Published in final edited form as:

J Card Fail. 2012 July ; 18(7): 524–533. doi:10.1016/j.cardfail.2012.04.012.

The Worst Symptom As Defined By Patients During Heart Failure Hospitalization: Implications for Response to Therapy

Mahoto Kato, MD¹, Lynne W. Stevenson, MD², Maryse Palardy, MD³, Patricia M. Campbell, MD², Christopher W. May, MD⁴, Neal K. Lakdawala, MD², Garrick Stewart, MD², Anju Nohria, MD², Joseph G. Rogers, MD⁵, J. Thomas Heywood, MD⁶, Mihai Gheorghiade, MD⁷, Eldrin F. Lewis, MD², Xiaojuan Mi, PhD⁸, and Soko Setoguchi, MD, DrPH^{2,8}

¹National Cardiovascular Center, Osaka, Japan

²Brigham and Women's Hospital, Harvard Medical School, Boston, MA

³McGill University, Montreal, Quebec

⁴Inova Fairfax Hospital, Falls Church, VA

⁵Duke University Medical Center, Durham, NC

⁶Scripps Clinic, La Jolla, CA

⁷Northwestern University, Chicago, IL

⁸Duke Clinical Research Institute, Durham, NC

Abstract

Background—Patients perceive different symptoms of heart failure decompensation. It is not known whether the nature of the worst symptom relates to hemodynamic profile, response to therapy, or improvement in clinical trials.

Methods and Results—Patients in the ESCAPE trial were hospitalized with advanced heart failure, ejection fraction < 30%, and at least 1 sign and 1 symptom of elevated filling pressures.

Corresponding Author: Lynne W. Stevenson, M.D., Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, Phone: 617-732-7406, Fax: 617-264-5265, l Stevenson@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

Lynne Warner Stevenson, M.D. – no current relationships. During the time of the ESCAPE trial was a consultant to Medtronic Inc.

Maryse Palardy, M.D. – None

Mahoto Kato, M.D. – None

Garrick Stewart, M.D. – None

Patricia Campbell, M.D. – None

Christopher W. May, MD - None

Neal K. Lakdawala, MD - None

Anju Nohria, MD - None

Joseph G. Rogers, MD - None

J. Thomas Heywood, MD - None

Mihai Gheorghiade, MD - None

Eldrin F. Lewis, MD - None

Soko Setoguchi, MD - None

Visual analog scales (VAS) for symptoms were completed by 371 patients, who selected their worst symptom as difficulty breathing, fatigue, abdominal discomfort or body swelling and also scored breathing and global condition at baseline and discharge. The dominant symptom identified was difficulty breathing by 193 (52%) patients, fatigue by 118 (32%), abdominal discomfort and swelling each by 30 (8%) patients, combined as right-sided congestion for analysis. Clinical and hemodynamic assessments were not different between groups except that right-sided congestion was associated with more hepatomegaly, ascites, third heart sounds, and jugular venous distention. This group also had greater reduction in jugular venous distention and trend toward higher BUN after therapy. By discharge, average improvements in worst symptom and global score were 28 points and 24 points. For those with > 10 points improvement in worst symptom, 84% also improved global assessment > 10 points. Initial fatigue was associated with less improvement ($p=0.002$) during and after hospitalization, but improvements in symptom scores were sustained when re-measured during 6 months after discharge.

Conclusion—In most patients hospitalized with clinical congestion, therapy will improve symptoms regardless of the worst symptom perceived, with more evidence of baseline fluid retention and reduction during therapy for worst symptoms of abdominal discomfort or edema. Improvement in trials should be similar when tracking worst symptom, dyspnea, or global assessment.

Keywords

Quality of Life; Cardiomyopathy; Congestive Heart Failure; Hemodynamics

INTRODUCTION

Heart failure hospitalizations are usually triggered by worsening symptoms associated with elevated filling pressures.¹ If differences in the nature of the worst symptom connote differing underlying clinical profiles with implications for therapy, these could influence triage at the time of hospitalization.

Standard therapies usually provide dramatic relief of symptoms during hospitalization, but it has been difficult to demonstrate the impact of newer therapies on symptoms in recent trials of decompensated heart failure.²⁻⁶ This lack of clear signal could reflect differences between patients in the dominant symptoms they perceive. It is also possible that relief in the presenting symptoms could be counterbalanced later by increased awareness of other symptoms that detract from perception of global improvement. Better understanding of changes in symptoms as assessed by patients over time could facilitate selection of endpoints for trials in this population.

Unique information about the nature of dominant symptoms during decompensation is provided by the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial.⁷ Hospitalized patients with clinical evidence of elevated filling pressures were asked to select their “worst” symptom as difficulty breathing, abdominal discomfort, body swelling, or fatigue. At baseline and again after therapy, patients quantitated the same “worst” symptom, in addition to the specific symptom of shortness of breath (if not the worst symptom), and the overall global assessment.

The high rate of symptomatic improvement during hospitalization has been well documented, and shown by the ESCAPE trial to be similar whether hemodynamics were assessed invasively or clinically only.⁷ The aim of this analysis was to identify the specific symptoms perceived as “worst” during decompensation of advanced heart failure, and to determine whether the nature of the worst symptom predicts different hemodynamic profiles and different responses to acute therapy. Our hypotheses were that 1) the dominant symptom might distinguish patient populations with different hemodynamic profiles of cardiac output and filling pressures, 2) the nature of the dominant symptom during decompensation would predict likelihood of clinical improvement, and 3) the patients’ rating of improvement in their dominant symptom would correlate well with improvement in their global assessment.

Methods

Study Population and Design

We conducted a retrospective analysis using data from the ESCAPE trial, a randomized multicenter trial evaluating the efficacy and safety of pulmonary artery catheter-guided therapy versus clinical assessment in patients hospitalized with decompensation despite recommended therapy.⁷ Sites were selected for known expertise in invasive monitoring and clinical management of patients with heart failure. Criteria included current hospitalization with at least 1 symptom and 1 sign of congestion, left ventricular ejection fraction < 30 %, systolic blood pressure < 125 mmHg, and previous heart failure hospitalization or chronic daily dose of 160 mg furosemide. Patients were randomized to receive therapy guided by clinical assessment only or by clinical assessment and indwelling pulmonary artery catheter.

Therapy was adjusted in both arms with the goals of an estimated jugular venous pressure (JVP) of 8 cm H₂O and resolution of orthopnea and edema, assessed qualitatively using a 0 to 4 scale. Additional hemodynamic goals for patients receiving PAC were pulmonary capillary wedge pressure (PCWP) 15 mmHg and right atrial pressure (RAP) 8 mmHg. Therapy was adjusted to avoid progressive renal dysfunction or symptomatic hypotension.

Assessments of “Worst” Symptom

At the time of randomization, each patient was asked their worst symptom at admission: “Which of the following bothers you the most?” with choices from the list of ‘abdominal discomfort’, ‘difficulty breathing’, ‘body swelling’, and ‘fatigue’. For those patients who did not describe difficulty of breathing as their worst symptom, they were also asked to rate the ease of their breathing, from constant shortness of breath to breathing comfortably throughout the day. The global patient assessment ranged from “worst imaginable health state” to “best imaginable”. Each of these three was depicted by the patient using a line drawn thorough the visual analog scale (VAS) on a separated sheet, and assigned a score equal to the distance between the mark and 0, with 0 corresponding to the worst rating and 100 the best, representing freedom from the symptom. The same worst symptom defined initially was the one queried on subsequent assessments. Patients completed the symptom assessments again prior to hospital discharge. The protocol also included completion of the assessments again by patients returning for outpatient visits at 1, 3 and 6 months after

discharge, Only the patients completing all assessments for baseline, discharge, and 1, 3, and 6 month values were included in analysis of symptoms after discharge.

Assessment in Hospital

Signs were recorded as categorical variables in the ESCAPE trial as follows: rales (0; none, 1; $<1/3$, $1/3$, or $>2/3$), S3 (0;absent or 1;present), hepatomegaly (0;absent, 1; 2–4 finger breadths, 2; >4 finger breadths), peripheral edema(0; none to trace or 1; moderate to massive), hepatojugular reflux (0;none or 1;present). Jugular venous pulsation (JVP) was estimated as height of the visible venous pressure fluctuation above the right atrium, as <8 cm, 8-12, 13-16, and over 16 cm. We further collapsed the ordinal variables into binary variables: Rales $> 1/3$, JVP > 12 cm, hepatomegaly >2 finger breadths, peripheral edema $>3+$ (moderate or greater), and ascites $> moderate$). Routine admission laboratory values included electrolytes, serum sodium, creatinine, blood urea nitrogen (BUN), liver function tests, and hemoglobin, available in 371 patients. B-type natriuretic peptide (BNP) was measured using the Shionogi assay as previously described.⁸ Blood samples were obtained shortly after randomization, prior to or immediately after PAC placement, and were available in 371 patients. By protocol design, hemodynamic measurements were available only in the 196 patients randomized to the PAC group, in which the baseline was defined by the average of 3 measurements made from paper tracings prior to adjustment of therapy.

Statistical Analysis

We described patient characteristics for each group defined by the type of worst symptom and presented percent for categorical variables and mean for continuous variables. Due to the small numbers and similarities of the groups describing either abdominal discomfort or body swelling as worst symptoms, these two groups were combined for most subsequent analyses. We tested for differences among groups for binary and continuous variables across the groups using a chi-square test or one-way analysis of variance (ANOVA). When the tests for the null hypothesis of 3 groups being equal were rejected, we also conducted a test for pair-wise comparisons of our interest. Due to the multiple comparisons, we used the Bonferroni correction ($\alpha \sim 0.05/n$) to establish statistical significance of tests, where n is the number of a pair-wise comparison. Changes in symptom VAS score between baseline and discharge were assessed using paired t-tests.

To estimate symptom VAS scores change over time (admission, discharge, 1 month, 3 month, and 6 months) among 3 symptom groups, we used a linear mixed model taking into account the correlation between repeated measures. We used unstructured covariance pattern after comparing the fit statistics among unstructured, first-order autoregressive structure, Toeplitz and compound symmetry.

Kaplan-Meier survival curves were constructed and log-rank test was used to test for differences in outcomes between the symptom groups. A p value < 0.05 was considered statistically significant unless otherwise noted. All analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics Associated With Worst Symptoms

A dominant symptom was specified prior to randomization by 371 patients, which is defined as the population for this study. Age and male gender were characteristic of most referral heart failure populations, except for the higher proportion of 41% of the study population that was non-Caucasian. The study patients had a mean ejection fraction of $19\pm 7\%$, and systolic blood pressure of 106 ± 17 mmHg [Table 1]. Recommended therapies included diuretics and angiotensin converting enzyme inhibitors or angiotensin receptor blockers for almost all patients, with fewer patients tolerating beta adrenergic blocking agents.

The most common “worst” symptom was ‘difficulty breathing’ in 193 patients (52%). ‘Fatigue’ was the worst symptom in 118 patients (32%). ‘Abdominal discomfort’ and ‘body swelling’ were each the worst symptom for 8% of the study patients [Figure 1]. Due to the small numbers and clinical similarities between these 2 groups, they were subsequently considered together as one group, “right-sided congestion”.

The patient description of their worst symptom was consistent with the physical examination performed by the investigator prior to randomization [Table 2]. Compared to ‘difficulty breathing’ group, the group with a worst symptom of ‘fatigue’ less frequently had rales ($p < 0.016$). The group with right-sided symptoms of abdominal discomfort or body swelling contained more patients with JVP > 12 , and greater prevalence of hepatomegaly and ascites compared to the ‘difficulty breathing group’ ($p < 0.016$, Bonferroni correction). There were only 7 patients not on diuretics at baseline, 6 of whom described ‘fatigue’ as their worst symptom.

The global assessment of overall health was very similar between the 3 groups [Table 1]. Those patients with worst symptoms of abdominal discomfort or body swelling still described marked difficulty breathing although they scored it as less severe than the patients who described ‘difficulty breathing’ as their worst symptom ($p < 0.016$ for the pair-wise comparison). When comparing the 3 groups for baseline demographics and co-morbidities, there were no significant differences [Table 1] except that patients with ‘difficulty breathing’ as their worst symptom had lower creatinine and better estimated GFR than patients with ‘fatigue’ or right-sided symptoms, group and higher serum sodium than patients with worst right-sided symptoms group (all pair-wise comparison p values < 0.016).

By design, hemodynamic measurements were available only in the half of patients randomized to the PAC. There were no overall differences in measured hemodynamic profiles associated with “worst” symptoms [Table 3]. Patients with a worst symptom of ‘difficulty breathing’ had PCWP similar to the other groups at baseline. The cardiac index was similarly low (2.0 - 2.1 L/min/m²) in all 3 symptom groups at baseline.

Clinical Changes after Therapy

Therapy led to clinically meaningful and statistically significant improvement in most clinical or laboratory parameters [Table 4]. The changes were similar among all 3 groups, except for less reduction of systolic blood pressure in the patients with ‘fatigue’ compared to

‘difficulty breathing’ group ($p<0.016$ for the pair-wise comparison) [Table 4]. Although fewer than half of patients ($n=166$) had both initial and final hemodynamic measurements, there were no trends for differences between the symptom groups, all of whom had similar reduction of filling pressures and increases of cardiac index demonstrated during therapy guided by the PAC. Estimates of JVP were available for most patients ($n=332$). JVP was > 12 cm initially in 72% of patients with worst right-sided symptoms of congestion. A greater proportion of this group (59%) had JVP > 12 which was subsequently reduced to < 12 cm ($p<0.016$) compared to the dyspnea group. The right-sided symptom group also had a trend for greater weight loss ($p=0.08$) and a trend ($p=0.06$) for greater increase in BUN (by 8 mg/dl compared to 2.9 in the dyspnea group and 0.7 in the fatigue group). There was also a strong trend ($p=0.06$) for patients in this group to be discharged on higher doses of furosemide than patients in the other two groups (164+104 mg/day in the right-sided symptom group compared to 128+90 mg in the dyspnea group and 134+90 mg in the fatigue group).

Symptom Improvement With Therapy

Both worst symptoms and global assessment improved from the baseline at the time of discharge in all 3 groups. No significant differences were observed between the symptom groups in the magnitude of self-reported improvements from baseline to discharge, although there was a trend for more improvement in dyspnea than in fatigue (Figure 2, Table 4). For assessing longer term follow-up after discharge, the worst symptom VAS scores were available from admission, discharge, 1, 3, and 6 months in 176 patients. The “worst” symptoms assessed after discharge were stipulated to be the same as those defined by the patient at admission, and could not be re-defined later. The patients with complete symptom follow-up for all 6 months had slightly better baseline eGFR, serum sodium, and hemoglobin at baseline (data not shown) than the 176 patients who did not have complete questionnaires through 6 months. The improvement in worst symptom seen at discharge was slightly reduced by one month after hospitalization ($p<0.05$ in the mixed linear model), after which improvement was sustained at 3 and 6 months (p for trend = 0.82 (Figure 3). Compared to ‘difficulty breathing’ group, ‘fatigue’ group had numerically less improvement during hospitalization and significantly lower scores for freedom from their worst symptom ($p=0.002$) during follow-up after discharge. (Figure 3).

During long-term follow-up available in 176 patients, changes in the global assessment continued to correlate with those of the worst symptom ($R=0.53$, $p<0.01$) (Figure 4). For the 124 patients with improvement in their worst symptom at 6 months compared to baseline, 96 (77%) also had improvement in their global assessment score.

No significant differences were observed in freedom from all-cause mortality or the primary endpoint of all-cause mortality and re-hospitalization in groups defined by their worst symptom [Figure 5].

Discussion

This study shows that most patients hospitalized for decompensated chronic heart failure identified their dominant symptom as either ‘difficulty breathing’ (52%) or ‘fatigue’ (32%). After admission with clinical congestion, neither initial hemodynamic profile nor subsequent

degree of symptom improvement differed between these two groups. For patients describing worst symptoms of abdominal discomfort or body swelling, there was more initial evidence of elevated right sided pressures and more reduction in jugular venous pressures with therapy, and a trend for greater weight loss and more increase in BUN. Dyspnea was prominent and improved substantially even when not the worst symptom. For 176 patients followed through 6 months, symptom scores remained improved although initial fatigue was associated with less improvement. Improvement in patient global assessment tracked well with improvement in the worst symptom during hospitalization and during the next 6 months.

Dominant Symptoms of Dyspnea and Fatigue

Dyspnea and fatigue are the most common limiting symptoms in patients with advanced heart failure at the time of hospitalization. Among patients enrolled in the ADHERE (The Acute Decompensated Heart Failure National Registry) database, 89% described any dyspnea and 31% had fatigue at the time of hospital admission.² Although younger and restricted to heart failure with left ventricular ejection fraction < 30%, patients in the ESCAPE population described similar symptoms [Figure 1]. In the stable outpatient setting where most patients are clinically stable without evidence of congestion or hypoperfusion, dyspnea may indicate higher filling pressures and fatigue may indicate lower cardiac output,⁹⁻¹¹ although this has not been established. However, the current population was selected for decompensation of chronic heart failure, in which it has been shown that most hospitalizations are preceded by a gradual increase in left and right-sided filling pressures, regardless of precipitating symptom.^{1, 12} Once these patients had sufficient symptoms to require hospitalization and justify randomization to possible PAC, this study showed that hemodynamic measurements were almost the same whether fatigue or dyspnea was recognized as the dominant symptom. Furthermore, enrollment into the ESCAPE trial specifically required one symptom and one sign considered indicative of elevated filling pressures, so the population is biased by design for patients with obvious congestion. A symptom found to be particularly useful for severely elevated filling pressures was orthopnea.¹³ This study cannot determine if the dominant symptom is more revealing of the hemodynamic status and cardiac reserve in the ambulatory outpatient setting, where most patients during chronic heart failure management do not have clinical evidence of elevated filling pressures.

There is considerable variation in the threshold for symptoms and the perception of their source. Some people may perceive the effort required to breathe as dyspnea, while others may describe it as fatigue. This interrelationship of dyspnea and fatigue during the time of decompensation is further confirmed by the perception of significant dyspnea even in most patients who considered fatigue to be their worst symptom. Patients described similar severity regardless of the nature of the dominant symptom, and similar compromise of their global assessment.

The responses to intensive therapy during hospitalization were essentially the same between 'difficulty breathing' and 'fatigue'. As most patients had reductions in filling pressures, improvements in cardiac output, and relief of symptoms regardless of the dominant

symptom, it was not possible to relate or dissociate the degrees of hemodynamic and symptomatic responses.

It was possible to demonstrate in this study that there was significantly less perception of improvement in fatigue than in the other symptoms in the patients who provided serial assessments of symptoms after discharge. This could reflect a greater resolution of symptoms directly attributable to congestion than reduction of symptoms reflecting inadequate cardiac output reserve to support desired activity. It is also possible that the perception of fatigue is heightened by depression and other factors less responsive to acute therapy.

Dominant Abdominal Discomfort or Edema

The 68 patients with worst symptoms of abdominal discomfort or body swelling do not comprise a large enough group for definitive comparison across clinical characteristics, but they do appear to be a slightly different group. These symptoms of right-sided congestion had more specific correlates as found on physical examination for ascites and peripheral edema. The group with these dominant symptoms had higher right atrial pressure as estimated clinically by the jugular venous pressure. Although it could not be confirmed specifically in the small subset with measured right atrial pressures, previous analysis of the same dataset indicates good correlation between clinician-estimated and invasively measured right atrial pressures.¹³ Alternatively, the appearance of peripheral edema or hepatic enlargement could have influenced the examiner to perceive higher jugular venous pressure. The severity of these symptoms and of the associated global assessment score was similar to that for other “worst symptoms”, suggesting a common general level of discomfort and distress, regardless of the specific attribution.

During therapy to remove extra fluid, ascites and peripheral edema likely represent an extravascular volume reservoir that is more extensive than for patients with predominantly left-sided pressure elevations. Thus there may be more excess volume to be removed before the central circulating volume diminishes, as suggested by the trend for more weight loss during hospitalization. The trend for a greater increase in BUN in the patients with abdominal discomfort or symptomatic edema and the higher discharge furosemide doses would be consistent with recent data implicating systemic venous pressure elevation and greater sensitivity of BUN for the cardiorenal syndrome.^{14, 15}

Tracking Improvement in Symptoms

It is well-recognized that most patients experience clinical improvement in symptoms during hospitalization.²⁻⁶ However, the difficulty of demonstrating an impact of specific therapies on symptoms in controlled trials has led to questions about the validity of patient-perceived symptoms as endpoints. Multiple definitions of symptoms have been proposed, leading to variable prevalence of improvement without increasing sensitivity to treatment modality. Most commonly, patient assessments have focused on dyspnea and global distress, occasionally including “GI symptoms”.³ The relationship between changes in different symptoms and the global scores have not been well-characterized.

This study is the first to measure the patients' perception of the "worst symptom" and how it responds to therapy specifically guided to relieve evidence of congestion as in the ESCAPE trial, with average weight loss of 4 kg. The results clearly indicate that similar symptomatic improvement during hospitalization occurs regardless of the perceived dominant symptom.

It has not previously been established how global improvement tracks with the improvement in the initial worst symptom. It is conceivable that improvement in one symptom could unmask limitation from a second symptom, or that other symptoms could develop as a result of therapies during the hospitalization. This might explain in part why symptoms do not always track with hemodynamic changes.¹⁶ However, this trial demonstrates that the global assessment generally does improve in parallel with the worst symptom. This suggests that improvement during hospitalization may be assessed globally without a consistent mandate to parse out the specific symptoms that contribute to distress. Furthermore, these improvements remained relatively stable through the 6 months in the patients who had serial measurements following discharge. Over 80% of patients with a 10 point improvement in their worst symptom score had a similar improvement in their global assessment, and there were only 6% of patients in whom changes in the worst symptom and the global assessment during hospitalization moved in opposite directions. It still may occasionally be useful, however, to track specific symptoms if a therapy is expected to affect them differentially.

Limitations

Patient completion of the assessments was incomplete, as this aspect of trials has received less vigilance than the objective outcome measurements for primary endpoints. For the time during which this trial was conducted, however, collection of 87% of the assessment pairs during the hospitalization is a relatively high response rate. When completing multiple tests, there may be a tendency for patients to mark a line in similar places when completing two scales in succession. To minimize this tendency, the visual analog scales were presented on different pieces of paper, and without any numerical labels.

These conclusions are relevant only for patients such as enrolled in the ESCAPE trial, for which all patients were required to have one symptom and one sign typical of elevated filling pressures. The population with vague symptoms of fatigue, dyspnea, or renal dysfunction in the absence of obvious fluid overload would not be represented here. Neither would patients with other dominant symptoms such as chest pain or dizziness. Many hospitalizations include heart failure as a secondary diagnosis after presumed pulmonary or other systemic condition, which also would not be represented here. These results do not pertain to the outpatient heart failure management setting, where the relationship between the dominant symptom and the hemodynamic status may be more revealing as most patients are maintained free of clinical evidence of elevated filling pressures.

Perhaps the most unfortunate limitation is the relatively small size of the population with worst symptoms of abdominal discomfort or peripheral swelling. There is not enough data to demonstrate many statistical differences in their presentation or responses. The lack of consistent differences in this small sample should not lead to the conclusion that patients with worst symptoms related to right-sided congestion will have equivalent responses to

patients limited primarily by dyspnea or fatigue.. This distinction is particularly important in light of a growing prevalence of disproportionate right-sided heart failure.¹⁷

Conclusions

Patients most commonly describe either shortness of breath or fatigue as the “worst” symptom at the time of hospitalization, with fewer patients focusing on abdominal discomfort or body swelling. For patients who already show obvious clinical evidence of elevated filling pressures, the nature of the dominant symptom does not provide additional information regarding hemodynamic status or likelihood of response to therapy, although more information is needed to understand when renal function may worsen in patients with dominant right-sided symptoms. Most patients describe substantial dyspnea even when not rated as their worst symptom. For patients limited initially by fatigue, symptomatic improvement after therapy to relieve congestion may be less evident. For most patients undergoing repeat evaluation after therapy to relieve symptoms of congestion, similar improvements will be demonstrated whether tracked by worst symptom, dyspnea, or global assessment, and are likely to be sustained for the next 6 months.

Funding Sources

This study was supported by National Heart, Lung and Blood Institute (NHLBI) grant N01HV98177.

Dr. Palardy was the recipient of a research award from the Heart Failure Society of America. We are grateful for the expert manuscript preparation from Jerry Cornish.

References

1. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008; 118(14):1433–41. [PubMed: 18794390]
2. Fonarow GC, Corday E. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. *Heart Fail Rev*. 2004; 9(3):179–85. [PubMed: 15809815]
3. VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002; 287(12):1531–40. [PubMed: 11911755]
4. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002; 287(12):1541–7. [PubMed: 11911756]
5. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007; 297(12):1332–43. [PubMed: 17384438]
6. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA*. 2007; 297(17):1883–91. [PubMed: 17473298]
7. ESCAPE Investigators and Coordinators. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization. *JAMA*. 2005; 294:1625–33. [PubMed: 16204662]
8. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002; 40(5):976–82. [PubMed: 12225726]

9. Mauck HP Jr, Shapiro W, Patterson JL Jr. Pulmonary Venous (Wedge) Pressure. Correlation with Onset and Disappearance of Dyspnea in Acute Left Ventricular Heart Failure. *Am J Cardiol*. 1964; 13:301–9. [PubMed: 14128639]
10. Kleber FX. Dyspnea in heart failure. Introduction. *Basic Res Cardiol*. 1996; 91(Suppl 1):III. [PubMed: 8896737]
11. Drexler H, Coats AJ. Explaining fatigue in congestive heart failure. *Annu Rev Med*. 1996; 47:241–56. [PubMed: 8712779]
12. Stevenson LW, Zile M, Bennett TD, Kueffer FJ, Jessup ML, Adamson P, et al. Chronic ambulatory intracardiac pressures and future heart failure events. *Circ Heart Fail*. 2010; 3(5):580–7. [PubMed: 20562255]
13. Drazner MH, Hellkamp AS, Leier CV, Shah M, Miller LW, Russell SD, et al. Value of clinician assessment of hemodynamics in advanced heart failure. The ESCAPE trial. *Circ Heart Fail*. 2008; 1:170–7. [PubMed: 19675681]
14. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, et al. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol*. 2008; 51(13):1268–74. [PubMed: 18371557]
15. Maqsood F, Szerlip HM. Relationship of venous congestion to worsening renal function. *J Am Coll Cardiol*. 2009; 54(7):661–2. [PubMed: 19660700]
16. Shah MR, Hasselblad V, Stinnett SS, Kramer JM, Grossman S, Gheorghiade M, et al. Dissociation between hemodynamic changes and symptom improvement in patients with advanced congestive heart failure. *Eur J Heart Fail*. 2002; 4(3):297–304. [PubMed: 12034155]
17. Campbell P, Drazner MH, Kato M, Palardy M, Lakdawala N, Desai A, et al. Right-left mismatch in the ESCAPE Population: Discordance between right and left-sided filling pressures before and after therapy. *J Cardiac Failure*. 2009; 15(6S):S28.

Figure 1. Distribution of the worst symptoms: 84% of patients hospitalized for decompensated chronic heart failure identified their dominant symptom as either 'Difficulty Breathing' (52%) or 'Fatigue' (32%).

Figure 2.

The impact of therapies during hospitalization on symptoms: All symptom scores improved significantly during hospitalization. Note that the dyspnea VAS was not ascertained separately for patients who identified breathing as the worst symptom. This was the only group in whom the worst symptom improved more than the global assessment. Otherwise there were no significant differences between improvement in Global VAS, Worst symptom VAS and Dyspnea VAS within each group. There were no significant differences in the degree of improvement between symptom groups. VAS; visual analog scale. Changes were calculated as [VAS at discharge] – [VAS at randomization]. Bars represent 95% confidence intervals.

Figure 3.

The time course of Worst Symptom VAS score, with the higher score being greater freedom from the symptom. Patients included are the 176 for whom there is complete data for VAS scores from baseline to 6 months after randomization: 88 patients with initial worst symptom described by patients as ‘Difficulty Breathing’; 60 patients describing ‘Fatigue’; 28 patients describing ‘Abdominal Discomfort’ or ‘Body Swelling’ * (right-sided symptoms). Compared to the “Difficulty Breathing” group, those with fatigue as the worst symptom at baseline had lower scores after discharge ($p=0.002$), using a linear mixed model taking into account the correlation between repeated measures. VAS= visual analog scale,

Figure 4. The relationship between changes in global assessment and changes in the worst symptom for the 176 patients with complete information from baseline to 6 month re-assessment.

Figure 5.

Kaplan-Meier cumulative plot of all 371 patients during 180 days after randomization, showing freedom from (A) the primary endpoint of all-cause mortality and heart failure re-hospitalization and (B) all-cause mortality for groups characterized by worst symptoms at baseline. *Right-sided symptoms = abdominal discomfort or body swelling.

TABLE 1

Baseline Characteristics; Variables According to Worst Symptom

	All (n=371)	Worst Symptom			p-value
		Difficulty Breathing (n=193)	Fatigue (n=118)	Abdominal discomfort or body swelling (n=60)	
Age, mean (SD), years	56 (14)	56 (14)	58 (14)	53 (13)	0.11
Gender, female%	24	25	20	28	0.44
Race, white%	59	55	64	62	0.23
Ischemic etiology, %	49	47	53	45	0.46
Weight, mean (SD), kg	86 (21)	84 (19)	86 (22)	90 (23)	0.18
Ejection fraction, mean (SD), %	19 (7)	19 (6)	20 (7)	19 (7)	0.58
Hospitalization, median [IQR], days	11 [5, 22]	10 [5, 22]	11.5 [4, 21]	12 [6, 26]	0.76
Systolic BP, mean (SD), mmHg	106 (17)	107 (16)	104 (17)	106 (18)	0.48
Symptom, mean (SD), VAS score (0 is worst)					
Global assessment	42 (22)	44 (20)	40 (24)	40 (24)	0.27
Worst symptom	38 (22)	40 (21)	37 (24)	34 (23)	0.19
Dyspnea	43 (23)	40 (21)	46 (26)	48 (23)	0.01
Laboratory tests					
BUN, mean (SD), mg/dl	35 (23)	32 (22)	38 (24)	39 (21)	0.02
Creatinine, mean (SD), mg/dl	1.5 (0.6)	1.4 (0.6)	1.6 (0.6)	1.7 (0.6)	<0.01
eGFR, mean (SD), mL/min/m ²	60.1 (26.4)	64.5 (26.6)	56.4 (26.8)	53.3 (22.6)	<0.01
Sodium, mean (SD), mEq/dl	136.7 (4.3)	137.0 (4.0)	136.3 (4.5)	135.7 (4.4)	0.02
emoglobin, mean (SD), g/dl	12.6 (1.9)	12.6 (2.0)	12.5 (1.7)	12.7 (1.8)	0.77
BNP, mean (SD), pg/ml	1043 (1351)	984 (1380)	1134 (1483)	1048 (993)	0.70
Oral medication, n (%)					
Loop diuretics	364 (98)	192 (99)	112 (95)	60 (100)	<0.01
ACE-I or ARB	337 (91)	182 (94)	103 (87)	52 (87)	0.05
Beta blockers	222 (60)	110 (57)	74 (63)	38 (63)	0.51

	Worst Symptom				<i>p</i> -value
	All (n=371)	Difficulty Breathing (n=193)	Fatigue (n=118)	Abdominal discomfort or body swelling (n=60)	
Digoxin	272 (73)	150 (78)	77 (65)	45 (75)	0.05
Medical history, n (%)					
Hypertension	177 (48)	95 (49)	55 (47)	27 (45)	0.81
Atrial fibrillation	112 (30)	56 (29)	43 (36)	13 (22)	0.11
Diabetes	117 (32)	56 (29)	37(31)	24 (40)	0.28
COPD	66 (18)	36 (19)	20 (17)	10 (17)	0.90
Depression (treated with medication)	71 (19)	33 (17)	29 (25)	9 (15)	0.18

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR was calculated by MDRD equation.

* Original categories for orthopnea 1; Needs only 1 pillow, 2; Occasional orthopnea with 1 pillow, 3; Needs 2 pillows most of the time, 4; Needs 3 pillows most of the time, 5; Needs 4 pillows most of the time (sitting up).

p<0.016 vs.Difficulty Breathing

TABLE 2

Baseline Physical Examinations

	Worst Symptom			<i>p-value</i>
	Difficulty Breathing (n=193)	Fatigue (n=118)	Abdominal discomfort Or body swelling (n=60)	
Rales > 1/3, %	19	8 [¶]	13	0.02
S3 present, %	61	72	78 [¶]	0.02
JVP > 12cmH ₂ O, %	45	59 [¶]	72 [¶]	<0.01
Hepatomegaly 2fb, %	55	54	73 ^{¶§}	0.03
Peripheral edema > 2+, %	11	11	23	0.04
Ascites, moderate or massive %	12	19	32 [¶]	<0.01

Abbreviations: S3, 3 heart sound; JVP, jugular venous pulsation; fb, finger-breadths.

Original categories for signs and symptoms were as follows: Rales (None, <1/3, 1/3, >2/3), S3 (absent or present), JVP (Cannot measure, <8, 8-12, 12-16, >16cm above the right atrium), Hepatomegaly (Absent, 2-4, >4fb), Peripheral edema (None, 1+, 2+, 3+, 4+), Ascites (None, trace, moderate, massive).

[¶]p<0.016 vs.Difficulty Breathing

[§]p<0.016 vs.Fatigue.

TABLE 3**Hemodynamic Measurements**

Baseline	Worst Symptom			<i>p-value</i>
	Difficulty Breathing (n=97)	Fatigue (n=65)	Abdominal discomfort or body swelling (n=34)	
RAP, mean (SD), mmHg	14 (9)	13 (12)	15 (7)	0.79
PCWP, mean (SD), mmHg	26 (9)	24 (10)	25 (7)	0.58
Cardiac output, mean (SD), L/min	3.8 (1.3)	3.9 (1.4)	4.3 (1.6)	0.27
Cardiac index, mean (SD), L/min/m ²	2.0 (0.6)	2.0 (0.7)	2.1 (0.7)	0.81

PCWP = pulmonary capillary wedge pressure

RAP = right atrial pressure

Changes in Physical and Laboratory Parameters and Symptom VAS Before and After Therapy during Hospitalization

TABLE 4

	All Patients	<i>p</i> -value for change	Worst Symptom			<i>p</i> -value for group difference
			Difficulty Breathing	Fatigue	Abdominal discomfort or Body swelling	
Weight, mean (SD), kg (n=335)	-3.6 (4.9)	<0.01	-3.2 (4.0)	-3.5 (5.6)	-4.9 (6.2)	0.08
Systolic BP, mean (SD), mmHg (n=350)	-4.3 (17.3)	<0.01	-6.5 (16.9)	-1.0 (17.8) [¶]	-3.8 (16.9)	0.03
BUN, mean (SD), mg/dL (n=343)	3.2 (19.4)	<0.01	2.9 (18.9)	0.7 (18.4)	8.0 (20.5)	0.06
Creatinine, mean (SD), mg/dL (n=344)	0.0 (0.5)	0.1	0.1 (0.4)	0.0 (0.5)	0.1 (0.6)	0.14
eGFR, mean (SD), mL/min/m ² (n=344)	-2.4 (16.1)	0.01	-3.6 (17.5)	-1.0 (14.6)	-1.1 (14.1)	0.32
Sodium, mean (SD), mEq/dL (n=345)	-1.5 (4.1)	<0.01	-1.4 (3.9)	-1.4 (4.2)	-2.3 (4.0)	0.34
Hemoglobin, mean (SD), g/dL (n=278)	0.1 (1.6)	0.59	0.2 (1.8)	-0.2 (1.3)	-0.1 (1.3)	0.17
BNP, median [IQR], pg/mL (n=209)	-109 [-444, 18]	<0.01	-90 [-362, 8]	-64 [-444, 51]	-302 [-683, -71]	0.36
BNP, mean (SD), pg/mL (n=209)	-275 (1067)	<0.01	-338 (837)	-127 (1445)	-384 (743)	0.36
JVP > 12cmH ₂ O, % patients with (n=332)	-47	<0.01	-37	-54	-59 [¶]	0.01
Hepatomegaly 2 fb, % (n=339)	-40	<0.01	-37	-37	-44	0.66
Symptom, mean (SD), VAS score						
Global VAS (n=323)	24 (25)	<0.01	24 (23)	23 (25)	31 (29)	0.14
Worst symptom VAS (n=319)	29 (29)	<0.01	31 (25)	24 (32)	33 (34)	0.1

Abbreviations: IQR, interquartile range; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate (eGFR was calculated by MDRD equation); BNP, B-type natriuretic peptide; VAS, Visual analog scale; JVP, jugular venous pulsation; fb, finger-breaths.

[¶] *p*<0.016 vs. Difficulty Breathing

[§] *p*<0.016 vs. Fatigue.