The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study

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Aims
The vast majority of acute heart failure (AHF) trials to date have targeted dyspnoea. However, they enrolled patients relatively late and did not standardize their methods of dyspnoea measurement. URGENT Dyspnoea was designed to determine changes in dyspnoea in response to initial, standard therapy in patients presenting with AHF using a standardized approach.

Methods and results
URGENT Dyspnoea was an international, multi-centre, observational cohort study of AHF patients managed conventionally and enrolled within 1 h of first hospital medical evaluation. Patient-assessed dyspnoea was recorded in the sitting position at baseline and at 6 hours by Likert and visual analog scales. Less symptomatic patients were placed supine to determine whether this provoked worsening dyspnoea (orthopnoea). Of the 524 patients with AHF, the mean age was 68 years, 43% were women, and 83% received intravenous diuretics. On a 5-point Likert scale, dyspnoea improvement was reported by 76% of patients after 6 h of standard therapy. Supine positioning (orthopnoea test) led to worse dyspnoea in 47% of patients compared to sitting upright.

Conclusion
When sitting upright, dyspnoea in the sitting position improves rapidly and substantially in patients with AHF after administration of conventional therapy, mainly intra-venous diuretics. However, many patients remain orthopnoeic. Improving the methodology of clinical trials in AHF by standardizing the conditions under which dyspnoea is assessed could enhance their ability to identify effective treatments. Relief of orthopnoea is clinically valuable and may represent a useful goal for clinical trials.

Keywords
Acute heart failure • Dyspnoea • Orthopnoea

Introduction
Over 1 000 000 patients each year are hospitalized with heart failure in the USA, with similar rates of admission in countries represented by the European Society of Cardiology.1,2 Dyspnoea, or breathlessness, is the most common presenting symptom and distressing to patients.3,4 Its relief is an important goal for patients and physicians, as well as regulatory agencies such as the Food and...
Drug Administration and the European Medicines Agency. Consequently, relief of dyspnoea has been an endpoint in nearly every large acute heart failure (AHF) clinical trial. Despite the importance of relieving dyspnoea and its prominent role as an endpoint, standardized assessments of this symptom, including patient positioning during assessment, and the temporal relationship between initial pharmacological treatment and its improvement in the setting of AHF have not been well studied.

Our limited understanding of dyspnoea highlights the general lack of evidence and need for greater understanding of the pathophysiology and management of AHF. Common therapies such as loop diuretics and morphine continue to be used empirically, but with limited data to support their use. URGENT (Ularitide Global Evaluation in Acute Decompensated Heart Failure) dyspnoea was designed to describe the symptomatic response to initial, conventional therapy in patients with AHF very early in their hospital course.

To date, AHF clinical trials have enrolled patients relatively late, 24–48 h after admission. Despite substantial clinical trial data supporting the effectiveness of standard therapy to improve dyspnoea relatively late in the course of AHF, the efficacy during the initial phase of AHF is not well documented. Furthermore, no standard method for scoring the severity of dyspnoea or the effects of patient posture has been adopted, although a consensus proposal has been put forth. Typically, patients with severe dyspnoea owing to AHF cannot lie flat and become orthopnoeic. As patients are treated and improve, dyspnoea may be relieved in the sitting position; however, they may still have orthopnoea.

We hypothesized that in patients with AHF, conventional therapy would improve dyspnoea substantially within 6 h but that many patients would remain orthopnoeic.

Methods

Study design

The design and rationale for URGENT dyspnoea has been described previously. This was an international, multi-centre, observational, prospective cohort study designed to evaluate the effect of conventional therapy for AHF—typically oxygen, diuretics, and vasodilators—on patient-assessed dyspnoea during the initial management phase. Nesiritide or levosimendan was allowed in those countries where they are approved. No investigational agents were used.

Patients were enrolled within 1 h of first physician evaluation (for training institutions, this included physicians-in-training). As a result, the study was primarily conducted in emergency departments or other acute care settings. The final diagnosis of AHF was determined by each individual site investigator, based on all available data present at the 6 h assessment (e.g. history, physical examination, medical records, chest X-ray, B-type natriuretic peptide (BNP) or NT-proBNP, troponin, medications delivered, and so on).

Study population

Inclusion and exclusion criteria were broad and permitted enrolment of patients in whom AHF was suspected rather than established, reflecting daily clinical practice. Patients were 18 years or older, able to give consent, with signs and symptoms of AHF and able to self-assess dyspnoea. Our study complies with the Declaration of Helsinki and institutional review board, and/or ethics committee approval was obtained from each centre, with written informed consent obtained from each subject.

Dyspnoea measurements

The primary outcome was patient-assessed dyspnoea at 6 h. The effect of supine positioning (orthopnoea test) on patient-assessed dyspnoea was the secondary outcome. Dyspnoea was assessed at the time of enrolment (baseline) and 6 h later using three instruments. A 7-point Likert scale administered at 6 h was used to determine change from baseline: (i) markedly worse, (ii) moderately worse, (iii) minimally worse, (iv) no change, (v) minimally improved, (vi) moderately improved, and (vii) markedly improved. However, patients may not recall accurately how they felt at baseline or be uncertain about when baseline was supposed to be. Also, patients with severe symptoms who do not respond and patients whose symptoms were initially mild and have little room to improve may end up with similar change scores. Accordingly, symptoms were also assessed using two absolute scales. Change in dyspnoea can be calculated by subtracting scores. A 5-point Likert scale was used to document patients’ current status: (i) not short of breath, (ii) mildly short of breath, (iii) moderately short of breath, (iv) severely short of breath, and (v) very severely short of breath. A 100 mm visual analogue scale (VAS) was also used. A priori, this line was divided into 10 equal 1 cm increments, 0–10 (11-point VAS). If patients marked anywhere within a particular centimetre increment, the recorded result on the 11-point VAS was identical (i.e. 26 mm = 3 cm, 21 mm = 3 cm). Scales were translated into local language as needed.

Patients were initially studied in the sitting position (patients head was at minimum ≥60° relative to horizontal) and first answered the 5-point Likert scale questions followed by placing a mark on the VAS. If patients answered ‘severely’ or ‘very severely’ short of breath, they were not placed supine to avoid worsening their symptoms. Those patients who were not severely or very severely short of breath underwent the orthopnoea test (placed supine with head ≤20° relative to horizontal). After an equilibration period of 120 s, both the 5-point Likert and VAS were repeated. Those with worse dyspnoea score when supine compared with upright were categorized as ‘worse’, those who reported improved dyspnoea were categorized as ‘better’, and those patients who reported no change in their score...
<table>
<thead>
<tr>
<th></th>
<th>Patients with AHF at 6 h (n = 524)</th>
<th>Patients without AHF (n = 79)</th>
<th>Patients with uncertain diagnosis (n = 173)</th>
<th>P-value among three groups of patients</th>
<th>P-value between patients with and without AHFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups (%)</td>
<td>68 (64; 71)</td>
<td>10 (8; 13)</td>
<td>22 (19; 25)</td>
<td>0.07</td>
<td>0.08</td>
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<tr>
<td>Demographics (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age median (IQR)</td>
<td>70 (68–80)</td>
<td>67 (55–76)</td>
<td>66 (55–78)</td>
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<tr>
<td>Male (%)</td>
<td>57 (52; 61)</td>
<td>44 (33; 56)</td>
<td>59 (51; 66)</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF (%), median (IQR)</td>
<td>40 (38; 42)</td>
<td>48 (44; 52)</td>
<td>36 (32; 39)</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF unknown (%)</td>
<td>49 (45; 53)</td>
<td>35 (25; 47)</td>
<td>46 (38; 53)</td>
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<td>0.07</td>
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<tr>
<td>Cardiovascular co-morbidities (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td>62 (58; 66)</td>
<td>49 (38; 61)</td>
<td>78 (71; 85)</td>
<td></td>
<td>0.0001</td>
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<tr>
<td>De novo heart failure</td>
<td>38 (34; 42)</td>
<td>51 (39; 62)</td>
<td>22 (15; 29)</td>
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<td>0.0001</td>
</tr>
<tr>
<td>Coronary artery disease (CAD)</td>
<td>43 (39; 47)</td>
<td>46 (34; 57)</td>
<td>41 (34; 49)</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>25 (21; 29)</td>
<td>23 (14; 34)</td>
<td>23 (17; 30)</td>
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<td>0.08</td>
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<tr>
<td>Hypertension</td>
<td>75 (71; 79)</td>
<td>76 (65; 85)</td>
<td>64 (57; 71)</td>
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<tr>
<td>Valvular disease</td>
<td>16 (13; 20)</td>
<td>9 (4; 17)</td>
<td>14 (9; 20)</td>
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<td>0.2</td>
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<tr>
<td>Primary cardiomyopathy</td>
<td>14 (11; 17)</td>
<td>6 (2; 14)</td>
<td>21 (15; 28)</td>
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<td>0.01</td>
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<tr>
<td>PCI in past</td>
<td>11 (8; 14)</td>
<td>8 (3; 16)</td>
<td>8 (4; 13)</td>
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<td>0.4</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (6; 11)</td>
<td>6 (2; 14)</td>
<td>6 (3; 11)</td>
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<tr>
<td>Stroke</td>
<td>7 (5; 10)</td>
<td>6 (2; 14)</td>
<td>6 (3; 10)</td>
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<td>Non-CV co-morbidities (%)</td>
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<tr>
<td>Obesity</td>
<td>26 (22; 30)</td>
<td>32 (22; 43)</td>
<td>23 (17; 30)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>9 (6; 11)</td>
<td>6 (2; 14)</td>
<td>8 (4; 13)</td>
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<td>0.8</td>
</tr>
<tr>
<td>Asthma/chronic obstructive pulmonary disease</td>
<td>17 (14; 21)</td>
<td>25 (16; 36)</td>
<td>17 (12; 24)</td>
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<td>0.2</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>16 (13; 20)</td>
<td>14 (7; 24)</td>
<td>14 (10; 21)</td>
<td></td>
<td>0.8</td>
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<tr>
<td>Non-insulin-dependent diabetes</td>
<td>21 (18; 25)</td>
<td>24 (15; 35)</td>
<td>13 (9; 19)</td>
<td></td>
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<td>Renal insufficiency</td>
<td>26 (22; 30)</td>
<td>25 (16; 36)</td>
<td>21 (15; 28)</td>
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<td>0.4</td>
</tr>
<tr>
<td>Anaemia (Hgb &lt;12)</td>
<td>14 (11; 17)</td>
<td>16 (9; 26)</td>
<td>10 (6; 15)</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Cancer history</td>
<td>6 (4; 9)</td>
<td>16 (9; 26)</td>
<td>8 (4; 13)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Current prescriptions (%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Beta blocker</td>
<td>51 (47; 56)</td>
<td>42 (31; 53)</td>
<td>49 (41; 56)</td>
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<td>0.3</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>47 (42; 51)</td>
<td>30 (21; 42)</td>
<td>42 (34; 49)</td>
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<td>0.02</td>
</tr>
<tr>
<td>Angiotensin receptor blocker (ARB)</td>
<td>12 (10; 16)</td>
<td>11 (5; 21)</td>
<td>8 (4; 13)</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Statins</td>
<td>27 (24; 32)</td>
<td>24 (15; 35)</td>
<td>30 (23; 37)</td>
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<tr>
<td>Dihydropyridine Calcium channel blocker</td>
<td>14 (11; 17)</td>
<td>9 (4; 17)</td>
<td>12 (8; 18)</td>
<td></td>
<td>0.4</td>
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<tr>
<td>Nitrates</td>
<td>20 (17; 24)</td>
<td>11 (5; 21)</td>
<td>24 (18; 31)</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>11 (9; 14)</td>
<td>0 (0; 5)</td>
<td>13 (9; 19)</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Diuretics</td>
<td>65 (60; 69)</td>
<td>47 (36; 58)</td>
<td>62 (55; 70)</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Laboratory values (n, median, IQR)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>139, 867 (352–1935)</td>
<td>41, 195 (55.5–699.5)</td>
<td>93, 623 (245.5–1650)</td>
</tr>
<tr>
<td>Sodium</td>
<td>509, 138 (136–141)</td>
<td>76, 138 (136–141)</td>
<td>156, 139 (136–141)</td>
</tr>
<tr>
<td>Troponin I &gt;0.04</td>
<td>199, 0 (0.07–2.8)</td>
<td>29, 0 (0.05–0.36)</td>
<td>49, 0 (0.06–0.19)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>509, 1 (1–6)</td>
<td>77, 1 (0.9–1.5)</td>
<td>159, 1 (0.9–1.6)</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>474, 23 (16.0–33.9)</td>
<td>71, 21 (12.0–29.7)</td>
<td>139, 18 (12.0–28.0)</td>
</tr>
<tr>
<td>Therapy received during first 6 h (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>82 (79; 85)</td>
<td>48 (37; 60)</td>
<td>3 (1; 7)</td>
</tr>
<tr>
<td>IV Vasodilator (nitroglycerin, nitroprusside, nesiritide)</td>
<td>25 (22; 29)</td>
<td>22 (13; 32)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>IV Inotrope and/or vasopressor (dobutamine, dopamine, milrinone, enoximone, levosimendan, norepinephrine, epinephrine)</td>
<td>8 (6; 10)</td>
<td>0 (0; 5)</td>
<td>1 (0; 3)</td>
</tr>
<tr>
<td>Vital signs at admission (n, median, IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>524 (140) (119–163)</td>
<td>79 (135) (116–156)</td>
<td>168 (136) (112–155)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>523 (80) (70–94)</td>
<td>78 (73) (65–89)</td>
<td>167 (78) (66–90)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>523 (90) (75–106)</td>
<td>79 (97) (76–112)</td>
<td>166 (89) (75–104)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>513 (22) (18–26)</td>
<td>77 (24) (20–28)</td>
<td>164 (22) (20–27)</td>
</tr>
<tr>
<td>SpO2</td>
<td>472 (94) (90–97)</td>
<td>76 (96) (91–99)</td>
<td>168 (96) (93–98)</td>
</tr>
<tr>
<td>Dyspnoea at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likert 5-point$^*$ at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>517</td>
<td>79</td>
<td>172</td>
</tr>
<tr>
<td>SD</td>
<td>2.1 (1.2)</td>
<td>1.8 (1.4)</td>
<td>1.7 (1.9)</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
were categorized as 'unchanged'. Patients unable to tolerate lying flat were returned to a supine position and ranked according to their last completed assessment.

Statistical analysis

Our hypothesis was tested only in those patients diagnosed with AHF. Demographic and clinical characteristics of the cohort are reported with means and standard deviations for normally distributed continuous data or medians with interquartile ranges for non-normally distributed data. Proportions are described with 95% confidence intervals. Comparisons between groups of patients were performed by $\chi^2$ (or Fisher's exact test when cells had counts less than 5) for categorical variables or Kruskall–Wallis for continuous variables; if needed, post hoc analysis was performed by the Mann–Whitney $U$ test. Analyses were done using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and R.2.7.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

From 1 January 2007 to 31 August 2007, 776 patients from 35 sites in 18 countries were enrolled. Of these, 524 (68% (95% CI 64–71)) had the diagnosis of AHF confirmed by 6h, and 79 (10% (95% CI 8–13)) had not (Figure 1). For the remaining 173 (22% (95% CI 19–25)) patients, the diagnosis was either not clear or left unmarked on the case report form at the 6h point. The investigator made the diagnosis of AHF with full access to the patient and patient's medical records. Baseline characteristics are shown in Table 1. Patients with AHF were older, had a lower left ventricular ejection fraction (LVEF), were treated more often with digitalis or potassium, and were more often treated with higher BNP or NT-proBNP, and were more often treated with a beta blocker.

Statistical analysis

Table 1: Continued

<table>
<thead>
<tr>
<th>Patients with AHF at 6 h (n = 524)</th>
<th>Patients without AHF (n = 79)</th>
<th>Patients with uncertain diagnosis (n = 173)</th>
<th>$P$-value among the three groups of patients</th>
<th>$P$-value between patients with and without AHFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQR</td>
<td></td>
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<tr>
<td>VAS at baseline</td>
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<td></td>
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</tr>
<tr>
<td>n</td>
<td>523</td>
<td>79</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>5.7 (2.8)</td>
<td>5.0 (3.0)</td>
<td>5.1 (2.8)</td>
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<tr>
<td>Median</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>3.0–8.0</td>
<td>2.0–8.0</td>
<td>3.0–7.0</td>
<td></td>
</tr>
</tbody>
</table>

Data shown are proportions with 95% CI unless otherwise stated. SD, standard deviation.

The 5-point of the Likert scale received a number from 0 (no dyspnoea) to 4.

Table 2: Precipitating factors of acute heart failure

<table>
<thead>
<tr>
<th>Precipitating factors</th>
<th>Patients with AHF at 6 h (n = 524)</th>
<th>Patients without AHF at 6 h (n = 79)</th>
<th>Patients with uncertain diagnosis at 6 h (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndromes (%)</td>
<td>16.0 (13.0; 19.5)</td>
<td>6.0 (0.9; 13.7)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>16.4 (13.3; 19.9)</td>
<td>6.8 (0.9; 14.3)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Valvular dysfunction (%)</td>
<td>8.8 (6.5; 11.5)</td>
<td>6.8 (0.9; 14.3)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>21.0 (17.9; 24.4)</td>
<td>16.8 (13.0; 20.5)</td>
<td>10.7 (0.9; 20.4)</td>
</tr>
<tr>
<td>Medication non-compliance (%)</td>
<td>13.7 (10.9; 17.1)</td>
<td>6.8 (0.9; 14.3)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Dietary non-compliance (%)</td>
<td>10.3 (7.8; 13.3)</td>
<td>6.8 (0.9; 14.3)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Drug-induced HF (%)</td>
<td>1.9 (0.9; 3.5)</td>
<td>0.0 (0.0; 0.1)</td>
<td>0.0 (0.0; 0.1)</td>
</tr>
<tr>
<td>Post-surgical HF (%)</td>
<td>1.1 (0.4; 2.5)</td>
<td>0.0 (0.0; 0.1)</td>
<td>0.0 (0.0; 0.1)</td>
</tr>
<tr>
<td>Post-surgical HF (%)</td>
<td>2.9 (1.4; 4.7)</td>
<td>0.0 (0.0; 0.1)</td>
<td>0.0 (0.0; 0.1)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>29.0 (25.2; 33.1)</td>
<td>8.8 (6.5; 11.5)</td>
<td>4.0 (0.9; 9.5)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>5.9 (4.1; 8.3)</td>
<td>5.9 (4.1; 8.3)</td>
<td>5.9 (4.1; 8.3)</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>24.2 (20.6; 28.1)</td>
<td>24.2 (20.6; 28.1)</td>
<td>24.2 (20.6; 28.1)</td>
</tr>
</tbody>
</table>

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diuretic or inotropic agents than patients admitted for acute dyspnoea and non-AHF. They also reported worse dyspnoea compared with patients without AHF. Suspected precipitants of AHF, as determined by the investigator, are listed in Table 2.

**Relationship between dyspnoea and time**

Baseline dyspnoea by 5-point Likert was 2.1 ± 1.2 [median 2.0 (1.0–3.0)] and the baseline VAS 5.7 ± 2.8 [median 5.0 (3.0–8.0)] (Table 1). Patient responses utilized the entire scale for both the VAS and 5-point Likert, suggesting the use of the entire range of both scales.

By the 5-point Likert scale, fewer patients reported ‘very severe’ or ‘severe’ shortness of breath (SOB) and greater numbers of patients reported ‘mild SOB’ and ‘I am not SOB’ compared with baseline. (P < 0.0001) (Figure 2A). The mean (95% CI) VAS score at baseline in the sitting position was 5.7 (5.4–5.9), while the mean VAS at 6 h in the sitting position was 3.5 (3.4–3.7) (P < 0.0001) in AHF patients (Figure 2B).

By the 7-point Likert scale, 76% (95% CI 72–80) of those with AHF reported mild, moderate, or marked improvement and 58% (95% CI 54–63) reported moderate or marked improvement at 6 h (Figure 2C).

When comparing measurement instruments in the sitting position, a high degree of agreement was found between the 5-point Likert and VAS measurements at the baseline time point (correlation coefficient 0.891, P < 0.0001). A high degree of agreement was also found between the 5-point Likert and VAS measurements when used to calculate change (correlation coefficient 0.800, P < 0.0001 for both). However, when either the 5-point Likert or the VAS was compared with the 7-point Likert in terms of change from baseline measurement, less agreement was noted (correlation coefficients 0.512 and 0.500, respectively).

Figure 3A and B demonstrates the relationship between baseline dyspnoea score and magnitude of change at 6 h; patients reporting the worst baseline dyspnoea demonstrated the greatest improvement [VAS (correlation coefficient 0.672), 5-point Likert (correlation coefficient 0.272) (both P < 0.0001)].
Per protocol, only patients who initially reported ‘no SOB,’ ‘mild SOB,’ and ‘moderate SOB’ were placed in the orthopnoea position (postural stress), leaving 345 patients with baseline measurements in both the upright and supine position. Figure 4A and B represents patients’ response to postural stress, by both Likert and VAS measurements. Responses were initially recorded sitting upright and then re-recorded when placed supine. By 5-point Likert (Figure 4A), only nine [3% (95% CI 1–5)] AHF patients reported an improvement in their dyspnoea, 177 [51% (95% CI 46–57)] had no change, and 159 [46% (95% CI 41–52)] reported worse dyspnoea supine compared with sitting. By the VAS (Figure 4B), a greater number of AHF patients reported worsening dyspnoea [72% (95% CI 67–77)], with fewer patients reporting no change [24% (95% CI 19–28)] (P < 0.001) when compared with assessments by the 5-point Likert scale.

### Discussion

Dyspnoea in the sitting position rapidly improves in response to standard therapy for AHF, but resolution of orthopnoea lags behind. This may affect both the interpretation of past trials and the design of future clinical trials in AHF. By enrolling relatively late, previous trials may have enrolled a unique sub-set of AHF patients if dyspnoea was required as an inclusion criterion. The composition of this subset may include: (i) patients who were improperly, inadequately, or not treated, (ii) rebound dyspnoea—patients who got better, then relapsed, (iii) persistent dyspnoea—patients with mild dyspnoea improvement, and (iv)
refractory dyspnoea—patients who did not improve despite adequate therapy. Thus, the time-window of enrolment in previous clinical trials may have been too late to target unselected patients with dyspnoea. Timing of drug delivery could have been one factor contributing to the neutral outcomes seen in clinical trials in regards to dyspnoea. By inadvertently targeting refractory patients, the effectiveness of a new agent used as second-line therapy in patients refractory to standard treatments may be less than when it is used as first-line therapy. Trials of early interventions need to measure the speed with which symptoms resolve rather than merely measuring status late after the event.

Orthopnoea testing revealed a proportion of patients with persistent dyspnoea when placed under postural stress. Compared with baseline, fewer patients reported ‘severe’ or ‘very severe’ SOB at 6 h, and thus more patients underwent orthopnoea testing. Of those patients who underwent orthopnoea testing at 6 h, they reported less worsening of orthopnoea compared with baseline, further suggesting resolution of their dyspnoea overall.

When comparing instruments to measure dyspnoea, the present study shows a high degree of agreement between the 5-point Likert and VAS measurements (absolute values and changes compared with baseline) and less agreement between either the 5-point Likert or the VAS and the 7-point Likert in dyspnoeic patients in the sitting position. Furthermore, orthopnoea testing revealed a proportion of patients with persistent dyspnoea when placed under postural stress, which was better seen with the VAS compared with the 5-point Likert assessment. The VAS may more accurately represent change in AHF patients with dyspnoea when placed supine. Accordingly, the present study suggests equivalence between the 5-point Likert and the VAS in assessing dyspnoea in the sitting position, but the VAS appears to be superior when assessing patients in the orthopnoea position. These tools require further validation in the setting of AHF.

From a current regulatory approval standpoint, improvement of dyspnoea is still an important goal, and thus studies that address dyspnoea should consider additional means to best capture patient-reported dyspnoea. Standardization of the timing of dyspnoea measurement, patient positioning during dyspnoea measurement, and conditions under which dyspnoea is measured would ensure that variations within a study were minimized, and thus might better demonstrate the efficacy of a novel therapy on dyspnoea relief. Such standardization would also facilitate comparison between studies.

**Limitations**

Similar to other observational registries, various data elements are missing from patients, which may have affected baseline characteristics and self-assessed dyspnoea results. There was a bias towards enrolling patients who were symptomatic; however, obtaining consent in the severely dyspnoeic patient may be difficult, limiting their inclusion. In addition, AHF patients also present with symptoms other than dyspnoea, such as fatigue and weakness. These patients were not captured as part of this study. The diagnosis of AHF was either unclear or left unmarked on the reporting form at 6 h for 22% of our overall study population, which may have potentially skewed our results. Further, there was no independent adjudication process in terms of the diagnosis. If patients are enrolled early, improved diagnostic procedures will be required to ensure the recruitment of appropriate patients (e.g. bedside or point-of-care diagnostic testing). Such a requirement may have a significant impact on clinical trial design given the recent results from both the PROTECT Pilot and pre-RELAX clinical development programmes, which highlight a lower proportion of patients who improve with standard therapy alone when objective criteria for enrolment, such as elevated BNP levels, were required. Finally, six out of 18 countries enrolled less than 10 patients total and thus our results may not be representative across all countries. Three countries enrolled nine patients, with the three remaining countries enrolling less than five patients total. Most of the sites were initiated late, which may explain the limited enrolment.

**Conclusion**

The vast majority of clinical trials to date have targeted dyspnoea. However, many trials enrolled patients relatively late and did not standardize their methods of measurement. Based on the findings from this study, dyspnoea should be targeted early in a patient’s presentation, and the conditions under which it is measured should be standardized. As the most common symptom in AHF and the significant distress it causes patients, dyspnoea should remain an important therapeutic target. Recognition of the speed and extent to which patient-assessed dyspnoea improves with early standard therapy and the effect of orthopnoea testing on patient-assessed dyspnoea may influence future clinical trial design.

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**Appendix**

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**References**


CARDIOVASCULAR FLASHLIGHT

T-cell lymphoma and pigtail catheter drainage of a massive paraneoplastic pleuro-pericardial effusion in a child

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An 9-year-old black African boy was admitted for tachypnoea. His medical history was free of event. Clinical examination revealed abolition of vesicular murmur in the right lung, tachycardia, and mild jugular venous distension. Chest X-ray showed complete opacification of the right hemithorax due to massive pleural effusion. Pigtail catheter drainage yielded 4500 mL of an exudative fluid. A second massive pleural effusion. Pigtail catheter drainage revealed 4500 mL of an exudative fluid. A second massive pleural effusion. Pigtail catheter drainage of a massive paraneoplastic pleuro-pericardial effusion in a child. T-cell lymphoma and pigtail catheter drainage of a massive paraneoplastic pleuro-pericardial effusion in a child.

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