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

Permalink
https://escholarship.org/uc/item/4nx2w3hr

Journal
European journal of heart failure, 12(10)

ISSN
1388-9842

Authors
Metra, Marco
Teerlink, John R
Felker, G Michael
et al.

Publication Date
2010-10-01

DOI
10.1093/eurjhf/hfq132

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

Marco Metra1*, John R. Teerlink2, G. Michael Felker3, Barry H. Greenberg4, Gerasimos Filippatos5, Piotr Ponikowski6, Sam L. Teichman7, Elaine Unemori7, Adriaan A. Voors8, Beth Davison Weatherley9, and Gad Cotter9

1Cardiology, Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy; 2Division of Cardiology, University of California, San Francisco, CA, USA; 3Duke Clinical Research Institute, Durham, NC, USA; 4University of California, San Diego Medical Center, San Diego, CA, USA; 5Athens University Hospital, Athens, Greece; 6Department of Cardiology, Medical University, Clinical Military Hospital, Wrocław, Poland; 7Corthera, Inc. (part of Novartis Pharmaceutical Corp.), San Carlos, CA, USA; 8University Medical Center Groningen, Groningen, Netherlands; and 9Momentum Research Inc., Durham, NC, USA

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
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 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). 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. Briefly, this study enrolled patients aged ≥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 m²]. 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 ≥350 pg/mL or NT-proBNP ≥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 diuretic escape, 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 χ² 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. 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 ± 20.1 mm, by 14.3 ± 30.6 mm in the placebo group vs. 23.3 ± 29.8 mm in the overall relaxin group. The mean dyspnoea VAS AUC from baseline to Day 5 was 1679 ± 2556 mm h in placebo and 2412 ± 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 and 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

| Baseline characteristic | Early dyspnoea relief | Persistent dyspnoea relief | Worsening heart failure |
|-------------------------|------------------------|-----------------------------|-------------------------|
|                         | Yes (n = 58)           | No (n = 174)                | Upper tertile (n = 79)  | Lower 2 tertiles (n = 153) | No (n = 196) | Yes (n = 36) | P          |
| Age (years)             | 71 ± 9                 | 70 ± 11                     | 72 ± 10                 | 70 ± 11                     | 70 ± 11      | 73 ± 8     | 0.11       |
| Male (%)                | 48                     | 58                          | 52                      | 57                          | 55           | 58         | 0.72       |
| Body weight (kg)        | 83 ± 17                | 80 ± 17                     | 79 ± 18                 | 82 ± 17                     | 82 ± 17      | 78 ± 16    | 0.27       |
| COPD (%)                | 19                     | 16                          | 19                      | 16                          | 16           | 19         | 0.65       |
| Diabetes (%)            | 50                     | 41                          | 53                      | 39                          | 45           | 39         | 0.53       |
| Hypertension (%)        | 93                     | 83                          | 89                      | 84                          | 87           | 81         | 0.33       |
| Ischaemic heart disease (%) | 59                   | 73                          | 70                      | 70                          | 70           | 69         | 0.97       |
| Peripheral vascular disease (%) | 14             | 13                          | 16                      | 11                          | 11           | 12         | 0.07       |
| Stroke (%)              | 19                     | 15                          | 19                      | 15                          | 16           | 19         | 0.59       |
| Systolic BP (mmHg)      | 151 ± 18               | 143 ± 17                    | 147 ± 15                | 144 ± 19                    | 146 ± 17     | 144 ± 20   | 0.52       |
| Diastolic BP (mmHg)     | 84 ± 12                | 81 ± 11                     | 81 ± 11                 | 83 ± 12                     | 82 ± 12      | 82 ± 11    | 0.88       |
| Heart rate/min          | 83 ± 15                | 82 ± 15                     | 79 ± 12                 | 84 ± 16                     | 82 ± 15      | 82 ± 15    | 0.96       |
| Atrial fibrillation (%) | 43                     | 49                          | 40                      | 51                          | 47           | 53         | 0.50       |
| Respiratory rate/min    | 22 ± 3                 | 23 ± 3                      | 23 ± 4                  | 23 ± 4                      | 23 ± 3       | 24 ± 4     | 0.27       |
| Haemoglobin (g/dL)      | 13 ± 2                 | 13 ± 2                      | 13 ± 2                  | 13 ± 2                      | 13 ± 2       | 13 ± 2     | 0.15       |
| BUN (mg/dL)             | 27 ± 10                | 27 ± 12                     | 26 ± 11                 | 28 ± 12                     | 26 ± 11      | 31 ± 13    | 0.02       |
| Serum creatinine (mg/dL)| 1.4 ± 0.5              | 1.3 ± 0.5                   | 1.3 ± 0.5               | 1.3 ± 0.5                   | 1.3 ± 0.5    | 1.5 ± 0.5  | 0.03       |
| eGFR, screening (mL/min/1.73 m²) | 53 ± 16       | 54 ± 17                     | 54 ± 20                 | 53 ± 15                     | 54 ± 17      | 50 ± 14    | 0.15       |
| Sodium (mmol/L)         | 141 ± 4               | 140 ± 4                     | 140 ± 3                 | 141 ± 4                     | 141 ± 3      | 139 ± 5    | 0.01       |
| White blood cell count (× 10⁹/L) | 8.3 ± 2.6            | 8.7 ± 3.3                   | 8.6 ± 3.3               | 8.6 ± 3.1                   | 8.5 ± 3.0    | 9.1 ± 3.7  | 0.32       |
| Lymphocytes < 13% (%)   | 71                     | 71                          | 60                      | 76                          | 72           | 83         | 0.17       |
| BNP > 500 or NT-proBNP > 2000 pg/mL (%) | 86                | 70                          | 79                      | 72                          | 72           | 83         | 0.17       |
| Troponin > 0.10 ng/mL (%) | 16              | 17                          | 21                      | 15                          | 15           | 17         | 0.98       |
| ACE-inhibitor or ARB (%) | 67                   | 65                          | 67                      | 65                          | 65           | 69         | 0.59       |
| Nitrites (%)            | 24                     | 20                          | 22                      | 21                          | 21           | 22         | 0.86       |
| Hyaluronic acid (%)     | 5                      | 1                           | 4                       | 1                           | 2            | 0          | 0.33       |
| β-blocker (%)           | 57                     | 56                          | 59                      | 54                          | 56           | 58         | 0.76       |
| Calcium-channel blocker (%) | 12              | 16                          | 20                      | 12                          | 15           | 14         | 0.89       |
| Aldosterone inhibitor (%) | 21                   | 36                          | 19                      | 39                          | 32           | 33         | 0.89       |
| Digoxin (%)             | 19                     | 21                          | 10                      | 26                          | 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

| Predictor                              | 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 (0.70–1.87) | 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 (0.69–1.26) | 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) | 0.0002 | −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                             | 0.97      | 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 (0.24–2.06) | 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 (0.24–2.08) | 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 (0.81–1.70) | 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 |

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’s rank correlation (P-value) | Change in dyspnoea VAS from baseline |
|---------------------------------------|-------------------------------------|
| | 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 | $0.5656 (<0.0001)$ | $0.4493 (<0.0001)$ | $0.4481 (<0.0001)$ |
| Change in dyspnoea on exertion | $0.5266 (<0.0001)$ | $0.4678 (<0.0001)$ | $0.3163 (<0.0001)$ |
| Change in oedema | $-0.0125 (0.1786)$ | $-0.0106 (0.1405)$ | $-0.0152 (0.8261)$ |
| Change in JVP | $0.0523 (0.0411)$ | $0.0523 (0.4463)$ | $0.0874 (0.2039)$ |
| Change in weight | $0.0217 (0.7468)$ | $-0.0106 (0.1405)$ | $-0.0152 (0.8261)$ |

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 cm; Rales: 0, no rales; 1, rales, 1/3; 2, rales 1/3–2/3; 3, rales 2/3+.
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. 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, 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,
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, and confirmed in Pre-RELAX-AHF.

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 as well as with post-hoc analyses from EVEREST and the PROTECT pilot study 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. 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, 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 enrolled 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 and from the present trial, 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 enrolled 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 enrolled 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.

References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Pioro SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–989.
2. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol 2009;53:557–573.
3. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michi K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1–e90.
4. Metra M, Ponikowski P, Dickstein K, McMurray JJ, Gavazzi A, Bergh CH, Fraser AG, Jaarsma T, Ptits A, Mocahsi P, Böhm M, Anker S, Dargie H, Brutsaert D, Komajda M, Heart Failure Association of the European Society of Cardiology. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11:684–694.
5. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531–1540.
6. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O’Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainiis M, Kribin I, VERITAS Investigators. Effects of tezosan- tan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007;298:2009–2019.
7. Gheorghiade M, Konstam MA, Burnett JC Jr, Girinieldi L, Maggioni AP, Swedberg K, Udellion JE, Zannaf F, Cook T, Koyang J, Zimmer C, Orlandi G, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–1343.
8. O’Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M, Demographics, clinical characteristics, and outcomes of patients hospitalized for decompen- sated heart failure: observations from the IMPACT-HF registry. J Card Fail 2005;11:200–205.
9. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. ADHERE Scientific Advisory Committee, Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
Dyspnoea in acute heart failure

10. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M, ADHERE Scientific Advisory Committee, Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49:1943–1950.

11. Cotter G, Dittrich HC, Weatherly BD, Bloomfield DM, O'Connor CM, Metra M, Massie BM, Protect Steering Committee, Investigators, Coordinators. The PROTECT pilot study: a randomized, placebo-controlled, dose-finding study of the adenosine A1 receptor antagonist rolodafylline in patients with acute heart failure and renal impairment. J Card Fail 2008;14:631–640.

12. Mebazaa A, Pang PS, Tavares M, Collins SP, Storror AB, Lanbi S, Andre S, Courtney DM, Hsa A, Spinaj M, Hasp M, Peacock WF, Sliva K, Gayet E, Filipatos G, Cleland JG, Gheorghiade M. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J 2010;31:832–841.

13. Hogg KJ, McMurray JJ. Evaluating dyspnoea in acute heart failure: progress at last. Eur Heart J 2010;31:711–712.

14. Weatherley BD, Milo-Cotter O, Michael Felker G, Uriel N, Kaluski E, Vered Z, O'Connor CM, Adams KF, Cotter G. Early worsening heart failure in patients admitted with acute heart failure—a new outcome measure associated with long-term prognosis? Fundam Clin Pharmacol 2009;23:633–639.

15. Cotter G, Metra M, Weatherby BD, Dittrich HC, Massie BM, Ponikowski P, Bloomfield DM, O'Connor CM. Physician-Determined Worsening Heart Failure: a novel definition for early worsening heart failure in patients hospitalized for acute heart failure—association with signs and symptoms, hospitalization duration, and 60-day outcomes. Cardiology 2009;115:29–36.

16. Torre-Amione G, Milo-Cotter O, Kaluski E, Perchenet L, Kobrin I, Frey A, Rund MM, Weatherly BD, Cotter G. Early worsening heart failure in patients admitted for acute heart failure: time course, hemodynamic predictors, and outcome. J Card Fail 2009;15:639–644.

17. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail 2006;8:105–110.

18. De Luca L, Mebazaa A, Filipatos G, Parisis JT, Böhm M, Voors AA, Nieminen M, Zannad F, Rhodes A, El-Banayosy A, Dickstein K, Gheorghiade M. Overview of emerging pharmacologic agents for acute heart failure syndromes. Eur J Heart Fail 2008;10:201–213.

19. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherby BD, Marmar A, Katz A, Grzybowski J, Umemori E, Tsichan SL, Cotter G. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multi-centre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. Lancet 2009;373:1429–1439.

20. Metra M, Teerlink JR, Voors AA, Felker GM, Milo-Cotter O, Weatherby B, Dittrich H, Cotter G. Vasodilators in the treatment of acute heart failure: what we know, what we don’t. Heart Fail Rev 2009;14:299–307.

21. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boccardi WJ. ADHERE Scientific Advisory Committee, Study Group, Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–580.

22. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2008;156:662–673.

23. Harjola VP, Pollath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L, Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail 2010;12:239–248.

24. Stevenson LW, Hellkamp AS, Leier CV, Sopko G, Koelling T, Warnica JW, Abraham WT, Kasper EK, Rogers JG, Califf RM, Schramm EE, O'Connor CM. Changing preferences for survival after hospitalization with advanced heart failure. J Am Coll Cardiol 2008;52:1702–1708.

25. Teerlink JR. Dyspnoea as an end point in clinical trials of therapies for acute decompensated heart failure. Am J Cardiol 2003;91(Suppl. 2):526–533.

26. Gheorghiade M, Adams KF, Cleland JG, Cotter G, Felker GM, Filipatos GS, Fonarow GC, Greenberg BH, Hernandez AF, Khan S, Komajda M, Konstam MA, Liu PP, Maggioni AP, Massie BM, McMurray JJ, Mehm M, O’Connell J, O’Connor CM, Pang PS, Piria IL, Sabbah HN, Teerlink JR, Udelson JE, Yancy CW, Zannad F. Acute Heart Failure Syndromes International Working Group. Phase III clinical trial end points in acute heart failure syndromes: a virtual roundtable with the Acute Heart Failure Syndromes International Working Group. Am J Heart Fail 2009;157:957–970.

27. Pang PS, Cleland JG, Teerlink JR, Collins SP, Lindell CJ, Sopko G, Peacock WF, Fonarow GC, Aldean AZ, Kirk JD, Storror AB, Tavares M, Mebazaa A, Roland E, Massie BM, Maisel AS, Komajda M, Filipatos G, Gheorghiade M. Acute Heart Failure Syndromes International Working Group. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. Eur Heart J 2008;29:816–824.

28. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JE, Zimmer C, Teerlink JR, Maggioni AP, Burnett JC Jr, Grinfeld L, Ouyang J, Udelson JE. Gheorghiade M, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. Eur Heart J 2009;30:2333–2240.

29. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure—re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail 2008;10:165–169.

30. Milo-Cotter O, Adams KF, O’Connor CM, Uriel N, Kaluski E, Felker GM, Weatherley B, Vered Z, Cotter G. Acute heart failure associated with high admission blood pressure—a distinct vascular disorder? Eur J Heart Fail 2007;9:178–183.

31. Allen LA, Metra M, Milo-Cotter O, Filipatos G, Resin LH, Benenshir DM, Gronda EG, Colombo P, Felker GM, Cas LD, Kremastinos DT, O’Connor CM, Cotter G, Davison BA, Dittrich HC, Velazquez EJ. Improvements in signs and symptoms during hospitalization for acute heart failure follow different patterns and depend on the measurement scales used: an international, prospective registry to evaluate the evolution of measures of disease severity in acute heart failure (MEASURE-AHF). J Card Fail 2008;14:777–784.

32. Metra M, Cleland JG, Davison Weatherly B, Dittrich HC, Givertz MM, Massie BM, O’Connor CM, Ponikowski P, Teerlink JR, Voors AA, Cotter G. Dyspnoea in Patients with Acute Heart Failure. An analysis of its clinical course, determinants and relationship to 60 day outcomes in the PROTECT pilot study. Eur J Heart Fail 2010;12:499–507.

33. Hussein Blad V, Gattis Stough W, Shah PR, Lokhnytgyn T, O’Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–1069.

34. Thackray S, Eastaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure—a meta-regression analysis. Eur J Heart Fail 2002;4:515–529.