Il trattamento dello Scompenso Cardiaco in Emergenza Urgenza: sperimentazione con un farmaco innovativo

NAPOLI 20_11_2016

x congresso nazionale

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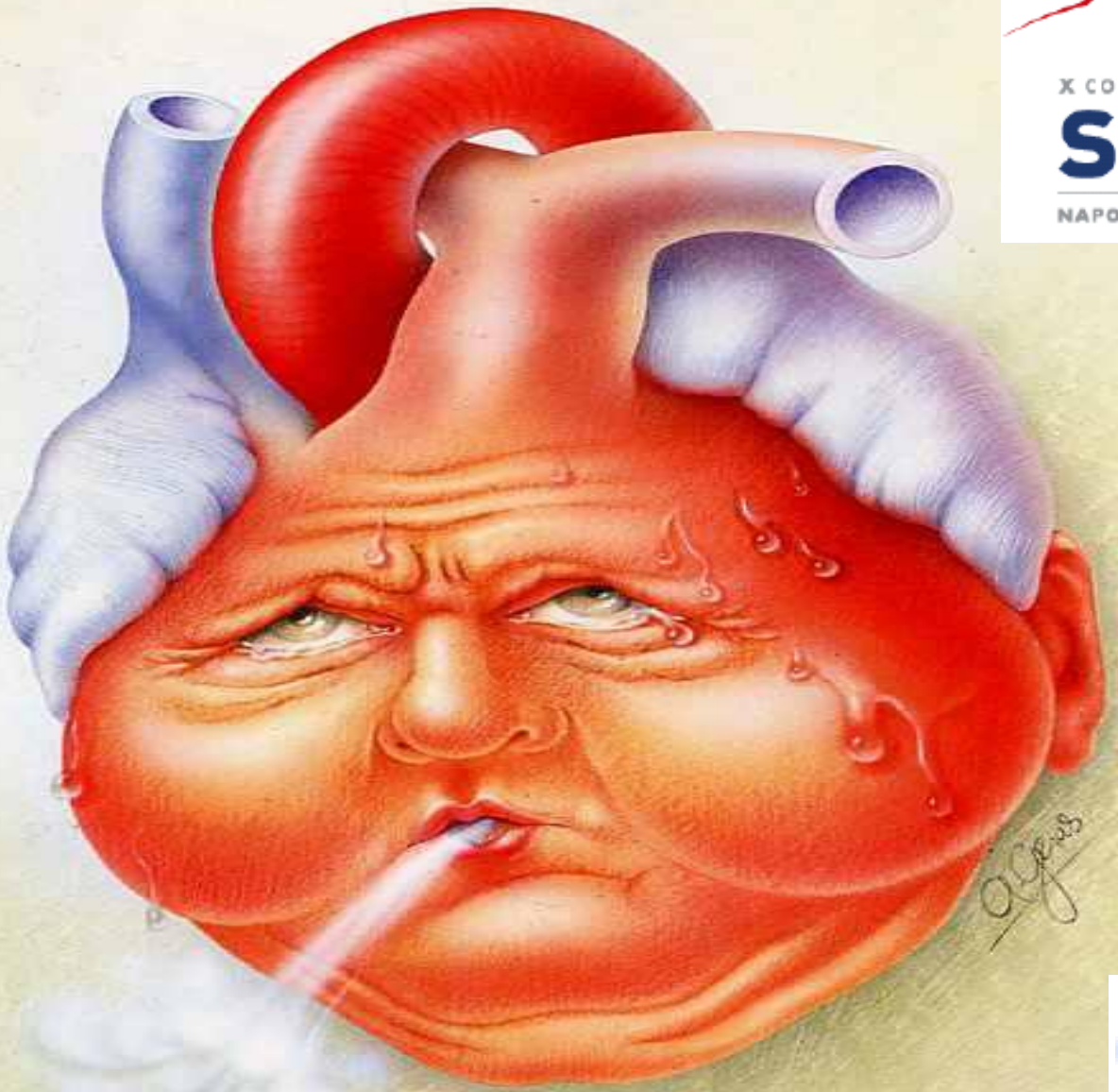
NAPOLI 18-20 NOVEMBRE 2016

x congresso nazionale
simeu
NAPOLI 18-20 NOVEMBRE 2016



Enzo Natale
SIMEU Calabria

DEFINIZIONE/ACC-AHA

"LO SCOMPENSO CARDIACO É UNA SINDROME CLINICA COMPLESSA

che può conseguire ad una qualsiasi

ANOMALIA STRUTTURALE

O

ANOMALIA FUNZIONALE CARDIACA IN GRADO DI ALTERARE LA CAPACITÁ DI RIEMPIMENTO O DI EIEZIONE DEI VENTRICOLI

caratterizzata da

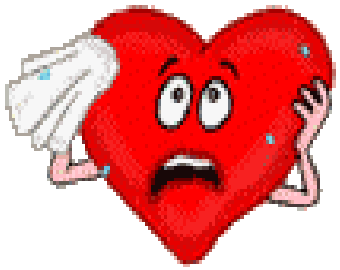
-SINTOMI SPECIFICI ALL'ANAMNESI (DISPNEA E AFFATICAMENTO)

e da

SEGNI SPECIFICI ALL'ESAME OBIETTIVO (RANTOLI, EDEMA PERIFERICO)"

ACC/AHA Practice Guidelines 2005

Lo scompenso cardiaco (HF) può a buon diritto essere definito l'epidemia del 21° secolo.



la principale causa di ricovero ospedaliero nel paziente di età ≥65 anni, assorbe oltre i due terzi dei costi diretti legati alla sindrome e rappresenta il 3-5% della spesa sanitaria totale dei paesi occidentali.

Lo Scompenso Cardiaco Costituisce un Onere Consistente per la Società

Dati Nazionali

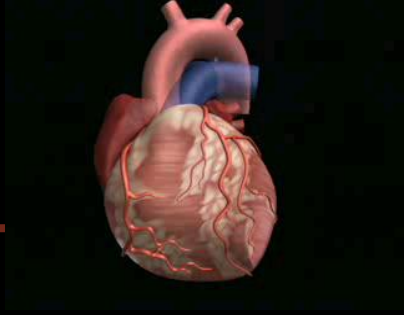
- Prevalenza: > 600.000 pazienti
- Incidenza: 87.000 nuovi casi/anno
- Ricoveri 2013: 190.340 (DRG 127)
- Giornate di degenza 2013: 1.704.386 (DRG 127)

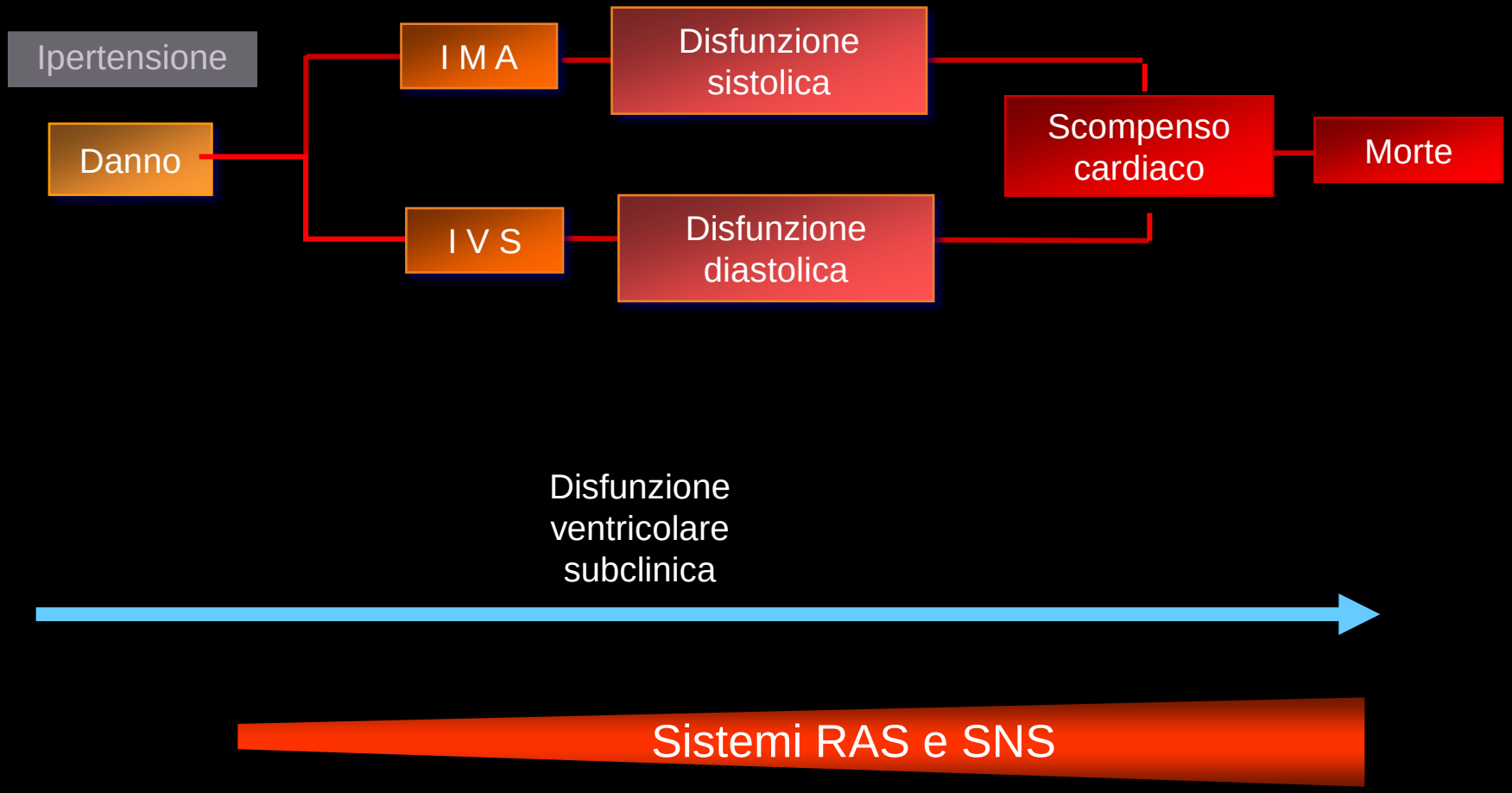
I pazienti ricoverati per scompenso cardiaco sono, infatti, aumentati quasi dell'8% negli ultimi 4 anni.

Ministero della Salute. Clinical Evidence: una sintesi delle migliori prove di efficacia. Ed Italiana Milano; Zadig, 2013

http://www.ministerosalute.it/programmazione/sdo/ric_informazioni/default.jsp

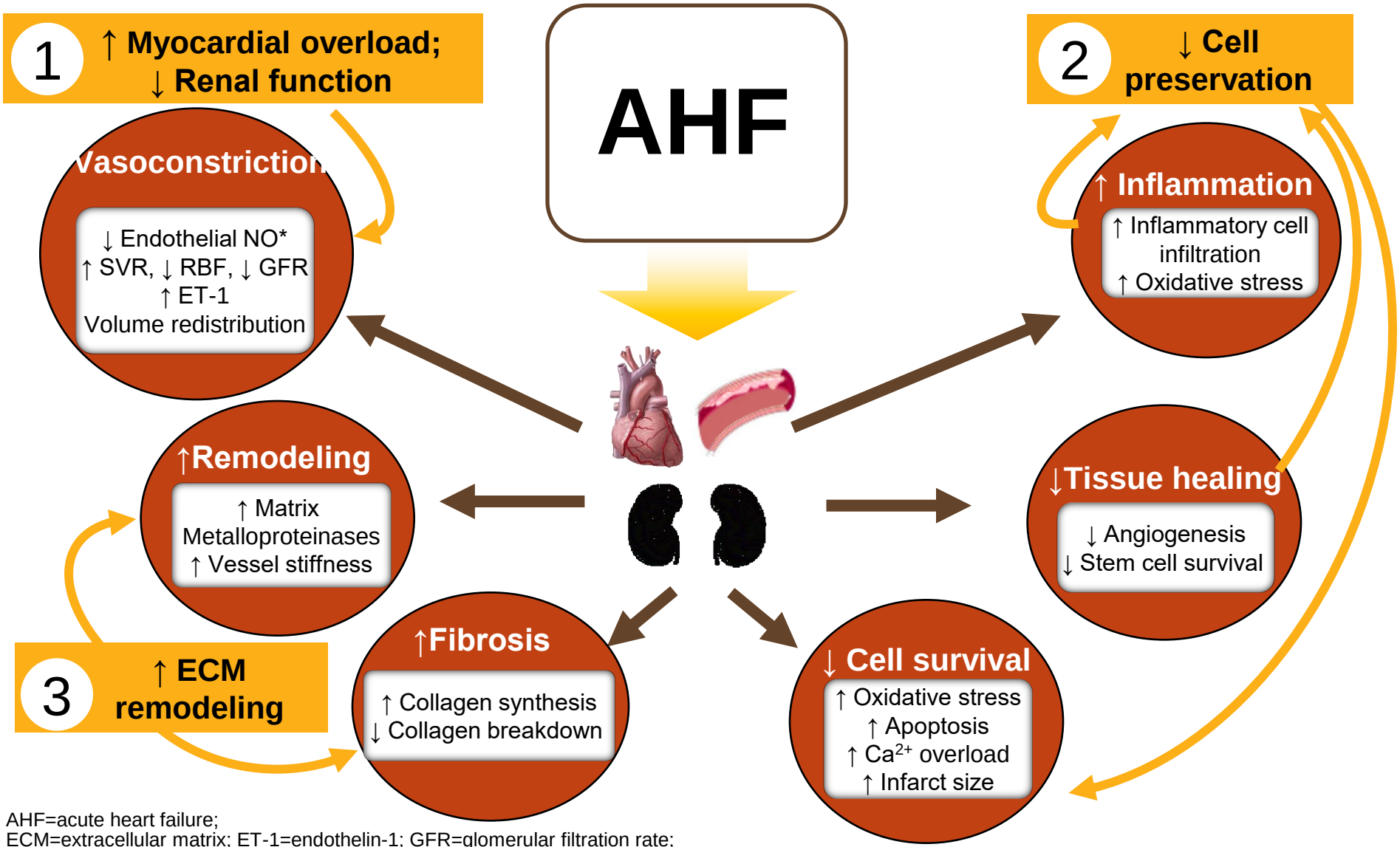
Continuum cardiovascolare





Dzau VJ, Gibbons GH. Endothelium and growth factors in vascular remodeling of hypertension. *Hypertension* 1991 suppl. 3): 115-21.

Pathophysiology of AHF

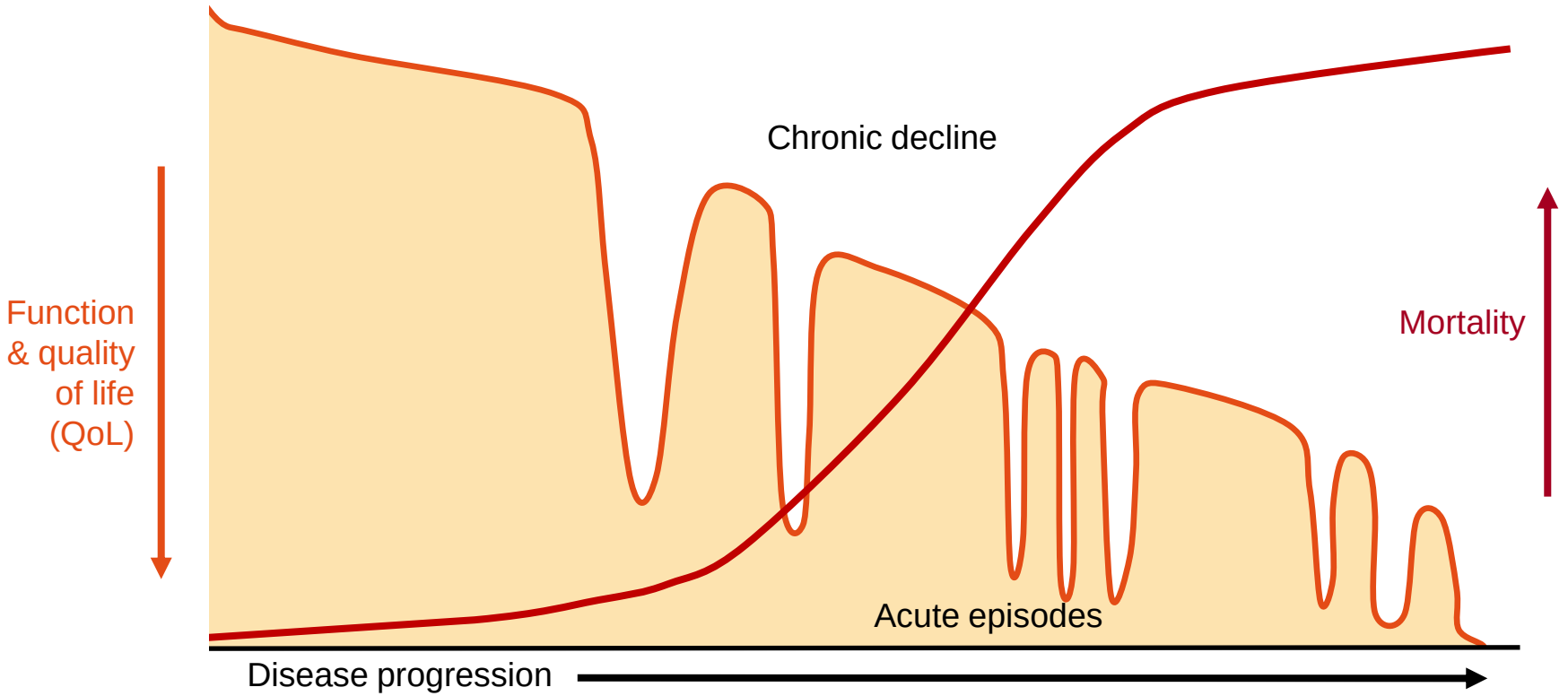


AHF=acute heart failure;
ECM=extracellular matrix; ET-1=endothelin-1; GFR=glomerular filtration rate;
NO=nitric oxide; RBF=renal blood flow; SVR-systemic vascular resistance

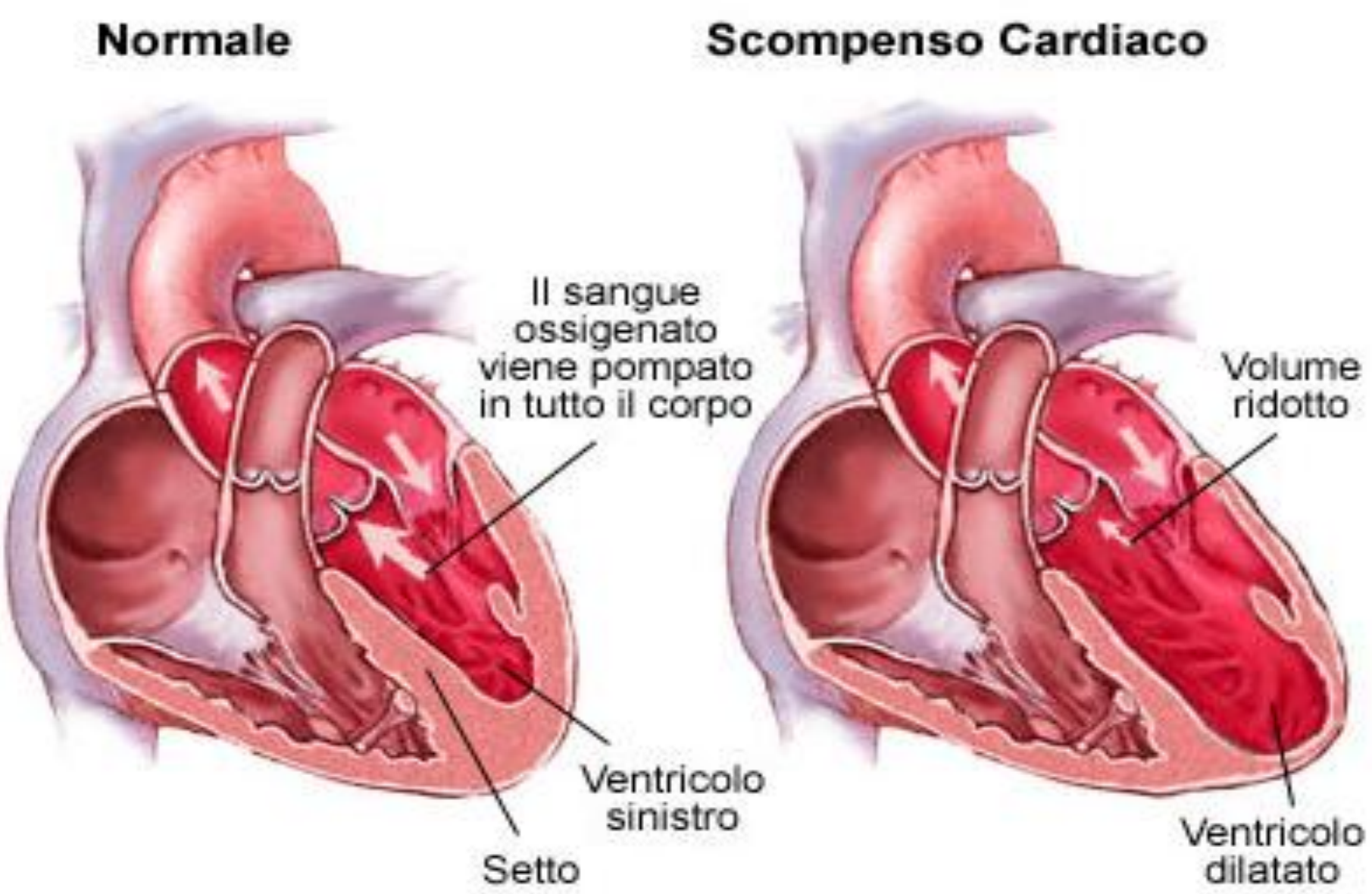
Adapted from Cotter Am Heart J 2008;155:9-18.

Heart failure is a progressive condition with high morbidity and mortality

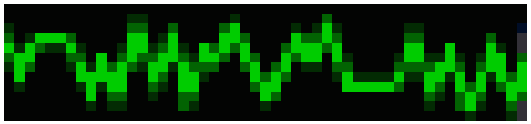
- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality
- With each acute event, myocardial injury may contribute to progressive LV dysfunction



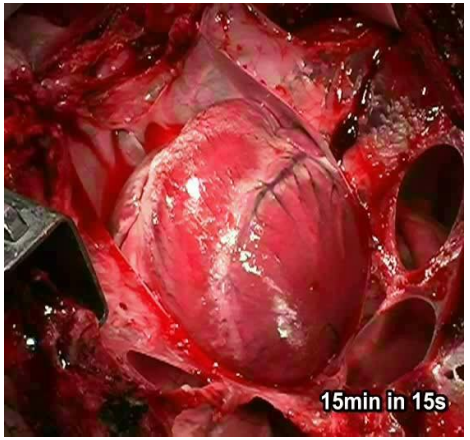
Gheorghiade et al. Am J Cardiol 2005;96:11G–17G;
Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73


Normale
Scompenso Cardiaco
Il sangue ossigenato viene pompato in tutto il corpo
Volume ridotto
Ventricolo sinistro
Setto
Ventricolo dilatato

Scompenso Cardiaco e Morte Improvvisa



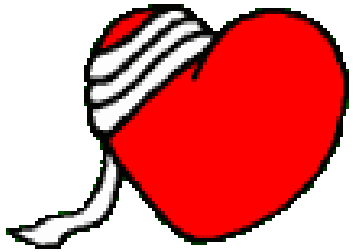
- Mortalità >45% entro 5 anni dalla diagnosi
- 50% della mortalità è improvvisa (TV/FV)
- La frequenza di morte cardiaca improvvisa tra i pazienti con scompenso cardiaco è **da 6 a 9 volte** più alta di quella tra la popolazione generale



American Heart Association. ***Heart and Stroke Statistical –2007 Update*****.**
Dallas, Tex.: American Heart Association: 2006.

INSUFFICIENZA CARDIACA ACUTA
(AHF)

L'invecchiamento della popolazione e il miglioramento della sopravvivenza da malattie cardiovascolari aumentano ulteriormente la prevalenza dell'HF. Gli operatori dell' **emergenza** svolgono un ruolo significativo nella gestione dei pazienti con



NUOVI ORIZZONTI E VECCHIE DIFFICOLTA’

NUOVI ORIZZONTI: CRITICITA’

L’eterogeneità clinica dello scompenso acuto è la principale causa

della mancanza di accordo sugli obiettivi del trattamento,

della poca chiarezza sulla gestione più appropriata di questi pazienti,

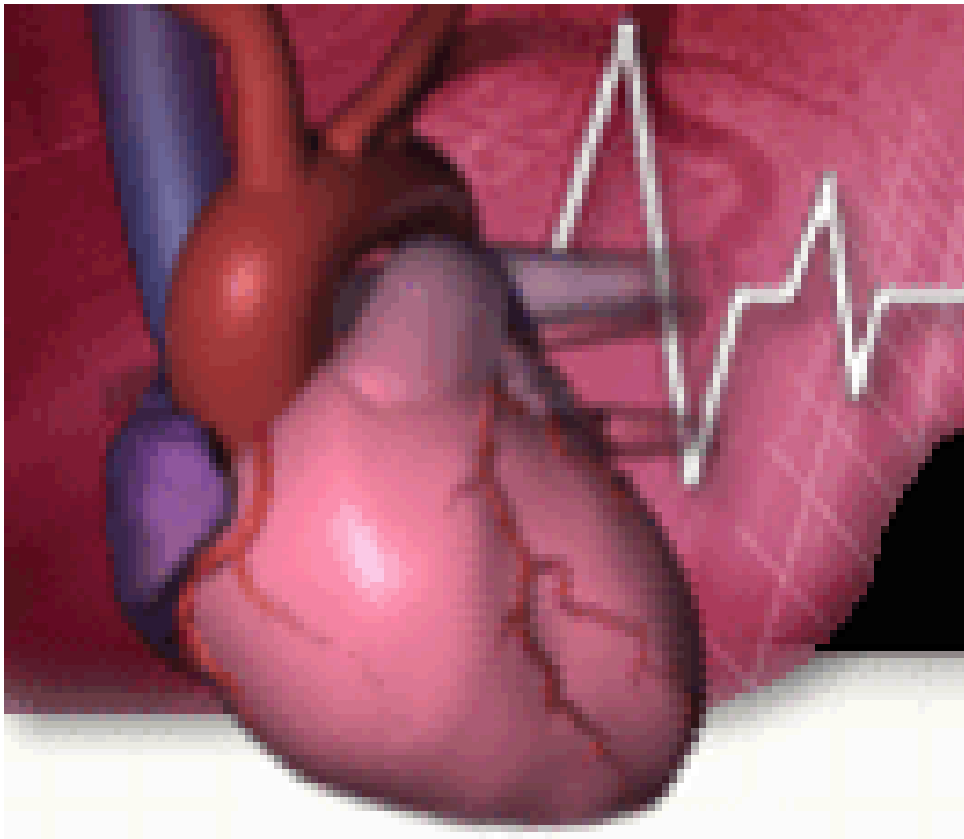
della difficoltà a raccogliere solide evidenze sui farmaci attualmente impiegati nella terapia di questa sindrome

NUOVI ORIZZONTI: CRITICITA’

Nonostante questi importanti progressi nella terapia farmacologica, la nostra comprensione dei meccanismi della malattia di base di HF da punti di vista epidemiologici, clinici, fisiopatologici, molecolari, genetiche resta incompleta.

Terapia dello scompenso cardiaco acuto

- 1 Ridurre l'iperventilazione
- 2 Ridurre il sovraccarico volumetrico ventricolare
- 3 Ridurre le resistenze periferiche
- 4 Migliorare l' ossigenazione
- 5 Controllare i problemi clinici associati

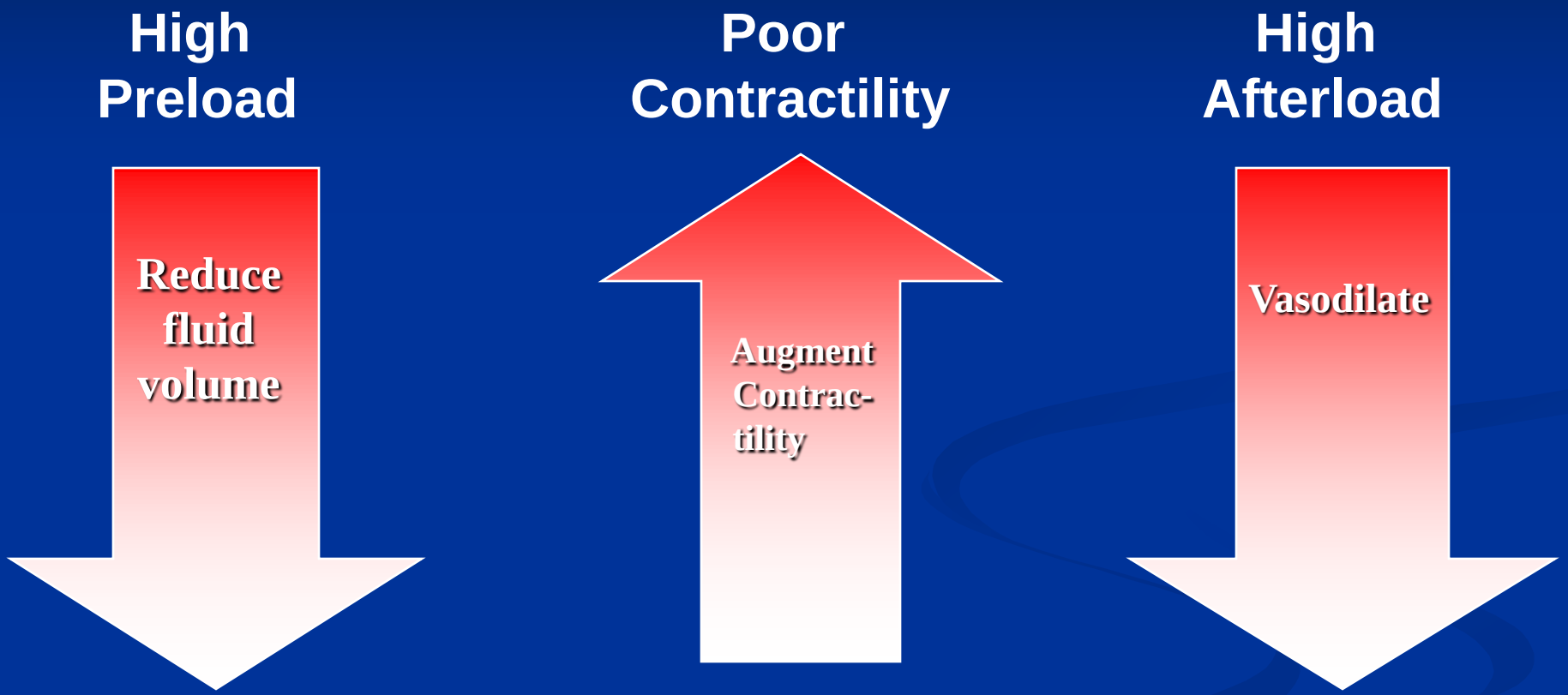


OBIETTIVI DEL TRATTAMENTO dell'insufficienza cardiaca acuta

- Stabilizzare il paziente
- Ripristinare le funzioni emodinamiche
- Migliorare la sopravvivenza

- Eliminare la causa
- Prevenire l'insorgenza e la progressione
- Migliorare sintomi e qualità di vita

Current Treatment of Acute Heart Failure



Principi di Trattamento dello Scompenso

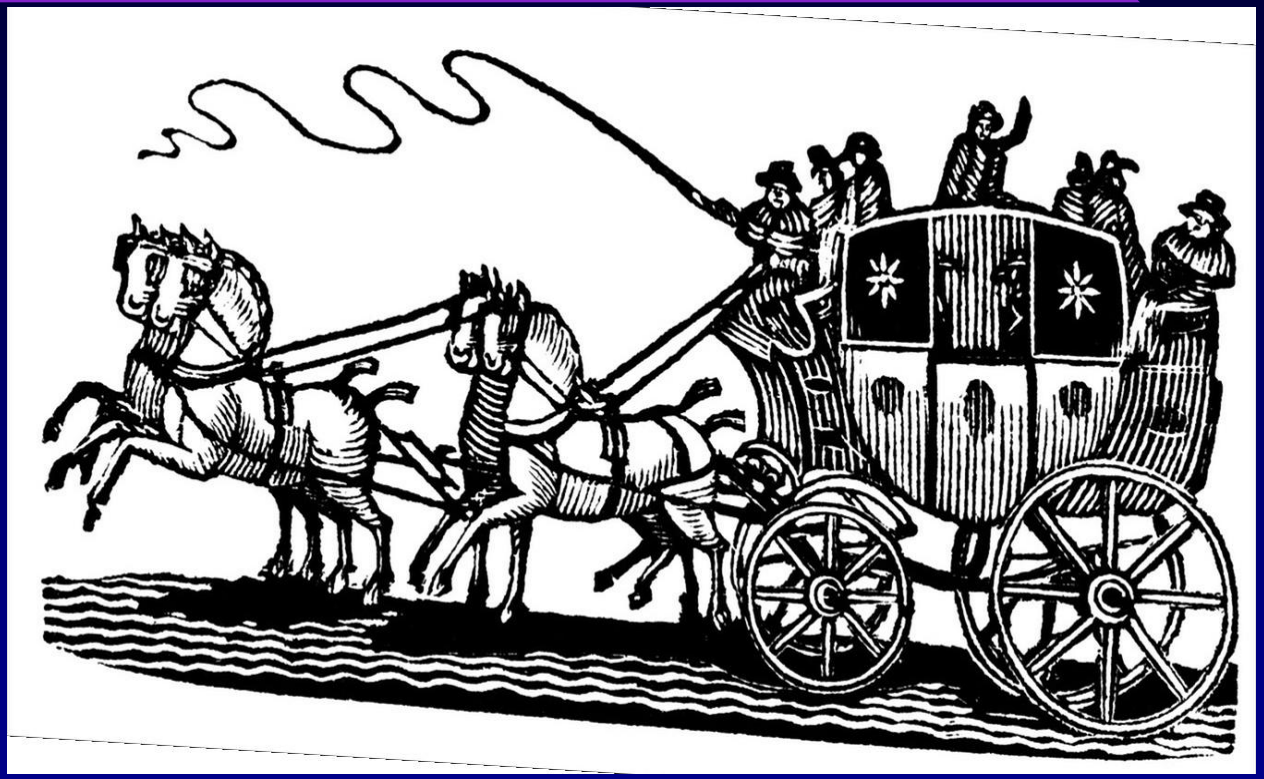
- Cavalli:
  - Cuore
- Salita:
  - Post-carico (pressione arteriosa)
- Persone a bordo:
  - Pre-carico (volemia)

Diuretici

Riduzione del lavoro cardiaco

Riduzione degli edemi, migliorano i sintomi: inutili nei pazienti asintomatici, cioè con disfunzione non scompenso

Inotropismo



Scompenso acuto/refrattario: trattamento ospedaliero, di solito farmaci in vena, per breve periodo.

NUOVI INOTROPI

Fra i nuovi inotropi con diverso meccanismo d'azione, il calcio-sensibilizzatore **levosimendan** aumenta la contrattilità miocardica ma non incrementa i livelli di calcio nel citosol; in studi clinici controllati, in pazienti con scompenso acuto ha documentato effetti emodinamici e **neurormonali favorevoli senza aumento della mortalità**.

21 Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol 2009; 53: 557-73.

Vasodilatatori

Riduzione del lavoro cardiaco
Marcata riduzione della mortalità, famiglia di farmaci obbligatoria

The evidence base for many commonly used AHF treatments is limited with no proven long-term benefits

Group	Medication	Class of recommendation	Level of evidence† (A–C)
Diuretics	IV loop diuretics	I	B
Vasodilators	IV nitrates	IIa	B
	Sodium nitroprusside	IIb	B
IV opiates	Morphine	IIa	C
Inotropes*		IIa or IIb	C

"The treatment of acute heart failure remains largely opinion-based with little good evidence to guide therapy"

"Intravenous nitrates—efficacy and safety still uncertain"

†A=data derived from multiple RCTs or meta-analyses; B=data derived from a single RCT or large non-randomized studies; C=consensus of opinion of the experts and/or small studies, retrospective studies, registries
*Inotropic agents are not recommended unless the patient has hypotension (systolic blood pressure [SBP] <85 mmHg), hypoperfusion or shock due to safety concerns
IV=intravenous; RCT=randomized controlled trial

Adapted from McMurray et al. Eur Heart J 2012;33:1787–847

E‘ fondamentale che medici e altri operatori dell’emergenza coinvolti nella gestione comprendano gli ultimi sviluppi **terapeutici**.

Inoltre, gli studi clinici devono essere condotti in il DE al fine di migliorare la base di conoscenze e guidare la **terapia iniziale ottimale** per AHF.

SEAN COLLINS, MD, MSc
Journal of Cardiac Failure Vol. 21 No. 1 2015

NUOVI ORIZZONTI: CRITICITA’

recentemente sono stati condotti studi randomizzati, controllati con placebo

Questo divario di conoscenze è particolarmente evidente per quanto riguarda **HF acuta scompensata**
e **HF con normale (conservata) FEVS**.
Per questi fenotipi clinici, nessun farmaco ha dimostrato di ridurre i tassi di eventi clinici a lungo termine in modo sostanziale.

NUOVI ORIZZONTI: CRITICITA’

la insufficienza cardiaca cosiddetta con **frazione di eiezione conservata** ha alti tassi di mortalità e morbilità.

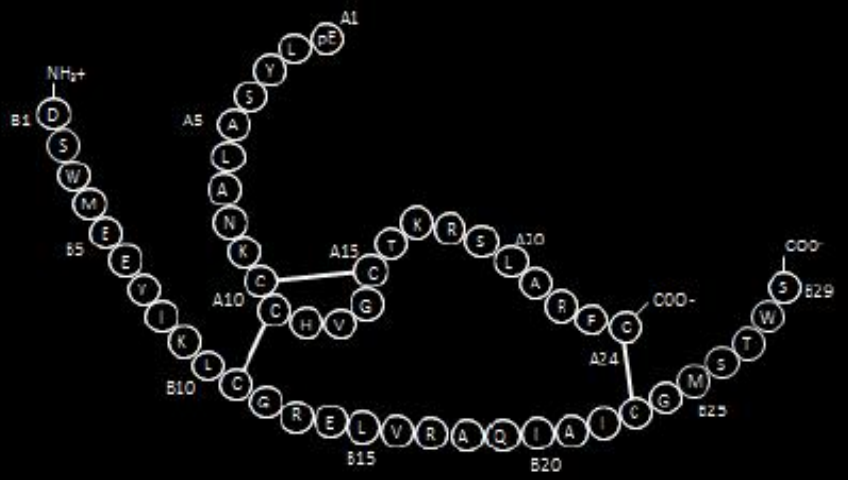
Quindi, sono assolutamente necessarie nuove terapie

Serelaxin nei pazienti con scompenso cardiaco acuto con frazione di eiezione ventricolare sinistra preservata

REVIEW ARTICLE
Serelaxin: A Novel Therapy for Acute Heart Failure with a Range of Hemodynamic and Non-Hemodynamic Actions
Javier Dı´ez
Published online: 4 March 2014
Am J Cardiovasc Drugs (2014) 14:275–285

SERELAXIN IS A RECOMBINANT FORM OF HUMAN RELAXIN-2

Structure of native and manufactured human relaxin-2



Structure of human relaxin-2:
53 amino acids (two chains connected by two disulphide bonds)

LGR=leucine-rich repeat containing G-protein-coupled receptor;
RXFP=relaxin family peptide

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

Serelaxin is a recombinant form of human relaxin-2

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

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

- Human relaxin-2 contributes to the adaptation of the renal and cardiovascular systems during pregnancy:

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

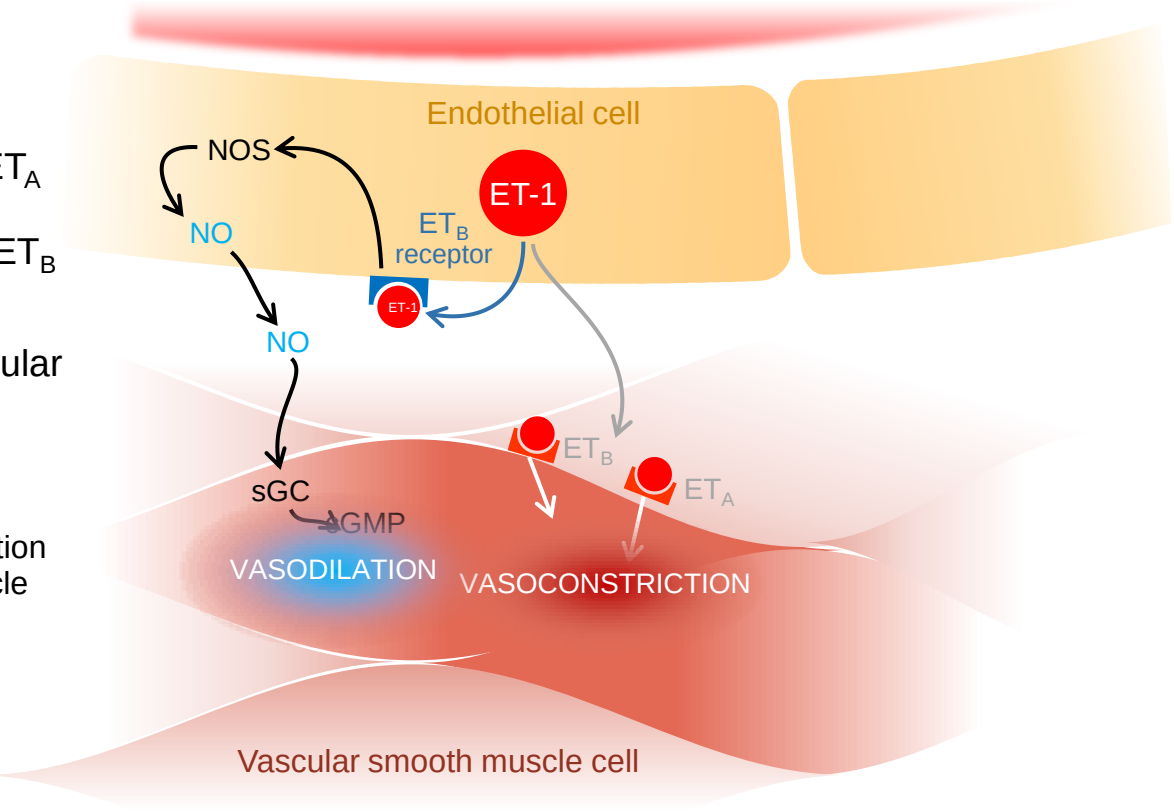
Pharmacologic use of relaxin may produce these beneficial effects in HF

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

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

The endothelin (ET) system has a key role in regulating vascular tone

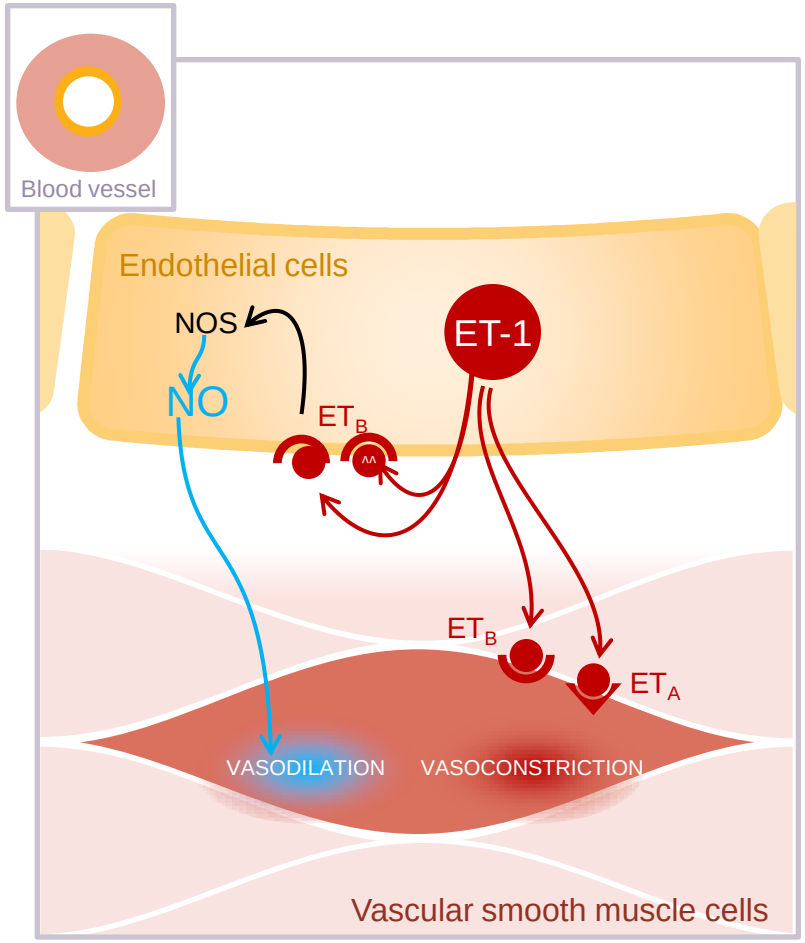
- The ET system is important in regulating normal vascular tone
- ET-1 is synthesized by vascular endothelial cells.[1] ET-1 stimulates ET_A and ET_B receptors, which reside on vascular smooth muscle cells and ET_B receptors on endothelial cells [2,3]
- The ET_A and ET_B receptors on vascular smooth muscle cells mediate vasoconstriction,[2] whereas the endothelial ET_B receptor mediates:
  - Increased systemic and renal vasodilation via relaxation of vascular smooth muscle cells through release of NO
  - Natriuresis/diuresis
  - Clearance of ET-1[4,5]
- Dysregulation of the ET system can lead to serious vascular disorders, such as HF



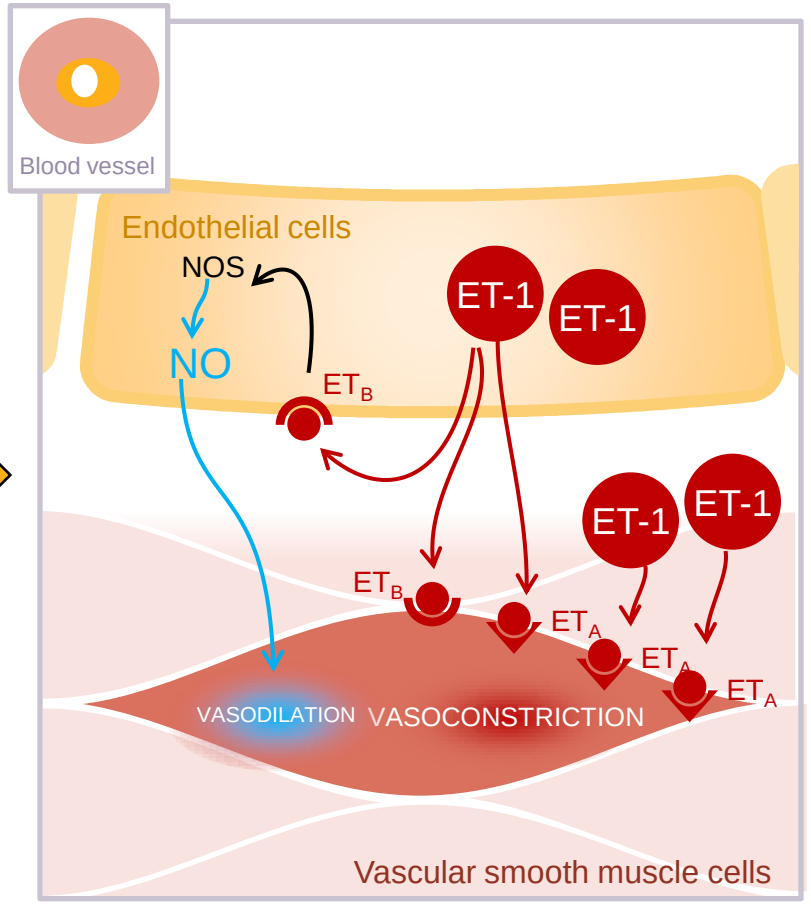
1. Teerlink et al. Circ Res 1994;74:105–14; 2. Schneider et al. Ann Rev Pharmacol Toxicol 2007;47:731–59;
3. Haynes et al. J Hypertens 1998;16:1081–98; 4.McMurray et al. Circulation 1992;85:1374–9;
5. Goddard et al. Circulation 2004;109:1186–93

In acute HF, expression of ET-1 and ET receptors is dysregulated

Under normal conditions, the ET system helps regulate basal vascular tone by mediating both vasodilation and vasoconstriction

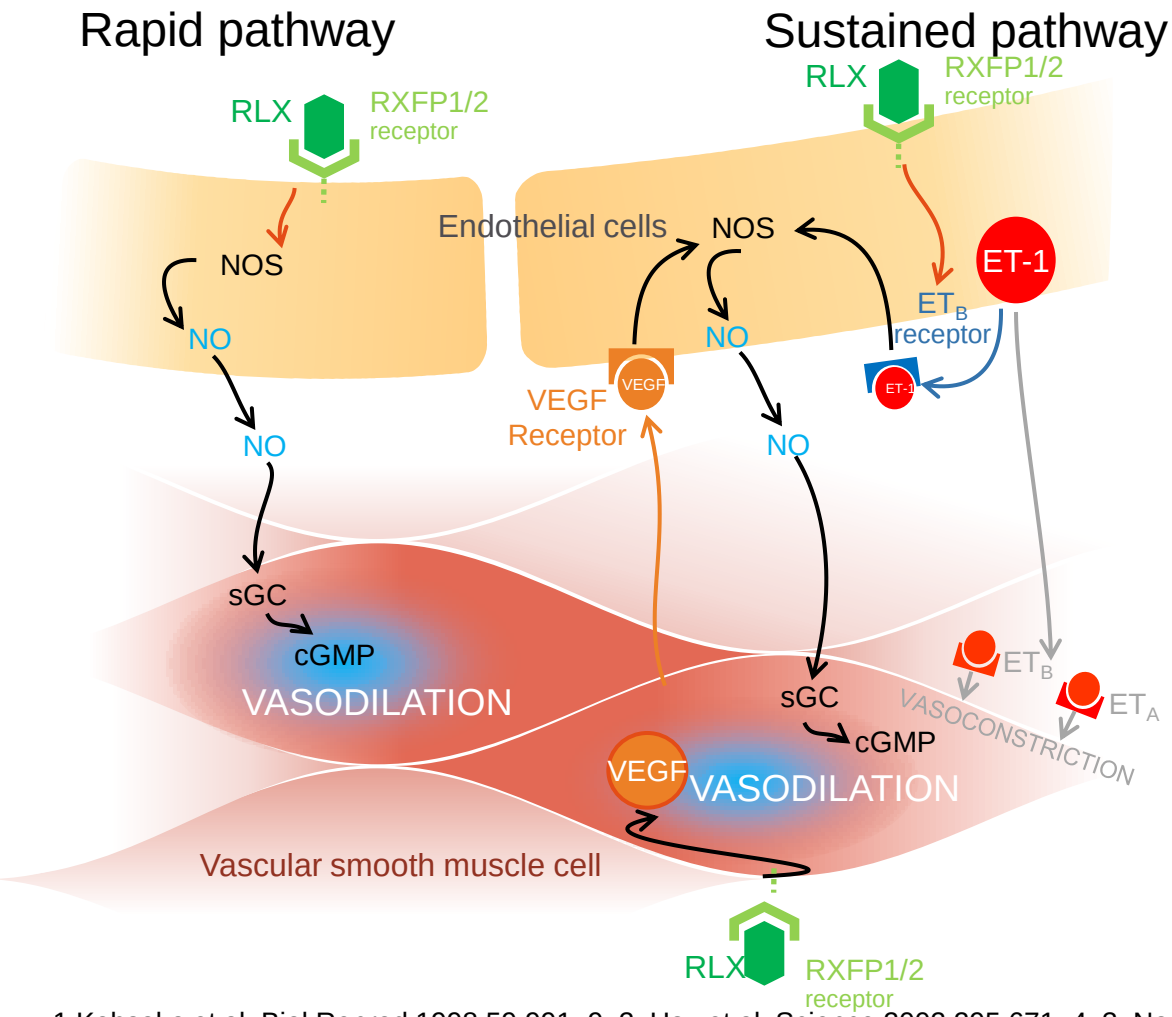


In HF, circulating ET-1 levels and the expression of ET_A receptors are increased, while ET_B receptors may be decreased, leading to systemic and renal vasoconstriction as well as salt and water retention



Schneider et al. Ann Rev Pharmacol Toxicol 2007;47:731–59; Haynes & Webb. J Hypertens 1998;16:1081–98; McMurray et al. Circulation 1992;85:1374–9; Asano et al. J Molec Cell Cardiol 2002;34:833–45; Sørensen, Madsen Am Physiol Soc 1994;166:F411–18; Vuurmans et al. Hypertension 2003;41:1253–58

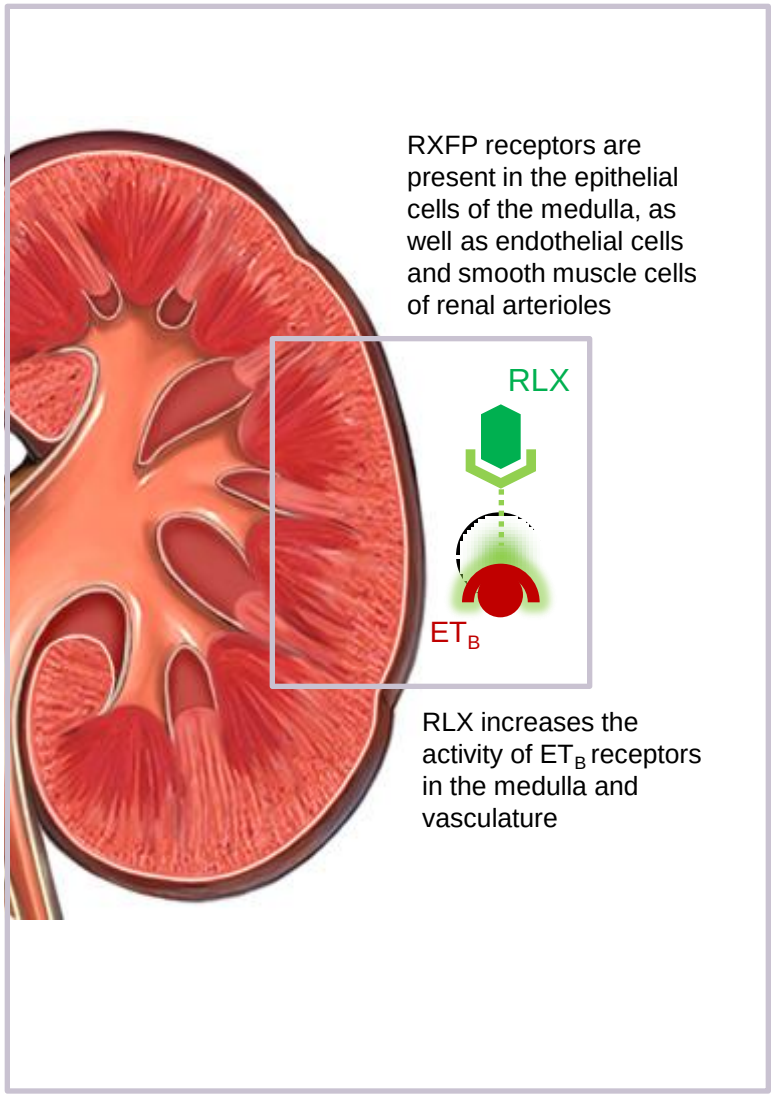
Serelaxin stimulates vasodilation via both rapid and sustained NO- mediated pathways

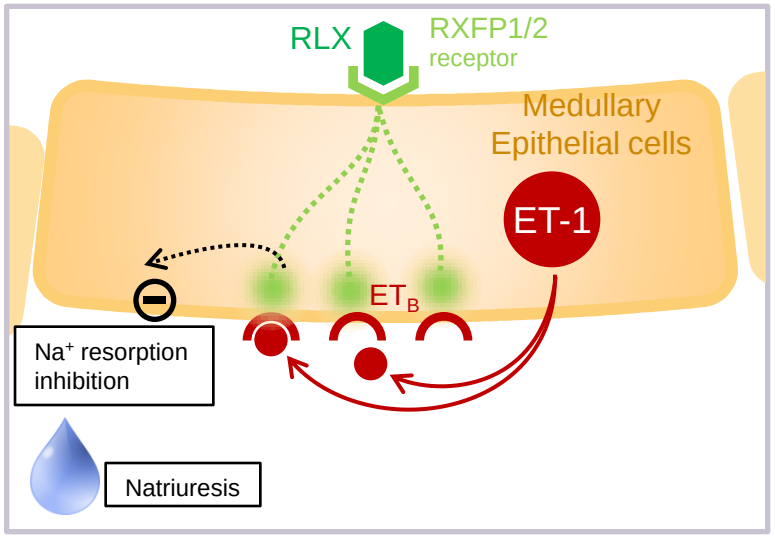


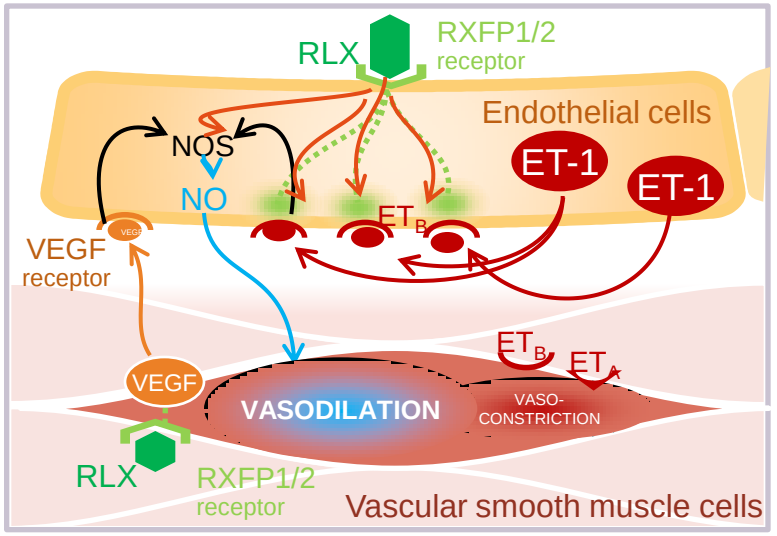
- Serelaxin binds to its receptors on vascular endothelial cells and smooth muscle cells in specific vascular beds[1–4]
- Within minutes of serelaxin treatment, vasodilation occurs via rapid phosphorylation of NOS and production of NO[5]
  - NO is released from the endothelial cells and acts on adjacent smooth muscle cells to cause rapid relaxation[6]
- Within hours of serelaxin treatment, a sustained NO-mediated vasodilation is induced[7] via increased endothelial ET$_B$ receptor[8,9] and VEGF (vascular endothelial growth factor) activity[10] and is maintained for up to 24 hours after treatment cessation[11]

1.Kohsaka et al. Biol Reprod 1998;59:991–9; 2. Hsu et al. Science 2002;295:671–4; 3. Novak et al. FASEB J 2006;20:2352–62;
4. Conrad, Shroff. Curr Hypertens Rep 2011;13:409–20; 5. McGuane et al. Endocrinology 2011;152:2786–96;
6. Schneider et al. Ann Rev Pharmacol Toxicol 2007;47:731–59; 7. Danielson,Conrad. J App Physiol 2003;95:1509–14;
8.Danielson et al. Am J Physiol 2000;279:R1298–304; 9. Dschietzig et al. Circ Res 2003;92:32–40;
10. McGuane et al. Hypertension 2011;57:1151–60; 11. Dschietzig et al. J Card Failure 2009;15:182–90

Renal effects: serelaxin increases renal blood flow and stimulates natriuresis/diuresis







1. Teichman et al. Curr Heart Fail Rep 2010;7:75–82
2. Schneider et al. Ann Rev Pharmacol Toxicol 2007;47:731–59

RELAX-AHF study

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

Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF study: patient reported change in dyspnea

	Placebo	Serelaxin	Treatment effect (95% CI)	p value
Change from baseline in dyspnoea VAS score (mm)				
Hour 6	8·9 (16·1)	10·2 (16·9)	1·3 (–0·6, 3·2)*	0·173†
Hour 12	13·2 (19·7)	15·2 (18·9)	1·9 (–0·3, 4·2)*	0·089†
Day 1	17·1 (25·0)	20·3 (21·7)	3·2 (0·5, 5·9)*	0·021†
Day 2	20·5 (28·9)	24·2 (23·9)	3·8 (0·7, 6·8)*	0·016†
Day 5	23·6 (33·3)	28·2 (27·8)	4·6 (1·1, 8·1)*	0·011†
Day 14	21·0 (36·5)	24·4 (32·4)	3·4 (–0·6, 7·4)*	0·093†
Dyspnoea VAS AUC (mm × h)				
Baseline to day 14	7131 (10112)	8442 (8443)	1311 (238, 2384)*	0·017†
Day 1 to day 5	2033 (2772)	2436 (2290)	403 (111, 696)*	0·007†
Day 1 to day 14	6855 (9846)	8122 (8199)	1266 (223, 2310)*	0·017†
Patients with markedly or moderately improved dyspnoea per Likert scale				
Hour 6	180 (31%)	205 (36%)	1·22 (0·95, 1·56)‡	0·113§
Hour 12	256 (45%)	288 (50%)	1·26 (1·00, 1·59)‡	0·051§
Day 1	362 (63%)	389 (68%)	1·24 (0·97, 1·58)‡	0·086§
Day 2	412 (72%)	438 (76%)	1·28 (0·98, 1·67)‡	0·064§
Day 5	446 (77%)	469 (82%)	1·31 (0·98, 1·75)‡	0·064§
Day 14	424 (73%)	433 (75%)	1·10 (0·84, 1·43)‡	0·479§

(Continues on next page)

Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF study: effect on cardiac and renal biomarkers

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 61, No. 2, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.11.005

EXPEDITED PUBLICATION

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

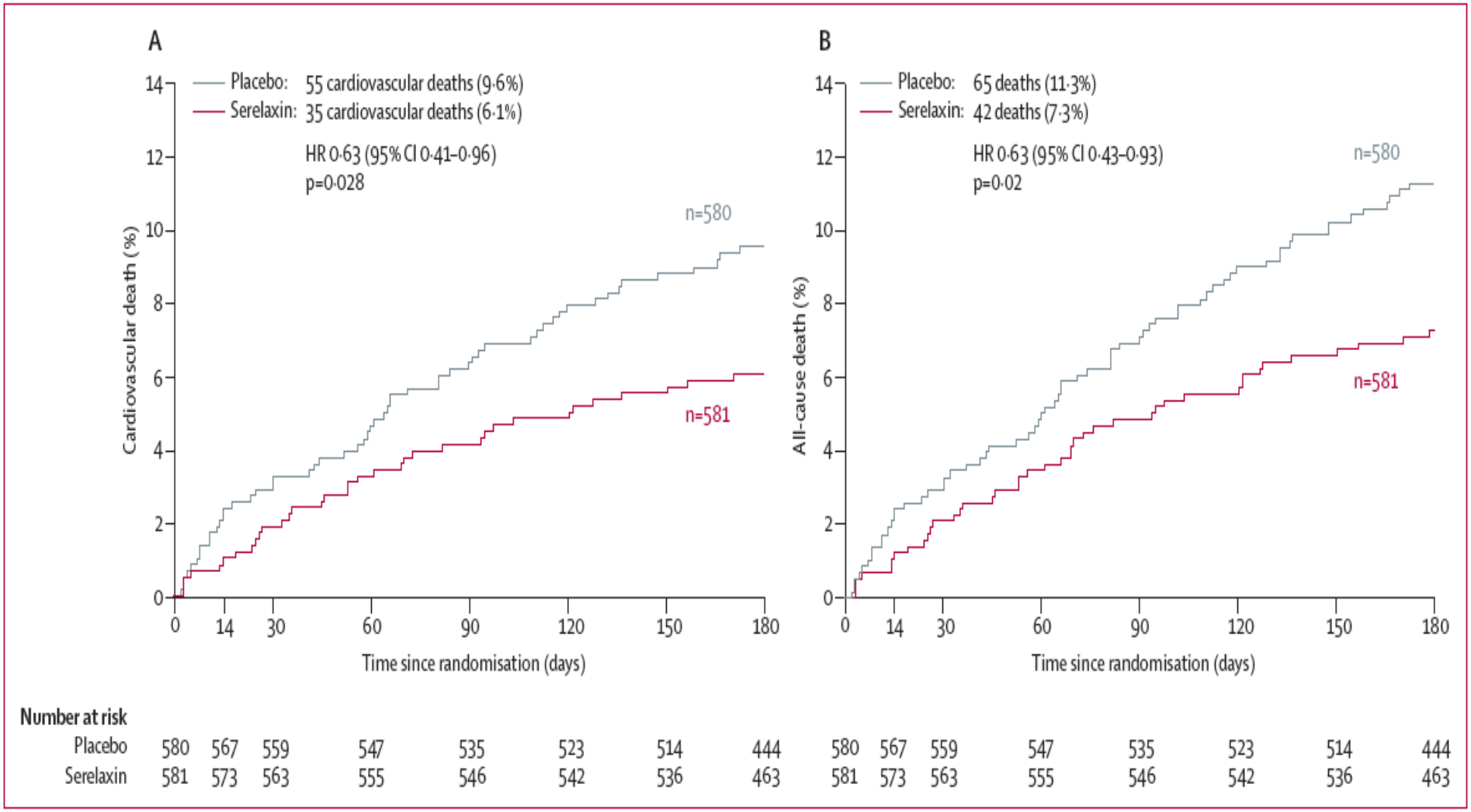
Correlation With Outcomes

Marco Metra, MD,* Gi... MD,† ... MHS,‡
Gerasimos Filippatos, MD,§ Barry H. Greenberg, MD,‖ Piotr Ponikowski, MD, PhD,¶
Elaine Unemori, PhD,# Adriaan A. Voors, MD, PhD,** Kirkwood F. Adams, Jr, MD,††
Maria I. Dorobantu, MD,‡‡ ... MD,§§ Guillaume Jondeau, MD, PhD,‖‖

Lo studio RELAX-AHF (Relaxin in Acute Heart Failure) ha valutato gli effetti della Serelaxina sui cambiamenti a breve termine nei marcatori di danno d'organo e di congestione, e li ha messi in relazione con la mortalità a 180 giorni nei pazienti con insufficienza cardiaca acuta.

Metra et al. J Am Coll Cardiol 2013;61:196–206

RELAX-AHF study: Kaplan-Meier analysis of death



Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF: incidence of AEs/SAEs

	Placebo (N=570) n (%)	Serelaxin (N=568) n (%)
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 AE (to Day 14)	**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 14)	27 (4.7)	28 (4.9)
Renal impairment-related AE (through Day 14)	51 (8.9)	32 (5.6)*
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.
Non-serious AEs were collected through Day 5, SAEs through Day 14

*p=0.03 vs placebo
AE=adverse event; RELAX-AHF=RELAXin in Acute Heart Failure; SAE=serious AE

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

Pre RELAX-AHF and RELAX-AHF studies

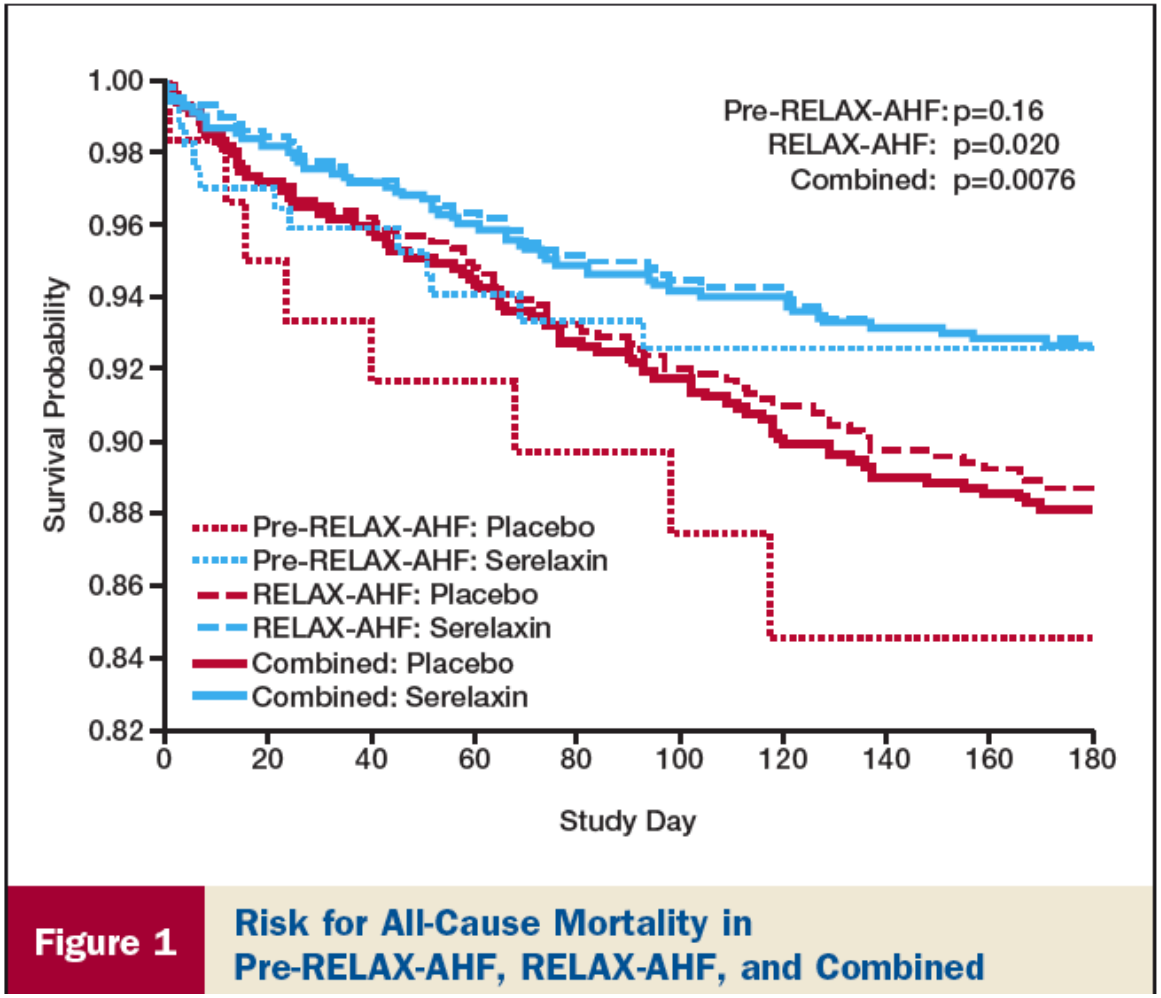
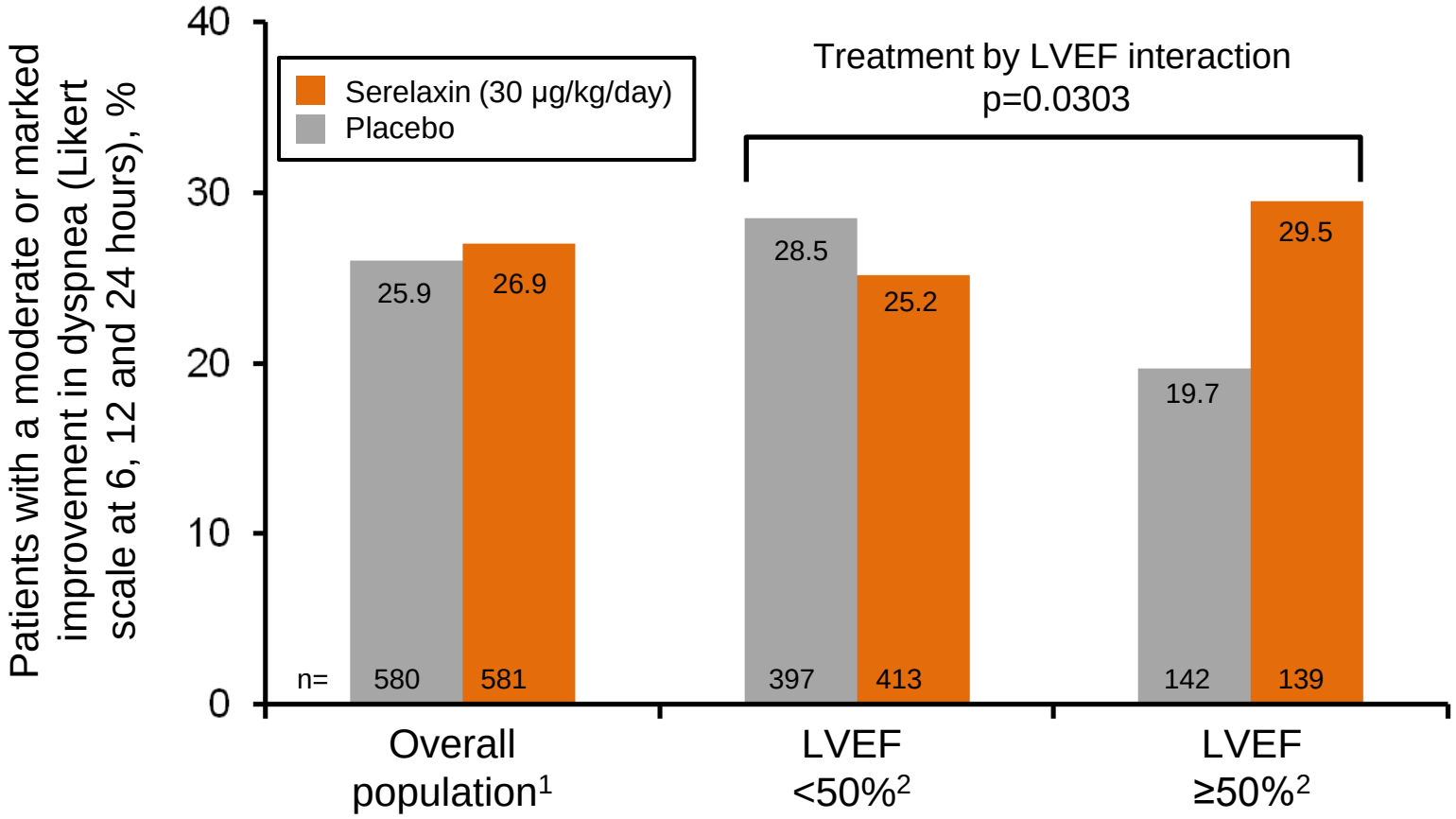


Figure 1 **Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and Combined**

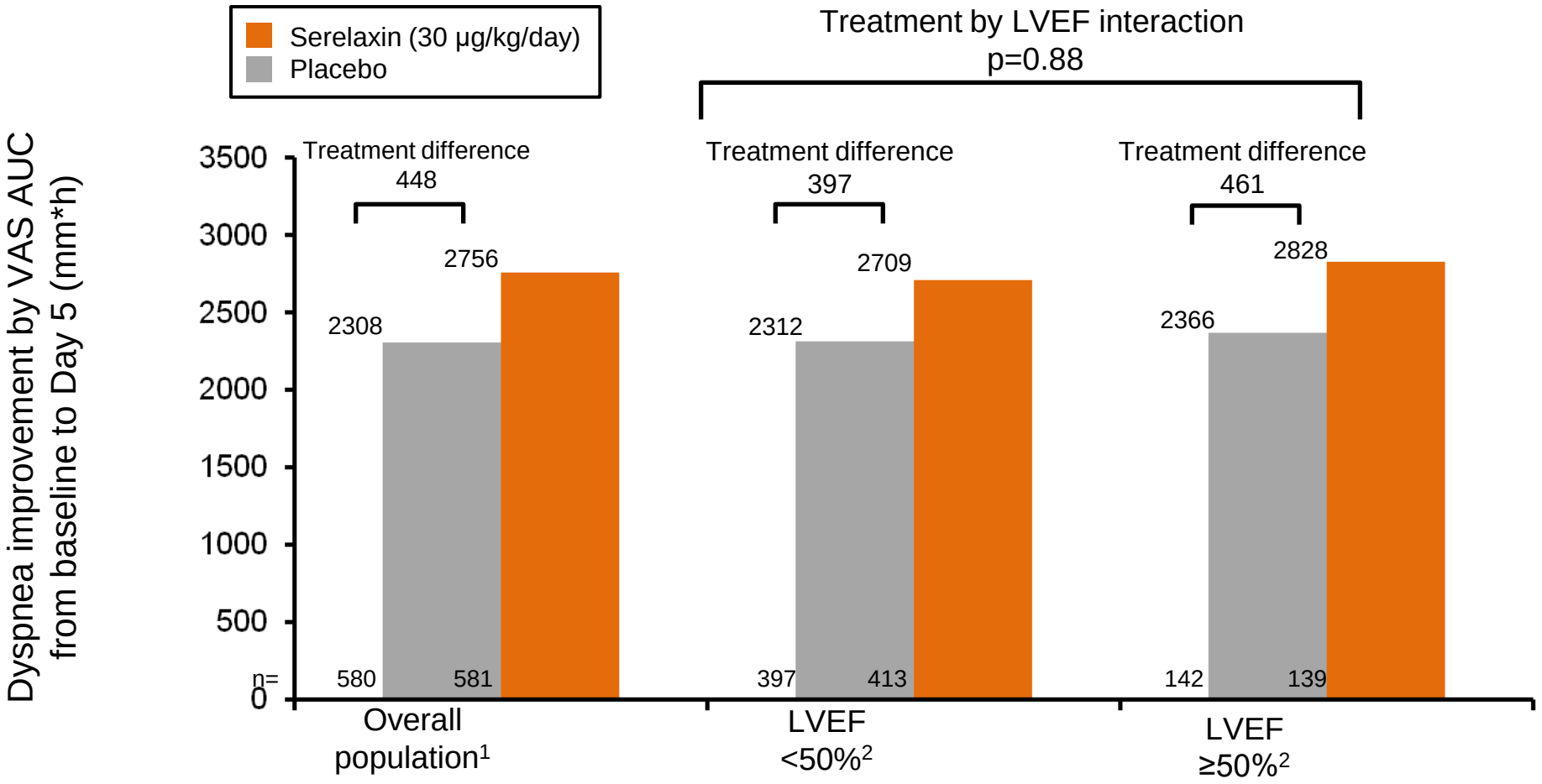
1. Teerlink et al. Lancet 2009;373:1429–39; 2. Teerlink et al. Lancet 2013;381:29–39;
3. Metra et al. J Am Coll Cardiol 2013;61:196–206;

RELAX-AHF: dyspnea relief to 24 hours (Likert scale), according to ejection fraction



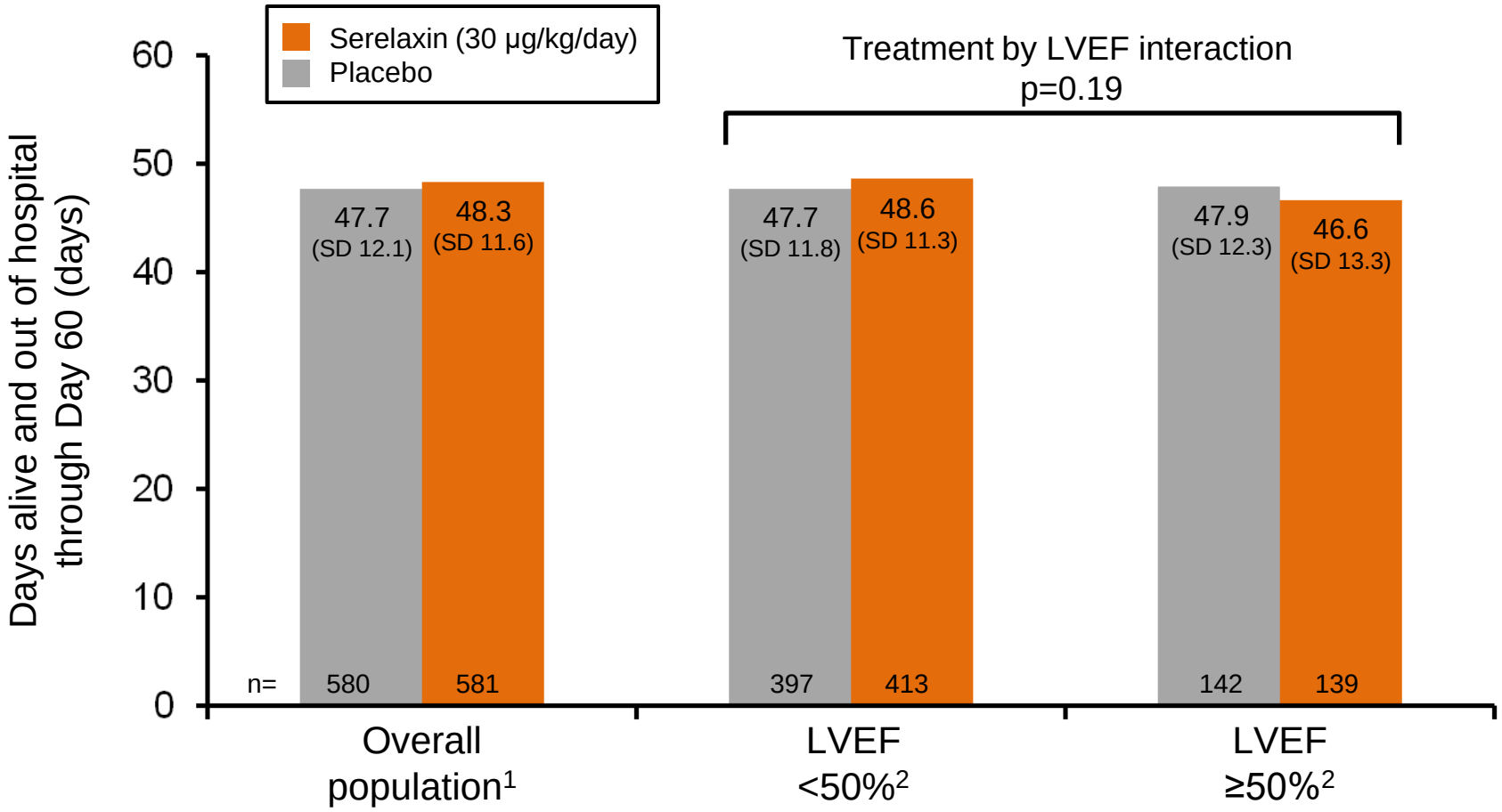
1. Teerlink JR, et al. Lancet 2013;381:29–39
2. Filippatos G, et al. Eur Heart J. 2014 Apr;35(16):1041-50.

RELAX-AHF: dyspnea relief (VAS AUC from baseline to Day 5), according to ejection fraction



1. Teerlink JR, et al. Lancet 2013;381:29–39
2. Filippatos G, et al. Eur Heart J. 2014 Apr;35(16):1041-50.

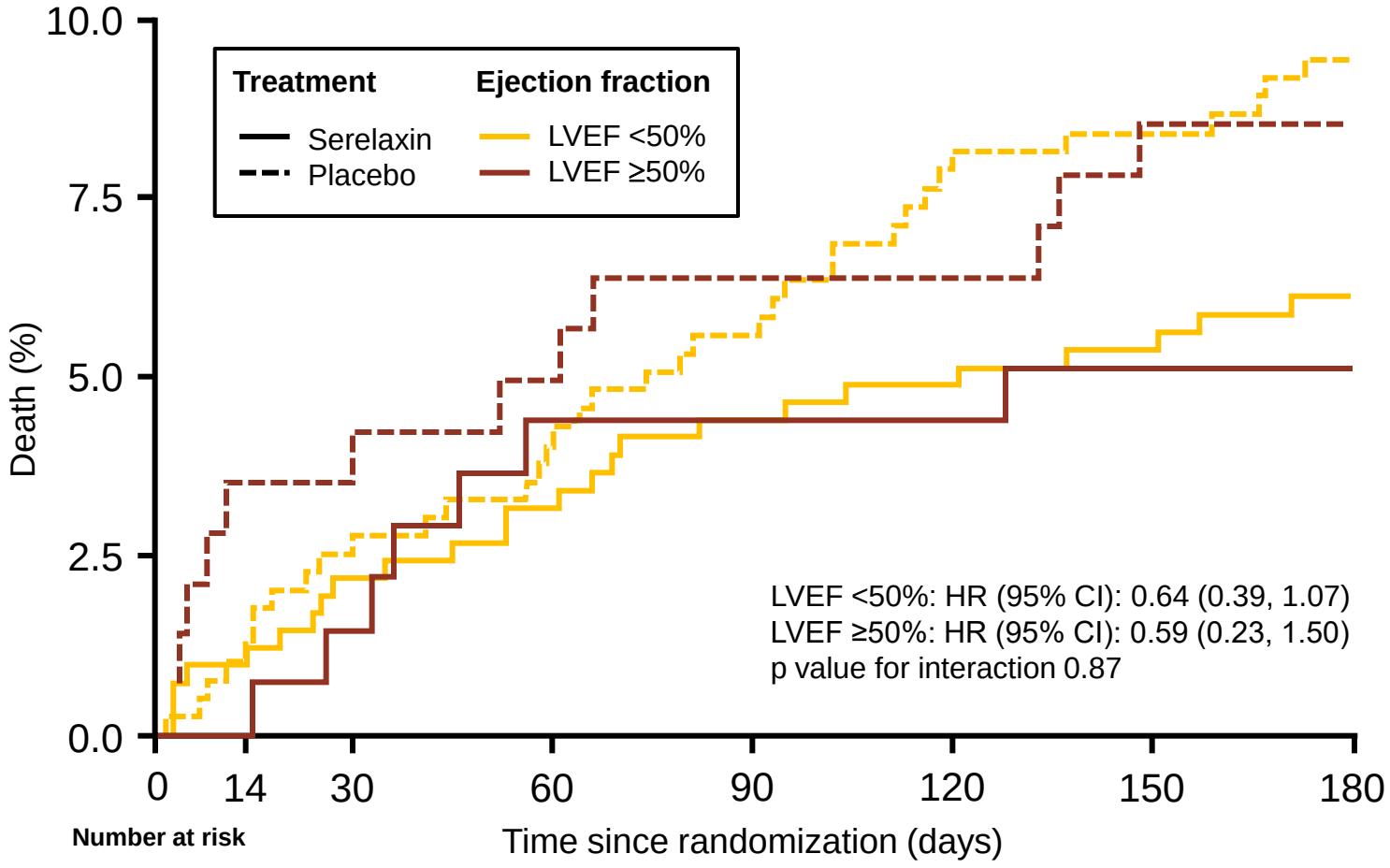
RELAX-AHF: days alive and out of hospital through Day 60, according to ejection fraction



AHF=acute heart failure; LVEF=left ventricular ejection fraction; SD=standard deviation

1. Teerlink JR, et al. Lancet 2013;381:29–39
2. Filippatos G, et al. Eur Heart J. 2014 Apr;35(16):1041-50.

RELAX-AHF: CV death through Day 180 (efficacy endpoint), according to ejection fraction



Number at risk

Serelaxin/LVEF ≥50%	139	139	135	131	131	131	127	127
Serelaxin/LVEF<50%	413	405	400	396	390	388	383	380
Placebo/LVEF ≥50%	142	137	135	133	131	131	127	127
Placebo/LVEF <50%	397	391	385	377	371	357	355	350

CI=confidence interval; CV= cardiovascular; HR=hazard ratio; LVEF=left ventricular ejection fraction

1. Teerlink JR, et al. Lancet 2013;381:29–39
2. Filippatos G, et al. Eur Heart J. 2014 Apr;35(16):1041-50.

Summary

- These data suggest that serelaxin is equally effective at:
  - relieving dyspnea through Day 5, irrespective of LVEF (<50% or ≥50%).
  - improving short- and long-term outcomes, including survival, irrespective of LVEF

1. Teerlink JR, et al. Lancet 2013;381:29–39
2. Filippatos G, et al. Eur Heart J. 2014 Apr;35(16):1041-50.

Serelaxin:
Hemodynamic effects in acute heart failure

STUDIO CLINICO RLX030/Serelaxin

Studio multicentrico, prospettico, randomizzato in aperto per valutare l'effetto di serelaxina rispetto allo standard di cura in pazienti con scompenso cardiaco acuto

Natale V. e Coll. Medicina d'Urgenza e Pronto Soccorso P.O. Vibo Valentia

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STUDIO CLINICO RLX030/Serelaxin
Esperienza del Centro di Medicina d'Urgenza e Pronto Soccorso di Vibo Valentia

Natale V. e Coll. Medicina d'Urgenza e Pronto Soccorso P.O. Vibo Valentia

STUDIO CLINICO RLX030/Serelaxin
Esperienza del Centro di Medicina d'Urgenza e Pronto Soccorso di Vibo Valentia

37 Pazienti arruolati

Primo centro in Italia per pazienti arruolati

Natale V. e Coll. Medicina d'Urgenza e Pronto Soccorso P.O. Vibo Valentia

Studio, multicentrico prospettico internazionale,randomizzato in aperto

SCOPO è valutare l'efficacia, la sicurezza e la tollerabilità della infusione endovenosa di Seralaxina somministrata per 48 ore, in aggiunta alla terapia standard, in pazienti ospedalizzati per scompenso cardiaco acuto

Il protocollo definisce endpoint primario il peggioramento dello scompenso cardiaco (WHF) durante il ricovero ospedaliero che richiede terapia di emergenza e/o decesso per qualsiasi causa fino al Giorno 5.

Studio, multicentrico prospettico internazionale,randomizzato in aperto

- OBIETTIVO PRIMARIO

è valutare l'effetto, la sicurezza di Seralaxina come terapia aggiuntiva allo standard di cura (*Standard of care* – SOC) rispetto a solo SOC, nella riduzione del peggioramento dello scompenso cardiaco in corso di ricovero che richiede terapia di emergenza o nel decesso per qualsiasi causa, dalla randomizzazione fino al giorno 5.

Visita di SCREENING (Visita 0)

Lo screening ha inizio formale quando il paziente accetta lo studio firmando il consenso informato. Valutazioni per la diagnosi di AHF possono essere effettuate prima della firma del consenso come da normale pratica clinica.

Consenso informato
Valutazione criteri Inclusione/Esclusione (**prelievo screening, Eco/X-ray**, NT-proBNP, serologia et al.)
ECG
Segni vitali (**Altezza**, **Peso**, Temperatura, FR, FC, Sistolica e Diastolica)
Dati demografici
Storia medica paziente
Registro delle medicazioni assunte dal paziente

IWRS →Patient Screening form

Inclusion criteria	• Able to provide written informed consent before any study-specific assessment is performed.
	• Male or female ≥ 18 years of age
	• Systolic blood pressure ≥ 125 mmHg
	• Admitted/hospitalized for AHF. AHF is defined as including all of the following measured at any time between presentation and the end of screening:
	  • Dyspnea at rest or with minimal exertion.
	  • Pulmonary congestion assessed with chest X-Ray, echocardiography or physical examination.
	  • N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥ 2000 pg/mL
	• Able to start serelaxin infusion within 16 hours from presentation to the hospital [presentation starts as the earliest of (1) time of presentation at either the ER/ED, ICU/CCU or ward; or (2) time of first IV loop diuretic for treatment of the current AHF episode prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department)
	• Received intravenous furosemide of at least 40 mg (or equivalent) at any time between presentation to emergency services and the start of screening for the study
	• Impaired renal function defined as an estimated glomerular filtration rate (eGFR) on admission defined as ≥30 and ≤75 mL/min/1.73 m^2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation. For France only: in case of recruitment in the ambulance the diagnosis of impaired renal function will be evaluated using the creatinine value obtained through the i-STAT device (bedside point of care device).

Visita di BASELINE (Visita 0-1)

Il paziente elegibile per lo studio viene randomizzato a ricevere SOC + Serelaxina oppure SOC (rapporto 2:1). Le valutazioni di questa visita devono essere effettuate dopo la randomizzazione del paziente e prima della somministrazione del trattamento farmacologico.

IWRS →PatientRandomizationform
Valutazione clinica di segni e sintomi HF (dispnea, ortopnea, rantoli, edemi, JVP)
Prelievo per sottostudio
Esame urine
Questionario EQ-5D-5L
Valutazione di eventuale WHF, SAE, AE
Somministrazione farmaco
Registro delle medicazioni concomitanti

Body weight (kg)	Serelaxin (mg)	Volume of serelaxin to be added to 250 mL IV bag of sterile 5% dextrose for intravenous infusion over a period of 24 hours
40-59 kg	2.0 mg	2.0 mL
60-74 kg	3.0 mg	3.0 mL
75-114 kg	3.5 mg	3.5 mL
115-160 kg	5.5 mg	5.5 mL (2 vials needed)

Studio, multicentrico prospettico internazionale,randomizzato in aperto

Visita 6h (Visita 1-1)
Visita 12h (Visita 1-2)
Visita 24h (Visita 1-3)
Visita 48h (Visita 1-4)

Visita Giorno 3 (Visita 1-5)

Visita Giorno 4 (Visita 1-6)

Visita Giorno 5 (Visita 2)

Visita Giorno 14 (Visita 3)

Follow up telefonico Giorno 30 (Visita 4)

Conclusions

- Serelaxin exerted marked hemodynamic effects in patients with AHF
- These effects may provide plausible mechanistic support for improvement in dyspnea and other signs and symptoms of congestion observed with serelaxin
- Serelaxin was well-tolerated in patients with AHF
- These results are consistent with previous studies of serelaxin in AHF

SOCIETA' ITALIANA MEDICINA D'EMERGENZA URGENZA

SEZIONE CALABRIA

Presidente Dr.ssa M.A. Rodolico

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V I B O 2016 Emergency Medicine

2-3 Dicembre 2016 Scuola Allievi Agenti Polizia di Sato Vibo Valentia

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