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

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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.”
AHF IS NOT A SINGLE DISEASE, BUT RATHER A HETEROGENEOUS FAMILY OF CLINICAL SYNDROMES, EACH WITH DISTINCT CLINICAL PRESENTATION, PROGNOSIS AND MANAGEMENT
AHF is the most frequent cause of hospitalization in subjects >65 years\textsuperscript{1}

Over 1 million hospitalizations with a primary diagnosis of HF occur each year in the USA\textsuperscript{2} and Europe\textsuperscript{5} alone

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

In-hospital mortality registries

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

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: age, low SBP and reduced renal function.
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)

HOSPITAL

- 4% in-hospital mortality rate

60 days

- 30–50% dead or rehospitalized within 60 days of admission

1 year

- ~25-35% mortality after 1 year

5 years

- ~40% mortality after 5 years

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

Gheorghiade et al. Eur J Heart F 2010
Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

Claudio Ronco¹,²*, Peter McCullough³, Stefan D. Anker⁴,⁵, Inder Anand⁶, Nadia Aspromonte⁷, Sean M. Bagshaw⁸, Rinaldo Bellomo⁹, Tomas Berl¹⁰, Ilona Bobek¹, Dinna N. Cruz¹,², Luciano Daliento¹¹, Andrew Davenport¹², Mikko Haapio¹³, Hans Hillege¹⁴, Andrew A. House¹⁵, Nevin Katz¹⁶, Alan Maisel¹⁷, Sunil Mankad¹⁸, Pierluigi Zanco¹⁹, Alexandre Mebazaa²⁰, Alberto Palazzuoli²¹, Federico Ronco¹¹, Andrew Shaw²², Geoff Sheinfeld²³, Sachin Soni¹,²⁴, Giorgio Vescovo²⁵, Nereo Zamperetti²⁶, and Piotr Ponikowski²⁷ for the Acute Dialysis Quality Initiative (ADQI) consensus group
Cardio-renal type I « acute »

Acute heart disease or procedures
- Acute decompensation
- Ischemic insult
- Coronary angiography
- Cardiac surgery

Acute renal injury
- Acute hypoperfusion
- Reduced oxygen delivery
- Necrosis/apoptosis
- Decreased GFR
- Resistance to ANP/BNP

Humorally mediated damage
- RAA activation,
- Na + H2O retention,
- Vasoconstriction

Hormonal factors
- BNP
- Natriuresis

Immune mediated damage
- Caspase activation
- Apoptosis

Exogenous factors
- Contrast media
- ACE inhibitors
- Diuretics

Decreased perfusion
- Increased venous pressure

Decreased CO

Hemodynamically mediated damage

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

Maria Nikolaou¹,²,³, John Parissis³, M. Birhan Yilmaz¹,⁵, Marie-France Seronde¹,²,⁴, Matti Kivistiko⁵,⁶, Said Laribi¹,²,⁷, Catherine Paugam-Burtz²,⁸, Danlin Cai⁹, Pasi Pohjanjouši⁶, Pierre-François Laterre¹⁰, Nicolas Deye¹,¹¹, Pentti Poder¹², Alain Cohen Solal¹,²,¹³, and Alexandre Mebazaa¹,²,¹⁴*

¹UMRS 942 Inserm, F-75010 Paris, France; ²Univ Paris Diderot; Sorbonne Paris Cité, F-75205 Paris, France; ³Heart Failure Unit, 2nd Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; ⁴Department of Cardiology, University Hospital Jean-Minjoz, Besançon, France; ⁵Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland; ⁶Orión Pharma, Kuopio, Finland; ⁷AP-HP, Department of Emergency Medicine, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; ⁸AP-HP, Department of Anesthesiology and Critical Medicine, Hôpital Bicêtre, F-94250 Clichy, France; ⁹Abbott Laboratories, Abbott Park, IL, USA; ¹⁰Department of Critical Care Medicine, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; ¹¹AP-HP, Medical ICU, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; ¹²First Department of Cardiology, North Estonia Medical Center, 12419 Tallinn, Estonia; ¹³AP-HP, Department of Cardiology, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; ¹⁴AP-HP, Department of Anesthesiology and Critical Care Medicine, Hôpital Lariboisière, 2 Rue A Paré F-75475 Paris Cedex 10, France; and ¹⁵Cumhuriyet 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)

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

Abnormal transaminases were associated with clinical signs of hypoperfusion

AHF-induced liver congestion (increased BNP)

isolated abnormal transaminases in 26%,

bile duct compression (increased AP)

bile duct compression (increased AP)

and cytolysis (acute centrilobular hepatocellular damage and necrosis) (increased transaminases)

Nikolaou et al Eur Heart Journal 2013 (in press)
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 $P < 0.001$).
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

<table>
<thead>
<tr>
<th>Clinical goals</th>
<th>Hemodynamic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of dyspnea and orthopnea</td>
<td>SBP ≥80 mmHg</td>
</tr>
<tr>
<td>Resolution of ascites and peripheral edema</td>
<td>Right atrial pressure ≤8 mmHg</td>
</tr>
<tr>
<td>JVP ≤8 cm H₂O</td>
<td>PCWP ≤16 mmHg</td>
</tr>
<tr>
<td>Control of hypertension</td>
<td>Systemic vascular resistance ≤1,200 dynes/s/cm⁻⁵</td>
</tr>
<tr>
<td>Minimize adverse effects of treatment, reduce duration and cost of stay</td>
<td></td>
</tr>
<tr>
<td>Initiate treatments that improve long-term outcome</td>
<td></td>
</tr>
</tbody>
</table>

JVP= Jugular Venous Pressure; PCWP=pulmonary capillary wedge pressure
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.
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
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-
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
Critical look – minimal dyspnea improvement
With worsening renal function and increased mortality
ASCEND-HF TRIAL
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization

Placebo vs. Nesiritide:
- 30-day Death/HF Rehospitalization: P=0.31
  - Placebo: 10.1
  - Nesiritide: 9.4
- 30-day Death:
  - Placebo: 4
  - Nesiritide: 3.6
- HF Rehospitalization:
  - Placebo: 6.1
  - Nesiritide: 6

Risk Diff 95 % CI:
- 30-day Death/HF Rehospitalization: -0.7 (-2.1; 0.7)
- 30-day Death: -0.4 (-1.3; 0.5)
- HF Rehospitalization: -0.1 (-1.2; 1.0)

-AHA 2010-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Regimen</th>
<th>Adverse effects</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitroglycerine</td>
<td>Acute PE; pulmonary congestion in normo or hypertensive AHF</td>
<td>10-20 ug/min, increase up to 200 ug/min</td>
<td>Hypotension, Headache</td>
<td>Tolerance is common after 24-48 h, requiring adjustment of dosing</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Pulmonary Edema Pulmonary congestion</td>
<td>1 mg/h, increase up to 10 mg/h</td>
<td>Hypotension, Headache</td>
<td>Tolerance as for nitroglycerine</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Acute hypertensive congestion</td>
<td>0.3μg/Kg/min, up to 5μg/Kg/min</td>
<td>Hypotension, Isocyanate toxicity</td>
<td>Light sensitive</td>
</tr>
<tr>
<td>nesiritide</td>
<td>Pulmonary edema Pulmonary congestion</td>
<td>Bolus and perfusion 0.015-0.030 ug/Kg/min</td>
<td>Hypotension, Worsening renal function</td>
<td>Not available in many ESC countries</td>
</tr>
</tbody>
</table>
There is a therapeutic need in acute heart failure

- The therapeutic approach to acute HF has not changed much in the last few decades¹
  - 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 years¹–³

- Acute HF has recently received attention from researchers, clinicians, regulatory agencies and the pharmaceutical industry, due to its unique diagnostic and management challenges²

- There is a need to identify new treatment strategies and regimens that have a beneficial effect in AHF patients ¹

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 \(^4, 5, 6\)

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

1. **Myocardial overload (preload and afterload)**
   - Vasodilation
     - Endothelial NO ↑
     - Systemic vascular resistance ↓
     - Cardiac index ↑

2. **Cell preservation**
   - Inflammation
     - Inflammatory cell infiltration ↓
     - Oxidative stress ↓

3. **Remodeling**
   - Remodeling ↓
     - CF-stimulated protein synthesis ↓
     - ANP expression ↑

4. **Fibrosis**
   - CF activation and proliferation ↓
   - Collagen synthesis ↓
   - Collagen breakdown ↑

5. **Cell survival**
   - Oxidative stress ↓
   - Apoptosis ↓
   - Calcium overload ↓
   - Infarct size ↓

6. **Tissue healing**
   - Angiogenesis ↑
   - Stem cell survival and coupling ↑

Adapted from Du et al. Nat Rev Cardiol 2010;7:48–58
Serelaxin Is NOT Just Another Vasodilator

Serelaxin (recombinant human relaxin-2)

↓ Inflammation  ↓ Fibrosis  ↑ Vasodilation  Renal effects  Angiogenesis

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

Serelaxin stimulates NO-mediated vasodilation via activation of the endothelial ET\textsubscript{B} receptor

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

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\item VEGF is also known to play a role in serelaxin-mediated vasodilation\textsuperscript{11}
\end{itemize}

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

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

Presentation <16 h

48 h study drug infusion

Double-blind randomized treatment period

Placebo (n=61)
Serelaxin 10 µg/kg/d (n=40)
Serelaxin 30 µg/kg/d (n=42)
Serelaxin 100 µg/kg/d (n=37)
Serelaxin 250 µg/kg/d (n=49)

Post-discharge evaluations

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

*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

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

John R Teelelink, 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.
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.

**RELAX-AHF: study design**

- **Randomized:** 1,161 patients hospitalized with AHF, normal to elevated BP and mild-to-moderate renal impairment
- **Screening:** Screening occurred after ≥40 mg i.v. furosemide
- **All pts had SBP > 125 mmHg**
- **Presentation:** <16 h
- **Double-blind randomized treatment period:**
  - Placebo (n=580)
  - Serelaxin 30 µg/kg/d (n=581)

In addition to standard HF therapy‡

‡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

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

19.4% increase in AUC with serelaxin from baseline through day 5 (Mean difference of 448 mm/hr)

AUC with placebo, 2308 ± 3082
AUC with serelaxin, 2756 ± 2588
*P = .0075

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

Worsening of Heart Failure

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

Cumulative Proportion of WHF to Day 5 (%)

- Placebo (N = 573)
- Serelaxin (N = 570)

*P < .001 through Day 5

KM Estimate Day 14 for Time to WHF (%)

- HR 0.7 (0.51-0.96);
- P = .024

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
**CV Death Through Day 180**

- **NS up to day 60**

- 37% reduction on CV death

**KM Estimate CV Death (ITT) (%)**

- HR 0.63 (0.41-0.96); $p = .028$

- NNT = 29

**Number of Events, n (%)**

- Placebo (N = 580): 55 (9.6%)
- Serelaxin (N = 581): 35 (6.1%)

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

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
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.
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.
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
Team RELAX-AHF-2
(S. Cardiologia I, CHLN, E.P.E., Director: António Nunes Diogo)

- **PI:** Dulce Brito
- **Co-I** (alphabetical 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
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.
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
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
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/1.73m², calculated using the sMDRD equation
Study design
Randomized, placebo-controlled study in a selected AHF patient population

<table>
<thead>
<tr>
<th>Screening epoch</th>
<th>Randomized treatment epoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>I.V. infusion (0-48 hours)</td>
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</tbody>
</table>

Serelaxin 30 μg/kg/d

Placebo

Maximum 16 hr. between presentation & randomization

Standard HF therapy continued throughout the study

D1 0hrs  D1 6hrs  D1 12hrs  D1 24hrs  D2 48hrs  D3 72hrs  D4 96hrs  D5 120hrs

D14  D60  D120  D180

Randomization

Discharge*

* Weight-range based dosing regimen for serelaxin and matching placebo
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 $\geq$ 125 mmHg and especially $> 100$ mmHg and no end stage renal failure
In patients with heart failure, serelaxin…
Unloads the heart
Unloads the kidney and improves perfusion

RELAX-AHF-2
Conclusions

- AHF is a complex syndrome, multiple physiopathological mechanisms, different clinical presentations / different diseases. Multiple effects of vasodilator therapy.
- Classical vasodilators shown to be beneficial in AHF. However, these 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 vasodilator)
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
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.
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