Effects of Serelaxin on the Outcome of Patients with or without Substantial Peripheral edema: A Subgroup Analysis from the RELAX-AHF Trial

AUTHORS

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CG conceptualized the sub-group categorization, hypothesized and initiated the current analysis. MM, MF, GF, BG, Piotr P, AV, JT, GC and BD were former EC members of the main RELAX-AHF trial and have contributed to the original study design, execution and overall data interpretation of the main RELAX-AHF trial. They have provided intellectual contribution to the conception and interpretation of the data of the current sub-group analysis. Peter P and JC served as national leaders of the RELAX-AHF trial and have provided intellectual contribution to the conception and interpretation of the current data. CG, PS, TS, LBM and CCW have provided intellectual contribution to the current sub-group analysis and discussion. CCW has also provided statistical support.

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ABSTRACT

Background: Acute heart failure (AHF) is a heterogeneous disorder with most of the patients presenting with breathlessness along with varying degrees of peripheral edema. The presence of peripheral edema suggests that volume overload is the cause of decompensation leading to AHF, while breathlessness in the absence of edema may reflect a "vascular phenotype". This analysis investigated the characteristics, therapeutic response and outcome of patients with AHF, with and without overt peripheral edema in the RELAX-AHF trial.

Methods: Physician-assessed edema scores at baseline were used to categorize the population into those with no /mild edema (score 0 or 1+) and moderate/severe edema (score 2+ or 3+). The effect of serelaxin versus placebo was assessed within each subgroup.

Results: Patients with moderate/severe edema (n = 583; 50.5%) were more likely to have severe dyspnea, orthopnea (>30 degrees), rales (≥1/3) and elevated jugular venous pressure (>6 cm) than the patients with little or no peripheral edema (n=571; 49.5%) The relative benefits of serelaxin in terms of reduction in breathlessness, lower diuretic requirements, decreased length of initial hospital stay and days in ICU/CCU, and improved prognosis (180-day cardiovascular and all-cause mortality) were generally similar for patients with or without peripheral edema. However, as patients with moderate/severe peripheral edema had worse outcomes, the absolute benefit was generally greater than in patients with no/mild edema.

Conclusions: Overall, patients with AHF and moderate/severe peripheral edema have a worse prognosis but appear to receive similar relative benefit and perhaps greater absolute benefit from serelaxin administration.

Keywords: no/mild edema, moderate/severe edema, acute heart failure, serelaxin

INTRODUCTION

With a few recent exceptions, the outcomes of randomized clinical trials in acute heart failure (AHF) have been disappointing(1-5). Methodological aspects of clinical trials in terms of study design, endpoint- and patient-selection, as well as intrinsic properties of the experimental interventions could account for some of these unsatisfactory findings(6). As AHF is heterogeneous in its etiology, pathophysiology, and clinical presentation, it should perhaps not be treated as a single clinical entity. It is plausible that while some treatments may have better efficacy in certain patient populations, they may not be as effective in others and therefore, on average, fail. Hence, a better segmentation of the AHF patient population, and development of therapies that target specific pathophysiological mechanisms, might yield greater success than would a 'one-size-fits all' model.

The clinical presentation of AHF can be diverse (7). While dyspnea is typically the most common cause for patients seeking consultation, many patients with AHF also present with varying degrees of peripheral edema (8,9). The underlying pathophysiology and therapeutic needs for patients presenting with progressive increase in exertional dyspnea and severe peripheral edema may be different from those who present with a sudden onset of severe dyspnea at rest with little or no peripheral edema. Patients in the latter group develop symptoms and signs of pulmonary congestion without overt evidence of fluid retention. This suggests fluid redistribution into the lungs as the underlying pathophysiological mechanism requiring immediate medical intervention with vasodilator rather than diuretic agents (9-11). A minority of patients with AHF are also admitted with clear signs and symptoms of hypo-perfusion and low cardiac output (cardiogenic shock), representing a subgroup of patients with AHF with an ominous prognosis (7,8).

Serelaxin is a recombinant protein identical in structure to the naturally occurring human pregnancy hormone, relaxin-2 (1,2). Previous trials have shown that serelaxin improves dyspnea, signs of congestion and, subsequently, reduces cardiovascular (CV) and all-cause mortality for up to 6 months after completion of 48-hour intravenous (IV) infusion(1,2). Whether there are differences in baseline characteristics and outcomes in patients with peripheral edema versus those without is unknown. We therefore investigated the characteristics, therapeutic response, and outcome of patients enrolled in the RELAX-AHF trial who at baseline either had substantial peripheral edema, indicating progressive fluid accumulation, or mild/no peripheral edema, suggesting fluid redistribution as the dominant underlying pathophysiology (9).

METHODS

This is a post-hoc analysis of the RELAX-AHF trial (clinicaltrial.gov identifier: NCT00520806). RELAX-AHF was an international, multicenter study that compared the efficacy of serelaxin versus placebo, in addition to standard of care, in patients admitted with AHF. The trial design and results have been reported previously (1,12). Patients were randomized within 16 hours of hospital presentation to either receive IV serelaxin or matching placebo for 48 hours, in addition to the standard of care for AHF. Pre-specified eligibility criteria included breathlessness at rest or from minimal exertion, elevated plasma concentrations of natriuretic peptides (brain natriuretic peptide [BNP] ≥350 pg/mL or N-terminal fragment of pro-BNP [NT-pro-BNP] ≥1400 pg/mL), a chest X-ray with an evidence of pulmonary congestion, mild to moderate renal insufficiency (estimated glomerular filtration rate [eGFR] ≥30 to ≤ 75 ml/min/1.73m^2), SBP>125 mmHg, and should have received at least 40 mg of IV furosemide (or equivalent) therapy prior to screening (1,13). The key outcome measures for this analysis are

described in the statistical analysis section. The in-hospital phase focused on symptoms and signs at different time points, diuretic requirements, blood pressure (BP) and length of stay (LOS). Worsening heart failure (WHF) was assessed through Day 5 and morbidity and mortality were assessed up to 6 months.

Data Collection

During the RELAX-AHF trial, investigators assessed the signs and symptoms of AHF including dyspnea on exertion (New York Heart Association [NYHA] class), orthopnea, rales, jugular venous pressure (JVP), and the presence of peripheral edema at scheduled time points through Day 14. These physician assessments of signs and symptoms were scored as follows: dyspnea on exertion (none, mild or moderate) or at rest (severe) corresponding to NYHA class I-IV, clinical evidence of pulmonary congestion assessed by auscultation (no rales, rales <1/3, 1/3–2/3, or >2/3), orthopnea (none, 1 pillow, 2 pillows, or >30 degrees), and JVP (<6 cm, 6-10 cm, >10 cm or not evaluable). Peripheral edema was assessed on a 0–4 scale, with scores of 0 to 1+ classified as no or mild edema and 2+ and 3+ as moderate to severe edema. Only baseline edema was used to define the subgroups. Body mass index (BMI) was based on actual weight uncorrected for the severity of edema

Statistical Analysis

Baseline characteristics (including demographic, clinical and HF characteristics) were summarized using descriptive statistics (i.e. n, mean, standard deviation [SD], 95% confidence interval [CI], median, interquartile range [IQR], minimum, and maximum).

For continuous variables, subgroups were compared using two-sample t-tests or Wilcoxon rank sum test as appropriate, and categorical variables were compared using chi-square (χ^2) tests.

For each efficacy endpoint, within each of the subgroups, treatment effects were assessed using an analysis of covariance (ANCOVA) model for continuous outcomes and the least square mean (LSM) difference was reported accordingly. Logistic regression was used to assess the treatment effects for binary outcomes and the odds ratios (OR) was provided. For time-to-event outcomes, treatment effects were assessed by Cox proportional hazard regression analysis and the hazard ratios (HR) were reported.

The 95% CIs for each of the above estimated treatment effect along with the p-value for between-treatment comparisons were reported based on the aforementioned statistical models including treatment (serelaxin vs. placebo) as a major factor. Additionally, for each of the time-to-event outcomes, p-values for treatment effects based on the log-rank test were also reported within each subgroup. Possible subgroup-by-treatment interactions were assessed from a separate model including the two subgroups, treatment arms, and the subgroup-by-treatment interaction in the model. The p-value based on the type-3 χ^2 test for the subgroup-by-treatment interaction term was reported accordingly. Because the endpoints, 'length of initial hospital stay', 'days in intensive care unit/cardiac care unit (ICU/CCU)', and 'days alive out of hospital through Day 60' do not follow the normality assumption for parametric tests, the treatment effect was expressed as median difference and 95% CI based on Hodges-Lehmann estimation in addition to the LSM and 95% CI . The p-values were based on non-parametric Wilcoxon rank sum test.

Kaplan-Meier plots for the estimated cumulative event rate over time were provided for the two treatment arms within each of the two subgroups (a total of 4 curves) for the following time-to-event outcomes: all-cause and CV mortality through Day 180, and WHF through Day 5.

For all analyses, two-sided p values with an alpha level of 0.05 were considered as statistically significant. All analyses were conducted on an intent-to-treat basis. Statistical Analysis software (SAS) release 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

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RESULTS

Of the 1161 patients randomized in the RELAX-AHF trial, 1154 reported the presence or absence of peripheral edema at baseline. Of these, 583 (50.5%) had little or no edema (no/mild edema subgroup) and 571 (49.5%) had overt peripheral edema (moderate/severe edema subgroup).

Patients in the no/mild edema subgroup were slightly older, had a lower BMI, and were more often women, compared with those in the moderate/severe edemas subgroup (Table 1). Clinical signs, including BP, heart and respiratory rates and patient-reported severity of dyspnea at baseline (assessed by the visual analog scale [VAS] score) were similar in both the subgroups.

Time from presentation to randomization was shorter for the moderate/severe edema subgroup (7.3 hours) compared with the no/mild edema subgroup (8.5 hours; p<0.0001) (Table 1).

Physician assessment of signs and symptoms of HF at baseline indicated that a higher proportion of patients in the moderate/severe edema subgroup, compared with the no/mild edema subgroup had severe dyspnea (71.1% vs. 60.5%, respectively; p=0.0002), severe orthopnea (>30 degrees, 45.1% vs. 34.0 %; p< 0.0001) and overt signs of pulmonary congestion as demonstrated by the presence of rales ≥1/3 (60.6 % vs. 48.2 %; p <0.001). The proportion of patients with an elevated JVP (≥6 cm) was also higher in the moderate/severe edema subgroup than the no/mild edema subgroup (p <0.0001) (Table 1).

Table 1: Comparison of baseline characteristics between patients with no/mild edema (baseline edema score= 0/1) subgroup vs moderate/severe edema subgroup (baseline edema score = 2/3)

Baseline Characteristics	**No/mild (Total N=583)**	**Moderate/severe (Total N=571)**	**p-value**[†]
Demographics			
Age, years	72.9 (11.4)	71.2 (11.0)	0.0090*
Male: n (%)	345 (59.2)	374 (65.5)	0.0267*
White: n (%)	553 (94.8)	540 (94.6)	0.8297
Clinical characteristics			
BMI, kg/m^2	27.8 (5.2)	30.8 (5.8)	<.0001*
Systolic blood pressure, mmHg	142.0 (16.6)	142.4 (16.5)	0.6586

Diastolic blood pressure, mmHg	79.0 (14.2)	79.1 (14.3)	0.8987
Heart rate, bpm	80.5 (15.0)	78.9 (14.9)	0.0729
Respiratory rate, breaths per minute	21.6 (4.6)	22.2 (4.6)	0.0578
Physician assessment of signs and symptoms of HF			
Dyspnea on exertion[‡], n/N (%) Proportion of patients with severe dyspnea, including at rest	348/575 (60.5)	401/564 (71.1)	0.0002*
Orthopnea[§], n/N (%) Proportion of patients with orthopnea >30 degrees	198/583 (34.0)	257/570 (45.1)	0.0001*
Edema, n/N (%) Proportion of patients with edema score >1	339/583 (58.1)	571/571 (100.0)	< .0001*
Rales[‖], n/N (%) Proportion of patients with rales≥ 1/3	281/583 (48.2)	346/571 (60.6)	< 0.0001*
JVP[¶], n/N (%) Proportion of patients with JVP≥ 6 cm	371/569 (65.2)	478/556 (86.0)	< .0001*
Dyspnea by VAS scale	45.0 (19.7)	43.3 (20.2)	0.1445
Heart failure characteristics			
LVEF (%)	38.6 (14.2)	38.5 (14.9)	0.9018
Ischemic heart disease, n/N (%)	304/583 (52.1)	291/571 (52.0)	0.9647
Subjects with history of congestive heart failure, n/N (%)	404/583 (69.3)	452/571 (79.2)	0.0001*
NYHA class 30 days prior, among those with history of congestive HF[#], n/N (%)			

I	15/399 (3.8)	8/447 (1.8)	0.2290
II	142/399 (35.6)	159/447 (35.6)	
III	174/399 (43.6)	213/447 (47.6)	
IV	68/399 (17.0)	67/447 (15.0)	
Time from presentation to randomization, hours	8.5 (4.6)	7.3 (4.6)	<0.0001*
HF hospitalization in past year, n/N (%)	175/583 (30.0)	220/571 (38.5)	0.0023*
Number of HF hospitalizations in past year	1.5 (1.4)	1.7 (1.3)	0.2490
Comorbidities, n (%)			
Hypertension	495 (84.9)	504 (88.3)	0.0942
Diabetes mellitus	235 (40.3)	313 (54.8)	< .0001*
Stroke or other cerebrovascular event	80 (13.7)	76 (13.3)	0.8378
Asthma, bronchitis, or COPD	85 (14.6)	96 (16.8)	0.2970
Atrial fibrillation at screening	215 (36.9)	261 (45.7)	0.0023*
History of atrial fibrillation or flutter	281 (48.2)	318 (55.7)	0.0109*

Intention-to-treat set with non-missing baseline edema score, data are presented as mean (SD) unless otherwise specified, *significant difference between "no/mild edema" vs. "moderate/severe edema", $p < 0.05$

[†]p-values were based on two-sample t-test for continuous variables and chi-square test for categorical variables; [‡]Severity of dyspnea on exertion was assessed as none (score=0), mild (score=1), moderate (score=2), severe including dyspnea at rest (score=3); [§]severity of orthopnea assessed as none (score=0), 1 pillow, 10 cm (score=1), 2 pillows, 20 cm (score=2), >30 degrees (score=3); [‖]Rales assessed as no rales (score=0), rales <1/3 (score=1), rales 1/3-2/3 (score=2), rales >2/3 (score=3); [¶]JVP assessed as <6 cm (score=0), 6-10 cm (score=1), >10 cm (score=2);

[#]There were 2 subjects in the “no/mild edema” and 8 subjects in the “moderate/severe edema” subgroup with history of congestive heart failure but without NYHA classification

BMI, body mass index; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; JVP, jugular venous pressure; DOE, dyspnea on exertion; VAS, visual analogue scale; COPD, chronic obstructive pulmonary disease

There were no baseline differences between the two subgroups with regards to history of hypertension and ischemic heart disease, NYHA class prior to admission or left ventricular ejection fraction (LVEF) (Table 1). However, patients in the moderate/severe edema subgroup were more likely to have a prior history of congestive HF, were more likely to have been hospitalized for HF in the past year, had a higher prevalence of atrial arrhythmias and diabetes mellitus and were more likely to have an implantable cardiac defibrillator (ICD) with or without biventricular pacing ($p<0.05$ for all). Each subgroup received similar background treatment for HF at baseline (Table 2). Patients in the moderate/severe edema subgroup had higher plasma concentrations of creatinine ($p=0.032$), uric acid ($p=0.0018$), blood urea nitrogen (BUN) ($p=0.0002$) and Cystatin C ($p<0.0001$) than patients in the no/mild edema subgroup, while the eGFR was similar in both subgroups ($p=0.27$). Plasma BNP and NT-proBNP levels and the proportion of patients with an elevated troponin T levels at baseline were also similar between subgroups (Table 2). Analysis of NT-proBNP levels in patients with or without atrial fibrillation (AF) at baseline indicated that in patients without AF, plasma NT-proBNP was higher in the no/mild edema subgroup compared with the moderate/severe edema subgroup (median [IQR]: 5110 [2732.0, 9904.5] ng/L vs. 4124 [2379.0, 8147.0] ng/L; $p = 0.0257$). In contrast, no significant differences in NT-proBNP levels were observed between the two subgroups in patients with AF. (Table 2)

Table 2: Comparison of therapies and key laboratory variables at baseline between patients with "no/mild edema" and "moderate/severe edema" subgroups

Baseline Characteristics	No/mild (Total N=583)	Moderate/severe (Total N=571)	p-value†
Devices, n (%)			
Pacemaker	63 (10.8)	58 (10.2)	0.7192
Implantable cardiac defibrillator (ICD)	66 (11.3)	88 (15.4)	0.0410*
Biventricular pacing	42 (7.2)	71(12.4)	0.0028*
Medication (Day 0, except nitrates), n (%)			
ACE inhibitor	330 (56.6)	301 (52.7)	0.1845
Angiotensin-receptor blocker	83 (14.2)	102 (17.9)	0.0932
Beta-blocker	402 (68.9)	389 (68.1)	0.7621
Aldosterone antagonist	174 (29.8)	191(33.4)	0.1880
IV loop diuretics	583 (100.0)	571 (100.0)	-----
Digoxin	112 (19.2)	116 (20.3)	0.6376
Nitrates (at randomization)	43 (7.4)	38 (6.6)	0.6319
Baseline laboratory variables			
Sodium, mmol/L	141.0 (3.3)	140.7 (3.8)	0.2135
Hemoglobin, g/dL	12.9 (1.9)	12.6 (1.8)	0.0051*
White blood cell count, $\times 10^9$/L	8.6 (3.0)	7.8 (2.6)	<0.0001*

Lymphocyte, %	17.7 (8.0)	18.6 (7.6)	0.0533
Potassium, mmol/L	4.3 (0.6)	4.3 (0.6)	0.7394
Creatinine, umol/L	114.4 (33.8)	118.7 (32.3)	0.0321*
Uric acid, umol/L	463.3 (131.6)	488.5 (139.2)	0.0018*
BUN, mmol/L	9.3 (3.8)	10.2 (4.2)	0.0002*
eGFR‡, ml/min/1.73m^2	53.2 (15.5)	52.2 (15.8)	0.2691
Alanine aminotransferase, U/L	31.5 (36.5)	28.1 (29.0)	0.0882
Aspartate aminotransferase, U/L	32.2 (32.8)	30.5 (27.9)	0.3725
Cystatin-C, mg/L§ - Median (1st Quartile, 3rd Quartile)	1.4 (1.1, 1.7) (n=556)	1.5 (1.2, 1.8) (n=546)	<0.0001*
Troponin T, ng/mL§ - Median (1st Quartile, 3rd Quartile)	0.03 (0.02, 0.06) (n=543)	0.03 (0.02, 0.05) (n=532)	0.2797
NT-proBNP, ng/L§ - Median (1st Quartile, 3rd Quartile)	4997.0 (2826.5, 9323.5) (n=556)	4737.5 (2633.0, 8657.0) (n=546)	0.4148
• In patients without AF at screening (N=647)	5110.0 (2732.0, 9904.5) (n=352)	4124.0 (2379.0, 8147.0) (n=295)	0.0257*‖
• In patients with AF at screening (N=455)	4665.5 (2848.0, 8188.0) (n=204)	5406.0 (3159.0, 9009.0) (n=251)	0.1373‖

Continuous variables are expressed as mean (SD) or geometric mean (95%CI) and categorical variables as n (%),

*Significant difference between "no/mild edema" vs. "moderate/severe edema", $p < 0.05$

[†]p-values were based on two-sample t-test for continuous variables and chi-square test for categorical variables,

[‡]eGFR calculated by the simplified MDRD formula;

[§]For the biomarkers, the summary statistics of median and IQR (inter-quartile range) and P-values based on non-parametric Wilcoxon test are provided. [‖]P-value was based on analysis of variance including natural-log-transformed NT-proBNP at baseline as the dependent variable and subgroup as the major factor.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; IV, intravenous; IQR, interquartile; MDRD, Modification of Diet for Renal Disease; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

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Compared with placebo, serelaxin improved patient-reported dyspnea (VAS scores) in both subgroups, with a trend towards greater benefit in those with moderate/severe edema (Table 3). No difference was observed in the assessment of dyspnea by the Likert scale at 6, 12 and 24 hours in both subgroups (OR 0.99 and 1.10 in the moderate/severe and no/mild edema subgroups respectively, p for interaction = 0.6983).

Patients assigned to serelaxin received lower cumulative doses of diuretics in both the subgroups, with the difference being statistically significant in the moderate/severe edema subgroup (serelaxin vs placebo mean difference: no/mild edema subgroup, -22 mg; p=0.1845 and moderate/severe edema subgroup, -78 mg; p = 0.0179), although the test for interaction was not significant (p-value for subgroup-by-treatment interaction = 0.1249). For patients with moderate/severe edema, reductions in body weight were similar for those assigned to serelaxin or placebo (LSM difference [95 % CI] = -0.005 [-0.6, 0.6] kg) while in those with no/mild edema, a

larger decrease in body weight was noted in patients assigned to placebo (LSM difference (95 % CI): 0.48 (0.07, 0.9) kg, p = 0.0225).

In the no/mild edema subgroup, serelaxin-treated patients had a significantly shorter index LOS and time spent in ICU/CCU compared with the placebo group (mean LOS, serelaxin: 8.3 days vs placebo: 10.1 days, p=0.0035; ICU/CCU stay, serelaxin: 2.7 days vs placebo: 3.8 days, p=0.0282). However, no significant differences between the serelaxin and placebo arms were observed in the moderate/severe edema subgroup; further, no significant interaction between subgroup and treatment was observed (p=0.0667 for LOS and p=0.0835 for ICU/CCU stay).

No significant differences were observed in the days alive and out of hospital endpoint or in the composite endpoint of CV death or HF/renal failure re-hospitalization through Day 60 across subgroups and treatment arms. Overall, serelaxin reduced all-cause mortality through Day 180 compared with placebo. The effect trended in a positive direction in the no/mild edema subgroup (HR [95 % CI] = 0.69 [0.4, 1.2], p = 0.2248) and was statistically significant in the moderate/severe edema subgroup (HR [95 % CI] = 0.58 [0.34, 0.97], p = 0.0361; Figure 1A). Similarly, treatment with serelaxin trended to reduce CV death through Day 180 compared with placebo in both subgroups (HR [95 % CI] =0.55 [0.3, 1.1], p = 0.0758 in the no/mild and 0.66 [0.4, 1.16], p = 0.1451 in the moderate/severe subgroup; Figure 1B). In both subgroups, the incidence of WHF through Day 5 was lower for serelaxin-treated patients (no/mild edema: HR [95% CI]: 0.54 [0.3, 1.0], p = 0.0465; moderate/severe edema: 0.50 [0.3, 0.8], p = 0.0086; Figure 1C).

Table 3: Treatment effect (serelaxin vs. placebo) on various outcomes in patients with "no/mild edema" (baseline edema score = 0/1) and "moderate/severe edema" (baseline edema score= 2/3)

Outcome	No/mild edema (Total N=583)			Moderate/severe edema (Total N=571)			p-value[†] for interaction
	Treatment groups		Between-treatment comparison: Serelaxin vs. Placebo	Treatment groups		Between-treatment comparison: Serelaxin vs. Placebo	
	Placebo (N = 286)	Serelaxin (N=297)	Treatment effect (95% CI)[†]; p-value[†]	Placebo (N =291)	Serelaxin (N = 280)	Treatment effect (95% CI)[†]; p-value[†]	
Dyspnea improvement, Likert Scale at 6, 12 and 24 hours[§], n /N (%)	80/286 (28.0%)	89/297 (30.0%)	OR: 1.1 (0.77, 1.58); 0.5958	70/291 (24.0%)	67/280 (23.9%)	OR: 0.99 (0.68, 1.46); 0.9718	0.6983
Dyspnea improvement[‡] to Day 5, Mean (SD)	2612.0 (2973.7)	2792.8 (2699.0)	180.8 (-280.8, 642.4); 0.4421	2017.0 (3169.2)	2755.5 (2467.3)	738.5 (270.45, 1206.60) 0.0020*	0.0959
Total dose of IV loop diuretics before Day 5, mg, Mean (SD)	131.5 (195.7) n' = 283	109.6 (198.6) n' = 292	-21.8 (-54.2, 10.4) 0.1845	293.5 (452.6) n' = 287	215.6 (311.9) n' = 278	-77.9 (-142.3, -13.5) 0.0179*	0.1249
Change in bodyweight to Day 5, kg, Mean (SD)	-2.2 (2.7) n' = 275	-1.8 (2.3) n' = 284	0.48 (0.07, 0.9) 0.0225*	-3.7 (3.7) n' = 284	-3.7 (3.9) n' = 270	-0.005 (-0.6, 0.6) 0.9882	0.2063
Length of initial hospital stay, days							

Mean (SD)	10.1 (9.2)	8.3 (5.4)	-1.8 (-3.0, -0.6) 0.0035* Median Diff ‖,	10.8 (10.0)	11.0 (11.7)	0.19 (-1.6, 2.0) 0.8374 Median Diff ‖,	0.0667
Median (IQR)‖	8.0 (6.0, 11.0)	7.0 (5.0, 10.0)	-1.0 (0.0, 1.0) 0.0359*	8.0 (6.0, 12.0)	8.0 (5.0, 11.0)	-1.0 (-1.0, 0.0) 0.4250‖	
Length of stay ICU/CCU, days							
Mean (SD)	3.8 (7.2) n' = 286	2.7 (3.6) n' = 294	-1.0 (-2.0, -0.1) 0.0282* Median Diff ‖	4.0 (6.8) n' = 289	4.4 (9.4) n' = 278	0.4 (-0.9, 1.7) 0.5594 Median Diff‖, 0.0 (-1.0,	0.0835
Median (IQR)‖	2.0 (1.0, 4.0)	2.0 (0.0, 3.0)	0.0 (0.0, 0.0) 0.2904‖	3.0 (0.0, 4.0)	2.0 (0.0, 4.0)	0.0) 0.0478*	
WHF Through Day 5, n / N (%);KM%	28/286 (9.8%); KM#= 9.9%	16/297 (5.4%); KM#= 5.48%	HR: 0.54 (0.3, 1.0); 0.0465* (LR¶)	41/291(14.1%); KM#=14.24%	21/280 (7.5%); KM#= 7.55%	HR: 0.5 (0.3, 0.8); 0.0086* (LR¶)	0.8565
Days alive and out of hospital through Day 60							
Mean (SD)	48.5 (11.2)	49.5 (9.6)	0.99 (-0.7, 2.7); 0.2530 Median Diff ‖	46.8 (12.9)	47.0 (13.3)	0.17 (-2.0, 2.3); 0.8776 Median Diff ‖, 0.0 (-1.0,	0.5563
Median (IQR)‖	52.0 (46.0, 55.0)	53.0 (47.0, 55.0)	0.0 (-1.0, 0.0); 0.4244‖	52.0 (44.0, 54.0)	52.0 (44.5, 55.0)	1.0); 0.6881‖	
CV death or HF/RF hospitalization through	33/286 (11.5%); KM#=11.6%	30/297 (10.1%); KM#=10.2%	HR: 0.88 (0.5, 1.4); 0.6135 (LR¶)	42/291 (14.4%); KM#= 14.6%	45/280 (16.1%); KM#=	HR: 1.1 (0.7, 1.7); 0.5593 (LR¶)	0.4454

Day 60, n/N (%); KM %					16.2%		
All-cause death through Day 180: n/N (%); (KM)%	26/286 (9.1%); KM[#]= 9.1%	19/297 (6.4%); KM[#]= 6.5%	HR: 0.69 (0.4, 1.2); 0.2248 (LR[¶])	39/291 (13.4%); KM[#]= 13.6%	22/280 (7.9%); KM[#]= 7.9%	HR: 0.58 (0.3, 1.0); 0.0361* (LR[¶])	0.6351
CV death through Day 180: n / N (%);KM %	24/286 (8.4%); KM[#]= 8.4%	14/297 (4.7%); KM[#]= 4.8%	HR: 0.55 (0.3, 1.1); 0.0758 (LR[¶])	31/291 (10.6%); KM[#]= 10.89%	20/280 (7.1%): KM[#]= 7.2%	HR: 0.66 (0.4, 1.2); 0.1451(LR[¶])	0.7009

Continuous variables are expressed as mean (SD), categorical variables as n/N (%), and time-to-event variables as n /N (%) + (KM %); n' = number of subjects with non-missing data; *significant difference between "no/mild edema" vs. "moderate/severe edema", $p < 0.05$.

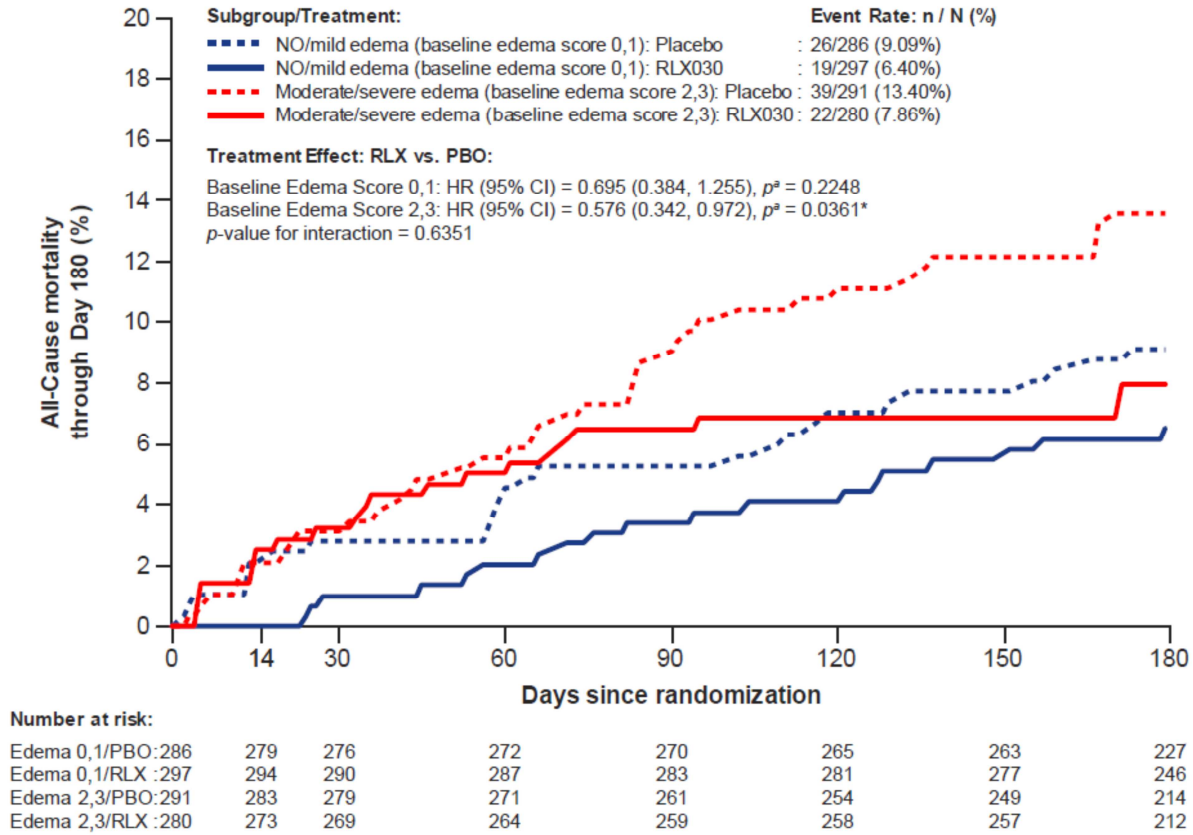
[†]Treatment effect represents LSM difference for continuous variables, odds ratio (OR) for dichotomous variables, and hazard ratio (HR) for time-to-event variables, estimated from analysis of covariance model (ANCOVA), logistic regression, and Cox regression models, respectively. The 95% confidence intervals (CIs) for the above estimated treatment effect along with p-value for between treatment comparison and subgroup-by-treatment interaction are reported based on the aforementioned statistical models respectively.;

[‡]Dyspnea improvement to day 5 as assessed by VAS-AUC; [§]Subjects with moderately or markedly better dyspnea as assessed by the Likert scale;

[‖]For the endpoints, "length of initial hospital stay", "days in IC/CCU", and "days alive out of hospital through Day 60", the summary statistics of median and IQR are also presented and the treatment effect is expressed as median difference and 95% CI based on Hodges-Lehmann estimation. P-value is based on non-parametric Wilcoxon rank sum test. [¶]LR: P-value of treatment effect for time-to-event endpoints is based on log-rank test; [#]Kaplan-Meier cumulative event rates ANCOVA, analysis of covariance; AUC, area under the curve; CV, cardiovascular; HF, heart failure; ICU/CCU, intensive care unit/ coronary care unit; IQR, interquartile range; IV, intravenous; KM, Kaplan-Meier; LSM, least square mean; LSM, least square mean; OR, odds ratio; RF, renal failure.; SD, standard deviation; VAS, visual analogue scale; WHF, worsening heart failure

Figure 1. Kaplan-Meier curves for (A) All-Cause Mortality through Day 180, (B) Cardiovascular Mortality through Day 180, and (C) Worsening Heart Failure through Day 5

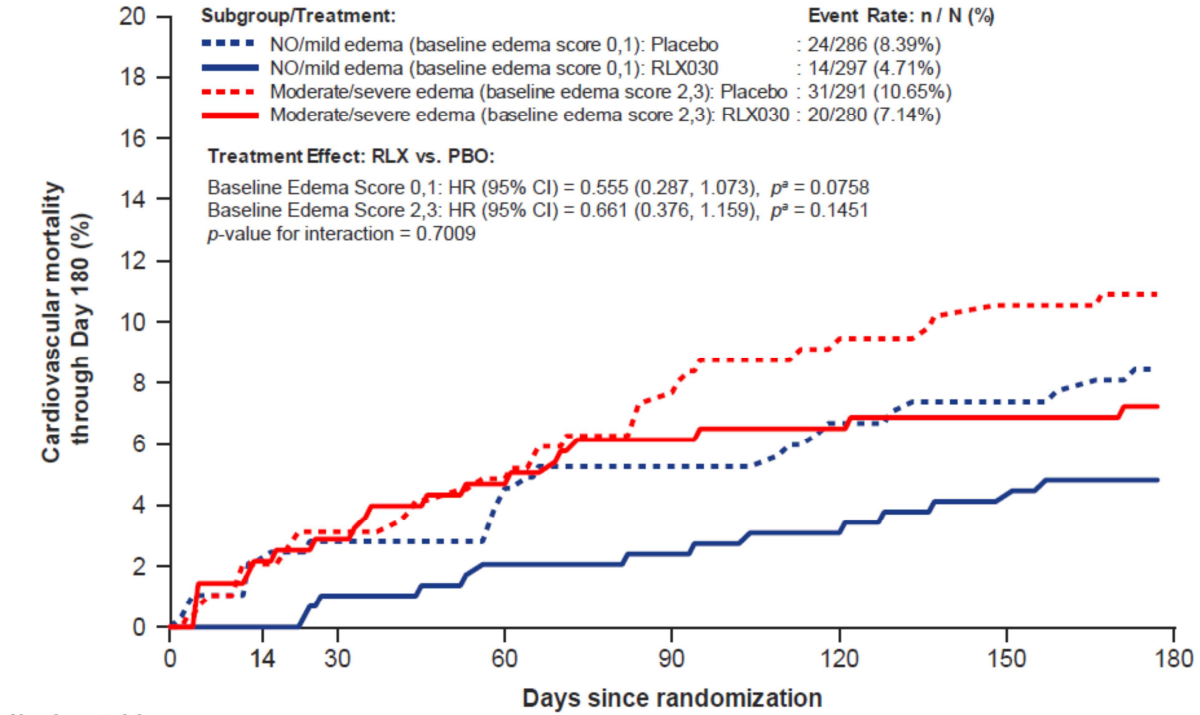
Figure 1A



Number at risk:

Edema 0,1/PBO:286	279	276	272	270	265	263	227
Edema 0,1/RLX :297	294	290	287	283	281	277	246
Edema 2,3/PBO:291	283	279	271	261	254	249	214
Edema 2,3/RLX :280	273	269	264	259	258	257	212

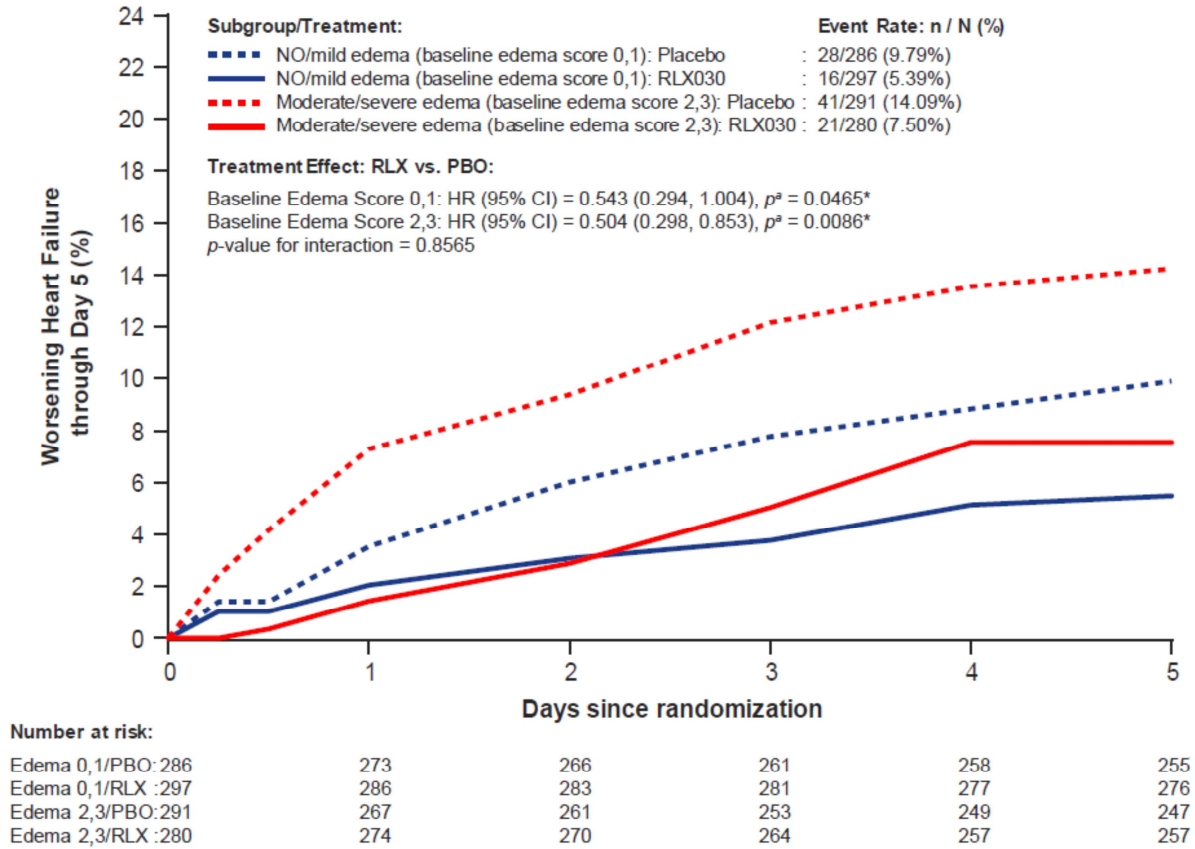
Figure 1B



Number at risk:

Edema 0,1/PBO:286	279	276	272	270	265	263	227
Edema 0,1/RLX :297	294	290	287	283	281	277	246
Edema 2,3/PBO:291	283	279	271	261	254	249	214
Edema 2,3/RLX :280	273	269	264	259	258	257	212

Figure 1C



HR, hazard ratio; PBO, placebo; RLX030, serelaxin

*significant difference between “no/mild edema” vs. “moderate/severe edema”, $p < 0.05$.

[a]*p* values for treatment effects based on log-rank test

DISCUSSION

In this post-hoc analysis, patients with AHF from the RELAX-AHF trial were classified into two subgroups based on the absence or presence of baseline peripheral edema: no/mild and moderate/severe. The subgroup definition was an attempt to discern two different phenotypes of patients with AHF, with possible differences in the underlying pathophysiology (fluid retention vs. fluid redistribution) based on a very simple clinical variable.

The analysis suggests that patients admitted with severe peripheral edema generally have worse outcomes but benefit from the administration of serelaxin as much in relative terms and perhaps, more in absolute terms, as do those admitted for breathlessness without an evidence of marked fluid retention. This suggests that serelaxin may not be acting solely as a vasodilator agent to reduce pulmonary capillary pressure and fluid redistribution. Improved renal function and reduction in diuretic requirements in patients treated with serelaxin point to a possible renal effect.

Importantly, the two subgroups in this analysis were of similar size. Some of the differences in baseline characteristics were not unexpected: a higher proportion of female representation, slightly older population, as well as lower BMI were observed in the no/mild subgroup. In the moderate/severe subgroup, the proportion of patients with a history of hospital admission due to HF within the last year was higher and statistically significant. This was consistent with their baseline characteristics of a past history of HF and, consequently, an increased proportion of associated comorbidities such as diabetes, AF, and higher levels of renal markers suggesting more severe chronic kidney dysfunction.

We observed higher NT-proBNP levels in patients without AF at screening in the no/mild edema group compared with moderate/severe edema group. These findings are somewhat counter

intuitive, as increased NT-proBNP levels would be expected both in patients with moderate/severe edema (as a consequence of the fluid overload), and in the subgroups with AF at screening as compared to those without, since AF is a known independent determinant of increased NT-proBNP. Although this observation could be a chance finding, it could also be due to differences in certain baseline characteristics such as renal function, paroxysmal AF post-screening, age, gender differences, etc.

Although we expected a higher LVEF in the no/mild group, the mean LVEF (approximately 38%) was similar in both subgroups. A chart review of echocardiograms as opposed to index visit echocardiograms may have contributed to this finding. The distribution of patients with AHF into those with mild or no peripheral edema vs. those with moderate to severe peripheral edema are consistent with previous registry data collected from more than 136000 patients during six years in England and Wales(14).

A similar useful and simplistic classification of patients with AHF into “puffers” and “bloaters” was described by Cleland et al (15,16). A classic “bloater” presents with increasing water retention, weight gain, peripheral edema and renal dysfunction. These patients have more severe pulmonary hypertension, right ventricular dysfunction and tricuspid regurgitation (17). Hepatic congestion impairs degradation of aldosterone which exacerbates sodium and fluid retention. These patients usually have a subacute presentation, and emergency treatment is often not required; yet they have a particularly poor prognosis. Some patients under the ‘bloaters’ group may not seek medical attention until pulmonary edema and severe breathlessness develop (15).

In contrast, many “puffers” have little evidence of fluid retention. Their underlying problem appears to be redistribution of fluid from the circulation to the pulmonary alveoli due to capillary hypertension, which is often associated with an increase in systemic vascular resistance and an increased afterload. This may be driven by a vicious cycle of increased sympathetic

activation driven in part by the distress caused by dyspnea. Patients in this group may be better treated by vasodilators rather than diuretic agents (15). They typically present with a short history of severe breathlessness, requiring urgent treatment for symptom control. Many patients, however, fall between the extremes of these two presentations.

While it can be argued that the presence of edema may be associated with multiple different clinical and pathophysiological conditions (e.g. nutrition and protein levels, endothelium integrity, venous competence, renal function etc.) and that the specificity of the evaluation is not very high, this "bedside assessment" is a simple clinical tool providing a first impression of the patient's phenotype. However, this must be confirmed by further assessments with complementary analyses(15,18,19).

While this classification is useful to understand the complexity of AHF presentation, it is not universally adopted. In the recently published European Society of Cardiology guidelines, an algorithm to characterize the hemodynamic profile of patients with AHF clearly shows that the presence of congestion (i.e. "wet") is the most common presenting feature representing nearly 95% of patients with AHF. The same algorithm also describes that the vast majority of patients are "wet" (congested) and "warm" (well perfused), typically presenting with normal or elevated BP. The algorithm further subcategorizes this population into vascular type-fluid redistribution (i.e. hypertension predominant) or cardiac type-fluid accumulation (i.e. congestion predominant)(18)

In the present analysis, a statistically significant positive effect of serelaxin on dyspnea was observed in the moderate/severe edema subgroup while a positive trend was also seen in the no/mild edema subgroup.

In accordance with our previous observations, no significant differences in the treatment effect were observed in the short to medium-term outcomes, as assessed by CV death through

Day 60 or the composite endpoint of CV death or HF/renal failure hospitalization at 60 days(1). A significant reduction in LOS was observed in the serelaxin-treated patients with no/mild edema.

Overall, the mean dose of IV diuretic up to Day 5 was lower in serelaxin-treated patients in both subgroups. Although no significant treatment differences in diuretic use was observed in the no/mild subgroup (serelaxin vs placebo), this was particularly evident, and statistically significant in the moderate/severe edema group. The serelaxin-treated patients in this subgroup required almost 80 mg less furosemide than did the placebo-treated patients, despite both treatment arms showing similar decreases in body weight. This finding is in contrast with previous analyses on the diuretic response, which did not identify any potentiation effect of serelaxin (20). However, the same study suggested that a better diuretic response is expected in patients with more peripheral edema, an assumption that is supported in the present analysis (20).

The reduction WHF through Day 5 is consistent with that seen in the main population (1). This is important for two reasons: (a) WHF has been recognized as a valid endpoint and has been demonstrated to have a good correlation with mortality(21), and (b) increased validity of the WHF endpoint for regulatory agencies. In the future, should these results be validated in prospective trials, this endpoint could be used as a surrogate for mortality.

In accordance with the earlier observations, all cause and CV mortality were lower in patients assigned to serelaxin (1) with similar relative benefits in each subgroup. Indeed, the absolute benefit with serelaxin on all-cause mortality and WHF appeared somewhat greater in those with more severe edema.

Contrary to what might be intuitively expected from a characteristic arterial vasodilator (i.e. a better response in those with fluid redistribution rather than fluid retention), this analysis suggests that benefits may be similar or greater in those with overt evidence of fluid retention.

Studies in pre-clinical models suggest a selective vasodilatory effect of serelaxin on certain venous vascular beds (such as renal and mesenteric beds)(22, 23). Further, pre-clinical and clinical evidence suggest that serelaxin reduces markers of renal and hepatic impairment possibly owing to its early decongestion effects and vasodilatory actions that improve perfusion and renal hemodynamics(24, 25). In accordance with these observations, we speculate that a putative target effect of serelaxin on these vascular beds could contribute to increased venous capacitance and decongestion of the kidney, liver and splanchnic tissue with potential long-term benefits. Alternatively, or in addition, specific effects on renal haemodynamics may improve diuretic responsiveness and unload the heart. This supports a targeted and specific mechanism of action that needs to be elucidated further.

LIMITATIONS

This was a post-hoc analysis and since the number of patients in each subgroup was small, the results should be interpreted with caution. Similarly, differences in the baseline characteristics of the population (e.g. different rates of AF across groups, and indicators of heart failure duration) could have contributed to the current observations. Some patients may have been misclassified either because of inter-observer variability or because of the arbitrary definition applied to what is possibly a continuous distribution. A larger study might allow more complex classifications to be applied with more granular subgroups.

CONCLUSIONS

Patients with AHF and more severe peripheral edema have a worse prognosis but appear to receive similar relative (and perhaps greater) absolute benefit from administration of serelaxin for several outcomes, including early WHF, CV and all-cause mortality. Future trials in AHF (particularly RELAX-AHF-2) will help to determine the validity of these observations.

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Figure titles and legends

Figure 1. Effect of serelaxin (vs. placebo) treatment on mortality and WHF in patients with or without peripheral edema. Kaplan-Meier curves for (A) All-Cause Mortality through Day 180, (B) Cardiovascular Mortality through Day 180, and (C) Worsening Heart Failure through Day 5.

HR, hazard ratio; PBO, placebo; RLX030, serelaxin

*significant difference between "no/mild edema" vs. "moderate/severe edema", $p < 0.05$.

[a]*p* values for treatment effects based on log-rank test