European Journal of Heart Failure (2010) **12**, 1130–1139
doi:10.1093/eurjhf/hfq132

Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study

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Received 6 February 2010; revised 23 April 2010; accepted 4 May 2010; online publish-ahead-of-print 22 August 2010

Aims Although dyspnoea is the most common cause of admission for acute heart failure (AHF), more needs to be known about its clinical course and prognostic significance.

Methods and results The Pre-RELAX-AHF study randomized 232 subjects with AHF to placebo or four doses of relaxin and evaluated early (6–24 h Likert scale) and persistent [change in visual analogue scale area under the curve (VAS AUC) through Day 5] dyspnoea relief. Worsening heart failure (WHF) was defined as worsening AHF signs and symptoms requiring additional therapy. Patients were followed until Day 180. Early dyspnoea relief was observed in only 25% of all patients, and VAS AUC at 5 days was 45% over baseline values in all patients (32% placebo; 50% all relaxin-treated patients). Worsening heart failure to Day 5 was observed in 16% of all patients (21% placebo; 14% relaxin). Lack of persistent dyspnoea relief and WHF were associated with a longer length of initial hospital stay and worse 60-day outcomes.

Conclusion Dyspnoea relief in patients admitted with AHF is often incomplete, and many may show WHF after the initial stabilization. Both lack of persistent dyspnoea relief and in-hospital WHF predict a longer length of stay and worse outcome.

Keywords Acute heart failure • Dyspnoea • Prognosis • Relaxin

Introduction

Although acute heart failure (AHF) remains the most common cause of hospitalization in people >65 years of age,[1–4] its treatment has changed minimally in the last few decades, with no new therapies approved and accepted globally in over 25 years.

Dyspnoea is the principal cause of hospitalization for patients with AHF and is often associated with signs of fluid overload, including pulmonary and/or peripheral congestion.[2,5–7] Recent AHF studies have shown that moderate to marked relief of dyspnoea occurs in only a relatively small percentage of patients (40–60%) in the first days after admission.[8–13] Furthermore, depending on the definition, 10–20% of patients may develop recurrent symptoms and signs of heart failure [worsening heart failure (WHF)][14–16] or die during the first few days from admission. These disappointing results are observed even when guideline-recommended therapies are fully implemented. Moreover, new agents for the treatment of AHF have not shown convincing benefits.[5–7,17,18] Although some AHF therapies have been associated with minimal or moderate improvement in dyspnoea, the absence of robust safety data have either prevented their regulatory approval or limited their use. Hence, rapid and

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persistent improvement of dyspnoea and congestion with no untoward effects on outcomes remains an important and unmet goal of AHF therapy.

The Preliminary study of RELAX in Acute Heart Failure (Pre-RELAX-AHF) assessed the efficacy and safety of the naturally occurring peptide relaxin, a vasodilator with multiple potentially beneficial effects, in patients hospitalized with AHF, mild to moderate renal dysfunction, signs of fluid overload, and increased plasma concentrations of brain natriuretic peptide (BNP) or N-terminal pro brain natriuretic peptide (NT-proBNP).[19] Relief of dyspnoea, death, or WHF during hospitalization were prospectively defined and assessed in this trial. The purpose of the current analysis was to characterize in depth the extent and time course of dyspnoea relief and assess its association with other clinical outcomes in patients with AHF.

Methods

Patients

Methods and results of Pre-RELAX-AHF have been detailed previously.[19] Briefly, this study enroled patients aged $\geq$18 years who were within 16 h of presentation to hospital for AHF, with a systolic blood pressure (BP) $>$125 mmHg at screening and impaired renal function [defined as an estimated glomerular filtration rate (eGFR) of 30–75 mL/min/1.73 m^2]. Acute heart failure was defined by the presence of dyspnoea at rest or with minimal exertion, pulmonary congestion on chest radiograph, and increased natriuretic peptide concentrations (BNP $\geq$350 pg/mL or NT-proBNP $\geq$1400 pg/mL) with the administration of at least 40 mg of intravenous furosemide (or equivalent loop diuretic) between presentation and screening. A systolic BP $>$125 mmHg was chosen as an inclusion criterion as likely associated with the best benefit to risk ratio for a study drug such as relaxin having vasodilating and, potentially, hypotensive effects and administered at a wide range of doses in the phase II Pre-RELAX-AHF trial.[1,2,20]

Patients were randomized within 16 h of presentation to receive placebo or 10, 30, 100, or 250 μg/kg/24 h of relaxin. Study medication was given as a continuous intravenous (IV) infusion over 48 h. Patients were allowed to receive other therapies at the treating physician's discretion, anytime after administration was initiated. At the time of randomization, IV nitrates were only allowed if the patient's systolic BP was $>$150 mmHg at screening. The Pre-RELAX-AHF study was approved by the appropriate regulatory authorities and Ethics Committees prior to patient enrolment, and written informed consent was obtained from each patient before study-specific procedures were performed.

Assessment of dyspnoea and worsening heart failure

Patients assessed their dyspnoea at baseline and then at 6, 12, and 24 h from randomization and then daily to Day 5, and then at Day 14, using patient-reported assessment tools, which included the following two main measures. (i) Absolute dyspnoea severity, assessed at each time point on a visual analogue scale (VAS) using a 100 mm vertical line, upon which patients were required to draw a horizontal line rating their breathing, with 100 representing the 'best imaginable health state' and zero 'the worst imaginable health state'. (ii) Additionally, relative changes in dyspnoea were captured using a 7-point Likert scale by which patients were required to rate their breathing as being markedly, moderately, or minimally better; no change; or minimally, moderately, or markedly worse compared with baseline.

Dyspnoea assessment was done at all-time points with the patient lying on the bed, with the head of the bed elevated to 30 degrees, legs on the bed, and oxygen withdrawn for 5 min. If the patient could not tolerate the position or being taken off oxygen for 5 min, these measures were discontinued, and the patient was requested to complete the dyspnoea assessment describing how they felt at the time the oxygen was withdrawn. Dyspnoea questionnaires were translated into all languages by certified translators.

After the assessment of dyspnoea, physicians were requested to perform, on a daily basis, additional clinical evaluations including assessment of orthopnoea, dyspnoea on exertion, as well as congestion by assessing jugular venous pressure (JVP), pulmonary rales, peripheral oedema, and body weight. After these clinical assessments, the physician was requested to specify whether the patient had worsening symptoms and/or signs of heart failure requiring the increase or re-institution of intravenous or mechanical therapy for heart failure (WHF). Physicians were instructed that either a pulmonary oedema event during the preceding 24 h or a gradual deterioration, both requiring addition of IV or mechanical therapy for heart failure, should be reported as WHF. On the other hand, addition of IV therapy for other reasons, such as control of hypertension or enhanced diuresis in the absence of worsening symptoms or signs of heart failure, was not considered WHF. Worsening heart failure through Day 5 was examined in the current analysis. Blood samples for central laboratory analysis, including serum creatinine, were collected daily through Day 5 and at Day 14.

Definitions of early dyspnoea relief and persistent dyspnoea relief

Early dyspnoea relief was defined as a moderately or markedly better dyspnoea assessed by the Likert scale at 6,12, and 24 h (all three time points) from study drug initiation.

Persistent dyspnoea relief was assessed using the VAS over 5 days. The area under the curve (AUC) representing the change in VAS score from baseline over time was computed from baseline to Day 5 for each patient by the trapezoidal rule. For the purposes of examining baseline characteristics and associations with other heart failure signs and symptoms, patients were classified as having persistent dyspnoea relief if their VAS AUC fell into the upper tertile of the overall distribution. For modelling purposes, the VAS AUC was examined as a continuous variable.

Follow-up

Patients were followed to Days 60 and 180 by telephone calls. At Day 60, all rehospitalizations and deaths were collected and the cause for each reported. At Day 180, all deaths between Day 60 and Day 180 were reported including cause of death as determined by the investigator.

Statistical methods

All data are shown as mean + standard deviation unless otherwise specified. Generally, groups were compared using *t*-tests for continuous variables and χ^2 tests for dichotomous variables. Univariable and multivariable logistic regression models were used to describe potential predictors of early dyspnoea relief and WHF; linear regression was used to examine potential predictors of dyspnoea VAS AUC. Variables considered were those shown in larger databases to be important prognostic factors in AHF. [4,21–23]. The last observation was carried forward for missing dyspnoea scores, except that the worst possible

score was carried forward from the time of death or WHF onset. Unimputed scores were used to evaluate correlations between dyspnoea changes and changes in other heart failure symptoms and signs. Spearman's rank correlation coefficients are presented, with *P*-values for the *t*-test of no correlation. Length of stay was imputed as the maximum length of stay plus 1 Day (33 days) for patients who died during the initial hospital admission. Linear regression was used to examine VAS AUC as a predictor of length of stay and days alive out of hospital. Kaplan–Meier estimates of the risks of death or the composite of death or rehospitalization are presented. The time to event was censored at last patient contact for patients without the event of interest. Survival analyses were restricted to patients with event times after Day 1 (where baseline was Day 0) for the analysis of early dyspnoea relief and to patients with event times after Day 5 for analyses of VAS AUC and WHF. Hazard ratios were estimated using Cox proportional hazards regression. Results for the four relaxin dose groups combined as compared with placebo are also described. No adjustment for multiple comparisons was made. Two-sided $P < 0.05$ was regarded as statistically significant.

Results

Rates of dyspnoea improvement

Of the 234 patients randomized at 54 centres in 8 countries, 232 had assessments of dyspnoea that allowed classification of early and persistent dyspnoea improvement. A total of 229 randomized patients were treated with relaxin or placebo and were included in treatment group for comparisons. Overall, moderately or markedly better dyspnoea was observed at 6, 12, and 24 h (early dyspnoea relief) in 25% of patients (23% on placebo and 26% assigned to relaxin at all doses combined). Overall only 70% of patients had moderately or markedly better dyspnoea at Day 14 (the last assessment in the study).

By Day 5, VAS increased from an average baseline of 42.3 $\pm$ 20.1 mm, by 14.3 $\pm$ 30.6 mm in the placebo group vs. 23.3 $\pm$ 29.8 mm in the overall relaxin group. The mean dyspnoea VAS AUC from baseline to Day 5 was 1679 $\pm$ 2556 mm h in placebo and 2412 $\pm$ 2721 mm h in all relaxin-treated patients. These AUCs correspond to average relative improvements from baseline over the 5 days of 31.7% in placebo and 50.0% in all relaxin patients.

The cumulative rate of WHF was 1% at 6 h, 4% at 12 h, 8% at 24 h, and 16% at Day 5. The rate of WHF to Day 5 was 21% in placebo and 14% in the combined active treatment groups.

Association with baseline characteristics

Baseline characteristics of patients with and without early or sustained dyspnoea relief or with WHF are presented in *Table 1*. Early dyspnoea relief was associated with a greater proportion of patients with high-BNP or NT-proBNP level, a lower mean respiratory rate, and a higher mean systolic BP at baseline. Persistent dyspnoea relief, assessed by VAS AUC, was also associated with a lower mean baseline respiratory rate. In contrast, absence of WHF was associated with lower mean baseline blood urea nitrogen (BUN) and serum creatinine levels as well higher mean serum sodium at baseline.

Univariable and multivariable models of the association of baseline characteristics with early dyspnoea relief, dyspnoea VAS AUC, and WHF are shown in *Table 2*. All the variables listed in this table were entered into the multivariable model. Few baseline characteristics were related to dyspnoea relief in both univariable and multivariable analyses. Early dyspnoea relief was associated with baseline systolic BP, and both early dyspnoea relief and dyspnoea VAS AUC were significantly related to baseline respiratory rate, after multivariable adjustment. Worsening heart failure remained correlated with lower sodium at baseline.

Association with changes in other signs and symptoms and treatment

Favourable changes in dyspnoea were significantly correlated with favourable changes in other heart failure signs and symptoms, including general well-being, orthopnoea, dyspnoea on exertion, and oedema (*Table 3*). Dyspnoea changes were less consistently correlated with changes in rales, JVP, and weight. Prescription rates for angiotensin-converting enzyme-inhibitors (ACE-I), angiotensin receptor blocker (ARBs), and beta-blockers at randomization were similar for patients who did and did not have dyspnoea relief (*Table 4*). Patients with dyspnoea relief and lack of WHF were more likely to receive ACE-I, ARBs, and beta-blockers at discharge and Day 14, although this did not reach statistical significance.

Association with short- and intermediate-term outcomes

Associations of early dyspnoea relief, dyspnoea VAS AUC, and WHF with length of stay and days alive and out of hospital to Day 60 are given in *Table 5*, and associations with rates of re-admission for heart or renal failure or cardiovascular death to Day 60 and cardiovascular death to Day 180 are presented in *Table 6*. Patients with lack of dyspnoea relief and WHF had trends, sometimes reaching statistical significance, for a longer length of stay, fewer days alive, and out of hospital and higher cardiovascular mortality.

Discussion

The present analysis of data from Pre-RELAX-AHF shows that early and persistent relief of dyspnoea are uncommon in these patients with AHF. About three-quarters of the patients studied did not have early dyspnoea relief, whereas persistent dyspnoea relief at Day 5 in the placebo group was limited to ~32% relative improvement over baseline. In addition, approximately a quarter of our patients developed recurrent symptoms and signs of heart failure during the initial hospitalization, necessitating increases or initiation of IV or mechanical therapy for heart failure (WHF). Dyspnoea improvement was, to some extent, predicted by higher systolic BP at baseline and a lower baseline respiratory rate. Freedom from WHF was predicted by a better renal function and higher serum sodium at baseline. Administration of relaxin was associated with early and more persistent dyspnoea relief and lower likelihood of WHF. Lack of dyspnoea relief and WHF tended to be associated with longer length of stay and poorer long-term outcome. However, these data need to be confirmed in larger study groups.

Table 1 Baseline characteristics of patients with and without early and persistent dyspnoea relief and worsening heart failure

	Early dyspnoea relief			Persistent dyspnoea relief			Worsening heart failure		
Baseline characteristic	**Yes (n = 58)**	**No (n = 174)**	***P***	**Upper tertile (n = 79)**	**Lower 2 tertiles (n = 153)**	***P***	**No (n = 196)**	**Yes (n = 36)**	***P***
Age (years)	71 + 9	70 + 11	0.67	72 + 10	70 + 11	0.16	70 + 11	73 + 8	0.11
Male (%)	48	58	0.19	52	57	0.41	55	58	0.72
Body weight (kg)	83 + 17	80 + 17	0.30	79 + 18	82 + 17	0.42	82 + 17	78 + 16	0.27
COPD (%)	19	16	0.61	19	16	0.52	16	19	0.65
Diabetes (%)	50	41	0.26	53	39	0.05	45	39	0.53
Hypertension (%)	93	83	0.07	89	84	0.37	87	81	0.33
Ischaemic heart disease (%)	59	73	0.03	70	70	0.99	70	69	0.97
Peripheral vascular disease (%)	14	13	0.82	16	11	0.25	11	22	0.07
Stroke (%)	19	15	0.54	19	15	0.44	16	19	0.59
Systolic BP (mmHg)	151 + 18	143 + 17	<0.01	147 + 15	144 + 19	0.29	146 + 17	144 + 20	0.52
Diastolic BP (mmHg)	84 + 12	81 + 11	0.11	81 + 11	83 + 12	0.42	82 + 12	82 + 11	0.88
Heart rate/min	83 + 15	82 + 15	0.68	79 + 12	84 + 16	0.03	82 + 15	82 + 15	0.96
Atrial fibrillation (%)	43	49	0.43	40	51	0.12	47	53	0.50
Respiratory rate/min	22 ± 3	23 ± 3	<0.01	22 ± 3	23 ± 4	<0.01	23 ± 3	24 ± 4	0.27
Haemoglobin (g/dL)	13 + 2	13 + 2	0.24	13 + 2	13 + 2	0.17	13 + 2	13 + 2	0.15
BUN (mg/dL)	27 + 10	27 + 12	0.79	26 + 11	28 + 12	0.26	26 + 11	31 + 13	0.02
Serum creatinine (mg/dL)	1.4 + 0.5	1.3 + 0.5	0.29	1.3 + 0.5	1.3 + 0.5	0.41	1.3 + 0.5	1.5 + 0.5	0.03
eGFR, screening (mL/min/1.73 m^2)	53 + 16	54 + 17	0.83	54 + 20	53 + 15	0.51	54 + 17	50 + 14	0.15
Sodium (mmol/L)	141 + 4	140 + 4	0.49	140 + 3	141 + 4	0.34	141 + 3	139 + 5	0.01
White blood cell count ($\times 10^9$/L)	8.3 + 2.6	8.7 + 3.3	0.53	8.6 + 3.3	8.6 + 3.1	0.93	8.5 + 3.0	9.1 + 3.7	0.32
Lymphocytes <13% (%)	71	71	0.99	60	76	0.02	73	59	0.12
BNP >500 or NT-proBNP >2000 pg/mL (%)	86	70	0.02	79	72	0.22	72	83	0.17
Troponin >0.10 ng/mL (%)	16	17	0.84	21	15	0.22	17	17	0.98
ACE-inhibitor or ARB (%)	67	65	0.75	67	65	0.72	65	69	0.59
Nitrates (%)	24	20	0.52	22	21	0.91	21	22	0.86
Hydralazine (%)	5	1	0.07	4	1	0.22	3	0	0.33
β-blocker (%)	57	56	0.88	59	54	0.45	56	58	0.76
Calcium-channel blocker (%)	12	16	0.52	20	12	0.08	15	14	0.89
Aldosterone inhibitor (%)	21	36	0.03	19	39	<0.01	32	33	0.89
Digoxin (%)	19	21	0.71	10	26	<0.01	18	33	0.04

Early dyspnoea relief was defined as a marked or moderate improvement in dyspnoea by the Likert scale at 6, 12, and 24 h from randomization. Persistent dyspnoea relief was measured on the basis of the changes in the AUC of VAS assessed at 5 days from randomization.

BP, blood pressure; BUN, blood urea nitrogen; COPD, Chronic Pulmonary Obstructive Disease; eGFR, estimated glomerular filtration rate.

Table 2 Univariable and multivariable regression analyses of predictors of early dyspnoea relief, dyspnoea visual analogue scale area under the curve to Day 5, and worsening heart failure to Day 5

		Early dyspnoea relief				Dyspnoea VAS AUC to Day 5				Worsening heart failure			
		Univariable model		Multivariable model		Univariable model		Multivariable model		Univariable model		Multivariable model	
	SD	OR (95%CI)	*P*	OR (95%CI)	*P*	Mean change (SE)	*P*	Mean change (SE)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	10.47	1.07 (0.79–1.44)	0.67	1.44 (0.90–2.29)	0.13	113 (177)	0.53	128 (229)	0.58	1.38 (0.93–2.04)	0.11	1.15 (0.70–0 1.87)	0.57
Male		0.67 (0.37–1.22)	0.20	0.36 (0.14–0.94)	0.04	−572 (354)	0.11	−403 (497)	0.42	1.14 (0.56–2.34)	0.72	0.85 (0.30–2.40)	0.76
History of myocardial infarction		0.77 (0.42–1.40)	0.38	0.96 (0.42–2.21)	0.93	−37 (356)	0.92	265 (420)	0.53	0.74 (0.36–1.51)	0.41	0.62 (0.26–1.51)	0.29
Pulse	14.96	1.06 (0.79–1.43)	0.68	1.04 (0.70–1.55)	0.85	−161 (177)	0.36	−194 (211)	0.36	0.99 (0.69–1.42)	0.96	1.03 (0.67–1.60)	0.88
Respiratory rate	3.59	0.59 (0.43–0.81)	<0.01	0.44 (0.29–0.67)	<0.01	−531 (174)	0.0026	−697 (204)	<0.01	1.23 (0.85–1.76)	0.27	1.58 (1.02–2.45)	0.04
Systolic blood pressure	17.87	1.52 (1.14–2.03)	<0.01	1.73 (1.14–2.64)	0.01	183 (177)	0.30	127 (226)	0.57	0.88 (0.61–1.28)	0.52	0.90 (0.56–1.42)	0.64
Sodium	3.92	1.12 (0.82–1.52)	0.49	1.23 (0.79–1.92)	0.36	161 (178)	0.37	242 (208)	0.25	0.66 (0.47–0.92)	0.02	0.63 (0.43–0.94)	0.02
BUN	11.46	0.96 (0.71–1.30)	0.79	0.76 (0.40–1.42)	0.38	−301 (177)	0.09	−359 (315)	0.26	1.46 (1.05–2.03)	0.03	1.20 (0.64–2.24)	0.57
Creatinine	0.47	1.17 (0.87–1.56)	0.29	1.48 (0.81–2.72)	0.20	−215 (173)	0.22	75 (323)	0.82	1.42 (1.02–1.96)	0.04	1.32 (0.71–2.46)	0.39
Haemoglobin at baseline	1.83	1.22 (0.87–1.70)	0.24	1.68 (1.06–2.65)	0.03	17 (190)	0.93	−58 (224)	0.80	0.76 (0.53–1.10)	0.15	0.84 (0.54–1.30)	0.44
WBC-lymphocytes %<13%		1.00 (0.49–2.06)	0.99	0.86 (0.36–2.04)	0.73	28 (424)	0.95	−73 (458)	0.87	0.54 (0.25–1.19)	0.12	0.62 (0.25–1.54)	0.30
Troponin positive		0.92 (0.41–2.08)	0.84	1.20 (0.45–3.20)	0.72	317 (481)	0.51	536 (509)	0.29	1.02 (0.39–2.65)	0.98	0.67 (0.22–2.03)	0.48
Admission BNP >500 or NT-proBNP >2000 pg/mL		2.66 (1.18–6.01)	0.02	1.59 (0.54–4.63)	0.40	−1.8 (404.3)	1.00	51 (486)	0.91	1.90 (0.75–4.82)	0.18	1.60 (0.55–4.67)	0.39

ORs and mean changes presented are for a standard deviation increase in continuous predictors and for a 1-unit change for dichotomous predictors from logistic regression models for early dyspnoea relief and worsening heart failure and from linear regression models for dyspnoea VAS AUC.

Table 3 Correlations between changes in dyspnoea and changes in other heart failure symptoms and signs

	Spearman' rank correlation (*P*-value)					
	Dyspnoea Likert			Change in dyspnoea VAS from baseline		
	Day 1 (24 h)	Day 5	Day 14	Day 1 (24 h)	Day 5	Day 14
Change in dyspnoea VAS	−0.5987 (<0.0001)	−0.4512 (<0.0001)	−0.3888 (<0.0001)	–	–	–
General well-being Likert	0.8761 (<0.0001)	0.8569 (<0.0001)	0.8068 (<0.0001)	−0.5656 (<0.0001)	−0.4493 (<0.0001)	−0.3939 (<0.0001)
Change in general well-being VAS	−0.4218 (<0.0001)	−0.4481 (<0.0001)	−0.3706 (<0.0001)	0.7642 (<0.0001)	0.8409 (<0.0001)	0.8377 (<0.0001)
Change in orthopnoea	0.3163 (<0.0001)	0.2854 (<0.0001)	0.3579 (<0.0001)	−0.2265 (0.0006)	−0.2145 (0.0016)	−0.2372 (0.0005)
Change in dyspnoea on exertion	0.2834 (<0.0001)	0.3472 (<0.0001)	0.4085 (<0.0001)	−0.2916 (<0.0001)	−0.1888 (0.0076)	−0.2867 (<0.0001)
Change in oedema	0.2566 (<0.0001)	0.1281 (0.0609)	0.1742 (0.0109)	−0.1598 (0.0160)	−0.1161 (0.0896)	−0.1684 (0.0139)
Change in rales	0.1895 (0.0041)	0.05221 (0.4463)	0.0874 (0.2039)	−0.2887 (<0.0001)	−0.1891 (0.0054)	−0.2263 (0.0009)
Change in JVP	−0.0217 (0.7468)	−0.1016 (0.1405)	−0.0152 (0.8261)	−0.0819 (0.2220)	0.0185 (0.7893)	−0.0057 (0.9343)
Change in weight	−0.0463 (0.4903)	0.1429 (0.0385)	0.2873 (<0.0001)	0.0886 (0.1862)	0.0526 (0.4481)	−0.0210 (0.7623)

Oedema: 0–3+; Jugular venous pulse (JVP): 0, <6 cm; 1, 6–10 cm; 2, >10 cm; Orthopnoea: 0, none; 1, 1 pillow (10 cm); 2, 2 pillows (20 cm); 3, >30°; Rales: 0, no rales; 1, rales <1/3; 2, rales 1/3–2/3; 3, rales >2/3 lung field.

Relief from dyspnoea and worsening heart failure in patients admitted for acute heart failure

Symptoms of heart failure, usually dyspnoea, are the main cause of hospitalization in AHF. These symptoms are so disabling that patients with advanced heart failure have professed acceptance of an increased risk of death for some improvement in symptoms.[24] The importance of dyspnoea is recognized by regulatory agencies and accepted as an important endpoint required for registration trials of new AHF medical treatments, provided there is sufficient evidence of safety.[25,26] Improved standardization of dyspnoea measurement has been proposed[27] and adopted in clinical trials, including in Pre-RELAX-AHF.[19]

Rates of early and persistent dyspnoea relief were surprisingly low in our study. This finding is at odds with previous trials where higher rates were reported. Using the Likert scale (similar to the one used in the current study), ~45% of patients enroled in the placebo arm of the VMAC study had moderate or marked improvement in dyspnoea by 3 h after enrolment.[5] Similar proportions (40–60%) of patients with improved dyspnoea were observed in the placebo arm of the REVIVE study at 6 h[17] and in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST).[7,28] Using the VAS in VERITAS,[6] major improvements in dyspnoea were observed at 3 and 24 h, surpassing those observed in the present study at Day 5. The lower proportion of patients with an early improvement in dyspnoea and the smaller improvements to Day 5 in the present study cannot be ascribed to the inclusion of patients known to be refractory to standard treatment, since we included only patients within 16 h from presentation (median 6 h).[19] We do not think that our findings can be ascribed to the demographic characteristics of our study group, as they were similar to those of previous trials, but, rather, to the enrolment criteria of Pre-RELAX-AHF. These included the need of IV diuretic therapy, mild to moderate renal dysfunction, signs of congestion at chest X-ray, and, most important, elevated natriuretic peptide plasma levels. These criteria allow the exclusion of patients with non-cardiac causes of symptoms as well as the enrolment of patients with more severe symptoms and worse prognosis.[4,10] Thus, our use of objective and more strict inclusion criteria may explain both the lower rate of dyspnoea relief as well as the unfavourable prognosis of our patients. Lastly, with respect to the comparison with EVEREST, it must also be noted that this trial included only patients with low left ventricular ejection fraction, whereas we included patients independently from left ventricular ejection fraction (more than half of our patients had a left ventricular ejection fraction >40%) and their history of heart failure.

In agreement with previous studies,[14,15] WHF during initial hospitalization (to Day 5 in this study) was observed in about one-fifth of patients on placebo. This finding emphasizes the high chance of relapse of AHF, with many patients worsening after an initial improvement both in hospital (our definition of WHF) and after discharge (leading to re-admissions). Overall, only a minority of the patients enroled in our study had a 'benign' course with early dyspnoea relief and no recurrence of heart failure.

Table 4 Relationships between changes in dyspnoea and medical treatment

	Early dyspnoea relief			Persistent dyspnoea relief			Worsening heart failure		
	Yes ($n = 58$)	No ($n = 174$)	P	Upper tertile ($n = 79$)	Lower 2 tertiles ($n = 153$)	P	No ($n = 196$)	Yes ($n = 36$)	P
ACE-I or ARB (%)									
One month prior to presentation	71	70	0.93	76	67	0.17	69	75	0.50
From presentation up to randomization	67	65	0.75	67	65	0.72	65	69	0.59
At discharge	84	78	0.30	86	76	0.08	81	72	0.22
At Day 14	83	79	0.57	87	76	0.05	82	69	0.08
Beta-blockers (%)									
One month prior to presentation	64	63.8	0.99	66	63	0.64	64	64	0.99
From presentation up to randomization	57	55.8	0.88	59	54	0.45	57	58	0.76
At discharge	88	81	0.23	83	82	0.82	85	72	0.07
At Day 14	88	81	0.23	83	82	0.82	85	72	0.07
Total dose of IV loop diuretics to Day 5—Mean (SD)	150 (330)	177 (271)	0.53	124 (194)	194 (322)	0.04	445 (499)	120 (189)	<0.01
Number of patients receiving IV dopamine, dobutamine, or milrinone to Day 5	1	6	0.68[a]	1	6	0.43[a]	2	5	<0.01[a]

[a]Fisher's exact test.

Table 5 Relationships between changes in dyspnoea and time in and out of the hospital

	Early dyspnoea relief			VAS AUC to Day 5		Worsening heart failure		
Selected outcome	Yes ($n = 58$)	No ($n = 171$)	P	Mean change per 117 mm h increase in AUC[a] (SE)	P	No ($n = 193$)	Yes ($n = 36$)	P
Length of initial stay	10.5 ± 6.8	11.2 ± 7.1	0.54	−0.094 (0.019)	<0.0001	10.1 ± 6.2	15.9 ± 8.9	0.0006
Days alive and out of hospital to Day 60	45.9 ± 13.4	47.0 ± 11.8	0.56	0.14 (0.034)	<0.0001	48.7 ± 9.4	36.2 ± 18.9	0.0004

[a]117 mm h corresponds to an average increase of 1 mm on the dyspnoea VAS over 5 days.

Determinants of relief of dyspnoea and worsening heart failure

Few variables predicted relief of dyspnoea in our study. This lack of association is consistent with our limited knowledge of the factors associated with this event.[29] More research is needed in larger databases to establish which factors predict dyspnoea relief in AHF. In the present study, dyspnoea relief was related to a higher systolic BP and a lower respiratory rate at baseline, with both variables likely consistent with a lower severity of cardiac dysfunction at baseline. Worsening heart failure was predicted by hyponatraemia and kidney dysfunction. These variables have been associated with worse outcomes in previous studies,[4,21,30] consistent with our findings of an important predictive power of symptoms and WHF for future events.

Assessment of dyspnoea in acute heart failure

In our study, dyspnoea was measured both by the Likert and the VAS scales. These two scales differ substantially, both with regard to the degree of granularity and with regard to how dyspnoea is measured, relative to baseline with the Likert scale, and as an absolute level with the VAS scale. Thus, the VAS scale measures the absolute severity of symptoms and measures them also at baseline. In addition, being based on a 100-point scale,

Table 6 Relationships between changes in dyspnoea and outcomes

Outcome	Early dyspnoea relief				Dyspnoea VAS AUC to Day 5		Worsening heart failure			
	Yes (*n* = 58)	No (*n* = 171)	HR (95% CI)	*P*-Value	HR (95% CI) (per 117 mm-h change in AUC)	*P*-Value	No WHF (*n* = 193)	WHF (*n* = 34)	HR (95% CI)	*P*-Value
60 days HF/RF re-admission or death	9 (15.8%)	18 (10.6%)	1.56 (0.70–3.48)	0.27	0.99 (0.97–1.01)	0.25	15 (7.9%)	9 (27.3%)	3.93 (1.72–8.98)	0.0012
30 days all-cause mortality	3 (5.2%)	6 (3.5%)	1.48 (0.37–5.93)	0.58	0.96 (0.94–0.99)	0.0053	3 (1.6%)	4 (11.8%)	7.70 (1.72–34.41)	0.0075
60 days CV mortality	2 (3.6%)	7 (4.1%)	0.87 (0.18–4.18)	0.86	0.99 (0.96–1.02)	0.35	4 (2.1%)	3 (9.2%)	4.56 (1.02–20.40)	0.047
60 days all-cause mortality	4 (7.0%)	11 (6.5%)	1.11 (0.35–3.48)	0.86	0.98 (0.96–1.00)	0.064	8 (4.2%)	5 (14.7%)	3.76 (1.23–11.50)	0.020
180 days CV death	2 (3.6%)	10 (6.6%)	0.64 (0.14–2.92)	0.56	0.98 (0.96–1.00)	0.094	5 (3.0%)	5 (16.5%)	6.04 (1.75–20.87)	0.0045

Presented are number of events (Kaplan–Meier estimate of event rate).

the VAS may be more sensitive to subtle changes in symptoms. On the other hand, the Likert scale seems closer to everyday clinical practice where symptoms are assessed rather roughly and mainly compared with baseline. The differences between the two methods explain why the Likert scale was more sensitive to early changes in symptoms, whereas the VAS was able to show persistent improvement, even late during the hospitalization. This was shown in a prospective registry, the Prospective Registry to Evaluate the Evolution of Measures of Disease Severity in Acute Heart Failure,[31] and confirmed in Pre-RELAX-AHF.[19]

Relation of changes in dyspnoea with other clinical symptoms and signs and outcomes

Changes in dyspnoea were correlated with changes in other symptoms and clinical signs of AHF in this small database. Our results are in agreement with data from registries[31] as well as with *post-hoc* analyses from EVEREST[28] and the PROTECT pilot study[32] and suggest that changes in dyspnoea are related to those in patients' congestion (both peripheral and central).

Relief of dyspnoea and lack of WHF were associated with trends, sometimes reaching statistical significance, towards improved outcomes such as shorter length of stay, more days alive, and out of hospital and lower mortality. These associations are important since they suggest that relief of dyspnoea and prevention of WHF, beyond being an important treatment goal for symptom improvement, are also markers of better outcome. Hence, prevention of in-hospital WHF may become a major goal of therapy in AHF. Given the lack of association between dyspnoea relief and baseline characteristics, these data suggest that early assessment of dyspnoea relief may add important prognostic information beyond the information available at the time of admission.

The reasons for the association between dyspnoea relief and outcomes are likely to be multiple. First, relief of dyspnoea may be a marker of the relief of congestion and of less severe disease. However, faster resolution of dyspnoea may also reduce the need for additional therapies (loop diuretics, intravenous vasodilators, and inotropes) that are aimed at symptom relief, yet may also have potential adverse effects on outcomes.[33,34] In agreement with this hypothesis, we observed greater use of known life-saving medications, such as ACE-I or ARBs, and beta-blockers, in the patients with dyspnoea relief (*Table 3*). These numbers are small, however, and require validation in larger studies.

Effects of relaxin administration

Administration of relaxin was associated with trends towards a greater likelihood of an improvement in persistent dyspnoea and prevention of WHF compared with placebo. As previously described,[19] we have assessed a large range of relaxin doses (25-fold, starting with 10–250 μg/kg/day). Some of these doses (especially the lowest and highest) were associated with smaller effects on dyspnoea relief and WHF. The most effective dose of relaxin (30 μg/kg/24 h) is being tested for efficacy on early and persistent dyspnoea relief, as well as intermediate-term outcomes, in the ongoing phase III RELAX-AHF study.

Study limitations

This analysis is hypothesis generating, due to the small number of patients enroled and of events during follow-up. These small numbers of patients and events have limited the power of our multivariable analysis to determine the relation between symptom changes and outcomes. However, given the lack of association of baseline characteristics known to affect outcomes in AHF with dyspnoea relief, it is likely that these effects are independent.

We chose to assess dyspnoea at Day 5 by the VAS AUC changes, rather than by the Likert scale, based on our analyses both from a registry[31] and from the present trial,[19] showing that VAS is more sensitive to long-term (i.e. 5–7 days from admission) changes. In contrast, data obtained by the Likert scale tend to remain stable after the first days from admission. Visual analogue scale area under the curve changes have, however, the limitations of a continuous variable making it difficult to compare groups of patients by quantitative measures. We have shown that increases in VAS score were related with better outcomes, namely, a shorter duration of hospital stay, more days alive outside of the hospital, and lower 30-day mortality, but no clinical cut-off can be provided.

Patients enroled in randomized clinical trials may have differences compared with those treated in everyday clinical practice. However, in our study, we used objective criteria for the diagnosis of AHF (increased natriuretic peptide plasma levels) and its severity (kidney dysfunction, pulmonary congestion, and elevated natriuretic peptides), and thus our patients may, actually, be better selected than in clinical practice when many patients may have a diagnosis of AHF despite having a non-cardiac cause of their dyspnoea. On the other hand, Pre-RELAX was restricted to those patients more likely to benefit from relaxin treatment (i.e. with high-systolic BP). Thus, our data cannot be extended to all patients admitted for AHF but only to patients with similar clinical characteristics to those enroled in our study.

Conclusions

Our study shows that the rate of early and persistent dyspnoea relief in patients with AHF may be low, with only 25% of patients showing early dyspnoea relief and $<50\%$ relative improvement of dyspnoea to Day 5. Moreover, 20% of patients may have recurrent WHF during the first 5 days after admission. Lack of dyspnoea relief and presence of WHF were associated with slower improvement in clinical signs of congestion and worse short- and intermediate-term outcomes. This suggests that, beyond being the main measure of AHF related to patients' symptoms, these endpoints are also related to prognosis and hence may be regarded as important and meaningful targets of therapy. The effects of relaxin administration suggest that a further improvement in symptoms and outcomes with new therapies is possible.

Funding

Pre-RELAX-AHF was funded by Corthera, Inc., USA. Funding to pay the Open Access publication charges for this article was provided by Corthera, Inc. (part of Novartis Pharmaceuticals Corp.).

Conflict of interest: All authors are members of the RELAX-AHF Executive Committee and receive grant support from Corthera. M.M has received honoraria and reimbursements for speeches and participation on Advisory Boards from Cardiokine, Corthera, Merck, and Otsuka. J.R.T. has received payments for working as a consultant on the design and implementation of the clinical trial and has served as Co-Principal Investigator and Co-Chair of the Steering Committee. G.M.F and B.H.G are consultants to Corthera. G.F is a member of the Executive Committee of the study and has received research grants. P.P has received honoraria from Corthera and Merck. S.L.T. and E.U. are employed by Corthera (now part of Novartis) the developer of relaxin for AHF. A.A.V has received consultancy fees from Corthera Inc. for participation as a Steering Committee member for pre-RELAX-AHF. B.D.W owns shares in and is an officer of Momentum Research Inc. which is paid by Corthera to consult and assist with the management of the RELAX-AHF study. G.C. is President and CEO of Momentum Research Inc. which received grants from Corthera to consult and assist with the management of the RELAX-AHF study.

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