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ORIGINAL PAPER

Serelaxin in acute heart failure patients with and without atrial fibrillation: a secondary analysis of the RELAX-AHF trial

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Abstract
Background Atrial fibrillation (AFib) is a common comorbidity in HF and affects patients' outcome. We sought to assess the effects of serelaxin in patients with and without AFib.
Methods In a post hoc analysis of the RELAX-AHF trial, we compared the effects of serelaxin on efficacy end points, safety end points and biomarkers in 1161 patients with and without AFib on admission electrocardiogram.
Results AFib was present in 41.3% of patients. Serelaxin had a similar effect in patients with and without AFib, including dyspnea relief by visual analog scale through day 5 [mean change in area under the curve, 541.11 (33.79, 1048.44), $p=0.0366$ in AFib versus 361.80 (−63.30, 786.90), $p=0.0953$ in non-AFib, interaction $p=0.5954$] and all-cause death through day 180 [HR = 0.42 (0.23, 0.77), $p=0.0051$ in AFib versus 0.90 (0.53, 1.52), $p=0.6888$ in non-AFib, interaction $p=0.0643$]. Serelaxin was similarly safe in the two groups and induced similar reductions in biomarkers of cardiac, renal and hepatic damage. Stroke occurred more frequently in AFib patients (2.8 vs. 0.8%, $p=0.0116$) and there was a trend for lower stroke incidence in the serelaxin arm in AFib patients (odds ratios, 0.31, $p=0.0759$ versus 3.88, $p=0.2255$ in non-AFib, interaction $p=0.0518$).
Conclusions Serelaxin was similarly safe and efficacious in improving short- and long-term outcomes and inducing organ protection in acute HF patients with and without AFib.

Keywords Serelaxin · Relaxin · Acute heart failure · Atrial fibrillation

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Introduction

Heart failure (HF) remains the most common reason for hospital admission in the elderly [1–4]. Although improvements in re-admission rates have been recently observed, outcomes for patients admitted for HF remain poor, with high post-discharge mortality and rehospitalization rates [2–7].

Atrial fibrillation (AFib) is a common comorbid state in HF patients, including those admitted for acute HF [8].

Table 1 Comparison of baseline characteristics between patients with and without atrial fibrillation (AFib) on admission

Baseline characteristic	AFib, $n=479$[a]	No AFib, $n=680$[a]	p value[b]
Demographics			
Age (years)	74.6 (9.5)	70.2 (12.0)	<0.0001
Male	284 (59.3)	440 (64.7)	0.0608
White/Caucasian	466 (97.3)	628 (92.4)	0.0003
Geographic region			<0.0001
Eastern Europe	266 (55.5)	295 (43.4)	
Western Europe	89 (18.6)	115 (16.9)	
South America	26 (5.4)	45 (6.6)	
North America	23 (4.8)	90 (13.2)	
Israel	75 (15.7)	135 (19.9)	
Heart failure characteristics			
Left ventricular EF	40.3 (14.5)	37.5 (14.5)	0.0015
EF < 40%	217 (48.9)	380 (58.9)	0.0011
Ischemic heart disease	226 (47.2)	376 (55.3)	0.0065
Time from presentation to randomization (h)	7.6 (4.6)	8.1 (4.7)	0.0768
CHF 1 month prior	362 (75.6)	497 (73.1)	0.3414
NYHA class 30 days before admission			0.1274
I	128 (26.8)	195 (29.0)	
II	115 (24.1)	187 (27.8)	
III	180 (37.7)	209 (31.1)	
IV	54 (11.3)	81 (12.1)	
Clinical signs			
Body mass index, kg/m^2	29.3 (5.3)	29.2 (6.0)	0.7501
Syst. blood pressure, mmHg	141.5 (16.2)	142.6 (16.8)	0.2523
Diast. blood pressure, mmHg	80.6 (13.8)	77.9 (14.5)	0.0018
Heart rate, beat per minute	83.0 (15.9)	77.3 (13.8)	<0.0001
Respiratory rate, breaths per minute	21.9 (4.7)	21.9 (4.6)	0.8515
HF hospitalization past year	161 (33.6)	235 (34.6)	0.7378
Congestion at baseline			
Edema	395 (83.0)	513 (75.9)	0.0037
Orthopnea	459 (96.4)	645 (95.4)	0.3962
Jugular vein distension	359 (76.7)	489 (74.5)	0.4054
Dyspnea on exertion	469 (99.8)	665 (99.6)	0.6468
Dyspnea by VAS	43.7 (20.5)	44.5 (19.6)	0.4915
Rales	453 (95.2)	640 (94.5)	0.6336
Comorbidities			
Hypertension	417 (87.1)	587 (86.3)	0.7181
Hyperlipidemia	223 (46.6)	392 (57.6)	0.0002
Diabetes mellitus	196 (40.9)	353 (51.9)	0.0002
Cigarette smoking	35 (7.3)	118 (17.4)	<0.0001
Stroke or other cerebrovascular event	66 (13.8)	91 (13.4)	0.8460
Peripheral vascular disease	62 (12.9)	93 (13.7)	0.7181
Asthma, bronchitis, or COPD	77 (16.1)	106 (15.6)	0.8229
History of Atrial fibrillation or flutter	454 (94.8)	148 (21.8)	<0.0001
History of CRT or ICD procedures	112 (23.4)	182 (26.8)	0.1925
Myocardial infarction	141 (50.5)	262 (60.0)	0.0132
Depression	14 (2.9)	46 (6.8)	0.0036
Medication			
ACE inhibitor	244 (50.9)	388 (57.1)	0.0394
ACEi or ARBs	314 (65.6)	472 (69.4)	0.1662
Angiotensin-receptor blocker	83 (17.3)	101 (14.9)	0.2563

Table 1 (continued)

Baseline characteristic	AFib, $n=479$[a]	No AFib, $n=680$[a]	p value[b]
Beta-blocker	344 (71.8)	448 (65.9)	0.0325
Aldosterone antagonist	166 (34.7)	199 (29.3)	0.0517
Oral loop diuretic 30 days prior	42.3 (59.9)	46.4 (68.7)	0.2900
Digoxin	152 (31.7)	76 (11.2)	<0.0001
Nitrates at randomization	31 (6.5)	50 (7.4)	0.5623
Devices			
Pacemaker	66 (13.8)	55 (8.1)	0.0018
Implantable cardiac defibrillator	42 (8.8)	112 (16.5)	0.0001
Biventricular pacing	33 (6.9)	80 (11.8)	0.0059
Baseline laboratory findings			
Hemoglobin, g/dL	12.83 (1.71)	12.77 (1.95)	0.5721
White blood cell count, $\times 10^9$/L	7.909 (2.723)	8.370 (2.916)	0.0082
Lymphocyte, %	18.15 (7.27)	18.18 (8.19)	0.9433
Glucose, mmol/L	7.29 (3.01)	8.07 (3.89)	0.0002
BUN, mmol/L	9.80 (4.03)	9.75 (4.03)	0.8340
Creatinine, umol/L	114.3 (31.5)	118.1 (34.2)	0.0621
Cystatin C, mg/L	1.47 (1.43, 1.51)	1.44 (1.41, 1.47)	0.2294
eGFR, mL/min per 1.73 m^2	53.20 (12.98)	53.72 (13.06)	0.5097
Sodium, mmol/L	141.0 (3.8)	140.7 (3.4)	0.3074
Potassium, mmol/L	4.27 (0.63)	4.27 (0.64)	0.9697
Calcium, mmol/L	2.26 (0.14)	2.27 (0.16)	0.5059
Alanine aminotransferase, U/L (log transformed)	23.4 (22.2, 24.7)	23.7 (22.5, 24.9)	0.7569
Albumin, g/L	40.41 (3.93)	40.11 (4.59)	0.2407
Total cholesterol, mmol/L	3.94 (1.07)	4.20 (1.22)	0.0001
CRP, mg/L (log transformed)	8.56 (7.57, 9.68)	8.49 (7.73, 9.31)	0.9101
Uric acid, umol/L	478.4 (132.3)	473.8 (138.2)	0.5751
NT-proBNP, ng/L (log transformed)	5279 (4919, 5665)	4905 (4553, 5284)	0.1599
Troponin T, ug/L (log transformed)	0.031 (0.028, 0.033)	0.038 (0.036, 0.041)	<0.0001
GDF-15, ng/L (log transformed)	4598 (4329, 4883)	4167 (3953 4392)	0.0165

[a]Mean (SD), or geometric mean (95% CI) if log transformed, presented for continuous variables, and n (%) for categorical variables (% based on the total number of patients with a non-missing value of the end point)

[b]p value was based on t test (with Satterthwaite correction if unequal variances), Chi-square test, or Fisher's exact test

Acute HF registries report a prevalence of AFib ranging between 27 and 45% [2]. There is a bidirectional pathogenetic relationship linking HF with AFib [9]. On one hand, HF leads to increased atrial pressures and neurohormonal activation, resulting in structural and electrical atrial remodeling: factors that constitute the ideal substrate for the development of AFib [10, 11]. On the other hand, AFib doubles the risk for HF development. It is a frequent trigger for HF decompensation resulting in a high overall risk of cardiovascular complications, including a fivefold higher risk of stroke [2, 12]. The presence of AFib directly affects the outcomes of HF patients, predicting a worse prognosis [13].

Serelaxin, a recombinant form of human relaxin-2, improves symptoms and outcomes in patients admitted for acute HF, as reported by the RELAX-AHF trial [14–18]. In this study, 53% of patients had a history of AFib, while 41% had AFib on screening electrocardiogram performed on admission [19, 20]. A previously published sub-group analysis showed no differential effects of seralaxin based on the presence or absence of a history of AFib or AFib at screening on key study end points [19]. In the present study, we sought to expand our knowledge on the efficacy and safety of serelaxin in acute HF patients with and without AFib at the time of presentation by addressing all pre-specified efficacy and safety end points, adverse events and biomarkers of organ damage. We further analyzed the clinical profile of patients with AFib as well as the independent prognostic significance of AFib on patient outcomes.

Methods

The design and primary results of the RELAX-AHF trial are described in detail elsewhere [21]. 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. The study was approved by the institutional review boards and all subjects enrolled gave informed consent.

In the present analysis, we compared the effects of serelaxin versus placebo on pre-specified efficacy end points, safety end points, and biomarkers indicative of organ damage, in patients with and without AFib. The presence of AFib was defined as evidence of either atrial fibrillation or atrial flutter on the screening electrocardiogram performed on admission.

The trial's primary efficacy end points were dyspnea improvement, defined as the area under the curve of dyspnea change from baseline on a 100-mm visual analog scale (VAS-AUC) through day 5 and the presence of moderately or markedly better breathing compared to baseline reported on a 7-point Likert scale at 6, 12 and 24 h. Adverse events (AEs) were collected through day 5, serious AEs through day 14, rehospitalizations through day 60, and vital status through day 180. Rehospitalizations and deaths were adjudicated by an independent, blinded committee. The trial's secondary efficacy end points 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 end point, and all-cause death through day 180 was a pre-specified safety end point. Stroke through day 180 was defined to include any AE of stroke (through day 14), any rehospitalization for stroke (through day 60), or death due to stroke (through day 180). Biomarkers indicative of congestion and/or organ damage, including high-sensitivity troponin T (hs-TnT), N-terminal beta-type natriuretic propeptide (NT-proBNP), cystatin C, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and growth differentiation factor-15 (GDF-15) were assessed serially using a central core laboratory.

Statistical analysis

Baseline characteristics were compared between patients with and without AFib, without imputation for missing values, using two-sample t test for continuous variables and Chi square or Fisher's exact test for categorical variables. Estimates of the serelaxin treatment effect (odds ratios, mean differences, or hazard ratios) for patients with and without AFib and an interaction test were obtained from separate regression models (logistic regression, analysis of covariance, or Cox proportional hazards). For the analyses of outcomes in patients with and without AFib and the analyses of treatment effects, two subjects with unknown AFib status were imputed as without AFib. Missing baseline covariates were also imputed as the mean for continuous variables or as the mode for categorical variables within the treatment group. Missing biomarker values were not imputed. Analyses were conducted on an intention-to-treat basis. All p values were two sided, and values <0.05 were considered to be statistically significant. Analyses were performed using SAS© release 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics in patients with and without AFib

From a total 1161 patients who underwent a screening electrocardiogram on admission, 479 patients had AFib (41.3%). In addition, 602 (51.9%) patients reported a history of AFib, although this was not used as a criterion for the present analysis. Patients with AFib were significantly older with a different race and geographic distribution than those without AFib (Table 1). Patients with AFib were less likely to have an ischemic etiology of HF or a reduced ejection fraction (HFrEF), but similar New York Heart Association (NYHA) class distribution when compared to patients without AFib. AFib patients had a higher resting heart rate than non-AFib patients, but similar systolic blood pressure. Symptoms and signs of congestion did not differ between the two groups with the exception of peripheral edema, which was more frequent in patients with AFib. Several comorbid conditions including hyperlipidemia, diabetes mellitus, smoking, history of myocardial infarction and depression were less frequent in patients with AFib. A history of hypertension, lung disease and cerebrovascular or peripheral arterial disease did not differ between the two groups. Regarding cardiovascular therapies, patients with AFib were more frequently prescribed beta-blockers and digoxin, and had more frequently undergone a pacemaker implantation. However, they were less likely to have a cardiac defibrillator or a biventricular pacing system. With respect to baseline laboratory findings, renal, liver function and natriuretic peptides did not differ between the two groups. Patients with AFib, however, had lower troponin T and higher GDF-15 levels.

Efficacy and safety of serelaxin in patients with and without atrial fibrillation

Atrial fibrillation was present in 233 of 580 (40.2%) patients in the serelaxin arm and in 246 of 579 (42.5%)

Table 2 Outcomes in patients with and without atrial fibrillation

Clinical end points	AFib, $n=479$ Estimate[a]	No AFib, $n=682$ Estimate[a,b]	Unadjusted effect of AFib (yes versus no)		Adjusted effect of AFib (yes versus no)	
			(95% CI)	p value[c]	(95% CI)	p value[c,d]
Dyspnea improvement by VAS to day 5, mm-h	2222.58 (1962.77, 2482.39)	2749.22 (2538.24, 2960.20)	−526.64 (−858.50, −194.78)	0.0019	−166.06 (−570.24, 238.11)	0.4207
Dyspnea improvement by Likert scale at 6, 12 and 24 h	110/479 (23.0%)	196/682 (28.7%)	0.74 (0.56, 0.97)	0.0282	–	–
Worsening heart failure (WHF)	53/479 (11.1%)	57/682 (8.4%)	1.34 (0.92, 1.96)	0.1258	1.13 (0.67, 1.91)	0.6446
Hospitalization length, days	11.82 (10.80, 12.84)	8.82 (8.26, 9.37)	3.00 (1.92, 4.08)	<0.0001	–	–
Cardiovascular death or HF/RF hospitalization through day 60	69/479 (14.5%)	82/682 (12.1%)	1.21 (0.88, 1.67)	0.2414	1.13 (0.81, 1.59)	0.4739
All-cause death through day 180	51/479 (10.7%)	56/682 (8.3%)	1.33 (0.91, 1.95)	0.1372	1.46 (0.98, 2.18)	0.0651
Cardiovascular mortality to day 180	43/479 (9.1%)	45/682 (6.7%)	1.40 (0.92, 2.12)	0.1170	1.71 (1.10, 2.67)	0.0173
Stroke through day 180	13/479 (2.8%)	5/682 (0.8%)	3.77 (1.34, 10.58)	0.0116	–	–

[a]Mean (95% CI), n (K-M %) and n (%) are presented for continuous outcome, survival outcome and binary outcome, respectively

[b]Two subjects with unknown AFib status were imputed as without AFib (treatment-specific mode)

[c]Treatment effect represents mean difference (from linear regression analysis), hazard ratio (from Cox proportional hazards model) and odds ratio (from logistic regression analysis) for continuous outcome, survival outcome and binary outcome, respectively

[d]Dyspnea VAS AUC to day 5 is adjusted for age, US-like, weight, dyspnea on exertion, hypertension, mitral regurgitation, history of atrial fibrillation or flutter, alkaline phosphatase, sodium, body temperature (linear spline at Q1), log2 troponin (linear spline at Q2), dyspnea by VAS (cubic), uric acid (cubic); WHF is adjusted for white race, height (linear spline at 173), diastolic BP(linear spline at 70), heart rate (trichotomized: <73, [73, 85), ≥85), respiratory rate, dyspnea by VAS, mm (cubic), coronary artery bypass graft, hyperthyroidism, total bilirubin, total cholesterol, albumin, troponin (log2 transformed, linear spline at −4.2); CV death or HF/RF rehospitalization through day 60 is adjusted for white race, NYHA class 30 days before systolic BP, respiratory rate, number of HF hospitalizations past year, orthopnea (ordinal), asthma or bronchitis or COPD, hyperthyroidism, lymphocytes %, BUN, phosphate (cubic), sodium, total protein (linear spline at 68); CV mortality through day 180 is adjusted for the following variables: US-like, systolic BP, orthopnea (ordinal), angina, hyperthyroidism, mitral regurgitation, atrial fibrillation/flutter at screening, white blood cell count, lymphocytes %, BUN, sodium, potassium, calcium, total protein, log2 troponin, log2 NT-proBNP. All-cause death to day 180 is adjusted for age, CHF 1 month previously, stroke or other cerebrovascular events, respiratory rate, systolic BP, edema (2/3 versus 0/1), orthopnea (2/3 versus 0/1), lymphocytes (%), sodium, creatinine and log2 troponin

patients in the placebo arm ($p=0.424$). Most of the study end points did not differ significantly between patients with and without AFib after multivariable adjustment, but AFib patients had a significantly higher incidence of cardiovascular mortality at 180 days (adjusted $p=0.0173$, Table 2).

The effect of serelaxin versus placebo on several study end points in patients with and without AFib is outlined in Table 3. There was no differential effect of serelaxin on dyspnea relief according to VAS scale up to day 5 (interaction $p=0.5954$; Table 3; Fig. 1) or by Likert scale at 6, 12 and 24 h (Table 3) Serelaxin induced a similar reduction in the incidence of worsening HF (interaction $p=0.7423$) irrespective of the presence or absence of AFib. Similarly, the length of hospital stay did not differ (interaction $p=0.3837$). Cardiovascular death or hospitalization for HF or renal failure through day 60 and all-cause death and cardiovascular mortality at 180 days were neither significantly affected by serelaxin in either of the two group interaction (interaction $p=0.1583$, 0.0643 and 0.1472, respectively; Fig. 2).

Stroke through 180 days occurred in 13 patients with AFib (2.8%) and 5 patients without AFib (0.8%, $p=0.0116$). There was a trend for a lower incidence of stroke in the serelaxin arm in patients with AFib [hazard ratio serelaxin versus placebo, 0.31 (0.09, 1.13) in AFib versus 3.88 (0.43, 34.71) in patients without AFib, interaction $p=0.0518$].

The effect of serelaxin versus placebo on AEs in patients with and without AFib is shown in Table 4. The overall incidence of serious AEs did not differ based on the presence or absence of AFib (interaction $p=0.3905$). The same applied to the incidence of AEs indicative of hypotension

Table 3 Treatment effect (serelaxin versus placebo) on various outcomes in patients with and without atrial fibrillation (AFib)

Outcome	AFib, $n=479$			No AFib, $n=682$[c]			Interaction p value[d]
	Serelaxin, $n=233$[a]	Placebo, $n=246$[a]	Treatment effect (95% CI) p value[b]	Serelaxin, $n=348$[a]	Placebo, $n=334$[a]	Treatment, effect (95% CI) p value[b]	
Dyspnea improvement by VAS-AUC to day 5, mm-h[e]	2500.48 (2165.85, 2835.11)	1959.37 (1565.60, 2353.13)	541.11 (33.79, 1048.44) 0.0366	2926.41 (2654.92, 3197.90)	2564.61 (2239.43, 2889.79)	361.80 (−63.30, 786.90) 0.0953	0.5954
Dyspnea improvement by Likert scale at 6, 12 and 24 h	55 (23.6%)	55 (22.4%)	1.07 (0.70, 1.64) 0.7457	101 (29.0%)	95 (28.4%)	1.03 (0.74, 1.43) 0.8671	0.8784
Worsening heart failure	19 (8.2%)	34 (13.8%)	0.57 (0.32, 1.00) 0.0506	20 (5.8%)	37 (11.1%)	0.50 (0.29, 0.86) 0.0126	0.7423
Hospitalization length, days	11.12 (9.77, 12.48)	12.48 (10.96, 13.99)	−1.35 (−3.00, 0.30) 0.1085	8.62 (7.79, 9.45)	9.02 (8.28, 9.76)	−0.39 (−1.78, 0.99) 0.5761	0.3837
Cardiovascular death or HF/RF hospitalization through day 60[e]	30 (13.0%)	39 (16.0%)	0.80 (0.49, 1.28) 0.3486	46 (13.4%)	36 (10.9%)	1.27 (0.82, 1.96) 0.2866	0.1583
All-cause death through day 180	15 (6.5%)	36 (14.8%)	0.42 (0.23, 0.77) 0.0051	27 (7.9%)	29 (8.7%)	0.90 (0.53, 1.52) 0.6888	0.0643
Cardiovascular mortality through day 180[e]	13 (5.6%)	30 (12.4%)	0.44 (0.23, 0.85) 0.0139	21 (6.1%)	24 (7.3%)	0.84 (0.47, 1.52) 0.5713	0.1472
Stroke through day 180	3 (1.30%)	10 (4.23%)	0.31 (0.09, 1.13) 0.0759	4 (1.16%)	1 (0.32%)	3.88 (0.43, 34.71) 0.2255	0.0518

[a]Mean (95% CI) presented for continuous outcome, n (K-M %) for survival outcomes, n (%) for binary outcomes

[b]Treatment effect represents the mean difference estimated from linear regression models for continuous outcomes, the hazard ratio from Cox regression for time-to-event outcomes, and the odds ratio from logistic regression for binary outcomes

[c]Two subjects with unknown AFib status were imputed as without AFib (treatment-specific mode)

[d]Interaction p value is based on test of treatment by AF interaction from linear regression, Cox or logistic regression model as appropriate

[e]Result presented in [19]

or renal or hepatic impairment. It should be noted that there was no difference in anticoagulation use at baseline and from baseline through day 14 and day 60 among the study groups. In addition, CHA_2DS_2-VASc score was similar among the study groups (Table 5).

Effects of serelaxin on biomarkers of organ damage in patients with and without atrial fibrillation

The effects of serelaxin versus placebo on biomarkers of organ damage were similar irrespective of AFib presence at baseline (Table 6; all interaction p levels were nonsignificant). There was a less pronounced increase in cystatin C with serelaxin than with placebo treatment in both AFib groups, while creatinine decreased in the serelaxin group and increased in the placebo group. There were greater reductions in NT-proBNP, AST, ALT, and GDF-15 at 48 h in the serelaxin group than in the placebo group, both in patients with and without AFib. Serelaxin induced similar reductions in relative changes in troponin T; however, in patients with AFib troponin T increased in the placebo group and remained the same in the serelaxin group, while in patients without AFib troponin T stayed the same in placebo patients and decreased in serelaxin patients.

Atrial fibrillation during follow-up

Atrial fibrillation or flutter was reported in 13 patients by day 14; the incidence was similar in the serelaxin ($n=7$) and placebo ($n=6$) groups. Ten patients, seven in the serelaxin group and three in the placebo group, were rehospitalized for AFib through day 60. In patients without AFib

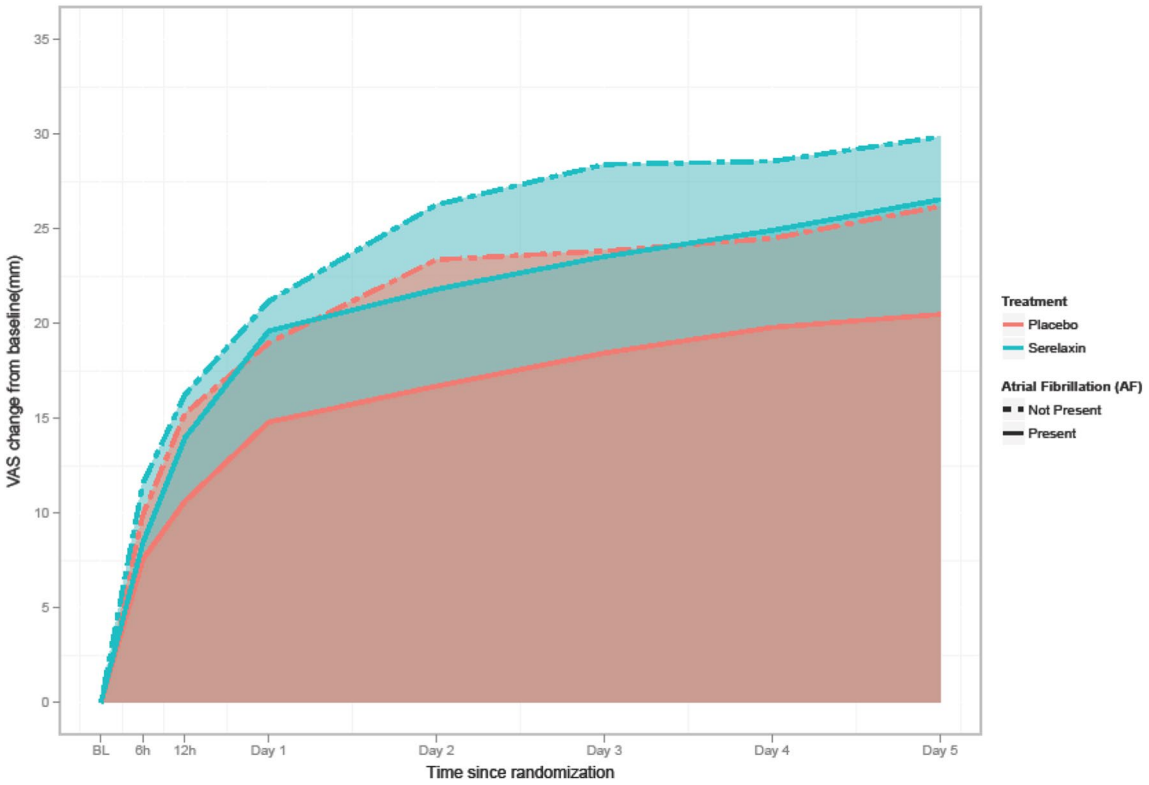

Fig. 1 Patient-reported dyspnea change (serelaxin versus placebo) in patients with and without atrial fibrillation (AF), according to visual analog scale from baseline to day 5

at baseline screening, there were eight episodes of AFib or flutter through day 14, including five (1.44%) in the serelaxin group and three (0.90%) in the placebo group [OR, 1.61, 95% CI (0.31, 10.4), $p=0.725$].

Discussion

A 48-h serelaxin infusion in patients with acute HF improved dyspnea and congestion, reduced early HF worsening and hospital stay and improved long-term outcome in terms of cardiovascular and all-cause mortality at 6 months [14]. The effects of serelaxin versus placebo on dyspnea relief to day 5, cardiovascular death or rehospitalizations for heart or renal failure at 60 days or all-cause or cardiovascular mortality at 180 days were further shown to be generally consistent across several patient subgroups, including a history of AFib and AFIb on admission [17]. In the present analysis, we expanded those results by addressing the interaction between treatment assignment (serelaxin or placebo) and the presence or absence of AFib on admission on all efficacy and safety end points, including dyspnea improvement at 6, 12 and 24 h, worsening HF, hospitalization length, all-cause and cardiovascular death at 180 days and incidence of stroke over the same time period.

Patients with AFib on admission enrolled in the RELAX-AHF trial differed in HF etiology and phenotype as well as in baseline comorbidities compared to patients without AFib. In addition, AFIb patients had a higher adjusted incidence of cardiovascular mortality at 180 days. However, dyspnea response to therapy, HF worsening and cardiovascular death or hospitalization for HF or renal failure through day 60 as well as all-cause death through day 180 were similar in the two subgroups after multivariable adjustment. This finding suggests that worse outcomes observed in acute HF patients with AFib may be partly influenced by the different profile of those patients rather than being wholly attributable to the arrhythmia per se.

Serelaxin was similarly safe in the two groups in terms of serious adverse events or events indicative of hypotension, or renal or hepatic impairment. Not only was serelaxin safe, but it also seemed to provide organ protection, as the previously documented beneficial effect of serelaxin on biomarkers of organ damage was consistent in patients with and without AFib. In addition, although the incidence of stroke was, as expected, higher in patients with AFib,

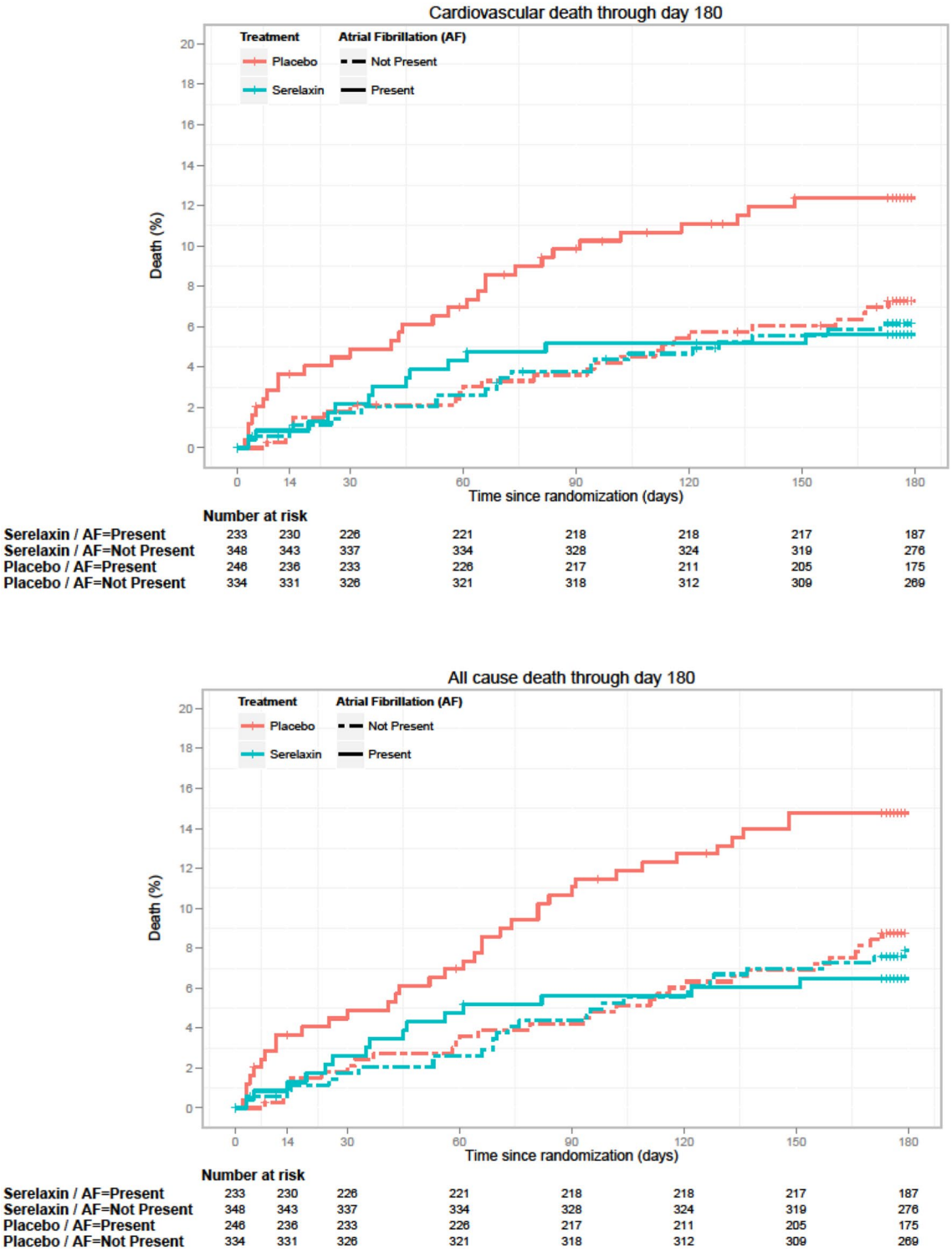

Fig. 2 Kaplan–Meier curves (serelaxin versus placebo) for cardiovascular death through day 180 (*upper panel*) and all-cause death through day 180 (*lower panel*) in patients with and without atrial fibrillation (AF)

interestingly serelaxin tended to reduce its incidence in those particular patients.

Atrial fibrillation is known to confer a fivefold increase in the risk of stroke [12]. Studies have shown that even subclinical AFib episodes as short as 6 min or perioperative AFib in patients undergoing non-cardiac surgery are followed by an increased long-term risk of stroke [22–25]. Stroke may be a devastating condition associated with

significant morbidity and mortality. The present post hoc analysis, despite the rather short follow-up period, confirmed a higher risk of stroke in AFib patients. Interestingly, serelaxin was followed by a lower incidence of stroke in those patients compared to placebo. Relaxin is a known vasoactive peptide that modifies beneficially arterial resistance and compliance. Regarding the cerebral vasculature, in particular, relaxin seems to have specific beneficial effects that have led to the hypothesis that it may play a protective role against ischemic stroke [26]. Experimental studies have shown that relaxin pretreatment reduced infarct size after middle cerebral artery occlusions in rats, an action accomplished through the activation of the relaxin family peptide receptor 3 (RXFP3), a process that also involved activation of the endothelial nitric oxide synthase (eNOS) pathway [27–29]. Those effects within the cerebral vascular bed may lead to vasodilation and improved brain tissue perfusion. In a small clinical study in 36 patients recovering from stroke, relaxin plus rehabilitation induced a greater recovery compared to rehabilitation alone at 20 and 40 days as indicated by measures of physical activity, cognitive function and global function [26]. It should be stressed however that the incidence rate of stroke was low and therefore those results should be interpreted with caution.

Besides its vasodilatatory and anti-ischemic actions discussed earlier, relaxin seems to possess anti-inflamatory and antifibrotic properties [30]. As inflammation and fibrosis are thought to be important aspects in the pathophysiology of AFib, it has been postulated that relaxin may have a role in the management of AFib [31]. In an experimental study in hypertensive rats, relaxin suppressed AFib triggered by programmed stimulation [32]. The suppression of AFib was achieved by increasing conduction velocity from a combination of reversal of atrial fibrosis and hypertrophy and by increasing Na^+ current density [32]. In RELAX-AHF, the occurrence of AFib during follow-up was not systematically recorded; there were only a few spontaneous reports of AFib as an adverse event. As a result, the effects of the drug on the occurrence of AFib could not be assessed, but this may be the aim of a future study.

The results of the present study should be cautiously treated as they are derived by a post hoc subgroup analysis of a randomized trial. In addition, the main RELAX-AHF study was not primarily designed and powered to assess medium and long-term prognostic outcomes and therefore the corresponding findings should be carefully interpreted.

In conclusion, serelaxin was overall similarly safe and efficacious in improving short- and long-term clinical outcomes and inducing organ protection in acute HF patients

Table 4 Treatment effect (serelaxin versus placebo) on adverse events (AE) in patients with and without atrial fibrillation (AFib)

Adverse event	AFib, $n=479$			No AFib, $n=680$			Interaction p value
	Serelaxin, $n=233$	Placebo, $n=246$	Oddsratio(95% CI) p value	Serelaxin, $n=347$	Placebo, $n=333$	Odds ratio (95% CI) p value	
Patients with any serious AE through day 14	26 (11.16%)	45 (18.29%)	0.56 (0.32, 0.97) 0.0293	43 (12.39%)	51 (15.32%)	0.78 (0.49, 1.24) 0.3172	0.3905
Patients with AE indicative of hypotension through day 14[a]	10 (4.29%)	9 (3.66%)	1.18 (0.42, 3.35) 0.8166	18 (5.19%)	18 (5.41%)	0.96 (0.46, 1.99) 1.0000	0.7769
Patients with AE indicative of renal impairment through day 14[b]	4 (1.72%)	12 (4.88%)	0.34 (0.08, 1.15) 0.0737	13 (3.75%)	20 (6.01%)	0.61 (0.27, 1.31) 0.2116	0.5189
Patients with AE indicative of hepatic impairment through day 14[c]	1 (0.43%)	7 (2.85%)	0.15 (0.00, 1.16) 0.0688	2 (0.58%)	4 (1.20%)	0.48 (0.04, 3.36) 0.4422	0.5491

AE adverse events

[a]Blood pressure decreased, dizziness, loss of consciousness, hypotension, orthostatic hypotension, presyncope, somnolence or syncope

[b]Azotemia, blood creatinine increase, oliguria, proteinuria, renal failure, acute renal failure or renal impairment

[c]Blood bilirubin increase, cholestasis, hepatic congestion, hepatic cyst, hepatic steatosis, hyperbilirubinemia, hypoalbuminemia, INR increase or liver disorder

Table 5 Comparison of anticoagulation therapy and CHADS2-VASc score among study groups

	AFib, $n=479$					No AFib, $n=680$					Interaction p value
	Serelaxin, $n=233$	Placebo, $n=246$	Treatment effect	95% CI	p value	Serelaxin$n=347$	Placebo$n=333$	Treatment effect	95% CI	p value	
Anticoagulant use at baseline[a]	119 (51.1)	136 (55.3)	0.84	(0.59, 1.21)	0.3560	90 (25.9)	102 (30.6)	0.79	(0.57, 1.11)	0.1744	0.8028
Anticoagulant use through day 14[a]	157 (67.4)	179 (72.8)	0.77	(0.52, 1.14)	0.1987	115 (33.1)	122 (36.6)	0.86	(0.63, 1.18)	0.3391	0.6878
Anticoagulant use through day 60[a]	165 (70.8)	186 (75.6)	0.78	(0.52, 1.17)	0.2364	124 (35.7)	132 (39.6)	0.85	(0.62, 1.16)	0.2936	0.7630
$CHADS_2$-VASc score at baseline[b]	4.41 (4.20, 4.61)	4.59 (4.41, 4.77)	−0.18	(−0.47, 0.11)	0.2171	4.26 (4.08, 4.44)	4.37 (4.19, 4.54)	−0.10	(−0.35, 0.14)	0.3993	0.6863

Mean (95% CI) and n (%) are presented for continuous outcome and binary outcome, respectively

[a]Treatment effect represents odds ratio (from logistic regression analysis). Each model includes the subgroup variable (AFib versus No AFib), treatment and treatment by subgroup interaction as covariates

[b]Treatment effect represents mean difference (from linear regression analysis). Each model includes the subgroup variable (AFib versus No AFib), treatment and treatment by subgroup interaction as covariates. Two patients had missing AFib values at screening. Anticoagulants include acenocoumarol, dalteparin, enoxaparin, fondaparinux, heparin, heparin-fraction, nadraparin, phenprocoumon, tinzaparin, warfarin

Table 6 Effect of treatment (serelaxin versus placebo) on biomarkers of organ damage in patients with and without atrial fibrillation (AFib)

Biomarker	AFib, $n=479$			No AFib, $n=682$[c]			Interaction p value[d]
	Serelaxin, $n=233$[a]	Placebo,$n=246$[a]	Treatment effect (95% CI) p value[b]	Serelaxin, $n=348$[a]	Placebo, $n=334$[a]	Treatment effect (95% CI) p value[b]	
Change to day 2 in cystatin C (log2 transformed)	1.01 (0.99, 1.04)	1.08 (1.06, 1.11)	0.93 (0.90, 0.96) <0.0001	1.04 (1.02, 1.06)	1.08 (1.05, 1.10)	0.96 (0.94, 0.99) 0.0071	0.1512
Change to day 2 in creatinine	−4.90 (−7.95, −1.85)	5.34 (2.55, 8.13)	−10.25 (−14.78, −5.72) <0.0001	−2.17 (−5.09, 0.75)	6.68 (3.85, 9.50)	−8.84 (−12.65, −5.04) <0.0001	0.6424
Change to day 2 in troponin (log2 transformed)	1.00 (0.95, 1.06)	1.08 (1.03, 1.13)	0.93 (0.85, 1.01) 0.0823	0.94 (0.89, 0.99)	1.00 (0.95, 1.06)	0.94 (0.87, 1.01) 0.0881	0.8281
Change to day 2 in NT-proBNP (log2 transformed)	0.54 (0.49, 0.58)	0.70 (0.65, 0.76)	0.76 (0.68, 0.86) <0.0001	0.46 (0.43, 0.50)	0.54 (0.50, 0.59)	0.85 (0.77, 0.94) 0.0019	0.1459
Change to day 2 in GDF 15 (log2 transformed)	0.77 (0.72, 0.82)	0.93 (0.88, 0.99)	0.82 (0.75, 0.90) <0.0001	0.80 (0.76, 0.85)	0.88 (0.84, 0.93)	0.91 (0.84, 0.98) 0.0091	0.0941
Change to day 2 in ALT (log2 transformed)	0.83 (0.80, 0.86)	0.91 (0.86, 0.96)	0.92 (0.87, 0.97) 0.0022	0.82 (0.80, 0.85)	0.87 (0.85, 0.90)	0.94 (0.90, 0.99) 0.0115	0.4777
Change to day 2 in AST (log2 transformed)	0.84 (0.80, 0.87)	0.91 (0.86, 0.96)	0.92 (0.86, 0.98) 0.0088	0.78 (0.76, 0.81)	0.87 (0.84, 0.90)	0.90 (0.85, 0.95) <0.0001	0.5810

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

[a]Mean (95% CI) change from baseline to day 2 or geometric mean (95% CI) – the ratio of day 2 to baseline – if log2 transformed

[b]Treatment effect represents mean difference or the ratio of the relative changes if log2 transformed

[c]Two subjects with unknown AFib status were imputed as without AFib (treatment-specific mode)

[d]Interaction p value based on test of treatment by AF interaction from linear regression

with and without AFib. However, prospective trials are required to confirm those findings.

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Compliance with ethical standards

Conflict of interest G. F. was a member of the steering committee of RELAX-AHF. D. F. has received consultancy and speaker fees from Servier and Novartis and an educational grant from Novartis. M. M. reports receiving honoraria as a consultant for Novartis and Bayer. G. C. and B. A. D. are employees of Momentum Research Inc., which received remuneration for conducting clinical studies from Novartis, Amgen, Cardio3, Trevena, Chan RX, Laguna Pharmaceuticals and Singulex. G. M. F. has received consulting and grant support from Novartis. B. H. G. is a consultant for Novartis and Janssen. T. A. H. and T. A. S. are employees of Novartis. P.S.P. is or has been in the past year a consultant for: Janssen, Medtronic, Novartis, Trevena, scPharmaceuticals, Cardioxyl, Roche Diagnostics and Relypsa; received honoraria: Palatin Technologies; and research support: Roche and Novartis. P. P. is a consultant for Novartis, Cardiorentis and Bayer, and receives research grants from Singulex. A. A. V. was a member of the steering committee of RELAX-AHF and received consultancy, speaker fees and research grants from Novartis, and he received grants and or consultancy/speaker fees from Alere, AstraZeneca, Bayer, Cardio3Biosciences, Celladon, GSK, Merck/MSD, Servier, Stealth, Singulex, Sphingotec, Trevena and Vifor. J. R. T. receives research/consulting fees from Amgen, Madeleine, Mast Therapeutics, Novartis, Relypsa and Trevena. The rest of the authors report no conflicts of interest.

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