikko Haapio[13], Hans Hillege[14], Andrew A. House[15], Nevin Katz[16], Alan Maisel[17], Sunil Mankad[18], Pierluigi Zanco[19], Alexandre Mebazaa[20], Alberto Palazzuoli[21], Federico Ronco[11], Andrew Shaw[22], Geoff Sheinfeld[23], Sachin Soni[1,24], Giorgio Vescovo[25], Nereo Zamperetti[26], and Piotr Ponikowski[27] for the Acute Dialysis Quality Initiative (ADQI) consensus group

Ronco et al. Eur Heart Journal 2010

Cardio-renal type I

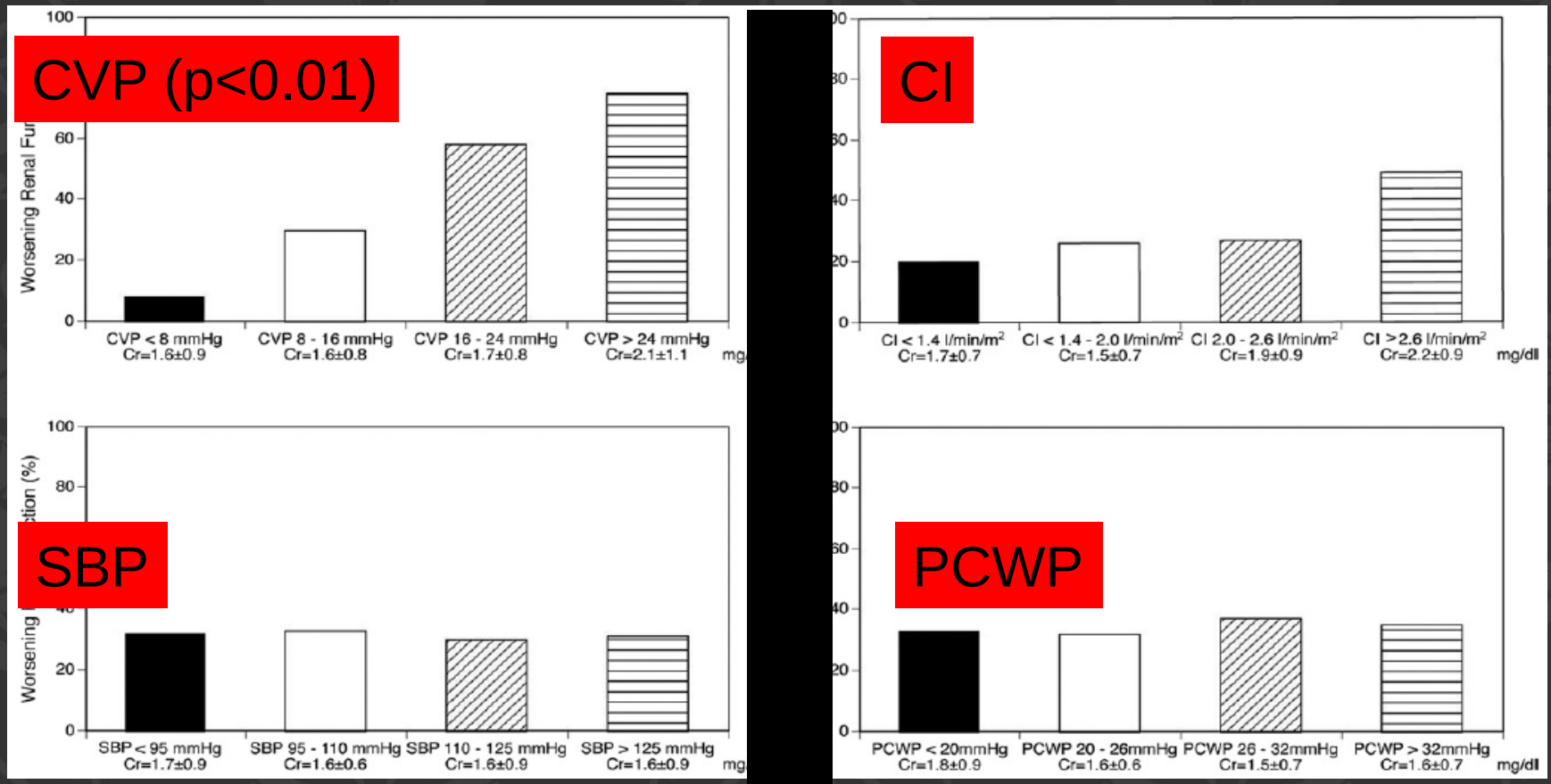
« acute »



Ronco et al. JACC 2008, 52:1527-39

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

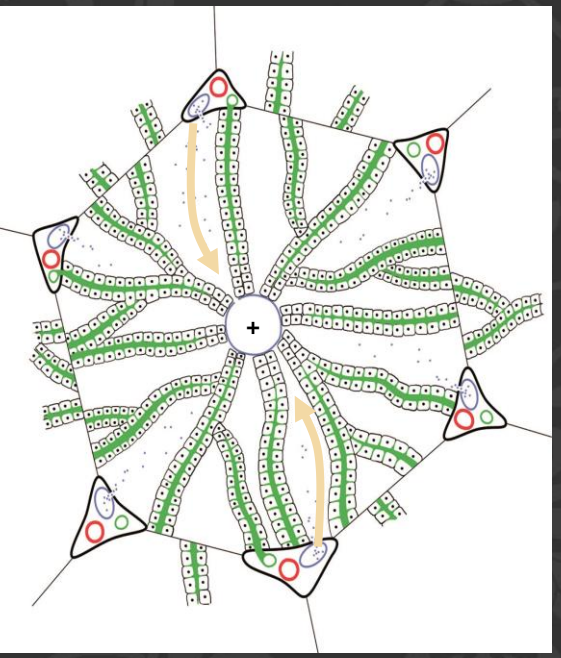
Mullens et al. JACC 2009, 53:589-596



Pts with ADHF with intensive medical R/ guided by PAC.
WRF was commonly observed despite hemodynamic improvements
This data imply that, apart from intrinsic renal dysfunction, the presence of venous congestion rather than reduced CO may be the primary hemodynamic factor driving WRF in this population

1134 patients with ADHF
Abnormal LFTs were seen in 46% of ADHF patients

Normal liver lobule



European Heart Journal Advance Access published October 22, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs332

CLINICAL RESEARCH

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

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

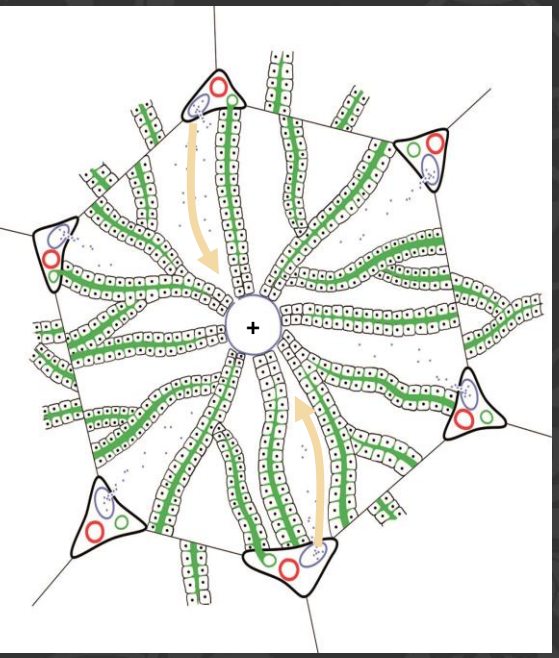
[1]UMRS 942 Inserm, F-75010 Paris, France; [2]Univ Paris Diderot, Sorbonne Paris Cité, F-75205 Paris, France; [3]Heart Failure Unit, 2nd Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; [4]Department of Cardiology, University Hospital Jean-Minjoz, Besançon, France;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

Received 14 March 2012; revised 21 August 2012; accepted 12 September 2012

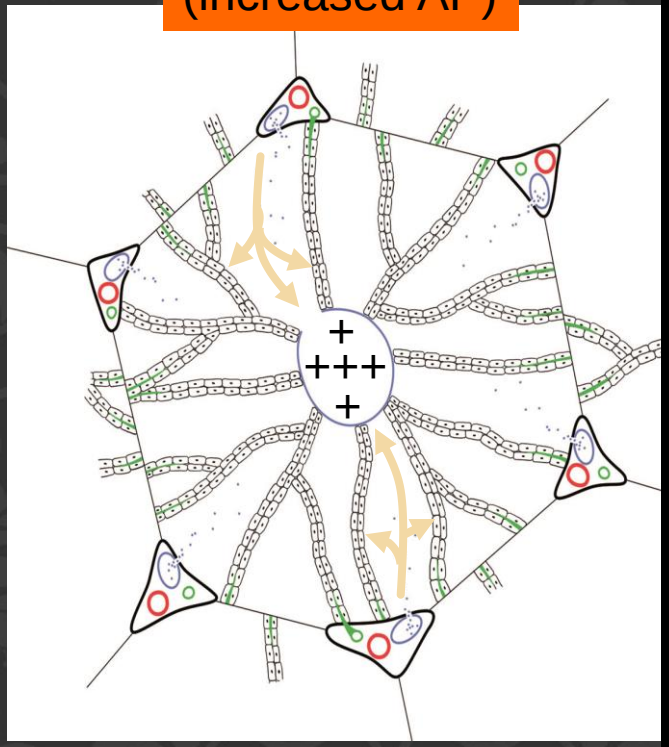
Nikolaou et al Eur Heart Journal 2013 (in press)

AHF-induced liver congestion
(increased BNP)

Normal liver lobule



bile duct compression
(increased AP)



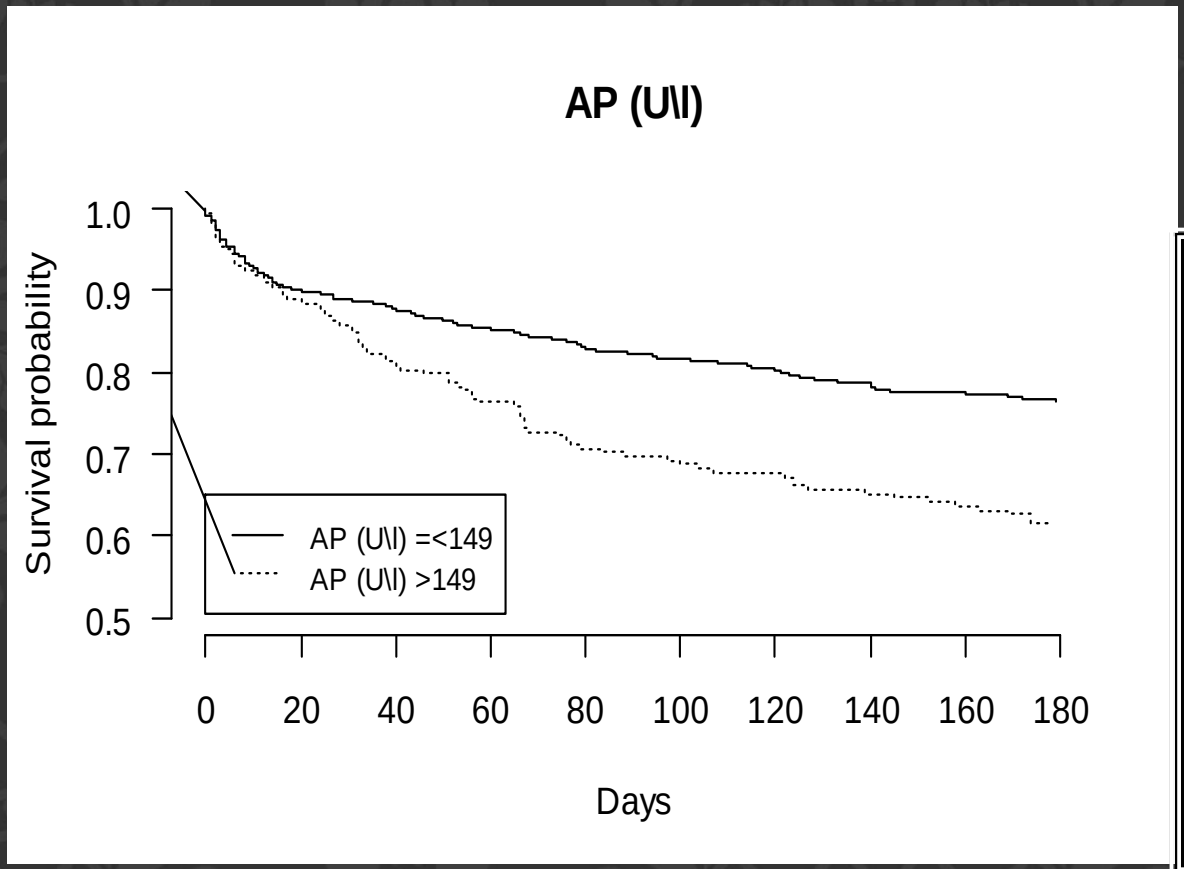
Isolated abnormal alkaline phosphatase (AP) was noted in 11%

Abnormal AP was associated with marked signs of systemic congestion and elevated right-sided filling pressure.

⇧Central Venous Pressure results in passive hepatic congestion and causes increase in alkaline phosphatase

Nikolaou et al Eur Heart Journal 2013 (in press)

6-month mortality as a function of cholestatis



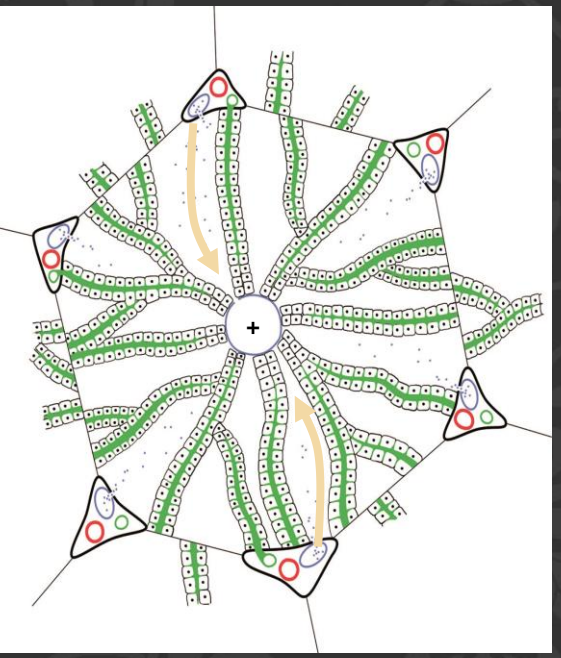
Abnormal alkaline phosphatase was associated with worse 180-day mortality (23.5 vs. 34.9%, P = 0.001 vs. patients with normal AP).

Nikolaou et al Eur Heart Journal 2013 (in press)

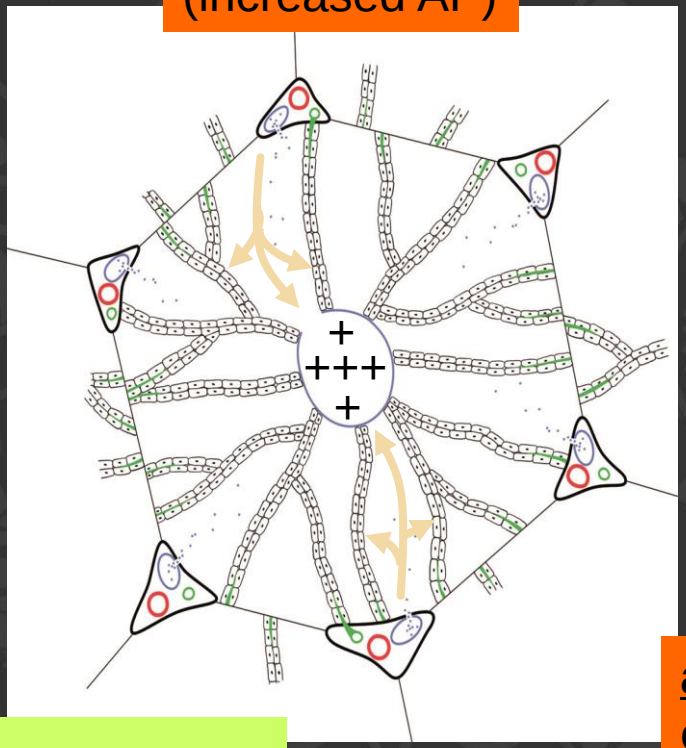
AHF-induced liver congestion
(increased BNP)

isolated abnormal transaminases in 26%,

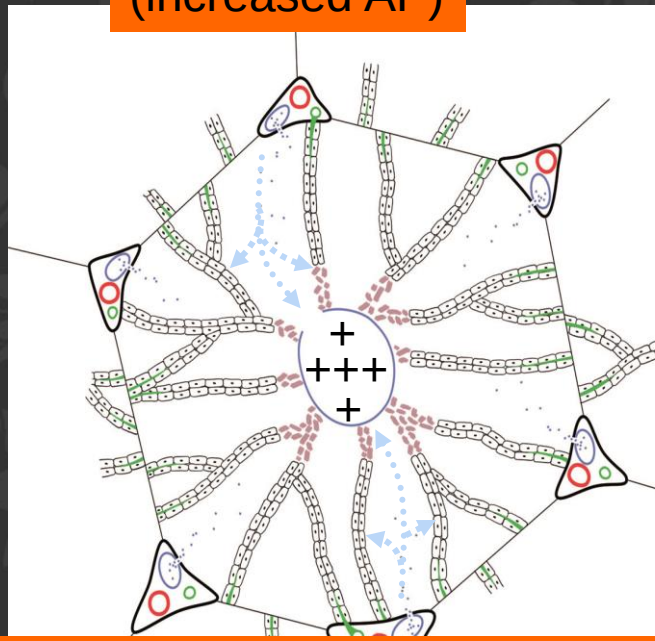
Normal liver lobule



bile duct compression
(increased AP)



bile duct compression
(increased AP)

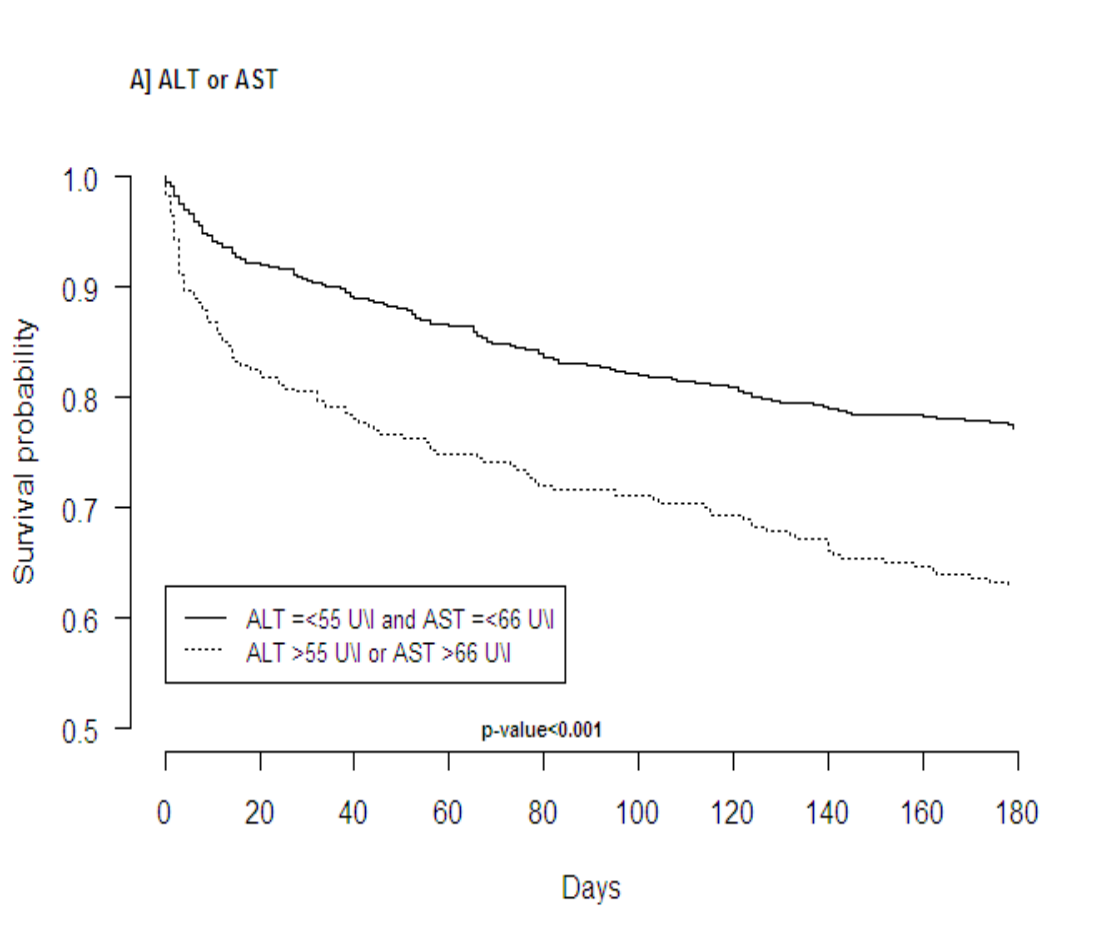


<u>and</u> cytolysis (acute centrilobular hepatocellular damage and necrosis)
(increased transaminanses)

Abnormal transaminases were associated with clinical signs of hypoperfusion

Nikolaou et al Eur Heart Journal 2013 (in press)

6-MONTH MORTALITY AS A FUNCTION OF LIVER CYTOLYSIS



Abnormal transaminase were associated with greater 31-day and 180-day mortality compared with normal transaminase profiles (17.6 vs. 8.4% and 31.6 vs. 22.4%, respectively; both P < 0.001).

Nikolaou et al Eur Heart Journal 2013 (in press)

TREATMENT OF ACUTE HEART FAILURE: IMMEDIATE, INTERMEDIATE AND LONG-TERM GOALS

Current guidelines split treatment goals into:[1–3]

Immediate (emergency department)
Relieve symptoms and stabilize the hemodynamic condition

Intermediate (in-hospital stabilization)
Initiate pharmacological therapy and minimize length of hospitalization

Long-term (post-discharge)
Prevent rehospitalization

Goals of in-patient therapy for acute HF:[4]

Clinical goals	Hemodynamic goals
Resolution of dyspnea and orthopnea	SBP ≥80 mmHg
Resolution of ascites and peripheral edema	Right atrial pressure ≤8 mmHg
JVP ≤8 cm H_2O	PCWP ≤16 mmHg
Control of hypertension	Systemic vascular resistance ≤1,200 dynes/s/cm^{-5}
Minimize adverse effects of treatment, reduce duration and cost of stay	
Initiate treatments that improve long-term outcome	

JVP= Jugular Venous Pressure; PCWP=pulmonary capillary wedge pressure

1. Gheorghiade et al. Circulation 2005;112:3958–68; 2. McMurrary et al. Eur Heart J 2012;33:1787–847
3. Hunt et al. J Am Coll Cardiol 2009;53:e1–90 4. Colucci (Ed.). Atlas of Heart Failure, 5th ed. Springer 2008

POTENTIAL BENEFITS AND RISKS OF VASODILATORS IN AHF NITRATES

May achieve clinical goals of in-patient therapy for acute HF:

Makes patients feel better, early and sustained relief of dyspnea, orthopneia, decrease CVP and control hypertension

May have a U-shaped dose-effects relationships, high doses may reduce their effectiveness , because of counter regulatory mechanisms, induce rebound neurohormonal activation potentially limiting short and long term efficacy.

In pts with AHF and reduced cardiac reserve, vasodilators may induce a steep reduction in BP, inappropriate vasodilatation, ischemia, renal failure and sometimes shock.

TRADITIONAL VASODILATORS

AHF without Hypotension/hypoperfusion (NTG and ISD)

Use with caution in pts who really need, with right doses, carefully monitoring and titulation

venodilator effect at low doses

and mild arteriolar effect at higher doses

↙ **R & LVF pressures, PVR, SVR, wall stress,** pulmonary congestion,
without compromising stroke volume or
increasing myocardial oxygen consumption

Decrease BP, but little or no change in HR

Reduces Mitral Regurgitation

NITROPRUSSIDE

Salt of complex molecule made up of ferric cyanide

Production of nitrosothiol and GMPc in vascular smooth muscle

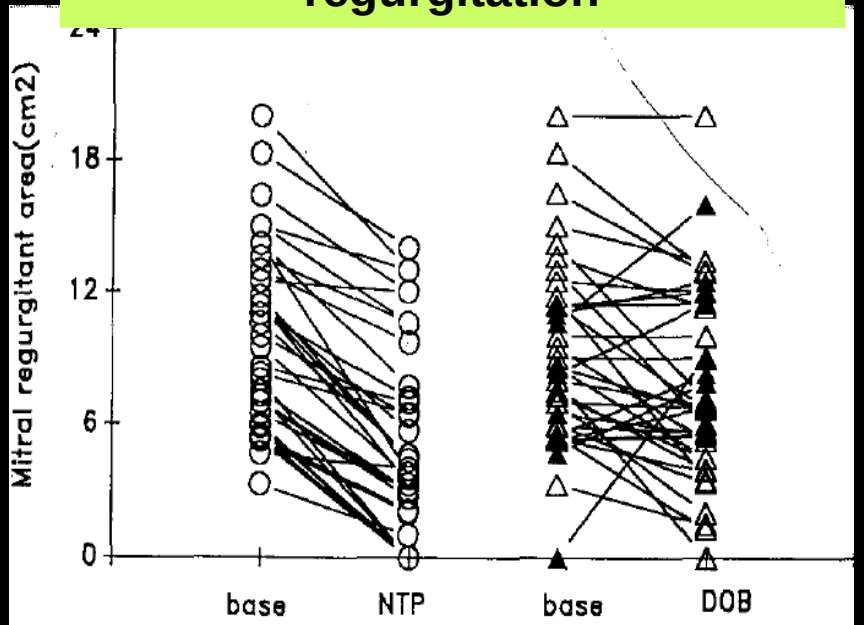
Reduces elevated filling pressures, Increase venous capacitance

Reduces afterload of right and LV

Significant reduction in BP, RAP, PCWP, SVR and PVR. Increase CO.

Effect on coronary blood flow in pts with CAD may be determinate by more vasodilator effect on non-obstructed coronary beds

Nitroprusside decreases mitral regurgitation



Changes of mitral regurgitant jet area after intravenous nitroprusside (*NTP*) and dobutamine (*DOB*) infusions. During nitroprusside infusion mitral regurgitation decreased in all patients, whereas during dobutamine infusion response was variable (*open triangles* indicate decrease in mitral regurgitation; *solid triangles* increase).

Capomolla S. et al. Am Heart J 1997; 134:1089-

NITROPRUSSIDE

Treatment of AHF with hypertension.

Can cause rebound effects; requiring gradual discontinuation

The incidence of side effects and toxicity is dose and duration related

Side effects of thiocyanate toxicity (> 6 mg): metabolic acidosis- can be removed by hemodialysis and treated with hydroxycobalamin

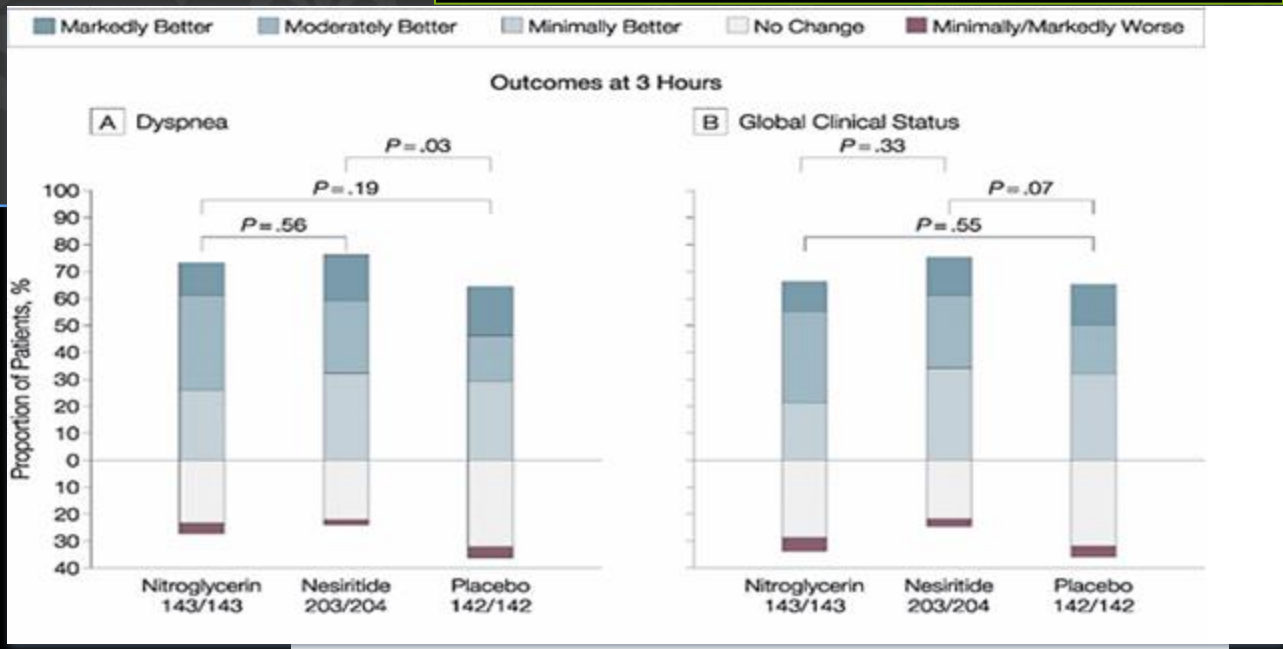
Conversion of cyanide to prussic acid increases methemoglobin levels

These effects are rare if we use NTP < 3 μg/Kg/min e < 72 hours

Nesiritide

Dyspnea Improvement in VMAC

Critical look – minimal dyspnea improvement With worsening renal function and increased mortality



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, Hal A. Skopicki and Keith D. Aaronson

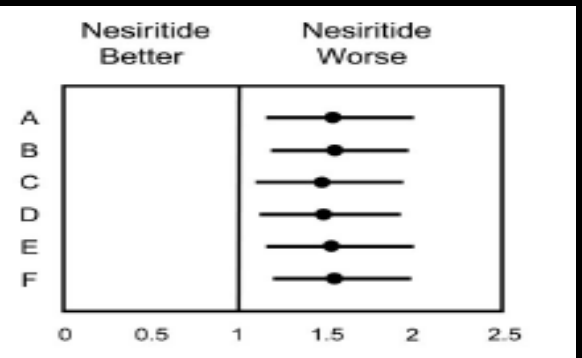
Circulation 2005;111;1487-1491; originally published online Mar 21, 2005;
DOI: 10.1161/01.CIR.0000159340.93220.E4
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75214

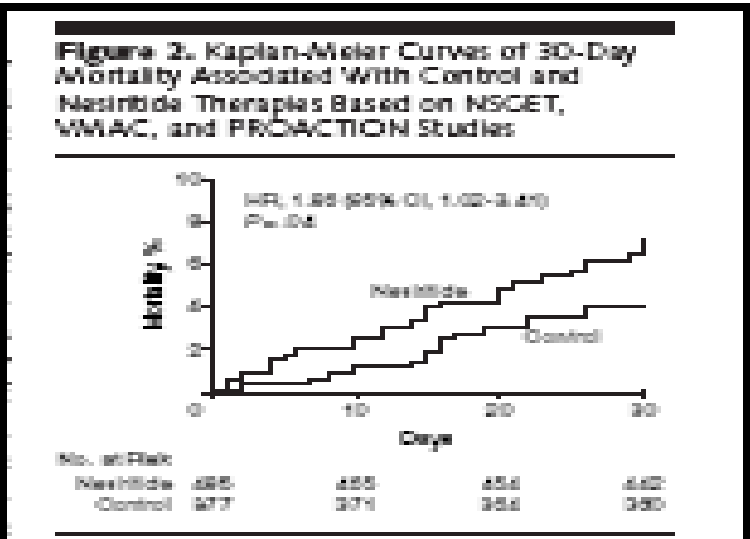
JAMA
Online article and related content current as of October 5, 2008.

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure: A Pooled Analysis of Randomized Controlled Trials

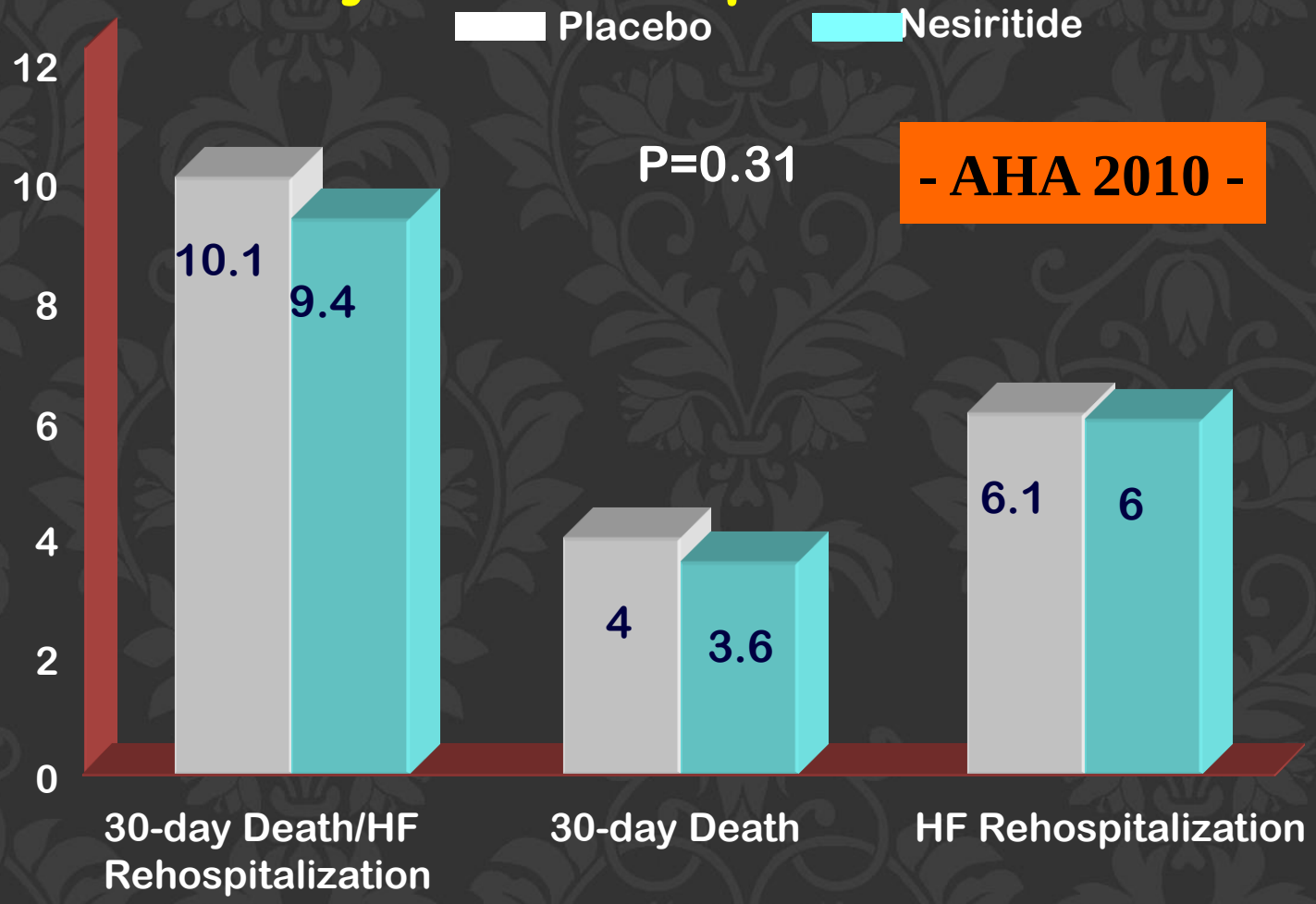
Jonathan D. Sackner-Bernstein; Marcin Kowalski; Marshal Fox; et al.

JAMA. 2005;293(15):1900-1905 (doi:10.1001/jama.293.15.1900)
http://jama.ama-assn.org/cgi/content/full/293/15/1900





ASCEND-HF TRIAL
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization



Risk Diff 95 % CI	-0.7 (-2.1; 0.7)	-0.4 (-1.3; 0.5)	-0.1 (-1.2; 1.0)

Drug	Indication	Regimen	Adverse effects	Limitations
nitroglycerine	Acute PE; pulmonary congestion in normo or hypertensive AHF	10-20 ug/min, increase up to 200 ug/min	Hypotension Headache	Tolerance is common after 24-48 h, requiring adjustment of dosing
Isosorbide dinitrate	Pulomonary Edema Pulmonary congestion	1 mg/h, increase up to 10 mg/h	Hypotension Headache	Tolerance as for nitroglycerine
Nitroprusside	Acute hypertensive congestion	0.3µg/Kg/min up to 5µ g/Kg/min	Hypotension Isocyanate toxicity	Light sensitive
nesiritide	Pulmonary edema Pulmonary congestion	Bolus and perfusion 0,015-0,030 ug/Kg/min	Hypotension Worsening renal function	Not available in many ESC countries

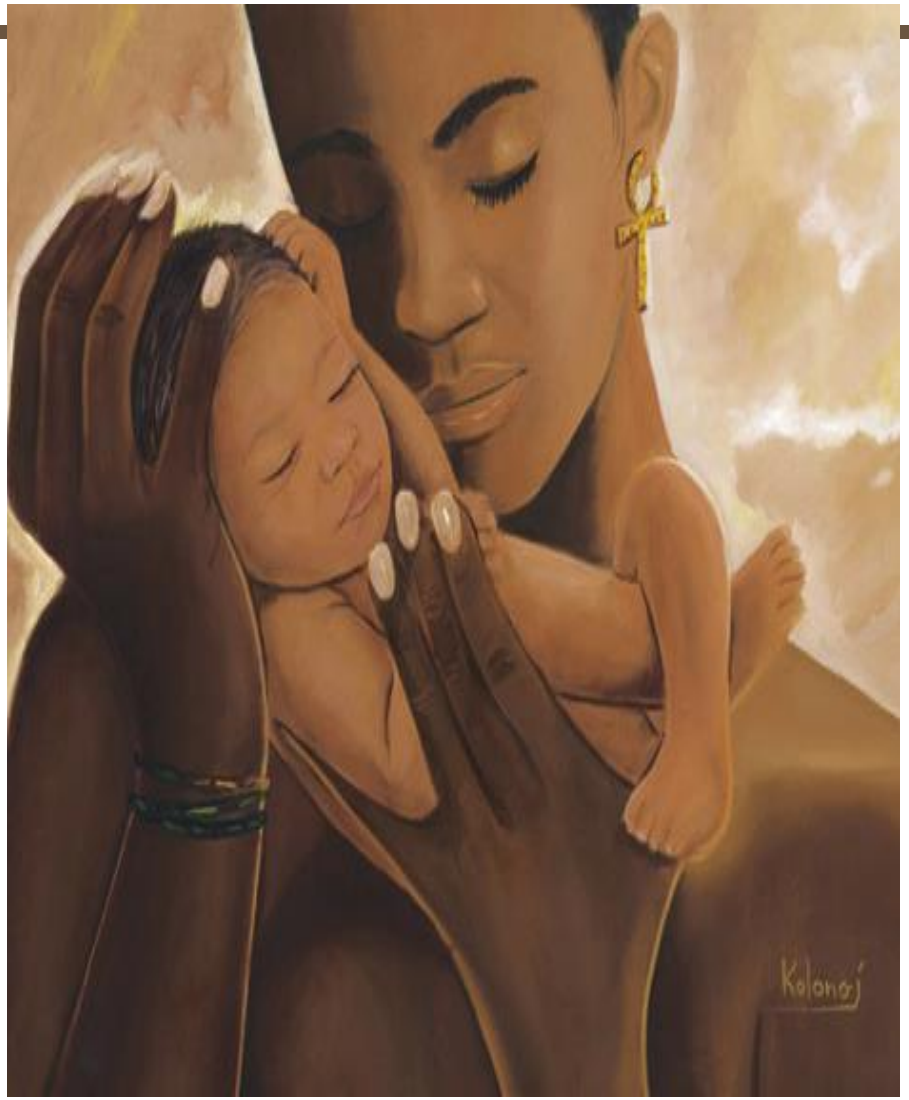
There is a therapeutic need in acute heart failure

- The therapeutic approach to acute HF has not changed much in the last few decades[1]
- few randomized controlled trials are available in this patient population
- the therapeutic portfolio available for patients with acute HF is limited
- only one drug in the USA and one drug in Europe have been approved in the last 15 years[1–3]
- Acute HF has recently received attention from researchers, clinicians, regulatory agencies and the pharmaceutical industry, due to its unique diagnostic and management challenges[2]
- There is a need to identify new treatment strategies and regimens that have a beneficial effect in AHF patients [1]

1. Felker et al. Circ Heart Fail 2010;3:314–25; 2. Gheorghiade et al. Circulation 2005;112:3958–68;
3. Hunt et al. J Am Coll Cardiol 2009;53:e1–90

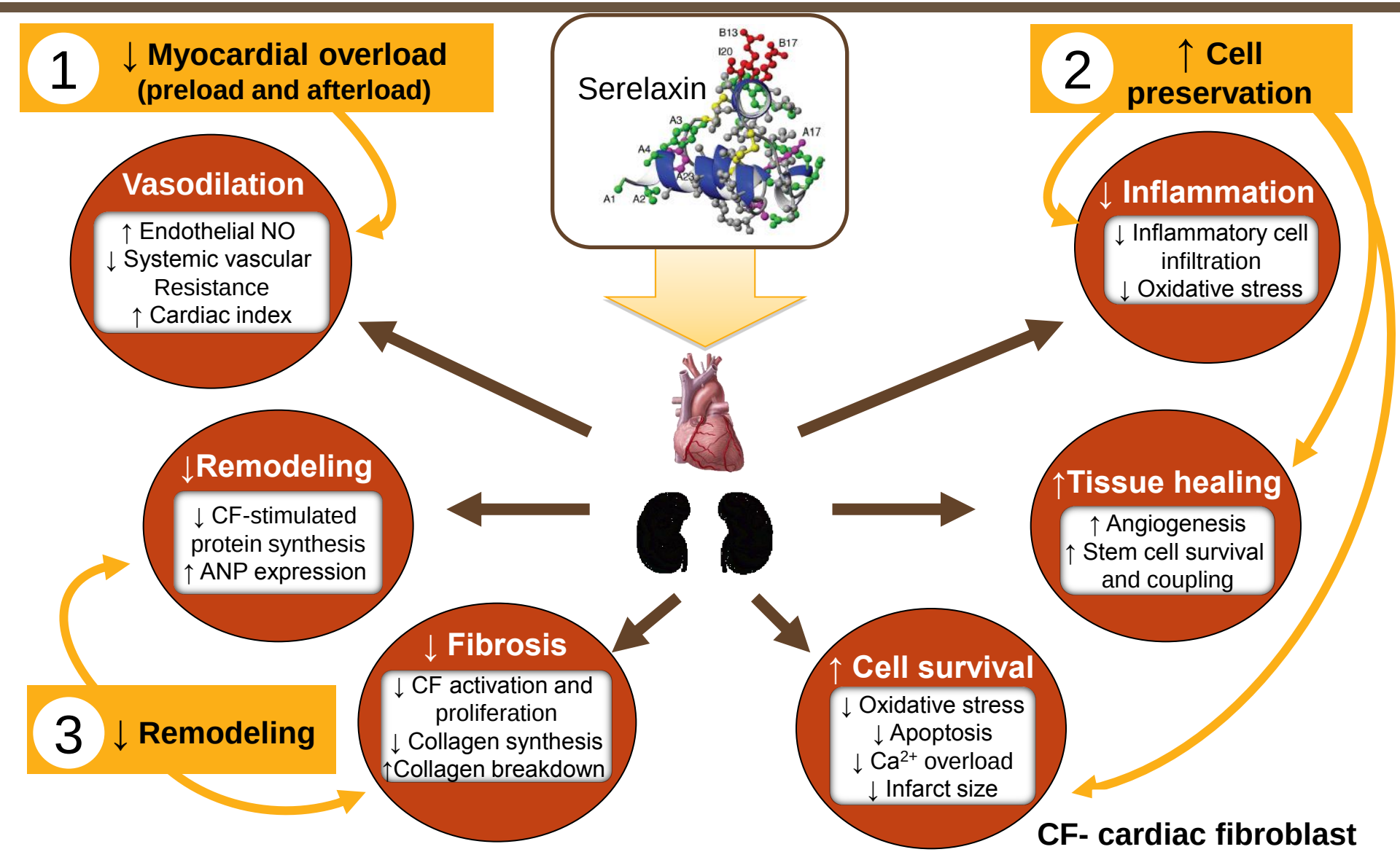
Serelaxin, recombinant form of human relaxin 2

- In women, the circulatory concentrations of relaxin rise in pregnancy along with notable physiological adjustments[4].
- These adaptations include a 20% increase in cardiac output, 30% decrease in systemic vascular resistance, 30% increase in global arterial compliance, and 50 to 80% increase in renal blood flow [4, 5, 6]



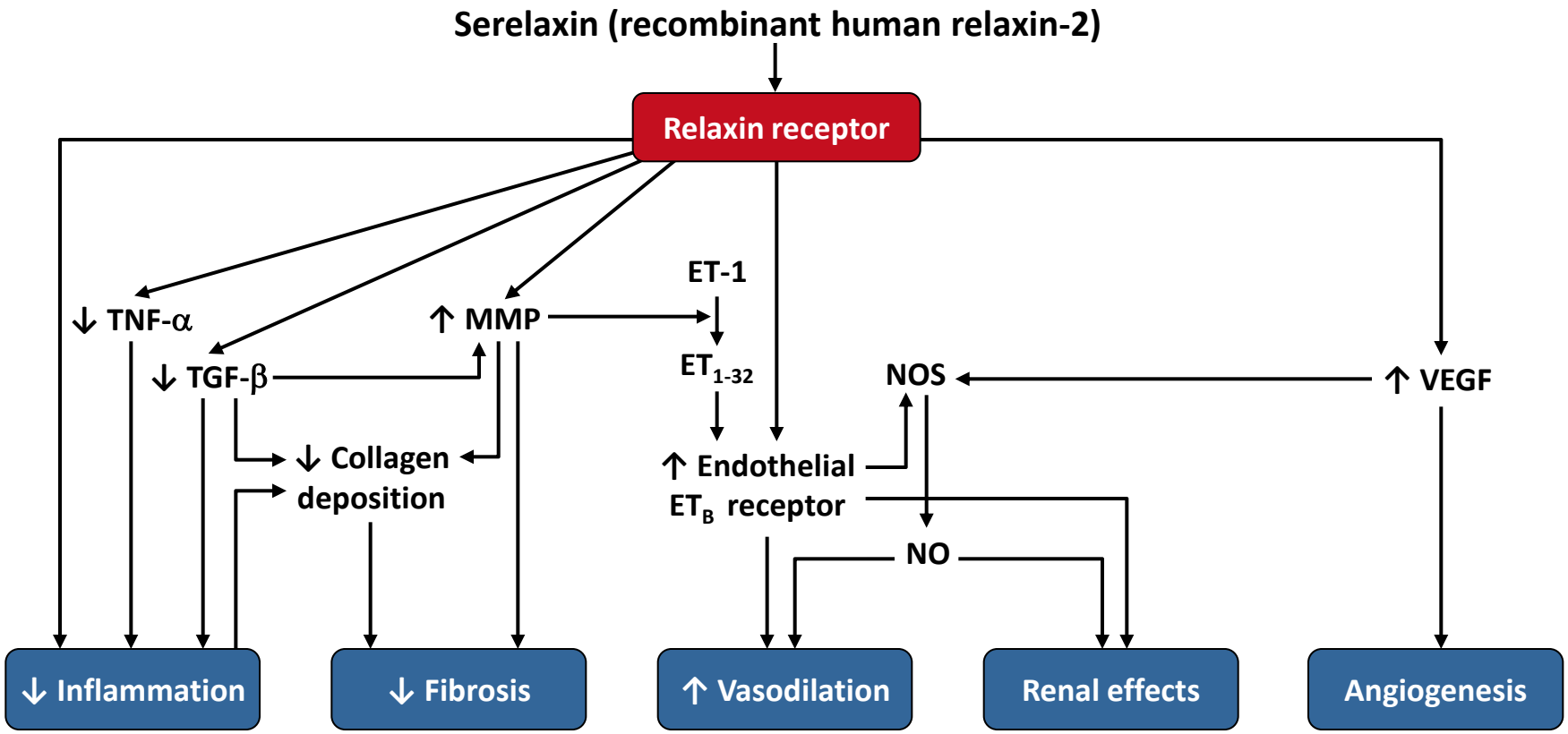
1. Hisaw FL, Proc Soc Exp Biol Med 1926, 23:661–663. 2. Teichman SL, et al Curr Heart Fail Rep. 2010;7:75-82. 3. Fevold et al. J Am Chem Soc 1930, 52:3340–3348. 4. Jeyabalan A, et al. Adv Exp Med Biol 2007, 612:65–87. 5. Schrier RW, et al. J Kidney Dis 1987, 9:284–289. 6. Baylis C, Am J Kidney Dis 1999, 34:1142–1145.

Serelaxin has potential multi-mechanistic effects which may address the pathophysiology of acute heart failure



Adapted from Du et al. Nat Rev Cardiol 2010;7:48–58

Serelaxin Is NOT Just Another Vasodilator

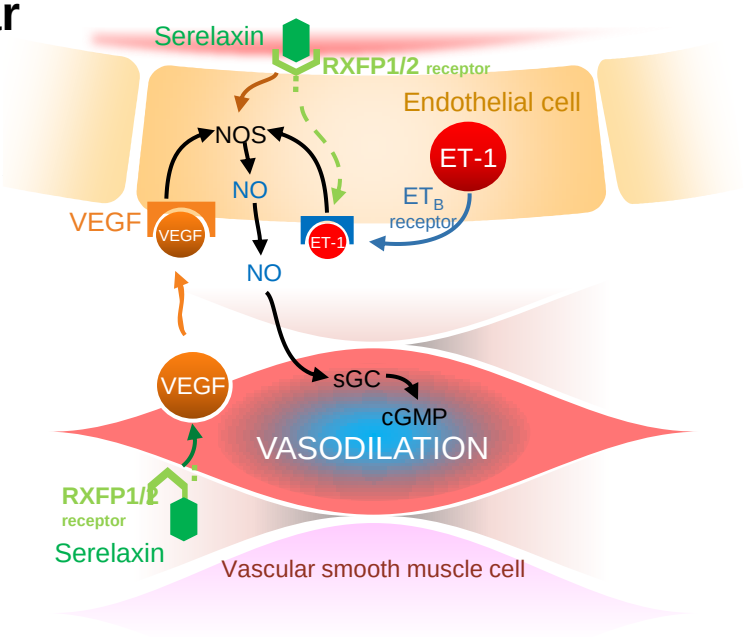


ET_B receptor = endothelin receptor type B; ET-1= endothelin-1; MMP = matrix metalloproteinase; NO = nitric oxide; NOS = nitric oxide synthase; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

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

Serelaxin stimulates NO-mediated vasodilation via activation of the endothelial ET_B receptor

- **Serelaxin binds to its receptors on vascular endothelial and smooth muscle cells[1–4]**
- **Binding of serelaxin to endothelial cell increases ET_B endothelial receptor activity[5–7] which mediates:**
  - **systemic and renal vasodilation via release of NO**
  - **clearance of ET-1, a potent vasoconstrictor**
  - **natriuresis/diuresis[8,9]**
- **In addition, serelaxin phosphorylates NOS directly in a rapid vasodilation pathway[10]**
- **VEGF is also known to play a role in serelaxin-mediated vasodilation[11]**



cGMP=cyclic guanosine monophosphate; ET=endothelin; NO=nitric oxide; NOS=nitric oxide synthase; RXFP=relaxin-2/serelaxin receptor; sGC=soluble guanylate cyclase; VEGF=vascular endothelial growth factor

1. Kohsaka et al. Biol Reprod1998;59:991–9; 2. Hsu et al. Science 2002;295:671–4; 3. Novak et al. FASEB J 2006;20:2353–62: 4. Conrad and Shroff. Curr Hypertens Rep 2011;13:409–20; 5. Teichman et al. Curr Heart Fail Rep 2010;7:75–82; 6. Danielson et al. Am J Physiol 2000; al. Circ Res 2003;92:32–40; 8. McMurray et al. Circulation 1992;85:1374–9; 9. Goddard et al. Circulation 2004;109:1186–9
Endocrinology 2011;152:2786–96; 11.McGuane et al. Hypertension 2011;57:1151–60

Pre-RELAX-AHF

Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study

John R Teerlink, Marco Metra, G Michael Felker, Piotr Ponikowski, Adriaan A Voors, Beth Davison Weatherley, Alon Marmor, Amos Katz, Jacek Grzybowski, Elaine Unemori, Sam L Teichman, Gad Cotter

Lancet 2009; 373: 1429–39

Published Online
March 29, 2009
DOI:10.1016/S0140-6736(09)60622-X

Phase IIb, multicenter (54 sites), international (8 countries), randomized, double-blind, placebo-controlled, parallel-group study

Pre-RELAX-AHF: study design

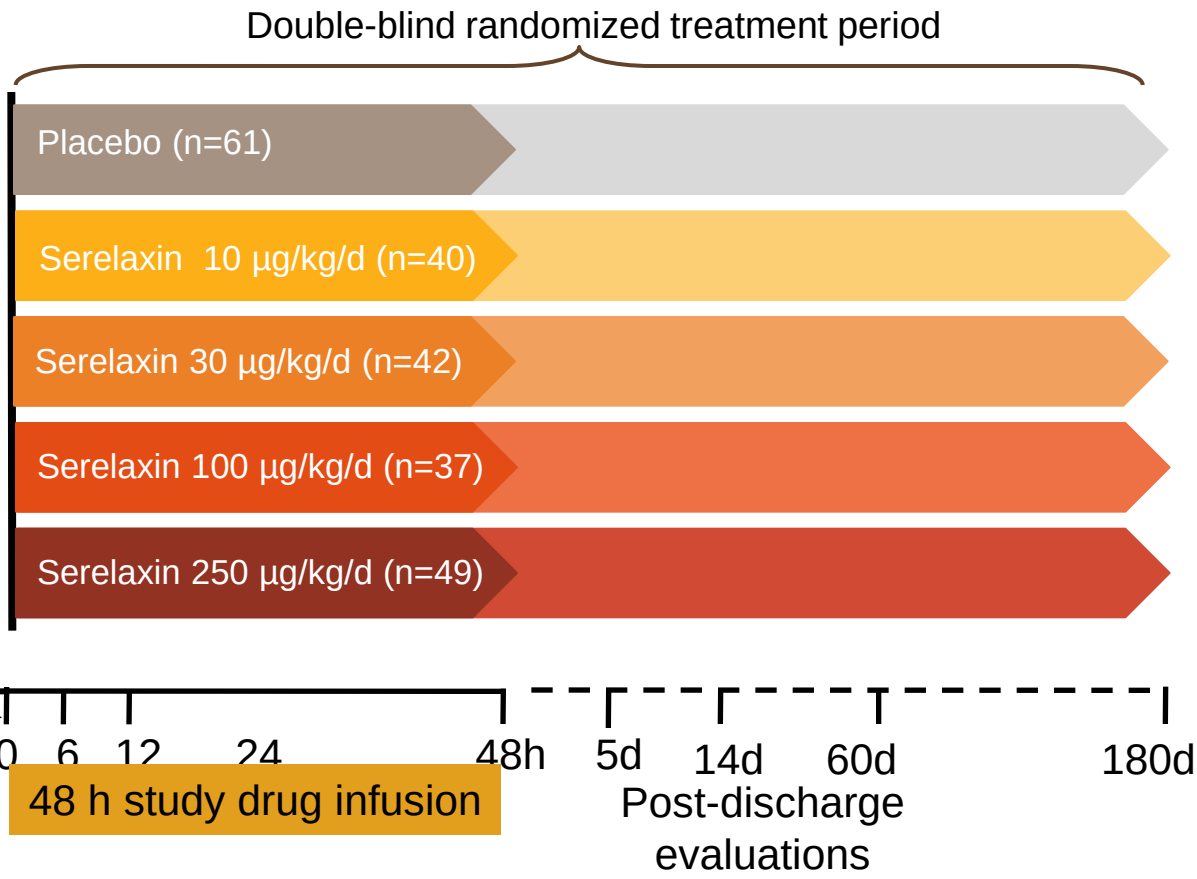
Randomized:

234 patients hospitalized with acute HF, dyspnea at rest or minimal exertion, normal to elevated blood pressure and mild-to-moderate renal impairment, high BNP, pulmonary congestion on chest RX

Screening

Screening occurred after ≥40 mg i.v. furosemide

Randomized 3:2:2:2:2
Stratified by site

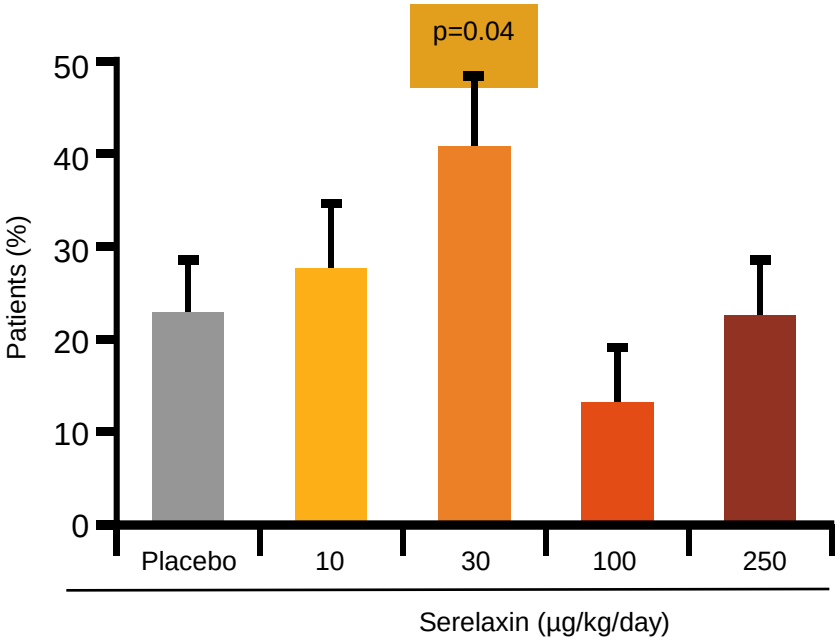


Teerlink et al. Lancet 2009;373:1429–39

Pre-RELAX-AHF: serelaxin is associated with rapid and sustained relief of dyspnea

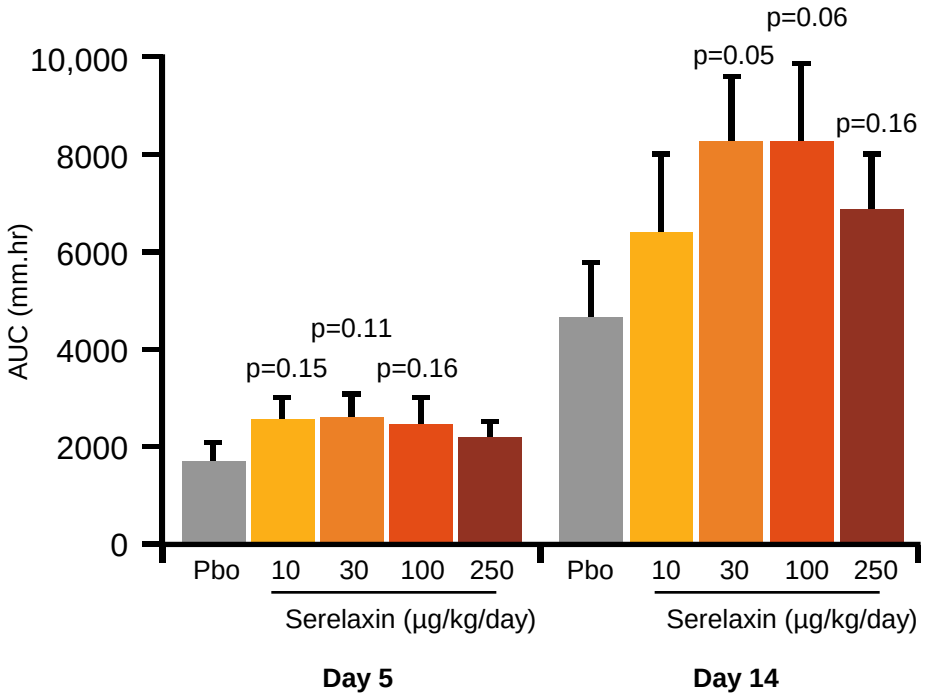
Rapid dyspnea improvement through 24 hours (Likert scale)

Proportion of patients with moderate/marked improvement in dyspnea at 6, 12 and 24 hr



Sustained dyspnea improvement through Day 14

Visual Analogue Scale AUC to Day 5 and Day 14

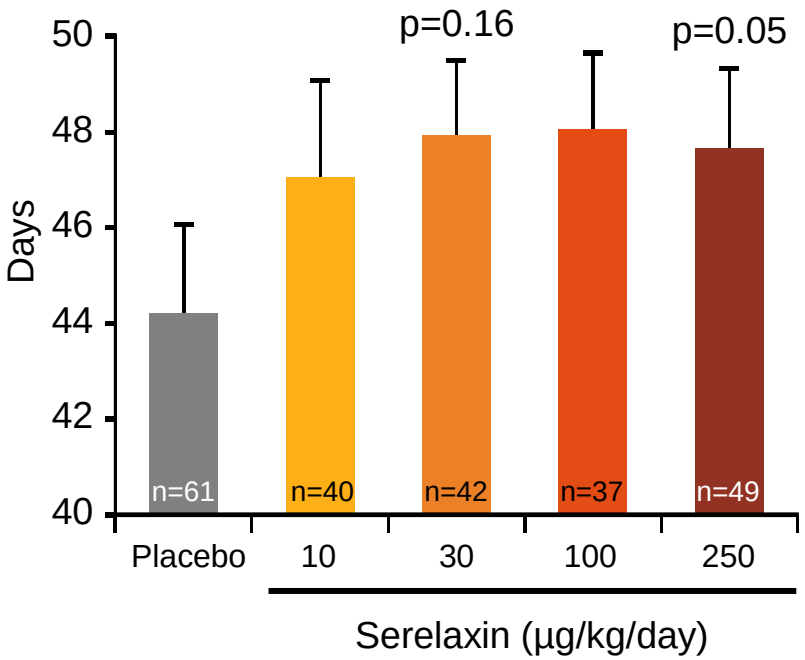


AUC=area under the curve

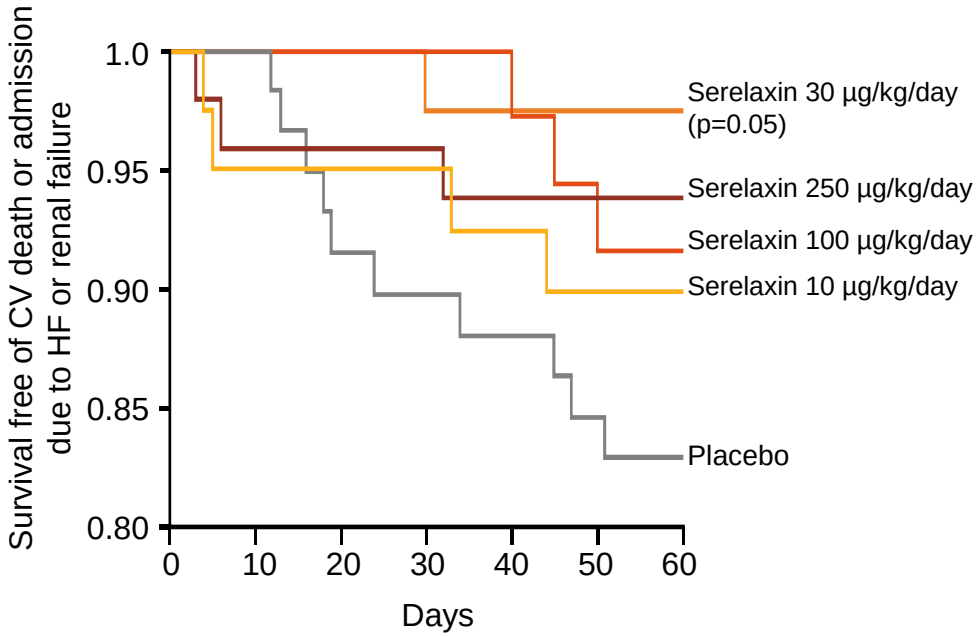
Teerlink et al. Lancet 2009;373:1429–39

Pre-RELAX-AHF: medium-term outcomes in AHF

Days alive and out of hospital to Day 60



CV Death or heart/renal failure re-hospitalizations to Day 60



***Trends* towards improvement in days alive and out of hospital and reduction in incidence of CV death or re-hospitalization due to heart failure or renal failure**

Teerlink et al. Lancet 2009;373:1429–39

RELAX-AHF

Lancet 2013; 381: 29–39
Published Online
November 7, 2012
http://dx.doi.org/10.1016/
S0140-6736(12)61855-8

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

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

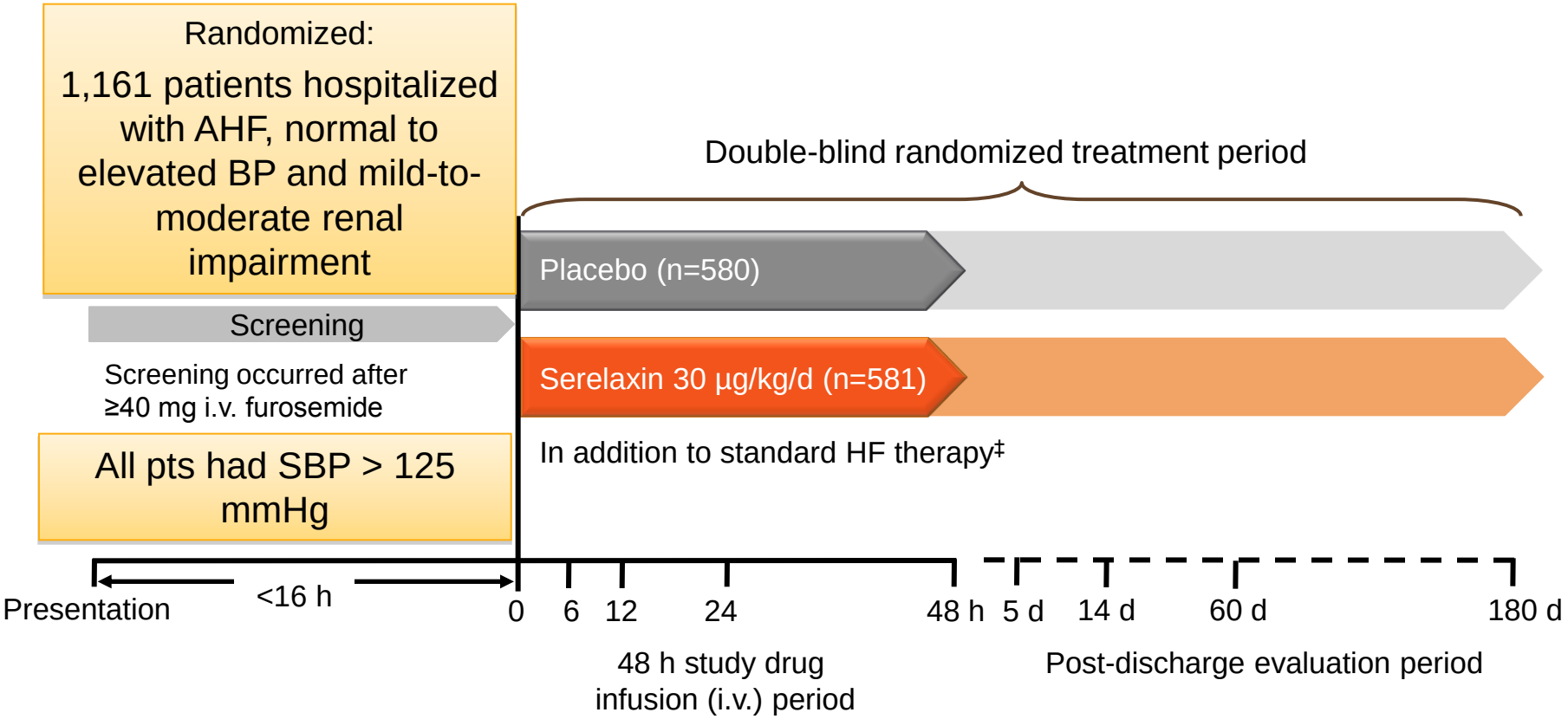
Primary end-points: dyspnea improvement (AUC of visual analogue scale (AVS) to day 5 and LIkert scale during first 24 hours

Secondary end-points*: 1) days alive and out of hospital to day 60 and 2) CV death at 6 months*

It was not prospectively designed or powered as a mortality trial

RELAX-AHF: study design

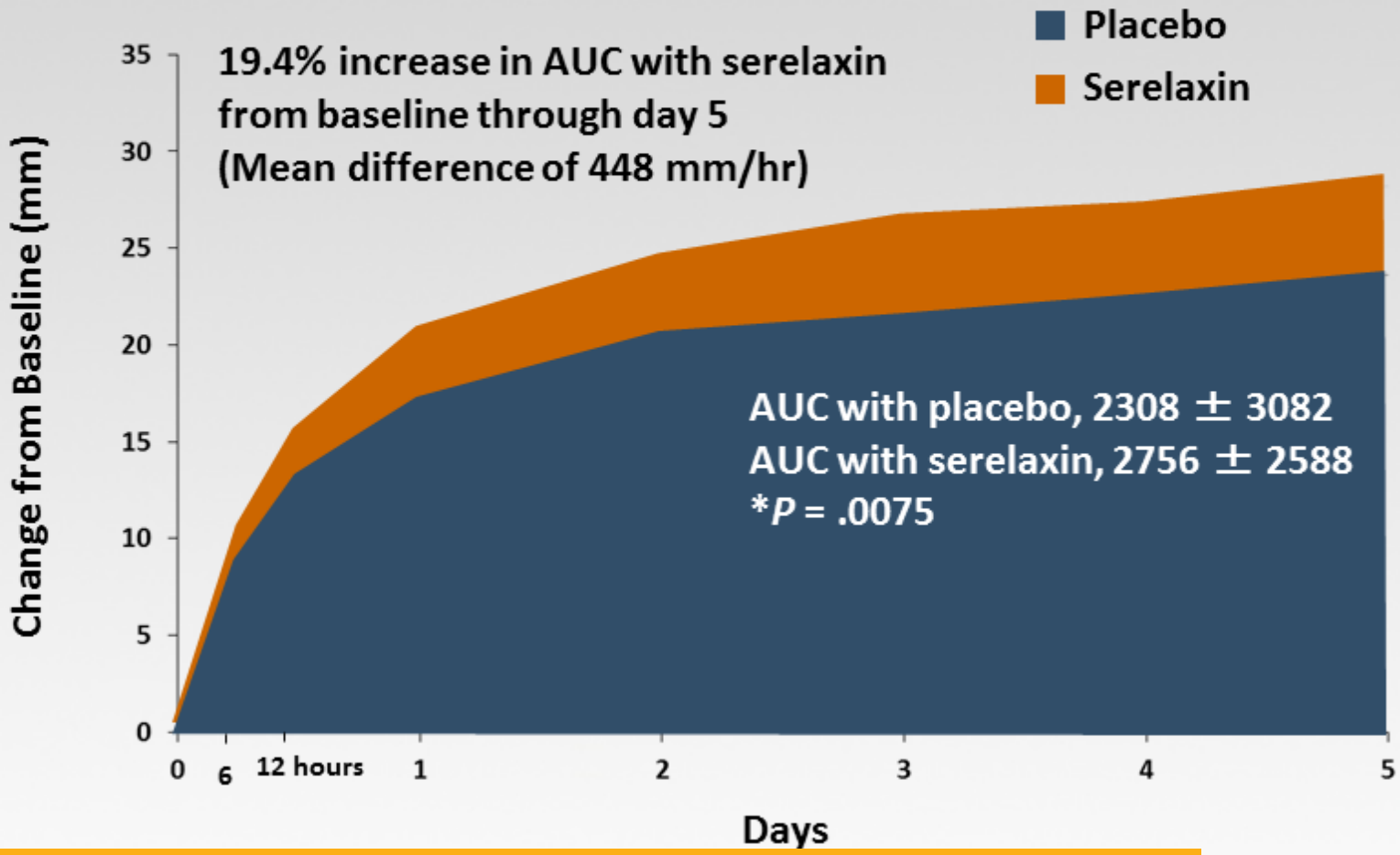
- A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of serelaxin, in addition to standard therapy, in subjects hospitalized for AHF. pts with a recent ACS, were excluded



‡Standard HF therapy permitted at physician's discretion
AHF=acute heart failure; BP=blood pressure; d=day; h=hour; i.v.=intravenous; RELAX-AHF=RELAXin in Acute Heart Failure
Teerlink et al. Lancet 2012 [Epub ahead of print]; Ponikowski et al. Am Heart J 2012;163:149–55.e1

First-Degree Endpoint: Dyspnea Relief (VAS AUC)

Improvement was noted in dyspnea starting at 6 h and persisting all 5 days

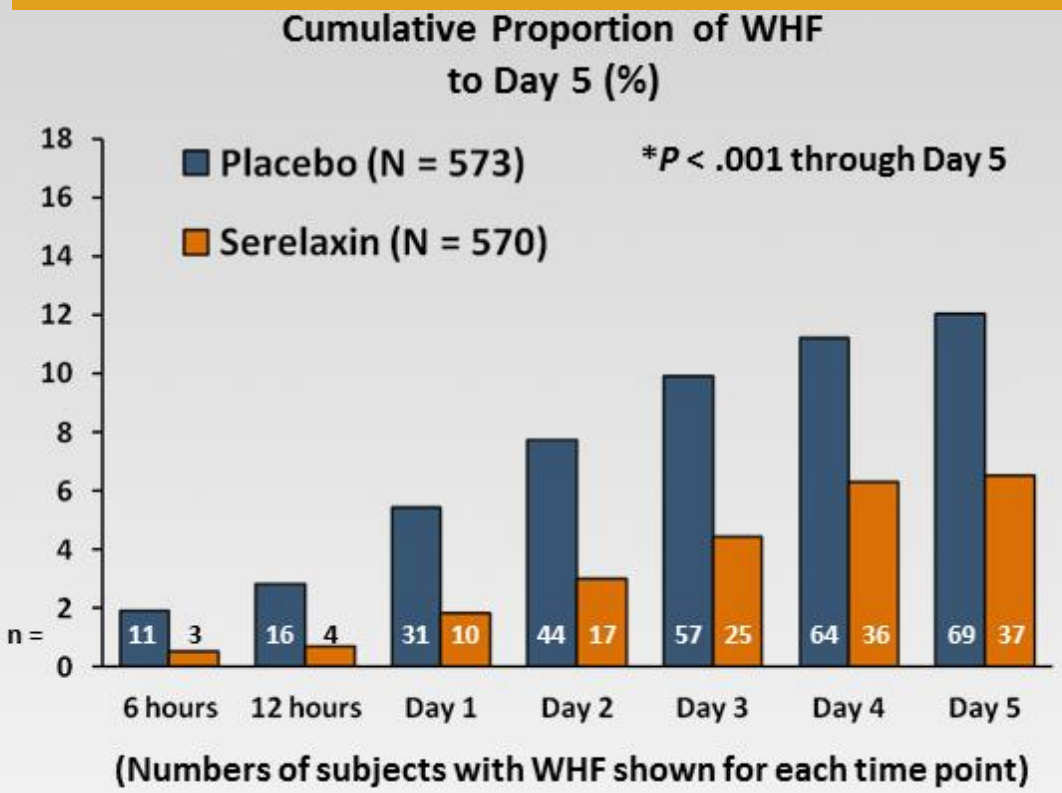


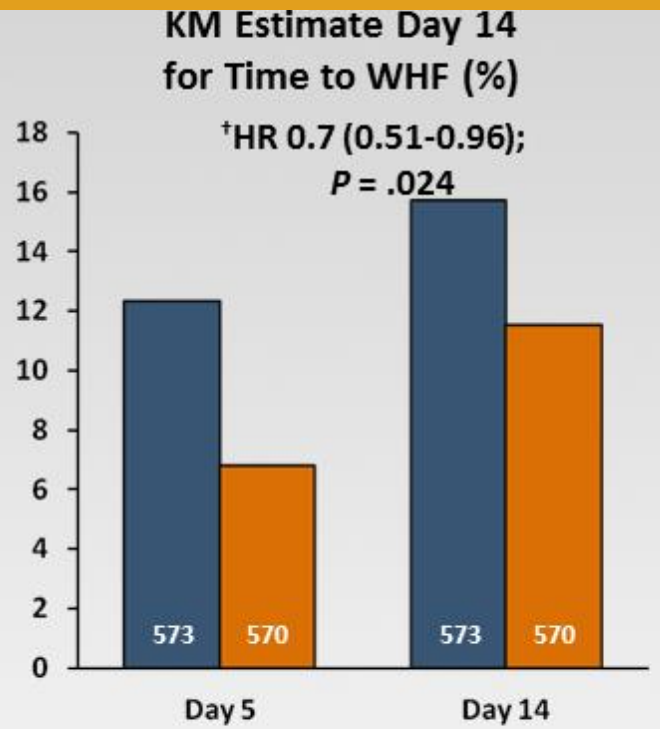
Pts in placebo group required iv diuretic more often at 3-5 days

From Teerlink JR, et al. *Lancet*. 2012 Nov 6.

Worsening of Heart Failure

30% reduced WHF by serelaxin up to day 14 and improvements in congestion by day 2





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**

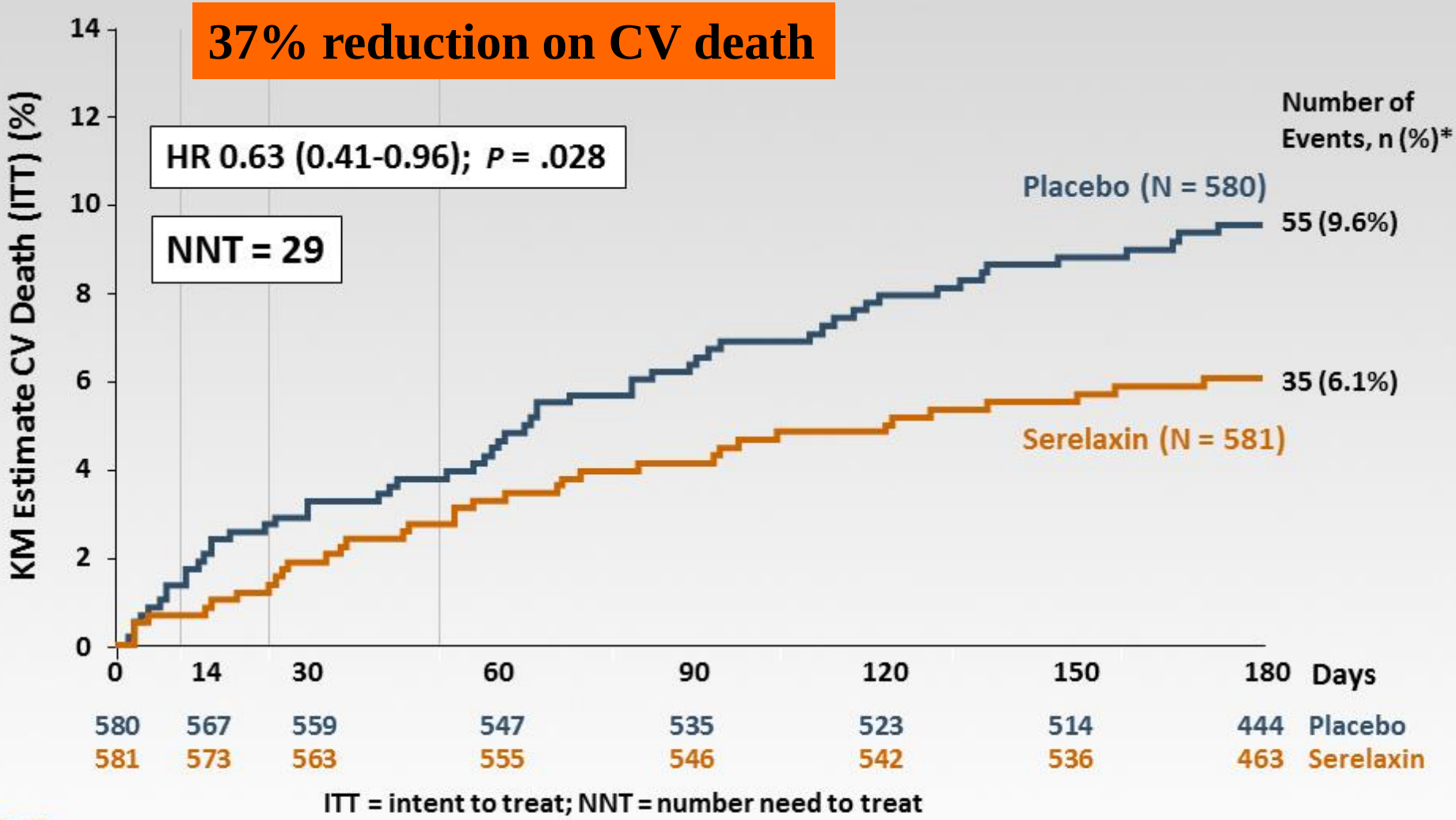
†P value by log rank test for serelaxin vs placebo; HR estimate by Cox model, HR < 1.0 favors serelaxin

Teerlink JR, et al. *Lancet.* 2012 Nov 6. [E

CV Death Through Day 180

NS up to day 60

37% reduction on CV death



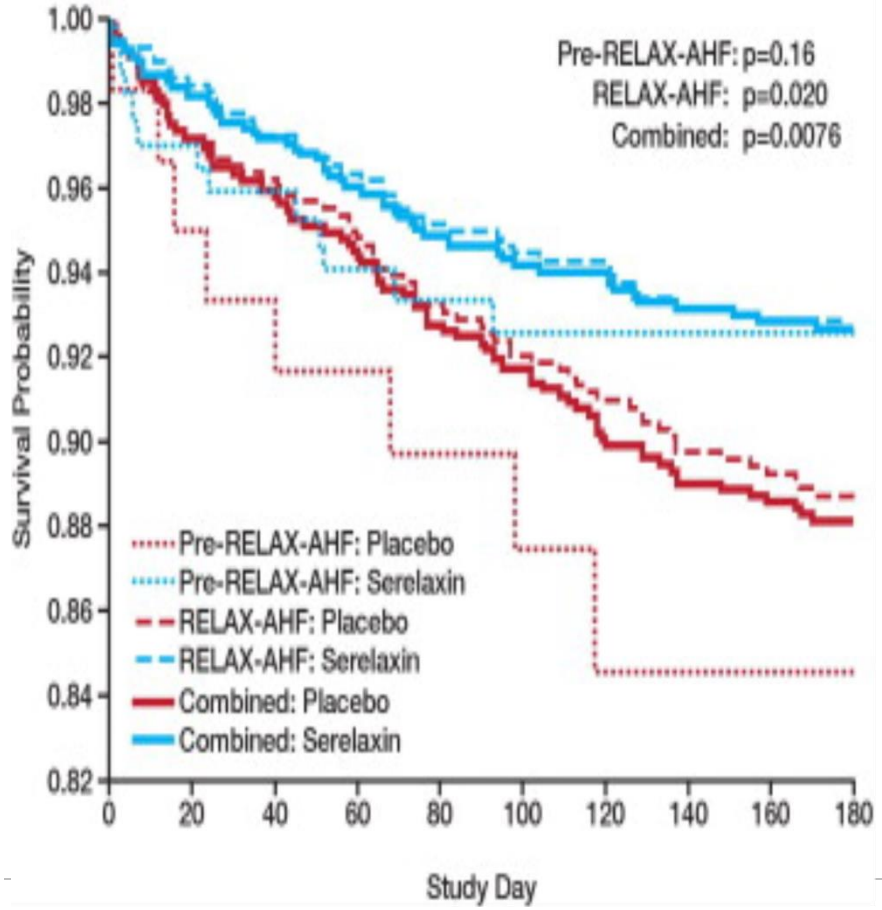
ITT = intent to treat; NNT = number need to treat

Heart failure

From Teerlink JR, et al. *Lancet*. 2012 Nov 6. [

: Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program: Correlation With Outcomes

P=0,0076



Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and combined studies : 1395 pts

The combined results represent stratified Kaplan-Meier estimates.

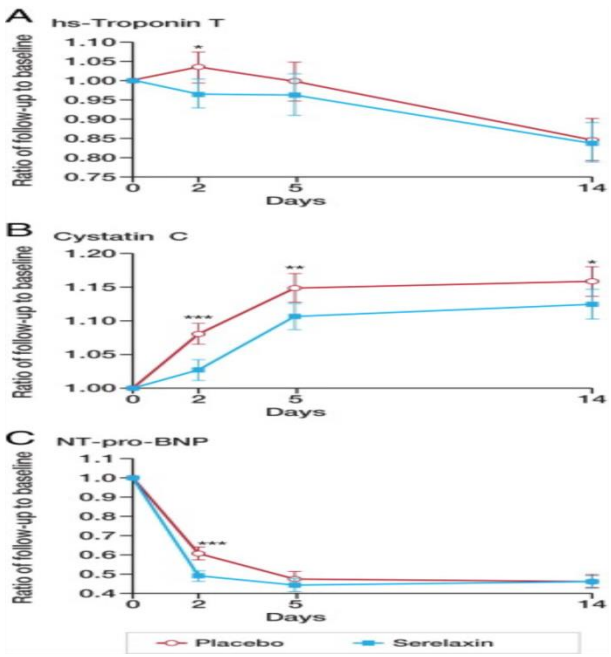
Survival curves began to separate after day 5 onward through day 180 (p = 0,0076)

NNT to save one life is 24.

Marco Metra et al. JACC 2013:196-206

From: Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program: Correlation With Outcomes

J Am Coll Cariol. 2013;61(2):196-206. doi:10.1016/j.jacc.2012.11.005



- Serelaxin was associated with significantly lower creatinine compared to placebo in the first 5 days.
- Serelaxin pts had larger mean decrease in hepatic damage (AST and ALT)
- Serelaxin reduces markers of cardiac (hs-Troponin T) renal (Cystatin C and creatinine) damage and congestion (NT-proBNP). These results were associated with 6 months mortality

Figure Legend:

Biomarker Changes From Baseline in the Placebo and Serelaxin Groups

Changes from baseline to each study day in the Relaxin in Acute Heart Failure study in high-sensitivity (hs) troponin T (A), cystatin-C (B), and N-terminal pro–brain natriuretic peptide (NT-proBNP) (C). *p < 0.05, **p < 0.005, and ***p < 0.001 by repeated-measures analysis of variance with adjustment for baseline value.

Marco Metra et al. JACC 2013:196-206

Comments on findings of pre RELAX-AHF and RELAX-AHF

Both trials showed that serelaxin improved dyspnoea, while significantly preventing worsening of HF

The observed reduction in mortality seems to be consistent with the emerging and growing concept that **AHF is associated with damage in multiple systems and organs, and that PROTECTION from these harmful effects can have favorable impact on survival.** Serelaxin reduced cardiac, renal and liver damage during first days after admission and these beneficial effects may be related with increase survival. However, **further studies are required to future explore the effects of serelaxin**

serelaxin
RLX030

Addressing Acute Heart Failure

RELAX-AHF-2 (RLX030A2301)

A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

NOVARTIS

Team RELAX-AHF-2

(S. Cardiologia I, CHLN, E.P.E. , Director: António Nunes Diogo)

- **PI: Dulce Brito**
- **Co-I** (alphabetic order):
  - **Susana Martins**
  - **Mónica Pedro**
  - **Fausto Pinto**
  - **Teresa Rodrigues (ED)**
  - **Jacques Santos (ED)**
- **Study Coordinators:**
  - **Inês Cabrita**
  - **Francisca Figueiras**
- **Nurse Study:**
  - **Filipe Florindo**
- **Logistics:**
  - **Paula Irene Camacho**
- **Pharmacists:**
  - **Vanessa Côdea**
  - **Ana Lima**
  - **Ana Sofia Cardoso**

NOVARTIS

Purpose

- To evaluate the efficacy, safety and tolerability of IV infusion of 30 ug/kg/day serelaxin administered by body weight category for 48 hours, when added to standard therapy, in ≈ 6,375 acute heart failure (AHF) patients.

- Efficacy will be determined based on the relative reduction in CV death and other clinical outcomes through a follow-up period of 180 days, as compared to placebo

- Data from this study is intended to replicate the reduction in mortality in AHF patients observed in the RELAX AHF trial

NOVARTIS

Study population

- Male and female patients (≥18 years old) admitted to the hospital for AHF, with systolic BP ≥125 mmHg, and mild-to-moderate renal impairment

NOVARTIS

Objectives

Primary objective

- To demonstrate that **serelaxin is superior to placebo** in **reducing CV death** in AHF patients during a follow-up period of **180 days**

Key secondary objectives

- **To demonstrate that serelaxin is superior to placebo in:**
  - reducing **all-cause mortality** during a follow-up period of 180 days
  - reducing **worsening heart failure** through Day 5
  - reducing the **length of total hospital stay** during the index AHF hospitalization
  - reducing the **composite endpoint of CV death or rehospitalization** due to heart failure/renal failure, during a follow-up period of 180 days

NOVARTIS

Inclusion criteria

1. **Male or female ≥18 years of age, with body weight ≤160 kg**
2. **Hospitalized for AHF;** AHF is defined as including **all** of the following measured at any time between presentation (including the emergency department) and the end of screening:
   - **Dyspnea at rest or with minimal exertion**
   - **Pulmonary congestion on chest radiograph**
   - **BNP ≥350 pg/mL or NT-proBNP ≥1,400 pg/mL**

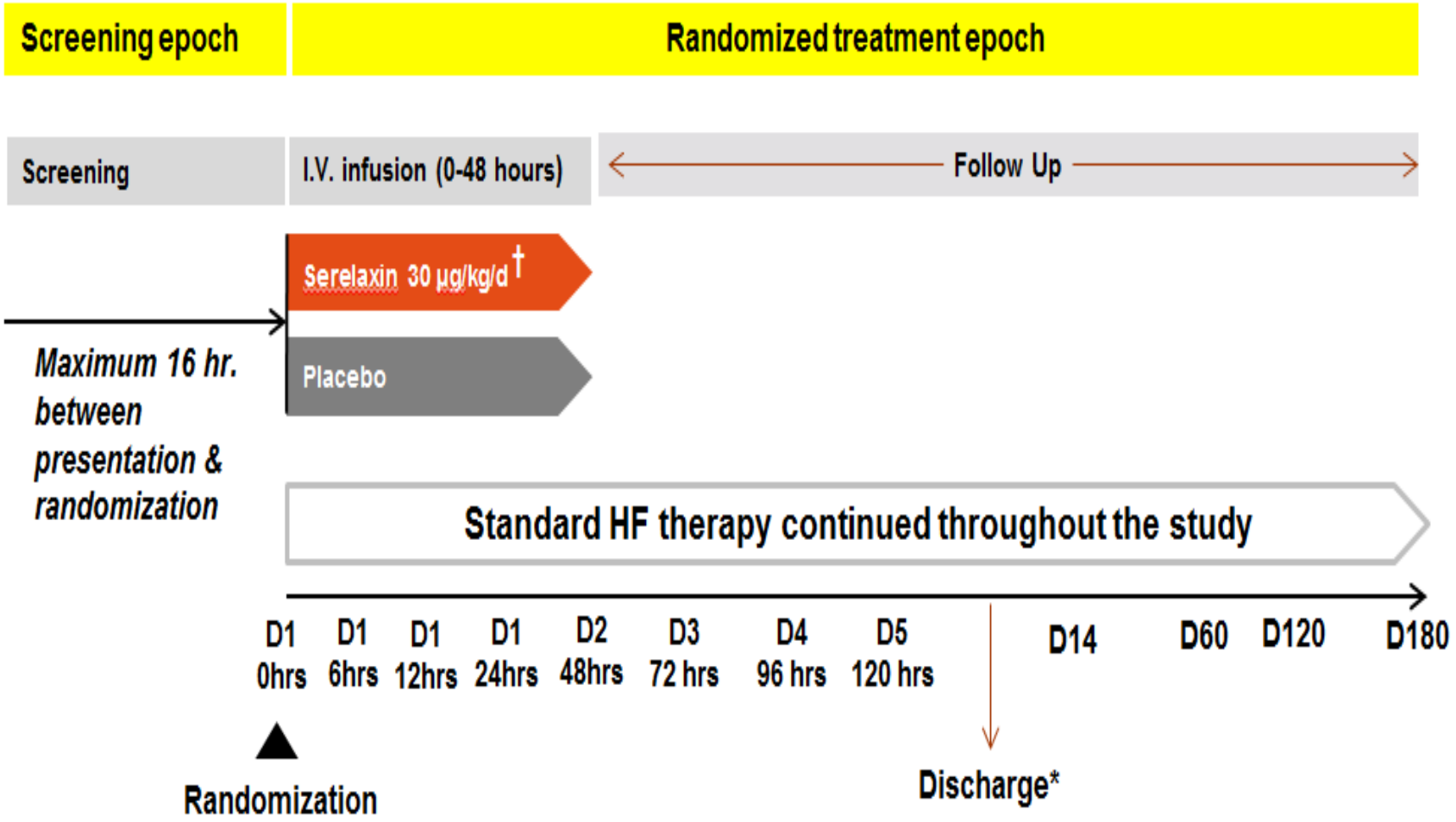
3. Systolic BP ≥125 mmHg at the start and at the end of screening

- 4. **Able to be randomized within 16 hours from presentation to the hospital**, including the emergency department
- 5. **Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation** (this includes outpatient clinic, ambulance, or hospital including emergency department) **and the start of screening for the study** for the treatment of the current acute HF episode.
- 6. **eGFR between presentation and randomization of ≥ 25 and ≤75mL/min/1.73m^2,** calculated using the sMDRD equation

NOVARTIS

Study design

Randomized, placebo-controlled study in a selected AHF patient population



*** Weight-range based dosing regimen for serelaxin and matching placebo**

NOVARTIS

The "ideal" RELAXIN patient should -

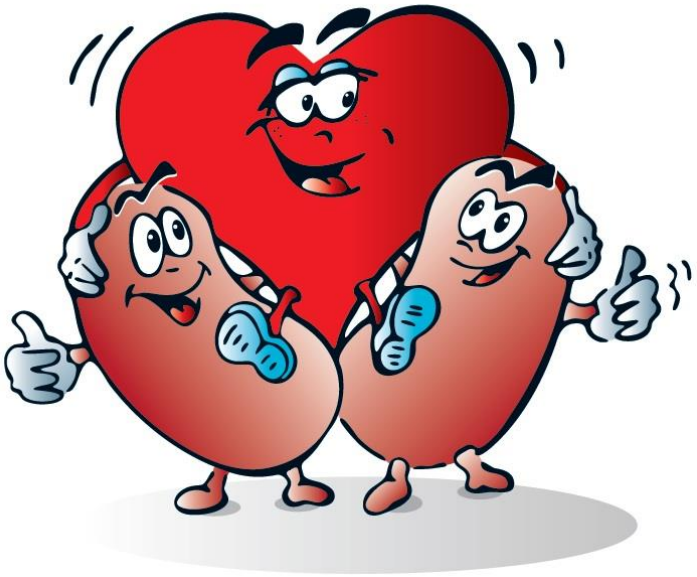
- Be admitted for AHF as manifested by worsening symptoms and signs and high BNP/NT-proBNP
- Be likely to benefit from Serelaxin clear congestion, clear renal impairment.
- Have no treatable cause for AHF such as arrhythmia, ischemia, pulmonary disease, pneumonia or sepsis or PE or severe primary valvular disease
- Should not be at risk for AEs – Sys BP >= 125 mmHg and especially > 100 mmHg and no end stage renal failure

NOVARTIS

In patients with heart failure, serelaxin…

- **Unloads the heart**
- **Unloads the kidney and improves perfusion**

RELAX-AHF-2



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Conclusions

- AHF is a complex syndrome, multiple physiopathological mechanisms, different clinical presentations / different diseases. Multiple effects of vasodilator therapy
- Classical vasodilators shown to be benefical in AHF. However, this agents have never been tested in prospective well-powered studies.
- We remain with:

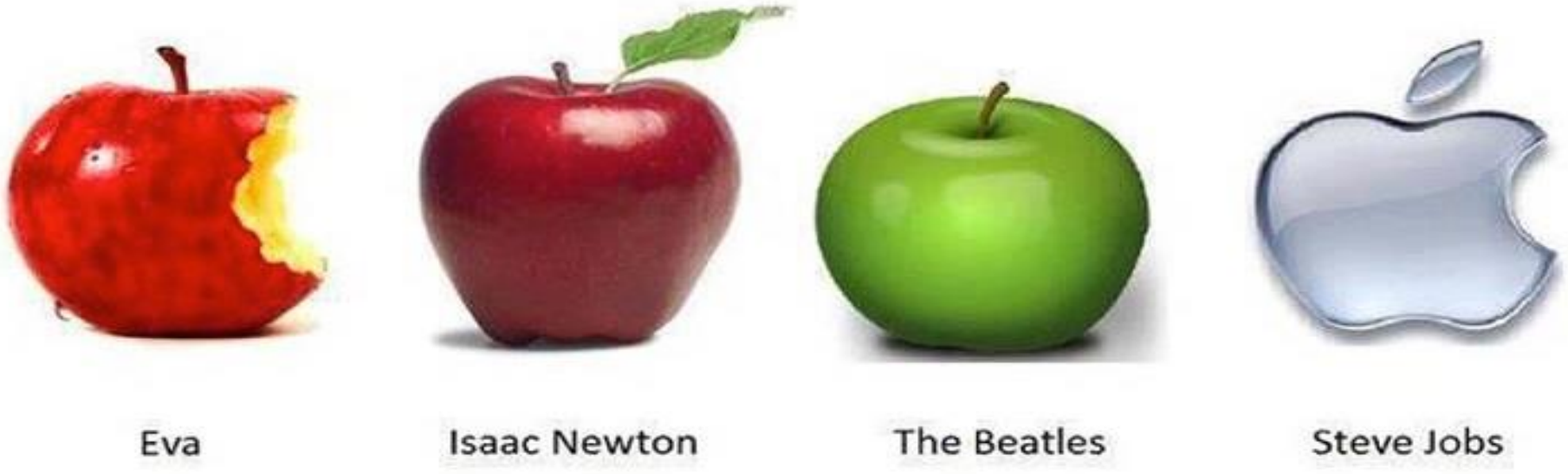
  Nitrates (class II a, Level B)

  Nitroprusside in selected patients

  Hope for serelaxin

  Waiting for more results with clevidipine (arterial vasodilatador)

waiting for “apples” that can change AHF world???



Exclusion criteria (1)

1. Dyspnea primarily due to non-cardiac causes

2. Temperature >38.5° C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment

3. Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment (elevated troponin alone, *per se* does not make a diagnosis of ACS!)

4. AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate <45 beats per minute, or atrial fibrillation/flutter with sustained ventricular response of >130 beats per minute

5. Patients with severe renal impairment defined as pre-randomization eGFR <25 mL/min/1.73m2 and/or those receiving current or planned dialysis or ultrafiltration

6. Patients with Hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding

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Exclusion criteria (2)

7. Significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm2 or mean gradient >50 mmHg on prior or current echocardiogram), and severe mitral stenosis

8. Current (within 2 hours prior to screening) or planned (through the completion of study drug infusion) treatment with any IV vasoactive therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (ETI, MV, IABP, VAD, HD, UF or UF) with the exception of IV furosemide (or equivalent), or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP >150 mmHg at screening.

9. Any major solid organ transplant recipient or planned/ anticipated organ transplant within 1 year

10. Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 30 days prior to screening

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Exclusion criteria (3)

11. History of malignancy of any organ system, within the past year with a life expectancy less than 1 year

12. Use of other investigational drugs within 30 days prior to screening

13. History of hypersensitivity to serelaxin

14. History of participating in serelaxin clinical studies

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