Novità Terapeutiche nello Scompenso Cardiaco

Giuseppe Campolongo
IRCCS San Raffaele Pisana

Roma, 6-7 Maggio 2016
POLICLINICO UMBERTO I
Auditorium I Clinica Medica
Treatment options for patients with chronic symptomatic HFrEF (NYHA class II-IV)
## Recommendation on Ivabradine

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivabradine</strong></td>
<td></td>
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<tr>
<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35%, a heart rate remaining ≥70 b.p.m., and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIa</td>
<td>B</td>
<td>112</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70 b.p.m. who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>
SHIFT: Ivabradine in Mild to Moderate HF

- Study population: 6658 patients, NYHA class II-IV, LVEF ≤35%
- Intervention: Ivabradine (up to 7.5 mg b.i.d.) vs. placebo
- Primary endpoint: CV death & HF hospitalisation

Treatment options for patients with chronic symptomatic HFrEF (NYHA class II-IV)

**Figure 4** Current and possible future evidence-based treatment of heart failure with reduced ejection fraction (HF-REF). ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator; Tx, heart transplantation; VAD, ventricular assist device. The pyramid structure illustrates the key drug, device, and surgical treatments for HF-REF. The drug therapies at the base of the pyramid are those that are indicated in the majority of patients with HF-REF with devices/surgery used on top of these (with the less commonly used devices/surgical interventions at the top of the pyramid). The drug therapies in the boxes either side of the pyramid are those that are indicated in selected patients (as is CABG).
Neurohormonal activation in HFrEF

**Natriuretic peptide system**

- NPRs ↔ NPs
  - Vasodilation
  - Blood pressure
  - Sympathetic tone
  - Natriuresis/diuresis
  - Vasopressin
  - Aldosterone
  - Fibrosis
  - Hypertrophy

**SNS**

- Epinephrine
- Norepinephrine
  - $\alpha_1, \beta_1, \beta_2$ receptors
- Vasoconstriction
- RAAS activity
  - Vasopressin
  - Heart rate
  - Contractility

**RAAS inhibitors (ACEI, ARB, MRA)**

- Ang II
- AT$_1$R
- Vasoconstriction
  - Blood pressure
  - Sympathetic tone
  - Aldosterone
  - Fibrosis
  - Hypertrophy

β-blockers

Natriuretic Peptides

- Predominantly present in the heart and circulates in plasma
- Expression increases in the atrium and ventricle in cardiac hypertrophy

ANP

- Predominantly present in the heart and circulates in plasma
- Expression increases in the atrium and ventricle in cardiac hypertrophy
- Ventricular synthesis regulated by volume overload

BNP

- Predominantly present in the central nervous system (CNS) and vasculature
- Does not behave as a cardiac hormone – levels extremely low in circulation

CNP

CNP=C-type natriuretic peptide
A Novel Concept: Neprilysin Inhibitor Sacubitril
Natriuretic peptides have potential beneficial actions in HF

Release of ANP and BNP from heart and CNP in vasculature

- \( \downarrow \) Sympathetic outflow
- \( \downarrow \) Vasopressin
- \( \downarrow \) Salt appetite and water intake

- \( \uparrow \) \( \text{Na}^+ / \text{H}_2\text{O} \) loss
- \( \downarrow \) Aldosterone
- \( \downarrow \) Renin

Natriuretic peptides have potential beneficial actions in HF

Figure 1 The conceptual therapeutic goal of angiotensin receptor nepriysin inhibition in heart failure with reduced ejection fraction (HF-REF). HF-REF can be considered as a state of relative neurohumoral imbalance, with relative underactivation of neurohumoral systems leading to vasodilatation, promoting renal sodium and water excretion and inhibiting pathological growth (hypertrophy and fibrosis). The aim is not only to block harmful neurohumoral pathways in heart failure but also to augment the activity and actions of potentially beneficial pathways.
The “Story” of augmentation of natriuretic peptides as a therapeutic strategy in HF

**Stand-alone neprilysin inhibition**
- Tested enhancing the effects of natriuretic peptides by reducing their breakdown through neprilysin inhibition\(^1\)
  - E.g. candoxatril\(^2\), thiorphan\(^3\)
- Ultimately not developed for clinical use in heart failure\(^1\)

**Omapatrilat (Neprilysin and ACE inhibition)**
- Omapatrilat developed to both inhibit neprilysin and suppress the RAAS, via ACE inhibition\(^4,5\)
- Demonstrated a trend towards reduced morbidity and mortality in HFrEF\(^5\)
- Development was halted due to increased frequency of angioedema\(^1,5\)

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The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John JV McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fraction (PARAMOUNT) Investigators

Solom S. Lancet, 2012
PARAMOUNT: Phase II LCZ696 in HFpEF

Inclusion criteria:
- NYHA II-III
- LVEF ≥45%
- NT-proBNP >400 pg/mL

Primary EP:
- Change in NT-proBNP from BL to w12

Treatment:
- LCZ696 (n=149) titrated to 200 mg b.d.
- Valsartan (n=152) titrated to 160 mg b.d.
- Treatment duration: 36 weeks

Results:
- LCZ696: NT-proBNP decreased from 783 (670-914) to 605 (512-714) pg/mL
- Valsartan: NT-proBNP from 862 (733-1012) to 835 (710-981) pg/mL, p=0.005
- LCZ696 was well tolerated.

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

Solom S., Lancet, 2012
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Changes in NYHA and clinical composite assessment showing percentage of patients who have worsened, remained unchanged, or improved for each measure. NYHA = New York Heart Association.
Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial (NT-proBNP) at 12 weeks
High-sensitivity troponin T (hs-TnT) levels by treatment group.

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*
PARADIGM-HF Study Design

Primary endpoint: CV death or HF hospitalization

Randomization
(N = 8,422 patients)
Single-blind run-in period

Double-blind randomized treatment period

Enalapril 10 mg bid
LCZ696 100 mg bid
LCZ696 200 mg bid

Testing tolerability to target doses of enalapril and LCZ696*

On top of standard heart failure therapy (excluding ACEIs and ARBs)

~ 21 to 43 months (event-driven)
Why enalapril was chosen as the comparator?

Because enalapril was the only ACEi shown to reduce mortality vs placebo in this broad spectrum of patients with HFrEF.
Why enalapril 10 mg BID was chosen as the appropriate comparator dose?

- Enalapril 10 mg BID is the regulatory ‘gold-standard’ ACEI based upon CONSENSUS and SOLVD-T trial data
- The mean daily dose achieved in PARADIGM was 18.9 mg

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Target dose (mg)</th>
<th>Mean daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>127</td>
<td>20 BID</td>
<td>18.4</td>
</tr>
<tr>
<td>SOLVD-T</td>
<td>1285</td>
<td>10 BID</td>
<td>16.6</td>
</tr>
<tr>
<td>SOLVD-P</td>
<td>2111</td>
<td>10 BID</td>
<td>16.7</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>403</td>
<td>10 BID</td>
<td>15.0</td>
</tr>
<tr>
<td>OVERTURE</td>
<td>2884</td>
<td>10 BID</td>
<td>17.7</td>
</tr>
<tr>
<td>CARMEN</td>
<td>190</td>
<td>10 BID</td>
<td>16.8</td>
</tr>
</tbody>
</table>
PARADIGM trial: a great challenge

• First trial in a new class (ARNI*)
• Greatest trial in HF, 8442 pts
• Phase 3 trial, great run-in phase

* Angiotensin Receptor Neprylisin Inhibitor
PARADIGM-HF: Entry Criteria

• NYHA class II-IV heart failure

• LV ejection fraction $\leq 40\% \Rightarrow 35\%$

• BNP $\geq 150$ (or NT-proBNP $\geq 600$), but one-third lower if hospitalized for heart failure within 12 months

• Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks

• Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists

• Systolic BP $\geq 95$ mm Hg, eGFR $\geq 30$ ml/min/1.73 m$^2$ and serum K $\leq 5.4$ mEq/L at randomization
# PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
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</table>
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

**Enalapril**
(n=4212)

**LCZ696**
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.00000002
Number needed to treat = 21
<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.00000002</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.000004</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td><strong>0.79 (0.71-0.89)</strong></td>
<td><strong>0.000004</strong></td>
</tr>
</tbody>
</table>
Clinical outcomes of cardiovascular death or heart failure hospitalization, cardiovascular death, heart failure hospitalization, and all-cause mortality by age category and treatment group.

Proportion of patients with a five-point or greater fall (deterioration) in Kansas City Cardiomyopathy Questionnaire at 8 months by age category and treatment.

A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure

John McMurray¹†, Milton Packer²†, Akshay Desai³, Janjian Gong⁴, Nicola Greenlaw⁵, Martin Lefkowitz⁴, Adel Rizkala⁴, Victor Shi⁴, Jean Rouleau⁶, Scott Solomon³, Karl Swedberg⁷, Michael R. Zile⁸, Karl Andersen⁹, Juan Luis Arango¹⁰, Malcolm Arnold¹¹, Jan Bělohlávek¹², Michael Böhm¹³, Sergey Boytsov¹⁴, Lesley Burgess¹⁵, Walter Cabrera¹⁶, Chen-Huan Chen¹⁷, Andrejs Erglis¹⁸, Michael Fu¹⁹, Efrain Gomez²⁰, Angel Gonzalez²¹, Albert-Alain Hagege²², Tzvetana Katova²³, Songsak Kiatchoosakun²⁴, Kee-Sik Kim²⁵, Edmundo Bayram²⁶, Felipe Martinez²⁷, Bela Merkely²⁸, Iván Mendoza²⁹, Arend Mosterd³⁰, Marta Negrusz-Kawecka³¹, Keijo Peuhkurinen³², Felix Ramirez³³, Jens Refsgaard³⁴, Michele Senni³⁵, Antonio S. Sibulo Jr³⁶, José Silva-Cardoso³⁷, Iain Squire³⁸, Randall C. Starling³⁹, Dragos Vinereanu⁴⁰, John R. Teerlink⁴¹, and Raymond Wong⁴², on behalf of the PARADIGM-HF Committees and Investigators
Putative placebo analysis - comparison network

SOLVD-T

PARADIGM-HF

Enalapril

Placebo

LCZ696

CHARM-Alternative

PARADIGM-HF

Candesartan

Placebo

LCZ696
CV mortality in SOLVD-T, CHARM-Alternative and PARADIGM-HF

- SOLVD-T
  - Hazard Ratio: 0.83 (0.73, 0.95)
  - p-value: 0.008

- CHARM-Alt.
  - Hazard Ratio: 0.85 (0.71, 1.02)
  - p-value: 0.072

- PARADIGM-HF putative placebo
  - from SOLVD-T
    - Hazard Ratio: 0.68 (0.55, 0.84)
    - p-value: 0.0001
  - from CHARM-Alt.
    - Hazard Ratio: 0.66 (0.56, 0.79)
    - p-value: <0.0001
Heart failure hospitalization in SOLVD-T, CHARM-Alternative and PARADIGM-HF

- SOLVD-T: Hazard Ratio (HR) 0.64 (0.55, 0.73), p < 0.0001
- CHARM-Alt.: Hazard Ratio (HR) 0.68 (0.57, 0.81), p < 0.0001
- PARADIGM-HF putative placebo from SOLVD-T: Hazard Ratio (HR) 0.51 (0.42, 0.61), p < 0.0001
- PARADIGM-HF putative placebo from CHARM-Alt.: Hazard Ratio (HR) 0.54 (0.44, 0.67), p < 0.0001
Recent findings regarding LCZ696 in HFrEF

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Description</th>
<th>Analysis Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desai A.S., et al (20)</td>
<td>PARADIGM-HF substudy on factors associated with dropout during the run-in period prior to randomization</td>
<td>Post-hoc analysis</td>
<td>Female patients with lower BP, higher creatinine, &amp; more severe HF were at higher risk for study drug intolerance during the run-in period</td>
</tr>
<tr>
<td>Bohm M, et al (21)</td>
<td>PARADIGM-HF substudy on the effect of LCZ696 compared with enalapril according to SBP</td>
<td>Post-hoc analysis</td>
<td>LCZ696 treatment effect on cardiovascular mortality was independent of baseline SBP</td>
</tr>
<tr>
<td>Cannon J, et al (22)</td>
<td>PARADIGM-HF substudy on possible dementia-related adverse effects with LCZ696</td>
<td>Post-hoc analysis</td>
<td>No evidence that LCZ696, compared with enalapril, increased dementia-related adverse events</td>
</tr>
</tbody>
</table>
### Recent findings regarding LCZ696 in HFrEF

| Study Authors          | PARADIGM-HF substudy                                     | Post-hoc analysis       | Outcome
|------------------------|---------------------------------------------------------|-------------------------|---------------------------------------------------
| Damman K, et al (23)   | PARADIGM-HF substudy on LCZ696 and renal function       | Post-hoc analysis       | LCZ696: neutral on renal dysfunction vs enalapril, but slows GFR decline |
| Gori M, et al (24)     | PARADIGM-HF substudy on the effect of LCZ696 on UACR and relation to outcomes | Post-hoc analysis       | Patients randomized to LCZ696 had better outcomes than those receiving enalapril despite modest, early, and stable UACR increases |
| Kristensen S, et al (25)| PARADIGM-HF substudy regarding LCZ696 efficacy across the glycaemic spectrum | Post-hoc analysis       | LCZ696 was similarly effective in normoglycaemia, prediabetes, as well as diabetes |
| Jhund P., et al (26)   | PARADIGM-HF substudy to determine the effect of LCZ696 on high sensitivity troponin T | Post-hoc analysis       | Elevated high sensitivity troponin was associated with poorer outcomes, reduced by LCZ696 |
Recent findings regarding LCZ696 in HFrEF

Valsartan/Sacubitril for Heart Failure
Reconciling Disparities Between Preclinical and Clinical Investigations

However, recent translational science studies involving the central nervous system and the eye suggest that other effects of valsartan/sacubitril might influence its use in some patients.
Numbers of Patients with Heart Failure Who Would Need to Be Treated to Reduce Any-Cause Mortality in Seven Clinical Trials.

![Graph showing numbers needed to treat to reduce any-cause death for each trial: U.S. Carvedilol Group 22, SOLVD-T 23, AHEFT 26, MADIT-CRT 220, SHIFT 72, EMPHASIS-HF 34, PARADIGM-HF 35.](image)
PARAGON: Phase III LCZ696 in HFpEF

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)

This study is not yet open for participant recruitment.

Verified November 2013 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01920711

First received: August 8, 2013
Last updated: November 22, 2013
Last verified: November 2013
History of Changes

Purpose

The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan in the reduction of cardiovascular death and heart failure (HF) hospitalizations in patients with HF with preserved ejection fraction.

Duration: November 2013 ... 2018

n = 4300
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

Summary
Background Serelaxin, recombinant human relaxin-2, is a vasoactive peptide hormone with many biological and haemodynamic effects. In a pilot study, serelaxin was safe and well tolerated with positive clinical outcome signals in patients with acute heart failure. The RELAX-AHF trial tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo.

Methods RELAX-AHF was an international, double-blind, placebo-controlled trial, enrolling patients admitted to hospital for acute heart failure who were randomly assigned (1:1) via a central randomisation scheme blocked by study centre to standard care plus 48-h intravenous infusions of placebo or serelaxin (30 μg/kg per day) within 16 h from presentation. All patients had dyspnoea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP, mild-to-moderate renal insufficiency, and systolic blood pressure greater
Pregnancy & Acute Heart Failure?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (L/min)</td>
<td>Increase by 20%</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn/s/cm²)</td>
<td>Decrease by 30%</td>
</tr>
<tr>
<td>Arterial compliance (mL/mmHg)</td>
<td>Increase by 30%</td>
</tr>
<tr>
<td>Renal blood flow (mL/min/1,73 m²)</td>
<td>Increase by 50-85%</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1,73 m²)</td>
<td>Increase by 40-65%</td>
</tr>
</tbody>
</table>

- These effects are mediated by the ovarian peptide relaxin; it also has anti-ischaemic, anti-inflammatory, and anti-fibrotic effects;
- Relaxin and its signalling cascade are present in both men and women;
- Serelaxin, a recombinant human relaxin-2, can mediate these effects in patients with acute heart failure.

Hypothesis of the RELAX-AHF Study Program

• To test the effectivity and safety of serelaxin in patients with acute heart failure;
• Hypothesis: serelaxin at a dose of 30 µg/kg/day IV improves dyspnoea better than placebo as assessed after 24 hours out to 5 days after admission.

Inclusion Criteria: RELAX-AHF

- Hospitalisation for acute heart failure;
- ≥40 mg fruosemide IV (or aequivalent);
- Systolic blood pressure >125 mmHg;
- Reduced kidney function with GFR: 30-75 mL/min/1,73 m²;
- Randomisation within 16 hours of hospital admission;
- Body weight <160 kg, age ≥18 years.

### Study Population: RELAX-AHF

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=580)</th>
<th>Serelaxin (n=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>72.5 (10.8)</td>
<td>71.6 (11.7)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>357 (62%)</td>
<td>368 (63%)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>552 (95%)</td>
<td>544 (94%)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>82.8 (18.7)</td>
<td>81.9 (18.5)</td>
</tr>
<tr>
<td><strong>Body-mass index (kg/m²)</strong></td>
<td>29.5 (6.1)</td>
<td>29.1 (5.3)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>282 (49%)</td>
<td>280 (48%)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>101 (17%)</td>
<td>103 (18%)</td>
</tr>
<tr>
<td>USA</td>
<td>55 (9%)</td>
<td>59 (10%)</td>
</tr>
<tr>
<td>Argentina</td>
<td>37 (6%)</td>
<td>34 (6%)</td>
</tr>
<tr>
<td>Israel</td>
<td>105 (18%)</td>
<td>105 (18%)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>142.1 (17.0)</td>
<td>142.2 (16.2)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>81.7 (13.2)</td>
<td>82.2 (14.2)</td>
</tr>
<tr>
<td><strong>Heart rate (beats per min)</strong></td>
<td>80.4 (14.9)</td>
<td>78.9 (15.0)</td>
</tr>
<tr>
<td><strong>Respiratory rate (breaths per min)</strong></td>
<td>22.0 (4.6)</td>
<td>21.8 (4.6)</td>
</tr>
<tr>
<td><strong>Admitted to hospital for heart failure in past year</strong></td>
<td>181 (31%)</td>
<td>216 (37%)</td>
</tr>
<tr>
<td><strong>Number of admissions for heart failure in past year</strong></td>
<td>1.5 (1.1)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td><strong>Most recent ejection fraction (%)</strong></td>
<td>38.6% (14.3)</td>
<td>38.7% (14.8)</td>
</tr>
<tr>
<td><strong>Ejection fraction &lt;40%</strong></td>
<td>295 (55%)</td>
<td>303 (55%)</td>
</tr>
<tr>
<td><strong>New York Heart Association class 30 days before admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>11 (3%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Class II</td>
<td>140 (33%)</td>
<td>164 (38%)</td>
</tr>
<tr>
<td>Class III</td>
<td>198 (47%)</td>
<td>191 (44%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>72 (17%)</td>
<td>63 (14%)</td>
</tr>
</tbody>
</table>

Primary Endpoint: Improvement of Dyspnoea

Visual Analog Scale

Primary Endpoint: Improvement of Dyspnoea

Likert-Skala

Secondary Endpoint: (Cardiovascular) Death

No effect on rehospitalisation rate.

Conclusions

- Dual inhibition of the renin-angiotensin-aldosterone system and neprilysin inhibition represent a novel approach to treating patients with HF.
  - LCZ (Valsartan & secubitril) have shown very promising effects in HFrEF
  - PARAGON trial in HFpEF ongoing

- Acute HF: serelaxin has shown beneficial effects
Management of co-morbidities

- Anaemia
- Angina
- Asthma/COPD
- Cachexia
- Cancer
- Depression
- Diabetes mellitus
- Erectile dysfunction
- Gout

- Hyperlipidaemia
- Hypertension
- Iron deficiency
- Kidney dysfunction
- Obesity
- Prostatic obstruction
- Sleep disturbance/ sleep disordered breathing
Teamwork is key to improving the management of heart failure.