Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial

Gerasimos Filippatos¹*, John R. Teerlink², Dimitrios Farmakis¹, Gad Cotter³, Beth A. Davison³, G. Michael Felker⁴, Barry H. Greenberg⁵, Tsushung Hua⁶, Piotr Ponikowski⁷, Thomas Severin⁸, Elaine Unemori⁹, Adriaan A. Voors¹⁰, and Marco Metra¹¹

¹Athens University Hospital Attikon, Athens, Greece; ²University of California-San Francisco and San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; ³Momentum Research, Inc., Durham, NC, USA; ⁴Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; ⁵Division of Cardiovascular Medicine, University of California at San Diego, San Diego, CA, USA; ⁶Novartis Pharmaceuticals, East Hanover, NJ, USA; ⁷Department of Heart Diseases, Medical University, Military Hospital, Wroclaw, Poland; ⁸Novartis Pharma AG, Basel, Switzerland; ⁹Corthera, Inc., A Member of the Novartis Group of Companies, San Carlos, CA, USA; ¹⁰Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; and ¹¹Cardiology, The Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

Received 28 August 2013; revised 30 October 2013; accepted 12 November 2013; online publish-ahead-of-print 6 December 2013

See page 1017 for the editorial comment on this article (doi:10.1093/eurheartj/eht567)

Aims
Serelaxin is effective in relieving dyspnoea and improving multiple outcomes in acute heart failure (AHF). Many AHF patients have preserved ejection fraction (HFpEF). Given the lack of evidence-based therapies in this population, we evaluated the effects of serelaxin according to EF in RELAX-AHF trial.

Methods and results
RELAX-AHF randomized 1161 AHF patients to 48-h serelaxin (30 μg/kg/day) or placebo within 16 h from presentation. We compared the effects of serelaxin on efficacy endpoints, safety endpoints, and biomarkers of organ damage between preserved (≥50%) and reduced (<50%, HFrEF) EF. HFpEF was present in 26% of patients. Serelaxin induced a similar dyspnoea relief in HFpEF vs. HFrEF patients by visual analogue scale-area under the curve (VAS-AUC) through Day 5 [mean change, 461 (−2195, 1117) vs. 397 (−10, 783) mm h, P = 0.87], but had possibly different effects on the proportion of patients with moderately or markedly dyspnoea improvement by Likert scale at 6, 12, and 24 h [odds ratio for favourable response, 1.70 (0.98, 2.95) vs. 0.85 (0.62, 1.15), interaction P = 0.030]. No differences were encountered in the effect of serelaxin on short- or long-term outcome between HFpEF and HFrEF patients including cardiovascular death or hospitalization for heart/renal failure through Day 60, cardiovascular death through Day 180, and all-cause death through Day 180. Similar safety and changes in biomarkers (high-sensitivity troponin T, cystatin-C, and alanine/aspartate aminotransferases) were found in both groups.

Conclusions
In AHF patients with HFpEF compared with those with HFrEF, serelaxin was well tolerated and effective in relieving dyspnoea and had a similar effect on short- and long-term outcome, including survival improvement.

Keywords
Serelaxin • Relaxin • Acute heart failure • Heart failure with preserved left ventricular ejection fraction • Diastolic heart failure • Dyspnoea

Introduction
Acute heart failure (AHF) is characterized by high morbidity and mortality. Several recent trials have evaluated novel vasoactive agents in this syndrome, but failed to provide any evidence on outcome improvement.⁵–⁸ Hence, the management of AHF patients is still based primarily on drugs that improve symptoms but have a neutral or even negative effect on patients’ prognosis.⁶

*Corresponding author. 28 DoukissisPlakentias, 11523, Athens, Greece, Email: geros@otenet.gr

© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
### Table 1  Comparison of baseline characteristics between patients with reduced (<50%) and preserved (≥50%) left ventricular ejection fraction

|                                | LVEF < 50 (n = 810) | LVEF ≥ 50 (n = 281) | P-value |
|--------------------------------|----------------------|----------------------|---------|
| **Demographics**               |                      |                      |         |
| Age, years                     | 70.5 (11.4)          | 75.4 (9.9)           | <0.0001 |
| Male                           | 571 (70.5%)          | 117 (41.6%)          | <0.0001 |
| **Geographic region (%)**      |                      |                      | 0.74    |
| Eastern EU                     | 412 (50.9)           | 132 (47.0)           |         |
| Western EU                     | 140 (17.3)           | 47 (6.7)             |         |
| South America                  | 38 (4.7)             | 14 (5.0)             |         |
| North America                  | 81 (10.0)            | 32 (11.4)            |         |
| Israel                         | 139 (17.2)           | 56 (19.9)            |         |
| **Heart failure characteristics** |                    |                      |         |
| LVEF                           | 31.7 (9.0)           | 58.7 (7.2)           | <0.0001 |
| Ischaemic heart disease        | 461 (56.9%)          | 120 (42.7%)          | <0.0001 |
| **NYHA class 30 days before admission (%)** | 0.13                |                      |         |
| I                              | 14 (2.3)             | 9 (4.5)              |         |
| II                             | 212 (34.8)           | 80 (39.8)            |         |
| III                            | 293 (48.1)           | 81 (40.3)            |         |
| IV                             | 90 (14.8)            | 31 (15.4)            |         |
| **Time from presentation to randomization, h** | 0.011               |                      |         |
| HF hospitalization past year   | 298 (36.8%)          | 83 (29.5%)           | 0.028   |
| Number of HF hospitalizations past year | 1.7 (1.4)          | 1.4 (0.8)            | 0.032   |
| **Clinical signs**             |                      |                      |         |
| Body mass index, kg/m²         | 29.2 (5.5)           | 29.7 (6.4)           | 0.24    |
| Systolic blood pressure, mmHg  | 140.8 (16.2)         | 145.7 (16.7)         | <0.0001 |
| Diastolic blood pressure, mmHg | 82.6 (13.6)          | 79.6 (13.9)          | 0.0015  |
| Heart rate, bpm                | 79.8 (14.5)          | 78.0 (16.0)          | 0.081   |
| Respiratory rate, breaths per minute | 21.9 (4.6)         | 21.8 (4.7)           | 0.58    |
| **Congestion at baseline (%)** |                      |                      |         |
| Oedema                         | 634 (78.7)           | 221 (79.5)           | 0.77    |
| Orthopnoea                     | 768 (95.4)           | 269 (96.4)           | 0.47    |
| JVP, mm Hg (<6 vs. ≥6)         | 601 (76.5)           | 200 (73.3)           | 0.29    |
| DOE                            | 795 (99.7)           | 274 (100)            | 1.00    |
| Dyspnoea by VAS                | 43.9 (19.8)          | 43.2 (19.7)          | 0.64    |
| **Comorbidities (%)**          |                      |                      |         |
| Hypertension                   | 684 (84.4)           | 262 (93.2)           | 0.0002  |
| Diabetes mellitus              | 394 (48.6)           | 130 (46.3)           | 0.49    |
| Stroke or other cerebrovascular event | 110 (13.6)         | 39 (13.9)            | 0.90    |
| Asthma, bronchitis, or COPD    | 130 (16.0)           | 44 (15.7)            | 0.88    |
| Atrial fibrillation at screening | 307 (38.0)          | 137 (48.8)           | 0.0016  |
| History of atrial fibrillation or flutter | 391 (48.3)         | 172 (61.2)           | 0.0002  |
| **Devices (%)**                |                      |                      |         |
| Pacemaker                      | 82 (10.1)            | 31 (11.0)            | 0.67    |
| Implantable cardiac defibrillator | 145 (17.9)          | 4 (1.4)              | <0.0001 |
| Biventricular pacing           | 101 (12.5)           | 7 (2.5)              | <0.0001 |

*Continued*
Heart failure with preserved ejection fraction (HFpEF) represents up to 50% of AHF patients, depending on the definition, and this proportion seems to be increasing because of aging of the general population.7 Despite the therapeutic advances in the medical therapy for the patients with chronic heart failure and reduced left ventricular ejection fraction (HFrEF), evidence on an effective therapy in HFpEF is still missing. Previous randomized trials in chronic HF failed to show efficacy, and no agent has been specifically evaluated in AHF patients with HFpEF.8–12 Serelaxin, a recombinant form of human relaxin-2, administered to AHF patients, caused in improvement of symptoms and prevention of organ damage with a reduction in 180-day mortality, compared with AHF patients, as recently available, including the one during the index hospitalization. The primary efficacy endpoints were dyspnoea improvement, defined as dyspnoea change from baseline in the visual analogue scale-area under the curve (VAS-AUC) through Day 5 and proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale at 6, 12, and 24 h. The secondary efficacy endpoints included cardiovascular death or rehospitalization for heart or renal failure and days alive and out of hospital through Day 60. Cardiovascular death through Day 180 was pre-specified as an additional efficacy endpoint, and all-cause death through Day 180 was a pre-specified safety endpoint. Biomarkers indicative of congestion and/or organ damage, including high-sensitivity troponin T (hs-TnT), N-terminal β-type natriuretic pro-peptide (NT-proBNP), cystatin-C, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), were assessed serially using a central core lab.14

### Patients and methods

The methods of the RELAX-AHF trial (NCT00520806) are described in detail elsewhere.13–15 Briefly, the study randomized 1161 AHF patients to 48-h intravenous infusion of serelaxin (30 μg/kg/day, n = 581) or placebo (n = 580) within 16 h from presentation. We compared the effects of serelaxin vs. placebo on the pre-specified efficacy endpoints, safety endpoints, and biomarkers indicative of organ damage, in patients with preserved in comparison to those with reduced LVEF, defined as ≥50 and <50%, respectively, according to the recently published guidelines.6 According to the study protocol, the recorded LVEF was the most recently available, including the one during the index hospitalization. The primary efficacy endpoints were dyspnoea improvement, defined as dyspnoea change from baseline in the visual analogue scale-area under the curve (VAS-AUC) through Day 5 and proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale at 6, 12, and 24 h. The secondary efficacy endpoints included cardiovascular death or rehospitalization for heart or renal failure and days alive and out of hospital through Day 60. Cardiovascular death through Day 180 was pre-specified as an additional efficacy endpoint, and all-cause death through Day 180 was a pre-specified safety endpoint. Biomarkers indicative of congestion and/or organ damage, including high-sensitivity troponin T (hs-TnT), N-terminal β-type natriuretic pro-peptide (NT-proBNP), cystatin-C, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), were assessed serially using a central core lab.14

### Statistical analysis

Baseline characteristics were compared between HFrEF and HFpEF patients using two-sample t-tests for continuous variables and χ² tests for categorical variables. An evaluation of the possible interaction between the effect of serelaxin on the two primary and key secondary efficacy endpoints and LVEF <40 vs. ≥40% was pre-specified. The cut-off of 50% to classify patients with HFrEF vs. those with HFpEF was selected

### Table I Continued

| Medication (Day 0, except nitrates) (%) | LVEF < 50 (n = 810) | LVEF ≥ 50 (n = 281) | P-value |
|--------------------------------------|---------------------|---------------------|--------|
| ACE inhibitor                        | 455 (56.2)          | 148 (52.7)          | 0.31   |
| Angiotensin-receptor blocker          | 131 (16.2)          | 46 (16.4)           | 0.94   |
| Beta-blocker                         | 586 (72.3)          | 174 (61.9)          | 0.0011 |
| Aldosterone antagonist               | 289 (35.7)          | 63 (22.4)           | <0.0001|
| Intravenous loop diuretics           | 808 (99.8)          | 280 (99.6)          | 1.0000 |
| Digoxin                              | 172 (21.2)          | 45 (16.0)           | 0.059  |
| Nitrates at randomization            | 46 (5.7)            | 26 (9.3)            | 0.038  |

Baseline labs

| Continuous variables are expressed as mean (SD) or geometric mean (95% CI) and categorical variables as n (%). | LVEF < 50 (n = 810) | LVEF ≥ 50 (n = 281) | P-value |
|----------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--------|
| Sodium, mmol/L                                                   | 140.7 (3.6)         | 141.3 (3.7)         | 0.026  |
| Haemoglobin, g/dL                                                | 13.03 (1.84)        | 12.14 (1.76)        | <0.0001|
| Haematocrit ratio                                                | 0.4213 (0.0565)     | 0.3929 (0.0539)     | <0.0001|
| White blood cell count, × 10⁹/L                                  | 8.140 (2.710)       | 8.215 (3.134)       | 0.71   |
| Lymphocyte, (%)                                                  | 18.30 (7.75)        | 18.18 (7.95)        | 0.84   |
| Potassium, mmol/L                                                | 4.31 (0.64)         | 4.21 (0.65)         | 0.031  |
| Creatinine, μmol/L                                               | 118.7 (34.2)        | 112.1 (30.5)        | 0.0050 |
| Uric acid, μmol/L                                                | 483.4 (142.2)       | 462.2 (121.4)       | 0.028  |
| Troponin T, μg/L                                                 | 0.037 (0.035, 0.039)| 0.030 (0.028, 0.034)| 0.0013 |
| BUN, mmol/L                                                      | 9.85 (4.02)         | 9.78 (4.23)         | 0.82   |
| Cystatin-C, mg/L                                                 | 1.44 (1.41, 1.47)   | 1.52 (1.47, 1.57)   | 0.0055 |
| Alanine aminotransferase, U/L                                    | 30.6 (35.0)         | 26.2 (20.4)         | 0.051  |
| Aspartate aminotransferase, U/L                                  | 32.1 (31.9)         | 27.5 (13.9)         | 0.025  |
| NT-proBNP, ng/L                                                  | 5535 (5194, 5897)   | 3992 (3632, 4388)   | <0.0001|
Results

An LVEF measurement was available for 1091 of the 1161 patients randomized; 281 of them (26%) had HFrEF. A comparison of baseline features between HFrEF and HPefEF patients is shown in Table 1. Patients with HFrEF were older and more often female compared with those with HFrEF. They were less likely to have a history of ischaemic heart disease or of a prior AHF hospitalization in the year before randomization and were more likely to have arterial hypertension and atrial fibrillation. Regarding medication, HPefEF patients had similar use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers but lower use of beta-blockers and mineralocorticoid receptor antagonists compared with patients with HFrEF. As expected, the use of device therapy was low in HFrEF. Upon presentation, the two groups did not differ in clinical signs and symptoms of congestion. However, HPefEF patients had higher systolic blood pressure and lower concentrations of NT-proBNP, troponin T and serum creatinine.

Efficacy

The effect of treatment (serelaxin vs. placebo) on several efficacy endpoints in HFrEF and HPefEF patients is presented in Table 2. Serelaxin induced a similar dyspnoea relief in HFrEF and HPefEF patients through Day 5 according to VAS-AUC (mean AUC change, 461 vs. 397 mm²×h, respectively, P for interaction = 0.8683; Figure 1A). A nominally statistically significant interaction was found for the proportion of patients with moderately or markedly improved dyspnoea at 6, 12, and 24 h on Likert scale (odds ratio 1.70 vs. 0.85, P for interaction = 0.030), which was not reflected at each individual time point (Figure 1B). Regarding short- and long-term outcome, serelaxin had a similar effect in HFrEF and HPefEF patients on cardiovascular death or hospitalization for heart or renal failure through Day 60 (hazard ratio, 1.08 vs. 1.10, P for interaction = 0.97, Figure 2). days alive and out of hospital through Day 60 (−1.28 vs. 0.86, P for interaction = 0.19), cardiovascular death through Day 180 (0.59 vs. 0.64, P for interaction = 0.87, Figure 3). While serelaxin appeared to reduce the risk of cardiovascular mortality by roughly the same extent in both HFrEF and HPefEF (Figure 3), the rate of rehospitalization for HF/RF was higher in the serelaxin group in both EF groups, particularly in patients with HFrEF, reflected in an apparently greater detrimental serelaxin effect on the composite outcome in the HPefEF group (Figure 2); however, given the smaller size of the HPefEF group, the role of chance in these findings cannot be ruled out. There was no difference between HFrEF and HPefEF patients in the effects of serelaxin on all additional endpoints such as total dose of intravenous loop diuretics to Day 5, change in weight through Day 5, and length of hospital stay or days in ICU/CCU (Table 2). An analysis reclassifying nine HPefEF patients with post hoc to be consistent with the guidelines. Estimates of the serelaxin treatment effect (odds ratio, mean difference, or hazard ratio) for patients with HFrEF and HPefEF and an interaction test were obtained from a separate regression model (logistic, analysis of covariance, or Cox) for each outcome that included the effects of serelaxin, LVEF (<50 vs. ≥50), and the serelaxin-by-ejection fraction interaction. Analyses were conducted on an intent-to-treat basis. All P-values were two-sided, and values <0.05 were considered nominally statistically significant. SAS® release 9.2 (SAS Institute, Cary, NC, USA) was used for analysis.
biventricular pacing and/or implantable cardiac defibrillator as HFrEF showed nearly identical results.

Using an LVEF cut-off of 40% to differentiate between HfPEF and HFrEF, 46% of patients were classified as HfPEF. In this case, the results regarding primary and secondary endpoints were similar, except for the difference in dyspnoea relief by Likert scale that was significant between HfPEF and HFrEF only with the 50% threshold.

**Safety**

The effect of treatment (serelaxin vs. placebo) on safety endpoints in HFrEF and HfPEF patients is presented in Table 3. Serelaxin had a

![Figure 1](image-url)  

**Figure 1** Patient-reported dyspnoea change (serelaxin vs. placebo) by category of left ventricular ejection fraction (LVEF), (<50% vs. ≥50%), according to visual analogue scale from baseline to Day 5 (A; increasing values represent improvement) and Likert scale during the first 24 h (B; interaction P values are for the proportions of patients with markedly or moderately improved dyspnoea).
similar effect in HFrEF and HFpEF patients on all-cause death through Day 180 (0.70 vs. 0.63, \( P \) for interaction = 0.82, Figure 3). There was no difference in the occurrence of confirmed blood pressure decrease or confirmed blood pressure decrease that led to dose reduction or to drug discontinuation following serelaxin between HFrEF and HFpEF patients (\( P \) for interaction, 0.17, 0.06 and 0.77, respectively). Furthermore, no differences between the two groups were observed in the occurrence of additional safety endpoints (Table 3).

**Biomarkers of organ damage**

The effect of treatment (serelaxin vs. placebo) on biomarkers indicative of organ damage in HFrEF and HFpEF patients is presented in Table 4. Serelaxin reduced plasma levels of NT-proBNP, cardiac troponin T, cystatin-C, serum creatinine and BUN and transaminases, compared with placebo, and there appeared to be no difference based on ejection fraction status (HFrEF vs. HFpEF) regarding the effects of serelaxin on any of these biomarkers measured from baseline to 48 h (all \( P \) for interaction > 0.05).

The results concerning efficacy and safety endpoints were similar when analyses were performed using an LVEF cut-off of 40%.

**Discussion**

In the RELAX-AHF study, a 48-h infusion of serelaxin in AHF patients improved dyspnoea and other symptoms and signs of congestion and reduced early AHF worsening and hospitalization length.\(^{13}\) The drug failed to improve post-discharge readmission rate, but provided a significant 37% reduction in 180-day cardiovascular and all-cause mortality and was well tolerated.\(^{13}\) In addition, serelaxin induced a short-term favourable effect on biomarkers of myocardial, renal, and hepatic injury, an effect that may be associated with increased survival.\(^{14}\) In the present trial, we showed that the aforementioned effects of serelaxin on symptoms, outcome, and organ protection were similar in patients with HFrEF and HFpEF. Although the treatment groups differed with respect to in-hospital IV loop diuretic use, the difference was similar in patients with preserved and reduced EF. Decreases in body weight, incidence of adverse events related to hypotension or renal failure, and changes in biomarkers were similar in the treatment groups and between subgroups. Further data with respect to post-randomization management of patients who may have affected outcomes and they may have differed in HFpEF patients, such HbA1c levels or conversion to sinus rhythm, are not available. Serelaxin was well tolerated in both subgroups. Serelaxin was even more effective in improving dyspnoea at 6, 12, and 24 h on Likert scale in patients with HFpEF compared with those with HFrEF, although this was not reflected at each individual time point or by VAS-AUC through Day 5 and therefore it may not represent a real effect.

Patients with HFpEF represent a population with particular demographic and clinical features. The HFpEF patients enrolled in RELAX-AHF are representative of the HFpEF population. In accordance with earlier registries such as the Acute Decompensated Heart Failure National Registry (ADHERE)\(^{16}\) or the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF)\(^{17}\) and the most recent Meta-analysis of Global Group in Chronic Heart Failure (MAGGIC) that concerned nearly 42,000 cases from 31 trials,\(^{18}\) the HFpEF patients are older and more often female and have a higher prevalence of arterial hypertension and atrial fibrillation and a lower prevalence of ischaemic aetiology, compared with the patients with HFrEF. Older age, female gender, and atrial fibrillation were among the strong risk factors for new-onset HFpEF according to recently released data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort study.\(^{19}\)
Given the lack of evidence-based therapies, the recently published findings of the Cardiovascular Research Network show that HFpEF patients are significantly less likely to be treated with multiple cardioactive drugs or multiple heart failure-related drug therapies. Accordingly, the present HFpEF population was treated less frequently with beta-blockers, mineralocorticoid receptor antagonists, or device therapies compared with the HFrEF subgroup. Upon presentation, the two subgroups had similar clinical signs of congestion, but HFpEF patients had higher systolic blood pressure and lower NT-proBNP. The presence of lower natriuretic peptide levels in acutely decompensated HFpEF in association with similar AHF severity compared with HFrEF has also been previously reported by a sub-analysis of the Diuretic Optimization Strategies Evaluation (DOSE) trial.

RELAX-AHF was the first trial to provide an intermediate-term mortality reduction in AHF and these results were obtained in a patient population including a meaningful proportion of patients with HFpEF. This is rather unique as several drug classes that

---

**Figure 3** Kaplan–Meier curves for cardiovascular death through Day 180 (A, upper panel) and all-cause death through Day 180 (B, lower panel) according to LVEF. HR, hazard ratio.
represent established therapies of HFrEF failed to provide similar benefits in HFpEF. Hence, none of the three earlier randomized studies on renin–angiotensin–aldosterone system inhibitors (peri-
dopril, candesartan, and irbesartan) in chronic HFpEF patients met their primary endpoints and the same applied to the two recently released trials testing the mineralocorticosteroid receptor antagonist spironolactone and the phosphodiesterase-5 inhibitor sildenafil, while no drug has been previously studied specifically in AHF with preserved LVEF.6–12 A number of reasons have been postulated for these neutral effects. The lack of a universally accepted definition of HFpEF and the heterogeneity of HFpEF population7,8 and the presence of mild haemodynamic, neurohormonal, or other pathogenetic changes in many of the patients enrolled in those trials have been postulated as potential explanations for the observed lack of clinical benefit. In addition, it may be that HFpEF becomes symptomatic mainly as AHF with the characteristics of an episodic disease.23 Thus, AHF might be a more appropriate setting to study the efficacy of treatment in these patients. In RELAX-AHF, all HFpEF patients were acutely decompensated and were required to have objective evidence of congestion and increased levels of natriuretic peptide, hence allowing more space for clinical improvement.

A main drawback of drugs used in AHF such as inotropes and diuretics is the induction of organ function deterioration and/or damage.24,25 Myocardial, renal, and hepatic injury, as depicted by corresponding biomarkers, has been associated with an adverse outcome in AHF.26–28 This may be the key to the neutral or negative effects of previous trials in AHF. On the other hand, it has been hypothesized that the prevention of these detrimental effects may improve patients’ prognosis and survival.13,14 The RELAX-AHF trial showed that serelaxin was followed by a reduction of biomarkers indicative of myocardial (troponin T), renal (cystatin-C), and hepatic (aminotransferases) injury.14 We showed herein that this effect was observed both in patients with HFpEF and in those with HFrEF. This favourable action may account at least in part for the observed beneficial outcome associated with serelaxin. Moreover, serelaxin was able to manage congestion effectively, as shown not only by the significant relief of dyspnoea and other symptoms and signs of congestion and the decreased heart failure worsening rate but also by the reduction of natriuretic peptide levels. The response of natriuretic peptides to AHF treatment has been associated with adverse prognosis in AHF.29,30 Additional pathogenetic mechanisms of AHF worsening that may theoretically be addressed by serelaxin and therefore may contribute to the observed benefit from the drug include increased LV afterload, inflammation, and oxidative stress.31

The present study bears the expected limitations of a post hoc subgroup analysis. Moreover, the main RELAX-AHF study was not primarily designed and powered to assess mortality.13,15 Given these limitations, the effects of serelaxin on HFpEF patients should be confirmed by subsequent trials.

In conclusion, serelaxin was well tolerated and effective in early dyspnoea relief and in improving multiple outcomes including 180-day mortality irrespective of LVEF. Future studies with larger sample sizes will be needed to confirm these findings.

Funding
The RELAX-AHF trial was supported by Corthera Inc., a member of the Novartis group of companies. Steve Winter of Novartis Pharma AG, Basel, Switzerland and Graham Alcock of CircleScience (Tytherington, UK) helped in the preparation of the figures, which was funded by Novartis Pharma AG, Basel, Switzerland. Funding to pay the Open Access publication charges for this article was provided by Novartis Pharma AG.

Conflict of interest: G.F. is an executive committee member and consultant to Corthera (a Novartis company), Bayer, Cardiorentis, and has received research grants from Amgen, Nanosphere, European Committee. J.R.T. has received research grants or consulting fees from Amgen, Bayer, Corthera, Cardio3 BioSciences, Cytokinetics, Merck, Novartis, Takeda, Teva, and Trevena. G.C. and B.A.D. are employees of Momentum Research, which has provided consulting services to NovaCardia, Merck, Corthera, Novartis, Singulex, ChanRx, Sorbent Therapeutics, Cardio3 BioSciences, Trevena, Amgen, and Anexon. G.M.F. reports

| Table 3 | Treatment effect (serelaxin vs. placebo) on safety endpoints in patients with reduced (<50%) and preserved (≥50%) left ventricular ejection fraction |
|-------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Outcome | LVEF < 50 (n = 793) | | LVEF ≥ 50 (n = 275) | | P-value for interaction |
| | Placebo (n = 388) (%) | Serelaxin (n = 405) (%) | Placebo (n = 141) (%) | Serelaxin (n = 134) (%) | |
| Patients with any SAE through Day 14 | 12.1 | 14.1 | 17.7 | 17.2 | 0.58 |
| Patients with SAE with an outcome of death through Day 14 | 1.5 | 1.5 | 4.3 | 3.0 | 0.71 |
| Total % of patients with AE indicative of hypotension through Day 14 | 4.9 | 4.7 | 4.3 | 5.2 | 0.69 |
| Total % of patients with AE indicative of renal impairment through Day 14 | 7.5 | 4.0 | 11.3 | 9.0 | 0.42 |
| Total % of patients with AE indicative of hepatic impairment through Day 14 | 2.6 | 1.0 | 4.3 | 0.7 | 0.52 |

SAE, serious adverse events; AE, adverse events.

aBlood pressure decreased, dizziness, loss of consciousness, hypotension, orthostatic hypotension, presyncope, somnolence, or syncope.
bAzotemia, blood creatinine increased, oliguria, proteinuria, renal failure, renal failure acute, or renal impairment.
cBlood bilirubin increased, cholestasis, hepatic congestion, hepatic cyst, hepatic steatosis, hyperbilirubinaemia, hypoalbuminaemia, INR increased, or liver disorder.
dHypotension through Day 14.
Serelaxin in AHF patients with preserved LVEF

1049

50%) and preserved (≥50%) left ventricular ejection fraction: the CHARM-Preserved Trial.

Outcome LVEF

50% (n = 810) LVEF

≥50% (n = 139)

Serelaxin (n = 413)

Placebo (n = 125)

Treatment effect (95% CI)

Placebo (n = 297)

Serelaxin (n = 413)

Treatment effect (95% CI)

Treatment effect represents ratio of relative changes or mean difference.

cTNT, cardiac troponin-T; NT-proBNP, N-terminal B-type natriuretic pro-peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Halpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lissibeth LD, Makuc DM, Marcus GM, Mearllo A, Matsui DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Pyntner NR, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Vrani SS, Wang ND, Woo D, Turner MB. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:62–220.

2. Gheorghide M, Konstant MA, Burnett JC Jr, Grinfeld L, Maggioli AP, Swedberg K, Udellslin J, Zannad F, Cook T, Ouyang Z, Zimmer C, Ondal C. Efficacy of Vasopres- sin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–1343.

3. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pacsoj SJ, Thakkar R, Padley RJ, Padler P, Kukko M. SURVIVE Investigators. Rososimod vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized Trial. JAMA 2007;297:1883–1891.

4. Massie BM, O’Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherby BD, Cleland JG, Givertz MM, Voors A, DeLuccia P, Manosor GA, Salerno CM, Bloomfield DM, Dittrich HC. PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419–1428.

5. O’Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Masie BM, Murray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanza MR, Dalhostu U, Deckelbaum Li, Diaz R, Dunlap ME, Ezeokwite AJ, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander J, Howlett JG, Hudson MP, Kociol RD, Krum H, Lauzévicus A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomos S, Teerlink JR, Triposiakis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Caill RRM. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2010;363:32–43.

6. Murray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filipatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kaber L, Lip GY, Magnoni AP, Parkhomenko A, Pieske BM, Popescu BA, Rannevik PK, Rutten RH, Schwieter J, Serofovic P, Stepins J, Trindade PT, Voors AA, Zannad F, Zehler A; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–1847.

7. Alla F, Zannad F, Filipatos G. Epidemiology of acute heart failure syndromes. Heart Fail Rev 2007;12:91–95.

8. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olsson B, Ostergren J. CHARM Investigators and Committees. Effects of candes- sarant in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
9. Cleland JG, Tendera M, Adkins J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investi-
gigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338 – 2345.
10. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, 
Donovan M, Iversen E, Staiger C, Ptaszynska A; PRESERVE Investigators. Irbesartan 
in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359: 
2456 – 2467.
11. Eddleman F, Wachter R, Schmidt AG, Kraigher-Kramer E, Colantonio C, Kanke W, 
Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dünge ND, Tschöpe C, 
Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investi-
gators. Effect of spironolactone on diastolic function and exercise capacity in 
patients with heart failure with preserved ejection fraction: the Aldo-DHF random-
ized controlled trial. JAMA 2013;309:781 – 791.
12. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, 
Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Redfield MM, 
Ponikowski P, Jorde IR, Ponikowski P, Metra M, Teerlink JR, Unemori E, Felker GM, 
Teerlink JR, Cotter G, Davison BA, Felker GM, O'Connor CM, Young JB; OPTIMIZE-HF Inves-
tigators and Hospitals. Characteristics, treatments, and outcomes of patients with 
heart failure: on behalf of the third Universal Definition of Myocar-
dial Infarction Global Task Force: Heart Failure Section. Eur Heart J 2012;33: 
2265 – 2271.
13. Teerlink JR, Cotter G, Davison BA, Felker GM, Filipatos G, Greenberg BH, 
Ponkowski P, Umemori E, Voors AA, Adams KF Jr, Dorobantu ML, Grinfeld LR, 
Jorde IR, Garmor M, Masaj P, Pang PS, Wardan K, Teichman SL, Trapani A, 
Bush CA, Saini R, Schumacher C, Severin TM, Metra M; RELAXin in Acute Heart 
Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for 
treatment of acute heart failure: a randomized, placebo-controlled trial. Lancet 2013;381: 
29 – 39.
14. Meta M, Cotter G, Davison BA, Felker GM, Filipatos G, Greenberg BH, 
Ponkowski P, Umemori E, Voors AA, Adams KF Jr, Dorobantu ML, Grinfeld LR, 
Jorde IR, Garmor M, Masaj P, Pang PS, Wardan K, Prescott MF, Edwards C, 
Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR; 
RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomark-
ers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: cor-
relation with outcomes. J Am Coll Cardiol 2013;61:196 – 206.
15. Ponkowski P, Metra M, Teerlink JR, Umemori E, Felker GM, Voors AA, Filipatos G, 
Greenberg BH, Teichman SL, Severin T, Mueller-Velten G, Cotter G, Davison BA. 
Design of the RELAXin in acute heart failure study. Am Heart J 2012;163:149 – 155.
16. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scien-
tific Advisory Committee and Investigators. Clinical presentation, management, and 
in-hospital outcomes of patients admitted with acute decompensated heart failure. 
An analysis of the Acute Decompensated Heart Failure National Registry (ADHERE) database. J Am Coll Cardiol 2006;47:76 – 84.
17. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, 
Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JR; OPTIMIZE-HF Investi-
gators and Hospitals. Characteristics, treatments, and outcomes of patients with 
preserved systolic function hospitalized for heart failure: a report from the 
OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768 – 777.
18. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of 
patients with heart failure with preserved or reduced left ventricular ejection frac-
tion: an individual patient data meta-analysis. Eur Heart J 2012;33:1750 – 1757.
19. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, 
Hillegé HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new 
onset heart failure with preserved vs. reduced ejection fraction in a community-based 
cohort: 11-year follow-up of PREVEND. Eur Heart J 2013;34:1424 – 1431.
20. Goldberg RJ, Gurwitz JH, Szczyglowski JS, Hsu G, McManus DD, Magid DJ, Smith DH, 
Go AS; CVRN PRESERVE HF Investigators. Comparison of medication practices 
in patients with heart failure and preserved versus those with reduced ejection frac-
tion (from the Cardiovascular Research Network [CVRN]). Am J Cardiol 2013;111: 
1324 – 1329.
21. Bishu K, Deswal A, Chen HH, LeWinter MM, Lewis GD, Semigran MJ, Borlaug BA, 
McNulty S, Hernandez AF, Braunwald E, Redfield MM. Biomarkers in acutely decomp-
ensated heart failure with preserved or reduced ejection fraction. Am Heart J 2012; 
164:763 – 770.
22. Cleland JG, Pellicori P. Defining diastolic heart failure and identifying effective ther-
apies. JAMA 2013;309:825 – 826.
23. Banerjee P, Clark AH, Nikitin N, Cleland JG. Diastolic heart failure. Paroxysmal or 
chronic? Eur Heart J 2004;6:427 – 431.
24. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation 
in patients with heart failure: on behalf of the third Universal Definition of Myocar-
dial Infarction Global Task Force: Heart Failure Section. Eur Heart J 2012;33: 
2265 – 2271.
25. Parissis JT, Farmakis D, Nieminen M. Classical inotropes and new cardiac enhancers. 
Heart Fail Rev 2007;12:149 – 156.
26. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. 
Troponin elevation in heart failure prevalence, mechanisms, and clinical impli-
cations. J Am Coll Cardiol 2010;56:1071 – 1078.
27. Meta M, Cotter G, Gheorghiade M, Diez C, Voors AA. The role of the kidney in 
heart failure. Eur Heart J 2012;33:2135 – 2142.
28. Ambrosy AP, Vaduganathan M, Huffman MD, Khan S, Kwasny MJ, Fought AJ, 
Maggioni AP, Swedberg K, Konstam MA, Zannad F, Gheorghiade M; EVEREST 
trial investigators. Clinical course and predictive value of liver function tests in patients 
hospitalized for worsening heart failure with reduced ejection fraction: an analysis of 
the EVEREST trial. Eur Heart J 2012;33:302 – 311.
29. Farmakis D, Parissis JT, Bistola V, Parissis JT, Bistola V, Parissis JT, Bistola V, 
Farmakis D, Parissis JT, Bistola V; RELAXin in Acute Heart Failure (RELAX-AHF) 
Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure: a randomized, placebo-controlled trial. Lancet 2013;381:196 – 206.
30. Ponkowski P, Metra M, Teichman SL, Severin T, Mueller-Velten G, Cotter G, Davison BA. 
Design of the RELAXin in acute heart failure study. Am Heart J 2012;163:149 – 155.
31. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scien-
tific Advisory Committee and Investigators. Clinical presentation, management, and 
in-hospital outcomes of patients admitted with acute decompensated heart failure with 
preserved systolic function: a report from the Acute Decompensated Heart 
Failure National Registry (ADHERE) database. J Am Coll Cardiol 2006;47:76 – 84.
32. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, 
Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JR; OPTIMIZE-HF Investi-
gators and Hospitals. Characteristics, treatments, and outcomes of patients with 
preserved systolic function hospitalized for heart failure: a report from the 
OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768 – 777.
33. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of 
patients with heart failure with preserved or reduced left ventricular ejection frac-
tion: an individual patient data meta-analysis. Eur Heart J 2012;33:1750 – 1757.