Title

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Journal

European Journal of Heart Failure, 15(4)

ISSN

1388-9842

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Publication Date

2013-04-01

DOI

10.1093/eurjhf/hfs188

Peer reviewed

European Journal of Heart Failure (2013) **15**, 456–464
doi:10.1093/eurjhf/hfs188

Predictors of early dyspnoea relief in acute heart failure and the association with 30-day outcomes: findings from ASCEND-HF

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Received 15 August 2012; revised 20 September 2012; accepted 5 October 2012; online publish-ahead-of-print 15 November 2012

Aims To examine the characteristics associated with early dyspnoea relief during acute heart failure (HF) hospitalization, and its association with 30-day outcomes.

Methods and results ASCEND-HF was a randomized trial of nesiritide vs. placebo in 7141 patients hospitalized with acute HF in which dyspnoea relief at 6 h was measured on a 7-point Likert scale. Patients were classified as having early dyspnoea relief if they experienced moderate or marked dyspnoea improvement at 6 h. We analysed the clinical characteristics, geographical variation, and outcomes (mortality, mortality/HF hospitalization, and mortality/hospitalization at 30 days) associated with early dyspnoea relief. Early dyspnoea relief occurred in 2984 patients (43%). In multivariable analyses, predictors of dyspnoea relief included older age and oedema on chest radiograph; higher systolic blood pressure, respiratory rate, and natriuretic peptide level; and lower serum blood urea nitrogen (BUN), sodium, and haemoglobin (model mean C index = 0.590). Dyspnoea relief varied markedly across countries, with patients enrolled from Central Europe having the lowest risk-adjusted likelihood of improvement. Early dyspnoea relief was associated with lower risk-adjusted 30-day mortality/HF hospitalization [hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.68–0.96] and mortality/hospitalization (HR 0.85; 95% CI 0.74–0.99), but similar mortality.

Conclusion Clinical characteristics such as respiratory rate, pulmonary oedema, renal function, and natriuretic peptide levels are associated with early dyspnoea relief, and moderate or marked improvement in dyspnoea was associated with a lower risk for 30-day outcomes.

Keywords Acute heart failure • Dyspnoea relief • Prognosis • Outcomes

Introduction

Heart failure (HF) is a major and growing public health problem worldwide.[1,2] Despite advances in the care of chronic HF, the prognosis of patients hospitalized for acute HF remains poor.[3] Fluid retention and congestion are responsible for the majority of HF hospitalizations,[4] and greater severity of congestion is associated with worse outcomes.[5] Several analyses have investigated the association between dyspnoea relief and acute HF outcomes.[6–8] These studies were relatively modest in size and investigated dyspnoea relief over the first several days of hospitalization. However, studies have suggested that dyspnoea relief with usual care may occur significantly earlier following hospitalization.[9–11] The patient characteristics associated with early dyspnoea improvement and the relationship between early dyspnoea relief and outcomes are not well characterized.

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Given the uncertainty surrounding dyspnoea in acute HF, we used data from the international ASCEND-HF trial[12] (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) to examine the characteristics of acute HF patients associated with moderate or marked dyspnoea relief at 6 h following study drug initiation. We also describe the regional variation in dyspnoea relief and the association of early dyspnoea relief with 30-day outcomes.

Methods

Study design

The design and results of the ASCEND-HF trial have been reported previously.[12,13] Briefly, the trial evaluated nesiritide vs. placebo in 7141 patients with acute HF enrolled within 24 h of the first i.v. HF-related treatment. Participants were required to have the following at the time of randomization: dyspnoea at rest or with minimal activity, ≥ 1 accompanying HF sign, and ≥ 1 objective measure of HF. Exclusion criteria germane to this analysis were severe pulmonary disease and clinically significant anaemia (the full criteria are available elsewhere).[12]

Study definitions, endpoints, and statistical analysis

Dyspnoea was measured with a self-reported 7-point categorical Likert scale, ranging from 'markedly better' to 'markedly worse' at 6 h after study drug initiation as compared with the degree of dyspnoea present at the start of study drug administration. For the present analysis, patients were classified as having early dyspnoea relief if they experienced moderate or marked improvement in dyspnoea at 6 h in comparison with other categories.

Post-hoc analyses were performed on the randomized population with complete dyspnoea data ($n = 6902$), with patients grouped based on early dyspnoea relief status. Demographics, physical and laboratory findings, medical history, and therapies were compared using the Student's *t*-test or Wilcoxon rank sum test for continuous variables, and χ^2 tests for categorical variables, as appropriate. Baseline characteristics of the study population were summarized as frequencies and percentages for categorical variables and by the medians and 25th and 75th percentiles for continuous variables.

Logistic regression modelling was used to assess the predictors of early dyspnoea relief. Pre-specified baseline factors were selected from the case report form (Supplementary Material, *Table S1*). The impact of these variables on dyspnoea relief was assessed. Stepwise selection was performed on the factors, using a criterion of ≤ 0.05 to be included in the model and to stay in the model. The linearity of relationships between outcome and continuous variables was evaluated. The restricted cubic spline model's likelihood ratio χ^2 statistic was compared with the model including a linear term exclusively. If the relationship between a predictor and outcome did not appear to be linear, then other transformations such as quadratic terms, log transformation, or linear splines were applied. No adjustments for multiple comparisons were made. We assessed the frequency of missing values for all candidate predictors and outcomes. Variables missing $\leq 20\%$ of values were identified, and Proc MI was used to impute the missing data. Imputation was not performed for BNP and NT-proBNP because they were missing $> 60\%$ of the values. To assess their importance in predicting dyspnoea at 6 h, these factors were added to the original model. We also used these methods to determine the predictors of moderate–marked dyspnoea relief at 24 h. The discrimination ability of each model was assessed using a C index. The C index and calibration for the models were internally validated using bootstrap resampling to adjust for overfitting optimism.

The downstream clinical endpoints for the present analyses were mortality/HF hospitalization, all-cause mortality, and mortality/hospitalization at 30 days. Multivariate logistic regression models were developed to assess which baseline factors were predictive of these three outcomes. Factors with *P*-values ≤ 0.01 were included in the final model. Rehospitalization and fatal events within 30 days after randomization were reviewed and categorized by an independent, blinded clinical events committee.[12] Univariate time to event comparisons between those with and without dyspnoea relief were made using log-rank tests. Kaplan–Meier estimates of the event rates were calculated over the entire follow-up period. Hazard ratios (HRs) and corresponding confidence intervals (CIs) were calculated relative to dyspnoea relief status using a Cox proportional hazards model with and without adjustment for baseline covariates. Statistical significance was assessed using two-sided *P*-values. A *P*-value <0.05 was considered statistically significant. All statistical computations were generated using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

Early dyspnoea relief occurred in 2984 patients (43%). There were 239 patients for whom evaluation was not done. Baseline characteristics based on dyspnoea relief status are shown in *Table 1*. Patients with early dyspnoea relief tended to be slightly older with lower NYHA class symptoms and less ischaemic aetiology for HF or HF hospitalizations in the previous year compared with those without dyspnoea relief (all $P < 0.01$). Patients with early dyspnoea relief also had slightly higher systolic blood pressure and serum haemoglobin, but lower serum blood urea nitrogen (BUN) and red cell distribution width compared with those without dyspnoea relief (all $P < 0.001$). At baseline, patients with early dyspnoea relief were less likely to be receiving aldosterone antagonists, loop diuretics, or nitrates. Time from hospitalization to randomization was shorter in those patients with early dyspnoea relief.

Multivariable predictors of dyspnoea relief

The multivariable model for the predictors of early dyspnoea relief is presented in *Table 2*. Lower BUN was a predictor of early dyspnoea relief. Additional independent predictors of dyspnoea relief included older age and oedema on chest radiograph; higher systolic blood pressure, respiratory rate, and natriuretic peptide level; and lower serum sodium and haemoglobin. Chronic respiratory disease and smoking status were not found to be independent predictors of early dyspnoea relief. C indexes were generated for the 25 imputed databases. The mean C index was 0.590, with a minimum value of 0.587 and a maximum of 0.594.

Table 3 presents the association between additional factors and early dyspnoea relief adjusted for the variables in *Table 2*. Chronic use of aldosterone antagonists, loop diuretics, and nitrates was associated with less dyspnoea relief ($P < 0.01$).

Table 1 Baseline clinical and demographic characteristics of heart failure patients with and without moderate/marked dyspnoea improvement at 6 h

Characteristic	No early dyspnoea improvement [*n* = 3918 (57%)]	Early dyspnoea improvement [*n* = 2984 (43%)]	*P*-value
Demographics			
Age, median (25th, 75th), years	66 (56, 76)	67 (57, 77)	0.01
Male, %	65.8	65.7	0.86
Race, %			< 0.001
White	55.5	55.8	
Black	14.8	15.3	
Asian	26.4	23.1	
Other	3.2	5.8	
Weight, median (25th, 75th), kg	78 (64, 95)	78 (65, 94)	0.72
Height, median (25th, 75th), cm	168 (160, 175)	168 (160, 175)	0.38
Region, %			<0.001
Asia-Pacific	26.3	23.1	
Central Europe	15.7	11.6	
Latin America	6.9	12.2	
Western Europe	6.9	6.6	
North America	44.1	46.5	
Medical history			
NYHA class III/IV, %	79.1	74.2	<0.0001
Ischaemic heart disease, %	61.5	58.3	0.01
HF hospitalization in past year, %	40.5	36.7	0.001
Ejection fraction, median (25th, 75th), %	30 (20, 36)	30 (20, 37)	0.62
LVEF <40% in past year, %	20.1	21.4	0.24
Hypertension, %	71.3	73.3	0.07
Diabetes, %	42.3	43.4	0.35
Coronary artery disease, %	55.7	53.2	0.03
Cerebrovascular disease, %	11.4	12.3	0.26
Peripheral arterial disease, %	10.3	10.7	0.56
Chronic respiratory disease, %	16.0	17.0	0.28
Atrial fibrillation, %	37.1	37.7	0.59
CRT, %	9.3	8.4	0.19
Baseline physical and laboratory findings, median (25th, 75th)			
Systolic BP, mmHg	122 (110, 138)	125 (110, 140)	<0.001
Heart rate, b.p.m.	82 (72, 95)	82 (72, 95)	0.68
Respiratory rate, breaths/min	24 (21, 26)	23 (21, 25)	0.01
Sodium, mg/dL	139 (136, 141)	139 (136, 141)	0.23
Potassium, mmol/L	4.1 (3.7, 4.5)	4.1 (3.7, 4.4)	0.45
BUN, mg/dL	26 (19, 40)	24 (17, 36)	<0.001
Creatinine, mg/dL	1.2 (1.0, 1.6)	1.2 (1.0, 1.6)	0.02
Haemoglobin, g/dL	12.6 (11.3, 13.9)	12.8 (11.5, 14.1)	<0.001
BNP, pg/mL	967 (520, 1820)	1000 (571, 1856)	0.19
NT-proBNP, pg/mL	4458 (2040, 9177)	4536 (2127, 9020)	0.35
RDW, %	15.4 (14.2, 17.1)	15.2 (14.0, 16.8)	<0.001
Medications before randomization, %			
ACE inhibitor/ARB	61.6	59.8	0.12
Beta-blockers	58.3	58.0	0.82
Aldosterone-blocking agents	29.1	26.2	0.01
Chronic loop diuretics	66.5	59.8	<0.001

Continued

Table 1 *Continued*

Characteristic	No early dyspnoea improvement [*n* = 3918 (57%)]	Early dyspnoea improvement [*n* = 2984 (43%)]	*P*-value
Chronic thiazide diuretics	6.5	6.9	0.49
Nitrates (oral or topical)	25.2	21.4	<0.001
Hydralazine	7.3	7.4	0.91
Digoxin	26.3	26.6	0.80
Calcium channel blockers	12.3	13.6	0.09
Oral anticoagulants	25.0	22.8	0.03
Aspirin	49.7	48.6	0.38
I.v. dobutamine	3.3	3.1	0.60
I.v. nitroglycerin	13.6	15.0	0.12
I.v. opiates	3.7	4.7	0.03
From qualifying episode to randomization (early hospital use)			
Loop diuretic from qualifying episode to randomization, %	88.8	89.8	0.18
Thiazide diuretic from qualifying episode to randomization, %	4.3	4.0	0.55
I.v. furosemide equivalent dosing from 0–6 h post-randomization, median (25th, 75th), mg	40.0 (40.0, 80.0)	40.0 (30.0, 60.0)	<0.001
I.v. furosemide equivalent dosing from 0–24h post-randomization, median (25th, 75th), mg	80.0 (40.0, 160.0)	80.0 (56.3, 124.8)	0.17
Time from hospitalization to randomization, median (25th, 75th), h	16.7 (5.7, 22.3)	13.7 (5.1, 21.2)	<0.0001

BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure; RDW, red cell distribution width.

Table 2 Multivariate clinical predictors of moderate–marked dyspnoea relief at 6 h

Variable	OR represents	OR	95% CI	*t*-statistic	*P*-value
Serum BUN, mg/dL	Doubling of BUN	0.84	0.79–0.90	−5.21	<0.0001
Systolic BP, mm Hg	10 units increase	1.07	1.04–1.11	4.25	<0.0001
Serum haemoglobin, g/dL	1 units increase	0.94	0.90–0.97	−3.45	<0.001
Age, years	10 year increase	1.06	1.02–1.10	3.16	<0.01
Respiratory rate, breaths/min	2 units increase	1.05	1.02–1.09	2.86	<0.01
Serum sodium, mg/dL	1 units increase	0.96	0.94–0.99	−2.51	0.01
Oedema on chest radiograph	Yes vs. no	1.17	1.02–1.34	2.26	0.02
NYHA class[a]					
II		0.73	0.55–0.96	−2.25	0.02
III		0.61	0.46–0.79	−3.69	<0.001
IV		0.73	0.56–0.96	−2.23	0.03
Race[b]					
Black		1.09	0.93–1.26	1.04	0.30
Asian		0.92	0.81–1.04	−1.38	0.17
Other		1.66	1.30–2.12	4.07	<0.0001
BNP, pg/mL	Doubling	1.06	1.02–1.09	8.3648	<0.01
NT-proBNP, pg/mL	Doubling	1.05	1.01–1.08	7.9264	<0.01

BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio.
[a]Reference group is NYHA class I.
[b]Reference group is white.

Table 3 Association between additional factors and moderate–marked dyspnoea relief at 6h[a]

Variable	OR	95% CI	χ^2	*P*-value
ACE inhibitor/ARB	0.92	0.84–1.02	2.37	0.12
Beta-blocker	0.99	0.90–1.09	0.1	0.82
Aldosterone antagonist	0.87	0.78–0.96	7.0	<0.01
Chronic loop diuretic	0.75	0.68–0.83	32.6	<0.0001
I.v furosemide equivalent dose[b]	0.92	0.87–0.98	6.52	0.01
Chronic thiazide diuretic	1.01	0.88–1.29	0.4691	0.49
Pre-randomization oral/topical nitrates	0.81	0.72–0.91	13.60	<0.001
Pre-randomization i.v. nitroglycerin	1.11	0.97–1.28	2.43	0.12
Pre-randomization nitroprusside	1.35	0.87–2.11	1.78	0.18
Pre-randomization hydralazine	1.01	0.84–1.21	0.0133	0.91
Pre-randomization dobutamine	0.93	0.71–1.22	0.28	0.60
Baseline RDW[c]	0.94	0.88–1.00	3.65	0.06
Prior CRT	0.61	0.39–0.96	4.73	0.03
World region[d]				
Central Europe	0.71	0.55–0.92	6.71	0.01
Western Europe	0.75	0.56–1.00	3.79	0.051
Asia	0.91	0.53–1.57	0.11	0.74
Latin America	1.19	0.90–1.58	1.46	0.23
Planned nesiritide	1.10	0.97–1.24	2.22	0.14
Time to treatment[e]	0.99	0.98–0.99	17.50	<0.0001

Overall test Wald χ^2 14.4420; $P = 0.0060$.
Variables in bold text are statistically significant (*P*-value <0.05).
CI, confidence interval; OR, odds ratio; RDW, red cell distribution width.
[a]Relationships are adjusted for all factors reported in *Table 2*.
[b]I.v. furosemide equivalent dose from 0 to 6 h post-randomization, per 40 mg increase.
[c]RDW, per 1 standard deviation increase (4.11).
[d]Reference is North America.
[e]Time from hospital presentation to study drug administration.

Table 4 presents the baseline predictors of dyspnoea relief at 24 h. Lower BUN, older age, and increased natriuretic peptide levels were associated with both 6 and 24 h dyspnoea relief. Several predictors were similar between the two time points, specifically pulmonary oedema on exam or chest radiograph, and higher blood pressure. Additional baseline predictors of dyspnoea relief at 24 h (but not 6 h) included atrial fibrillation or flutter, chronic respiratory disease, and HF hospitalization within the previous year. The mean C index for the 24 h dyspnoea model was 0.601, with a minimum value of 0.599 and a maximum of 0.603.

Early dyspnoea relief was the greatest in Latin America (57% of patients); intermediate in North American (45%), Western Europe (42%), and Asia-Pacific (40%); and lowest in Central Europe (36%). The geographical variation in early dyspnoea relief is presented in *Figure 1*.

Outcomes

Table 5 presents the association between early dyspnoea relief and outcomes. On univariate analysis, early dyspnoea relief was associated with reduced risk for 30-day mortality, mortality/HF hospitalization, and mortality/hospitalization. After risk adjustment, patients with early dyspnoea relief were at decreased risk for 30-day mortality/HF hospitalization (HR 0.81; 95% CI 0.68–0.96) and mortality/hospitalization (HR 0.85; 95% CI 0.74–0.99), but similar 30-day mortality.

Discussion

ASCEND-HF represents the largest experience in examining dyspnoea relief in patients with acute HF. Approximately 45% of randomized patients experienced moderate to marked dyspnoea relief 6 h after study drug initiation; however, there was significant regional variation. While there are several clinical characteristics such as age, renal function, and natriuretic peptide levels associated with early dyspnoea relief, the degree to which these factors account for dyspnoea relief is modest. The discrimination ability of the model was poor (C ndex <0.60), suggesting significant unexplained factors associated with dyspnoea improvement. Nevertheless, early improvement in dyspnoea may be a good prognostic indicator as it is associated with lower risk-adjusted 30-day outcomes of mortality or rehospitalization compared with patients with only minimal or no improvement in dyspnoea at 6 h. However, the lack of association between early dyspnoea relief and 30-day mortality on adjusted analysis suggests that the patient-reported outcome of dyspnoea relief is not strongly linked with the clinical outcome of mortality.

While nearly half of patients randomized had moderate to marked improvement in dyspnoea in 6 h, there was significant regional variation. There may be multiple explanations for such variation, including differences in patient profiles, cultural interpretation of dyspnoea, treatment strategies before randomization, and other factors. The impact of regional variation in the interpretation of dyspnoea and use of specific dyspnoea measurements warrants investigation especially considering that instruments used for dyspnoea have not been well validated.[14] For instance, variability around the timing of dyspnoea assessment and the persistence of dyspnoea despite ongoing therapy may influence the evaluation of dyspnoea in clinical trials.[15] Improved standardization of dyspnoea measurements has been proposed[15] and has recently been incorporated in clinical trials.[11,16] A recent ASCEND-HF investigation of the change in peak expiratory flow rate over the first 24 h during acute HF management and its association with dyspnoea improvement by Likert scale[17] supports the use of objective metrics for future dyspnoea evaluations. The RED-ROSE study (Reliable Evaluation of Dyspnoea in the Heart Failure Network ROSE Study) is investigating whether a provocative dyspnoea evaluation is a more sensitive index of variability in dyspnoea status than the dyspnoea visual analogue scale assessment (Clinicaltrials.gov: NCT01132846). In sum, future acute HF studies should consider a standardized provocative dyspnoea evaluation that incorporates baseline dyspnoea information as well as relative change in dyspnoea in combination with objective

Table 4 Multivariate clinical predictors of moderate–marked dyspnoea relief at 24h

Variable	OR represents	OR	95% CI	*t*-statistic	*P*-value
Serum BUN, mg/dL	Doubling of BUN	0.87	0.80–0.93	−4.18	<0.001
Diastolic BP, mm Hg	10 units increase	1.08	1.04–1.12	3.68	<0.01
Age, years	10 year increase				
Age <60 years		0.97	0.90–1.04	−0.89	0.38
Age >60 years		1.11	1.03–1.20	2.54	0.01
Jugular venous distension	Yes vs. no	1.12	1.02–1.23	2.12	0.03
Baseline AF/AFL	Yes vs. no	0.87	0.76–0.99	−2.32	0.02
HF hospitalization within 1 year	Yes vs. no	0.79	0.68–0.90	−4.30	<0.001
Chronic respiratory disease	Yes vs. no	0.75	0.62–0.89	−4.02	<0.001
Respiratory rate, breaths/min	2 units increase				
<26 breaths/min		1.01	0.97–1.05	0.52	0.60
>26 breaths/min		0.94	0.88–1.00	−2.11	0.04
Pulmonary oedema	Yes vs. no				
<1/3 lung field		1.40	1.24–1.57	4.13	<0.001
>1/3 lung field		1.50	1.35–1.66	5.12	<0.001
Race[a]					
Black		1.03	0.87–1.21	0.31	0.76
Asian		1.02	0.89–1.16	0.22	0.82
Other		2.57	1.86–3.57	5.68	<0.0001
BNP, pg/mL	Doubling	1.03	0.99–1.07	2.71	<0.01
NT-proBNP, pg/mL	Doubling	1.05	1.01–1.08	2.70	<0.01

AF/AFL, atrial fibrillation/flutter; BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; HF, heart failure; OR, odds ratio.
[a]Reference group is white.

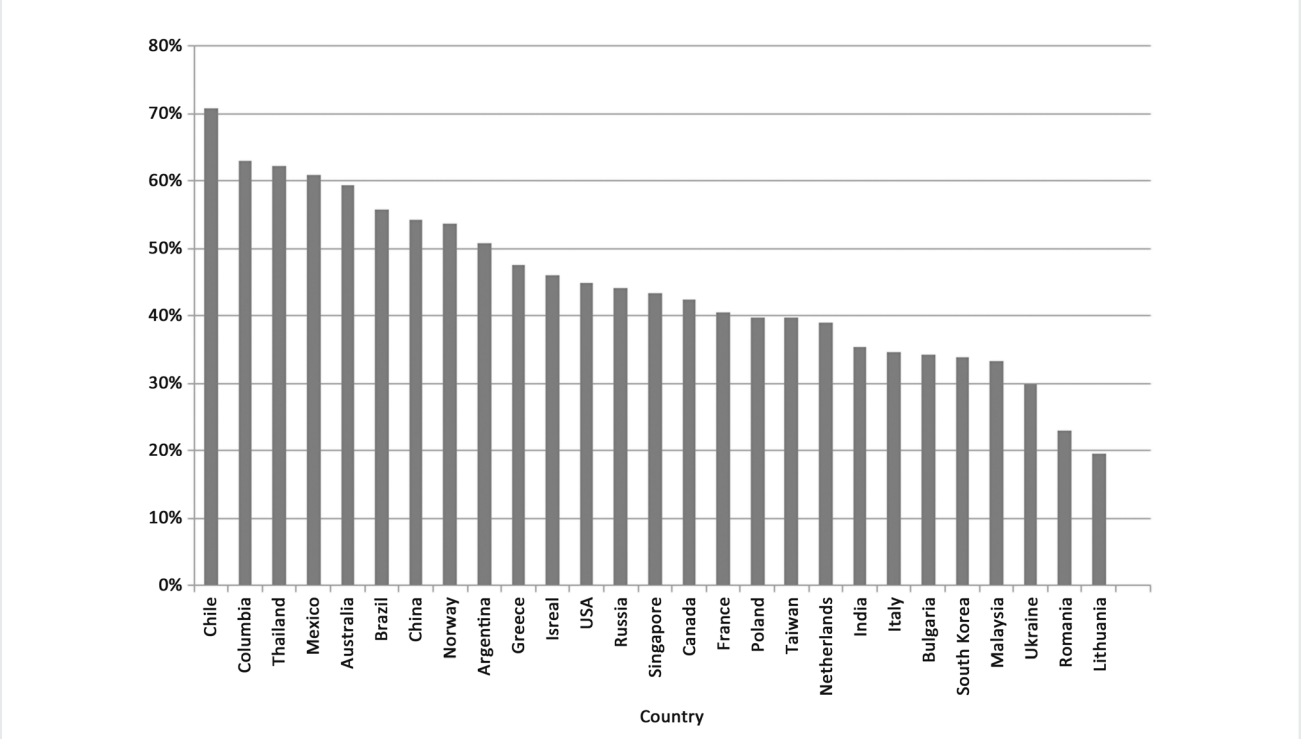

Figure 1 Observed moderate to marked improvement in dyspnoea at 6 h by country of enrolment.

Table 5 Association between moderate–marked dyspnoea improvement at 6 hand outcomes

Outcomes	Early dyspnoea improvement	No early dyspnoea improvement	Unadjusted		Adjusted[a]	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
30-day mortality	93/2980 (3.1)	167/3911 (4.3)	0.72 (0.56–0.94)	0.014	0.81 (0.62–1.07)	0.14
30-day mortality or HF hospitalization	240/2907 (8.3)	414/3834 (10.8)	0.74 (0.63–0.88)	0.0005	0.81 (0.68–0.96)	0.018
30-day mortality or hospitalization	397/2908 (13.7)	629/3837 (16.4)	0.81 (0.70–0.92)	0.002	0.85 (0.74–0.99)	0.031

BUN, blood urea nitrogen; CI, confidence interval; HF, heart failure; HR, hazard ratio.
[a]Adjustment variables were as follows.
Predictors of mortality by day 30 (at the $P \leq 0.01$ level): age, BUN, sodium, systolic blood pressure, baseline dyspnoea.
Predictors of mortality by day 30 and HF hospitalization (at the $P \leq 0.01$ level): age, BUN, baseline cerebrovascular disease, creatinine, depression, systolic blood pressure, baseline dyspnoea, HF hospitalization in the year prior to admission, serum sodium, elevated jugular venous pressure, and history of chronic respiratory disease.
Predictors of mortality by day 30 and all-cause hospitalization (at the $P \leq 0.01$ level): age, BUN, cerebrovascular disease systolic blood pressure, creatinine, depression, HF hospitalization in the year prior to admission, serum sodium, elevated jugular venous pressure, history of chronic respiratory disease, and baseline weight.

metrics (e.g. peak expiratory flow rate) and quality control oversight to minimize geographical variation.

Previous studies have identified few predictors of dyspnoea relief in acute HF,[6,7] and limited data exist with respect to dyspnoea relief in the early period following hospitalization. We found that BUN, natriuretic peptide levels, respiratory rate, and oedema on chest radiograph were associated with early dyspnoea relief. These characteristics may represent the degree of congestion. The association between neurohormonal activation, renal function, and BUN levels may explain, in part, the underlying pathophysiology.[18] More modest degrees of neurohormonal activation and preserved renal function, as captured in a lower BUN, may afford more rapid return to cardiac compensation with brisk diuresis upon initiation of acute HF therapies. Similarly, the association between lower haemoglobin and early dyspnoea relief may be due to relative haemodilution that responds to aggressive decongestion. This hypothesis is supported by data demonstrating the positive association between haemoconcentration, haemodynamic changes, and outcomes during the management of acute HF.[19] The association between the use of aldosterone antagonists, loop diuretics, and nitrates and a decreased likelihood of early dyspnoea relief may be related to greater severity of illness or chronicity of HF. Alternatively, aldosterone antagonists, loop diuretics, and nitrate use, which have known benefits on haemodynamics and pulmonary decongestion,[20,21] may not exert the same benefit in patients receiving these therapies chronically compared with treatment-naïve patients.[22] Therefore, the association between medication use, particularly post-randomization, and dyspnoea relief requires further prospective investigation.

Previous studies of characteristics associated with dyspnoea relief in acute HF are limited. In the PROTECT pilot study of 303 acute HF patients, only a history of pulmonary disease was associated with dyspnoea relief at 24–48 h.[6] A dyspnoea analysis in the Pre-RELAX-AHF study of 232 patients found that respiratory rate, systolic blood pressure, and baseline haemoglobin were associated with dyspnoea relief over the first 24 h.[7] Our study found similar relationships for respiratory rate and systolic blood pressure, but, in contrast, patients with lower haemoglobin had greater dyspnoea relief in ASCEND-HF. The modest predictive capacity of the ASCEND-HF model suggests that significant uncertainty remains with respect to the factors associated with dyspnoea relief. Focused studies to understand the underlying pathophysiology of this subjective patient-reported outcome are needed.

In a large international acute HF population, we demonstrated that early dyspnoea relief was associated with a 19% decreased risk for 30-day mortality/HF hospitalization and a 15% decreased risk for 30-day mortality/hospitalization, but similar mortality. Previous studies investigating the association between dyspnoea relief over the first several days following hospitalization and 30- to 60-day outcomes have been mixed.[6–8] In the PROTECT study[8] and the PROTECT pilot study,[6] dyspnoea relief at 2–3 days was associated with reduced mortality at 30 and 60 days, respectively. However, in Pre-RELAX-AHF,[7] dyspnoea relief within 24 h was not associated with a significant difference in mortality at 30 or 60 days. Moreover, in both the PROTECT pilot study and Pre-RELAX-AHF, dyspnoea relief was not associated with reduced 60-day composite endpoints including mortality or hospitalization. Importantly, a comparison of patients with and without dyspnoea relief at 6 h is different from a comparison between patients with and without dyspnoea relief within 24 h or at 2–3 days. In general, dyspnoea relief is not a surrogate for clinical outcomes, but is a patient-reported outcome or potentially a prognostic factor. Thus, evaluating a patient's symptoms of dyspnoea early in a hospitalization, in addition to other risk factors, may be used to identify patients at high risk of poor outcomes.

These results have applications to both the clinical and research enterprise. First, while there are clinical characteristics associated with early dyspnoea relief, much more research is needed to understand a patient's experience of dyspnoea as well as its association with downstream clinical outcomes. Certainly, those patients without dyspnoea relief are higher risk for poor outcomes and should be monitored more carefully. The implications of this analysis on dyspnoea improvement as a key endpoint for clinical

trials are several fold. The geographic variation in dyspnoea relief may indicate differences in patient experiences or perceptions which warrant further refinement and validation of instruments evaluating dypnoea as a patient-reported outcome. The Food and Drug Administration (FDA)-established guidelines in 2009 for patient-reported outcomes and future studies that use dyspnoea as a primary endpoint may require instruments that have content validation.[23] Those without early dyspnoea relief may also be used for selection of high-risk patients for acute HF trials.

Limitations

Our study should be interpreted in the context of several limitations. First, this was a retrospective analysis. Despite covariate adjustment, other measured and unmeasured factors may have influenced these findings. The study was from a clinical trial with inclusion and exclusion criteria, and may not be fully representative of the overall acute HF population. While the entry criteria may select a patient population that varies from other cohorts such as those entered into a registry, ASCEND-HF is the largest study to examine dyspnoea in acute HF, and previous registries have had limited evaluation of dyspnoea. Moreover, the presence of continental and regional differences in the aetiology, severity, and management of acute HF[24] highlights the importance of additional studies across geographical and cultural boundaries. Also, dyspnoea relief status was defined by a 7-point Likert scale at 6 h after study drug initiation. Since the median time from presentation to randomization was 15 h, our dyspnoea evaluation reflects an 'early' evaluation in a clinical trial but still represents a relatively later time point in a patient's hospital course.

Conclusion

In ASCEND-HF, nearly 45% of acute HF patients experienced early dyspnoea relief. Age, systolic blood pressure, respiratory rate, and serum BUN, sodium, and haemoglobin levels are modest predictors of early dyspnoea relief, which is associated with improved 30-day HF outcomes. Given the modest predictive capacity of baseline clinical variables for early dyspnoea relief, future investigations will need to clarify further the characteristics associated with early HF symptom improvement. The significant geographical variation in the percentage of patients with early dyspnoea improvement highlights the importance of standardization and validation of dyspnoea measurements.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

Funding

Johnson and Johnson provided funding for the overall ASCEND-HF trial.

Conflict of interest: J.R.T. has received research grants for his role as a Steering committee member in ASCEND-HF from Scios Inc., the sponsor of this trial. He received research support and/or consultation fees from Amgen, Bayer, Corthera, Cytokinetics, Novartis, and Trevena. R.C. has received research grants and consulting fees from Johnson & Johnson. All other industry relations are publicly displayed at www.dcri.org/about-us. J.E. is currently conducting research sponsored by Johnson & Johnson. B.M. has received consulting fees/honoraria from DCRI. G.M.F. has received consulting fees from Amgen, Trevena, Otsuka, Roche Diagnostics, Novartis, Merck, and BG Medicine, and research funding from NIH, Amgen, Otsuka, and Roche Diagnostics. P.P. has received fees in respect of consultancy and speaker's bureau from Scios Inc., Corthera, Novartis, Johnson & Johnson, and Bayer. All other authors declare no conflict of interest.

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