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

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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 (−195, 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.[1] Several recent trials have evaluated novel vasoactive agents in this syndrome, but failed to provide any evidence on outcome improvement.[2–5] 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]

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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	7.7 (4.6)	8.5 (4.7)	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/m^2	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

Table I *Continued*

	LVEF < 50 (n = 810)	LVEF ≥ 50 (n = 281)	P-value
Medication (Day 0, except nitrates) (%)			
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			
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, $\times 10^9$/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

Continuous variables are expressed as mean (SD) or geometric mean (95% CI) and categorical variables as n (%). EU, Europe; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; JVP, jugular venous pressure; DOE, dyspnoea on exertion; VAS, visual analogue scale; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

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 placebo.[13,14] A substantial proportion of patients in RELAX-AHF had a preserved left ventricular ejection fraction (LVEF). In the present study, we assessed the efficacy and safety of serelaxin in patients with HFpEF, compared with those with HFrEF.

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 χ^2 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 2 Treatment effect (serelaxin vs. placebo) on various outcomes in patients with reduced (<50%) and preserved (≥50%) left ventricular ejection fraction

Outcome	LVEF < 50 (*n* = 810)			LVEF ≥ 50 (*n* = 281)			*P*-value for interaction
	Placebo (*n* = 397)	Serelaxin (*n* = 413)	Treatment effect (95% CI)	Placebo (*n* = 142)	Serelaxin (*n* = 139)	Treatment effect (95% CI)	
Dyspnoea improvement by VAS-AUC to Day 5	2312.3 (3034.5)	2708.9 (2484.3)	396.67 (10.3, 783.0)	2366.4 (2963.3)	2827.5 (2827.9)	461.02 (−194.8, 1116.9)	0.87
Dyspnoea improvement by Likert scale at 6, 12, and 24 h	113 (28.5%)	104 (25.2%)	0.85 (0.62, 1.15)	28 (19.7%)	41 (29.5%)	1.70 (0.98, 2.95)	0.030
Total dose of IV loop diuretics before Day 5, mg	229.5 (399.2)	161.5 (268.8)	−68.0 (−112.6, −23.4)	176.3 (242.2)	167.9 (275.4)	−8.4 (−84.0, 67.3)	0.18
Change in bodyweight to Day 5, kg	−3.0 (3.4)	−2.8 (3.4)	0.2 (−0.3, 0.7)	−3.0 (3.4)	−2.4 (3.3)	0.6 (−0.2, 1.4)	0.38
Length of initial hospital stay, days	10.4 (9.3)	9.4 (8.6)	−1.0 (−2.3, 0.3)	10.7 (10.4)	10.6 (10.9)	−0.04 (−2.3, 2.2)	0.47
Days in ICU/CCU	3.7 (6.4)	3.4 (6.6)	−0.4 (−1.4, 0.6)	4.2 (8.1)	4.0 (8.9)	−0.1 (−1.8, 1.5)	0.82
Days alive out of hospital through Day 60	47.7 (11.8)	48.6 (11.3)	0.86 (−0.77, 2.49)	47.9 (12.3)	46.6 (13.3)	−1.28 (−4.05, 1.50)	0.19
Cardiovascular death or HF/RF hospitalization through Day 60	50 (12.64%)	56 (13.68%)	1.10 (0.75, 1.61)	18 (12.75%)	19 (13.85%)	1.08 (0.57, 2.06)	0.97
All-cause death through Day 180	44 (11.14%)	29 (7.08%)	0.63 (0.39, 1.00)	16 (11.32%)	11 (8.08%)	0.70 (0.32, 1.50)	0.82
Cardiovascular death through Day 180	37 (9.43%)	25 (6.12%)	0.64 (0.39, 1.07)	12 (8.53%)	7 (5.13%)	0.59 (0.23, 1.50)	0.87

Continuous variables are expressed as mean (SD) or geometric mean (95% CI), categorical variables as *n* (%), and time-to-event variables as *n* (K-M%). Treatment effect represents mean difference for continuous variables, odds ratio for dichotomous variables, and hazard ratio for time-to-event variables, estimated from ANCOVA, logistic regression, and Cox regression models, respectively. VAS, visual analogue scale; AUC, area under the curve; ICU/CCU, intensive care unit/coronary care unit; HF, heart failure; RF, renal failure.

post hoc to be consistent with the guidelines.[5,6] Estimates of the serelaxin treatment effect (odds ratio, mean difference, or hazard ratio) for patients with HFrEF and HFpEF 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.

Results

An LVEF measurement was available for 1091 of the 1161 patients randomized; 281 of them (26%) had HFpEF. A comparison of baseline features between HFrEF and HFpEF patients is shown in *Table 1*. Patients with HFpEF 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, HFpEF patients had similar use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers but lower use of beta-blockers and mineralocorticosteroid receptor antagonists compared with patients with HFrEF. As expected, the use of device therapy was low in HFpEF. Upon presentation, the two groups did not differ in clinical signs and symptoms of congestion. However, HFpEF 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 HFpEF patients is presented in *Table 2*. Serelaxin induced a similar dyspnoea relief in HFpEF and HFrEF patients through Day 5 according to VAS-AUC (mean AUC change, 461 vs. 397 mm × 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 HFpEF and HFrEF 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 HFpEF and HFrEF (*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 HFrEF group (*Figure 2*); however, given the smaller size of the HFpEF group, the role of chance in these findings cannot be ruled out. There was no difference between HFpEF and HFrEF 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 HFpEF patients with

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

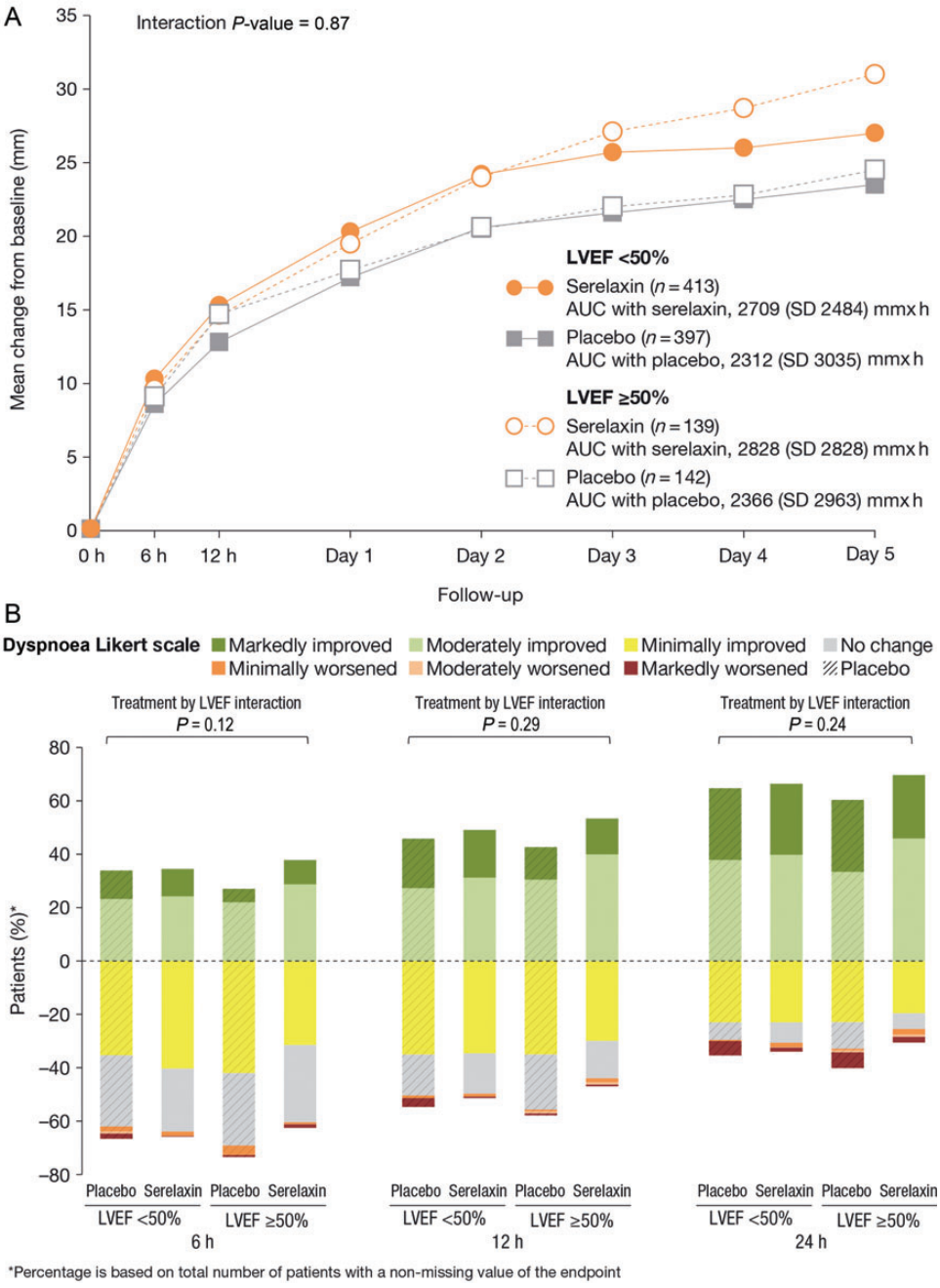


Figure 1 Patient-reported dyspnoea change (serelaxin vs. placebo) by category of left ventricular ejection fraction (LVEF), (<50% vs. ≥50%), according to visual analogue scale from baseline to Day 5 (*A*; increasing values represent improvement) and Likert scale during the first 24 h (*B*; interaction *P* values are for the proportions of patients with markedly or moderately improved dyspnoea).

similar effect in HFpEF and HFrEF 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]

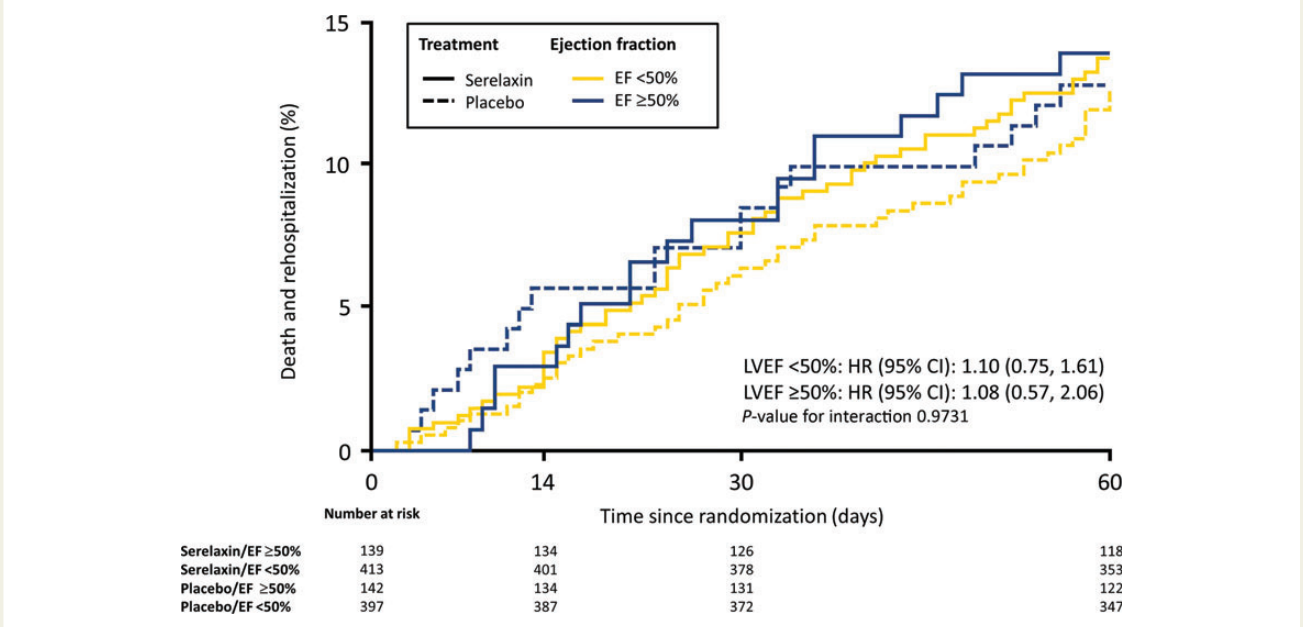
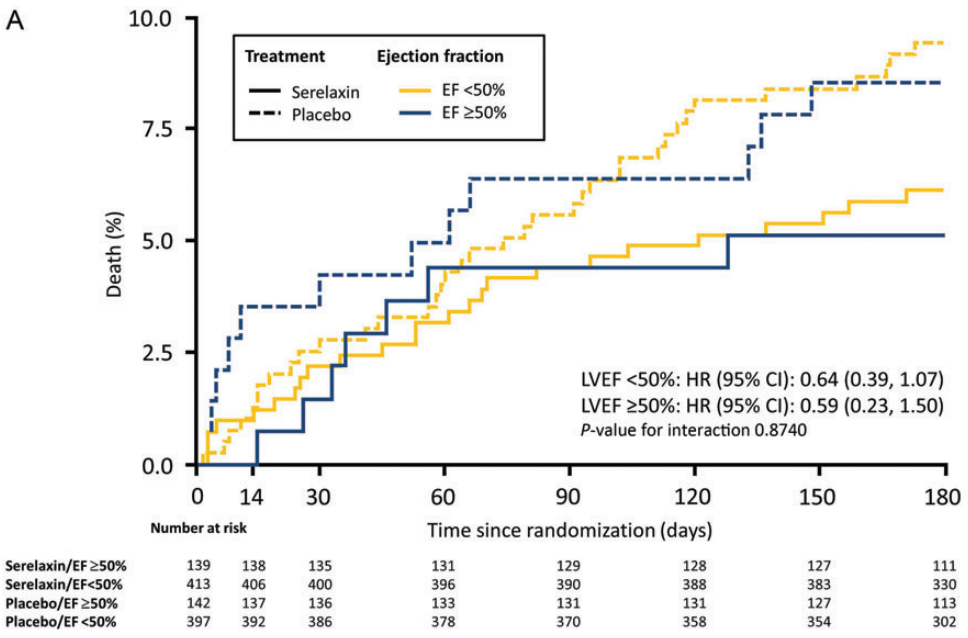


Figure 2 Kaplan–Meier curves for cardiovascular death or hospitalization for heart/renal failure through Day 60 according to LVEF. HR, hazard ratio.



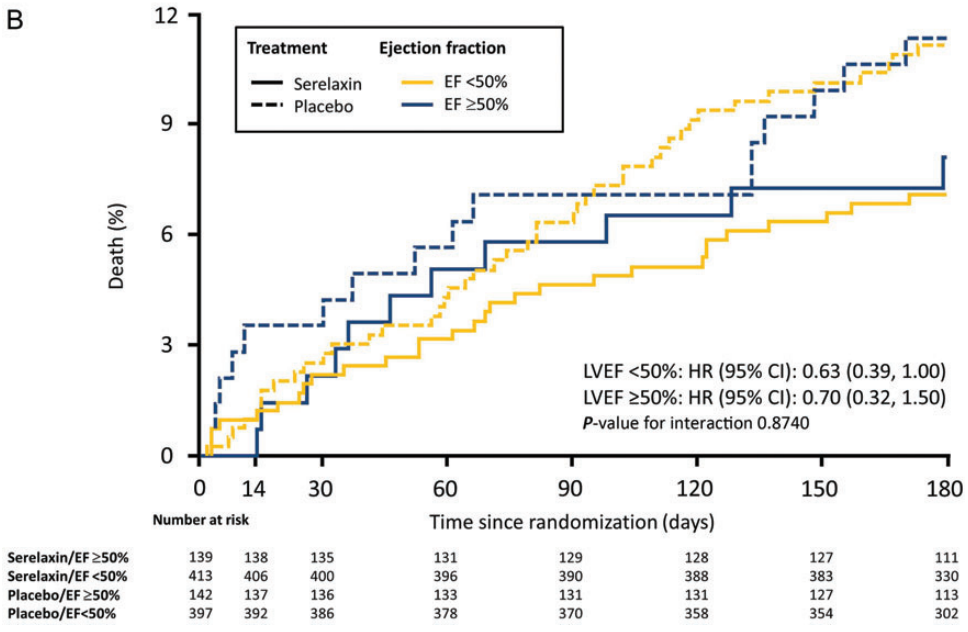


Figure 3 Kaplan–Meier curves for cardiovascular death through Day 180 (*A*, upper panel) and all-cause death through Day 180 (*B*, lower panel) according to LVEF. HR, hazard ratio.

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.[20] Accordingly, the present HFpEF population was treated less frequently with beta-blockers, mineralocorticosteroid 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.[21]

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

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[a]	4.9	4.7	4.3	5.2	0.69
Total % of patients with AE indicative of renal impairment through Day 14[b]	7.5	4.0	11.3	9.0	0.42
Total % of patients with AE indicative of hepatic impairment through Day 14[c]	2.6	1.0	4.3	0.7	0.52

SAE, serious adverse events; AE, adverse events.
[a]Blood pressure decreased, dizziness, loss of consciousness, hypotension, orthostatic hypotension, presyncope, somnolence, or syncope.
[b]Azotemia, blood creatinine increased, oliguria, proteinuria, renal failure, renal failure acute, or renal impairment.
[c]Blood bilirubin increased, cholestasis, hepatic congestion, hepatic cyst, hepatic steatosis, hyperbilirubinaemia, hypoalbuminaemia, INR increased, or liver disorder.

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 (perindopril, 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.[8–12] 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 population[22] 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.[13,27] 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 HFrEF and in those with HFpEF. 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 irrespectively of LVEF. Future studies with larger sample sizes will be needed to confirm these findings.

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Table 4 Treatment effect (serelaxin vs. placebo) on biomarkers of organ damage in patients with reduced (<50%) and preserved (≥50%) left ventricular ejection fraction

Outcome	LVEF < 50% (n = 810)			LVEF ≥ 50% (n = 281)			P for interaction
	Placebo (n = 397)	Serelaxin (n = 413)	Treatment effect (95% CI)	Placebo (n = 142)	Serelaxin (n = 139)	Treatment effect (95% CI)	
Ratio (95% CI) of change from baseline to 48 h							
Cystatin-C	1.07 (1.05, 1.09)	1.02 (1.00, 1.04)	0.95 (0.93, 0.97)	1.09 (1.06, 1.12)	1.03 (1.00, 1.07)	0.95 (0.91, 0.99)	0.96
cTNT	1.045 (0.997, 1.095)	0.955 (0.911, 1.002)	0.91 (0.86, 0.98)	1.002 (0.927, 1.083)	0.946 (0.888, 1.008)	0.94 (0.85, 1.05)	0.62
NT-proBNP	0.626 (0.583, 0.672)	0.498 (0.469, 0.529)	0.80 (0.72, 0.87)	0.555 (0.500, 0.615)	0.469 (0.409, 0.536)	0.84 (0.72, 0.99)	0.53
Mean (SD) change from baseline to 48 h							
AST, U/L	−0.7 (38.8)	−8.4 (28.4)	−7.69 (−12.07, −3.30)	−3.7 (8.1)	−5.3 (8.8)	−1.58 (−9.02, 5.87)	0.17
ALT, U/L	−1.0 (27.0)	−6.4 (19.3)	−5.44 (−8.41, −2.47)	−4.8 (9.1)	−5.9 (9.4)	−1.07 (−6.16, 4.02)	0.15

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.

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