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Evaluation of Novel Metrics of Symptom Relief in Acute Heart Failure: The Worst Symptom Score

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Abstract

Objective—To characterize a novel "worst" symptom visual analogue scale (WS-VAS) versus the traditional dyspnea visual analogue scale (DVAS) in an acute heart failure (AHF) trial.

Background—AHF trials assess symptom relief as a pivotal endpoint using dyspnea scores. However, many AHF patients' worst presenting symptom (WS) may not be dyspnea. We hypothesized that a WS-VAS may reflect clinical improvement better than DVAS in AHF.

Methods—AHF patients (n=232) enrolled in the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) Trial indicated their WS at enrollment and completed DVAS and WS-VAS at enrollment (BL), 24, 48 and 72 hours.

Results—Dyspnea was the WS in 61%, body swelling in 29% and fatigue in 10% of patients. Clinical characteristics differed by WS. In all patients, DVAS scores were higher (less severe symptoms) than WS-VAS and the change in WS-VAS over 72 hours was greater than DVAS (P<0.001). Changes in DVAS were smaller in patients with body swelling and fatigue than in patients with dyspnea as their WS (p=0.002) whereas changes in the WS-VAS were similar regardless of patients' WS. Neither score, nor its change was associated with available decongestion markers (change in N-terminal of the prohormone brain natriuretic peptide [NT-proBNP] or weight or cumulative 72 hour urine volume).

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Discussion—Many AHF patients have symptoms other than dyspnea as their most bothersome symptom. The WS-VAS better reflects symptom improvement across the spectrum of AHF phenotypes. Symptom relief and decongestion were not correlated in this AHF study.

Keywords

Acute Heart Failure; Clinical Trials; Quality of Life

INTRODUCTION

Dyspnea relief is a primary goal of acute heart failure (AHF) therapy,(1) a regulatory benchmark for the approval of novel therapeutic agents and a common endpoint in AHF clinical trials.(2) However, a previous trial of advanced HF patients reported that only 52% of patients cite dyspnea as their most bothersome symptom with the remainder citing fatigue and body swelling instead.(3) In a contemporary AHF trial, we hypothesized that the change in an individual patient's most bothersome symptom may be more closely linked to therapeutic responses than changes in dyspnea alone.

METHODS

Study Design

The Reliable Evaluation of Dyspnea in the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) study (RED-ROSE; ClinicalTrials.gov identifier: NCT01132846) was an ancillary ROSE-AHF study designed to assess novel symptom assessment tools in AHF. ROSE-AHF was performed within the National Heart Lung and Blood Institute (NHLBI)-sponsored Heart Failure Research Network (HFN). Its design and primary results have been published previously.(4) RED-ROSE was approved by the HFN data and safety monitoring board and by each site's institutional review board. Participants provided written informed consent.

Symptom assessment tools

Trained study coordinators used standardized scripts to administer each symptom assessment tool.

Dyspnea visual analogue scale (DVAS)—Patients indicated how their breathing felt "right now" on an analogue scale from 0 (worst possible) to 100 (no breathlessness) throughout the study [baseline (randomization), 24, 48 and 72-hours].

Worst symptom VAS (WS-VAS)—At enrollment, patients indicated their most bothersome symptom (choice of fatigue, body swelling or dyspnea). Patients with swelling or fatigue as their WS completed an additional 100-mm VAS (0, worst; 100, none) for that specific WS throughout the study.

Global well-being VAS (GVAS)—We also administered a global well-being VAS (GVAS) throughout the study where patients ranked their global health status from 0 (worst) to 100 (best).

Decongestion markers

Clinical markers of decongestion included weight change, cumulative urine volume and percent change in NT-proBNP from randomization to 72 hours.

Statistical Analysis

Differences in baseline characteristics and symptom scores between the group with dyspnea as a WS and those with fatigue or those with swelling as their WS was assessed with Wilcoxon rank test for continuous variables or Likelihood Ratio Chi-square for discrete variables. Nonparametric repeated measures test (Friedman) was used to assess whether the DVAS or WS-VAS scores differed over time. The Kruskal-Wallis test was used to analyze for differences in the change in symptom scores across all 3 groups. Subsequently, each of the fatigue and swelling groups were compared to the dyspnea group using the Mann Whitney test. Spearman correlation coefficients were used to examine the correlation between scores. The relationship between changes in scores and markers of clinical decongestion was examined using general linear models adjusting for baseline values of scores and baseline congestion markers. No imputation or carry forward was used to account for missing data. All analyses were conducted with SAS statistical software, version 9.2 or JMP, version 9.

RESULTS

Baseline Characteristics

RED-ROSE commenced after ROSE-AHF had started and enrolled 232 of the 360 ROSE-AHF patients. Baseline characteristics of the RED-ROSE participants were similar to those of the ROSE cohort (Table 1).

In RED-ROSE participants, 141 (61%) reported dyspnea, 24 (10%) fatigue and 67 (29%) body swelling as their WS at enrollment (Table 2). Compared to patients with dyspnea as their WS, those with fatigue were less likely to have been hospitalized for HF in the last year, be treated with renin-angiotensin system (RAS) antagonists, or report orthopnea but were more likely to be in atrial fibrillation. Compared to patients with dyspnea as their WS, those with body swelling were less likely to have been hospitalized for HF in the last year or have rales or orthopnea but were more likely to have severe edema and had worse renal function.

Symptom scores at baseline

At enrollment, the distribution of DVAS scores was slightly skewed towards higher scores while patients were more evenly distributed across the range of possible WS-VAS scores (Figure 1). As compared to patients with dyspnea as their WS, the DVAS was higher (less dyspnea) in patients with fatigue or body swelling as their WS (Table 2). As compared to those with dyspnea or fatigue as their WS, the WS-VAS was lower (more severe) in those with body swelling as their WS (Table 2). The median WS-VAS score was significantly lower (worse) than the DVAS in patients with fatigue (52.0 vs 77.0, $p=0.04$) or body swelling (32.5 vs 74.5, $p<0.001$) as their WS (Table 2).

Change in symptom scores over time

In patients with paired daily assessments (enrollment through 72 hours) of both symptom scores (n=206), both the DVAS and WS-VAS increased over time indicating symptom improvement (Figure 2 A–B). The change in DVAS from enrollment (BL) to 72 hours was lower in patients with body swelling and fatigue as their WS than in patients with dyspnea as their WS (Figure 2 C). The change in WS-VAS from BL to 72 hours was similar regardless of patients' WS (Figure 2 D). Overall, the BL to 72 hour improvement in the WS-VAS [19 (4,41)] was greater than that of the DVAS [13 (0,31); p<0.001] with the majority of improvement in both scores occurring in the first 24 hours compared to subsequent days (Figure 3).

Association of changes in symptom scores with decongestion markers

There were no clinically meaningful associations between changes in DVAS or WS-VAS from BL to 72 hours and extent of decongestion at 72 hours as the model R^2 values were all quite low (< 0.05; Table 3).

Global well-being

The WS-VAS and GVAS (n=206 with both scores at BL and 72 hours) were moderately correlated at BL (r=0.47, p<0.0001) and 72 hours (r=0.69, p<0.0001). The change from BL to 72 hours in the GVAS (18 (3–38)) was similar to that in the WS-VAS (20 (4–41); p=0.20). As with the WS-VAS, changes in the GVAS were similar in patients with dyspnea (20 (6–40)) or other (13 (0–32), p=0.15) symptoms as their WS.

DISCUSSION

Dyspnea assessment tools in AHF

The DVAS is a widely used measure of dyspnea severity in AHF trials and may be more sensitive to modest changes in dyspnea severity than a Likert based score in AHF(5, 6). In RED-ROSE, on average, changes in DVAS scores (16.5 mm) over 72 hours were modest and consistent with other AHF studies assessing dyspnea relief at 6 hours(7), 96 hours(8) or 5 days(6) where changes in DVAS ranged from 14 to 28 mm. The relatively modest improvement in DVAS here and in other AHF studies, despite aggressive therapy, supports the need for alternate measures of symptom relief in AHF.

Symptom specific assessment tools in AHF

In RED-ROSE, 39% of patients identified a symptom other than dyspnea as their WS, similar to findings in the ESCAPE trial of hemodynamic guided therapy on outcomes in advanced HF patients, where half of patients reported fatigue, abdominal discomfort or body swelling rather than dyspnea as their WS. In ESCAPE, patients with WS other than dyspnea also had worse renal function and more physical signs of right sided failure as observed in RED-ROSE. Importantly, in ESCAPE, hemodynamic profiles (cardiac index, pulmonary capillary wedge pressure and right atrial pressure) were similar across WS groups(3). While invasive hemodynamics were not assessed in RED-ROSE, together, these studies suggest that the hemodynamic perturbations associated with AHF and targeted in AHF therapy are

perceived differently by patients, potentially due to differences in the interplay of age, HF, comorbid conditions and affective conditions or simply differences in the perception or interpretation of physical limitations.(9, 10)

In RED-ROSE, the WS-VAS showed greater change over 72 hours than the DVAS and in contrast to the DVAS, changes were similar regardless of WS. Recognizing that distinct symptom clusters exist in AHF(10), some studies have utilized a global well-being scale to assess overall health status in AHF.(6, 11, 12) Here and in ESCAPE,(3, 12) changes in the GVAS correlated with changes in WS-VAS. These findings suggest that the WS-VAS or GVAS are more sensitive to symptom improvement than dyspnea focused symptom assessments across the spectrum of AHF phenotypes. Despite the correlation between the WS-VAS and GVAS, they may not provide similar information as GVAS may be more sensitive to affect and comorbid conditions whereas the WS-VAS assesses a single, HF related symptom which may be specifically impacted by AHF treatment.

Symptom relief and decongestion

In RED-ROSE, neither DVAS nor WS-VAS change at 72 hours were meaningfully correlated with changes in markers of decongestion. Our findings do not provide evidence that the use of the WS-VAS greatly strengthens the relationship between symptom relief and decongestion. Regardless of WS, the lack of correlation between extent of decongestion and symptom improvement may reflect the fact neither fluid output nor weight change were scaled to an assessment of the goal fluid or weight loss and thus, are only rough (but widely used) markers of decongestion. Further, symptom relief may require only a threshold degree of fluid loss as the greatest change in symptom severity occurred in the first 24 hours. Finally, symptom improvement may be affected by other therapeutic measures not impacting decongestion markers.

Limitations

Exclusion of AHF patients without significant renal dysfunction may have affected our findings. Patients were enrolled up to 24 hours after presentation and dyspnea may have been more severe prior to enrollment with change from presentation to enrollment not captured. Patients may have different symptoms that are most bothersome to them at different time points. Females were underrepresented in this cohort.

Conclusion

Approximately 40% of AHF patients have symptoms other than dyspnea as their most bothersome symptom. Worst symptom specific scores appear more sensitive than dyspnea specific scores to clinical improvement across the spectrum of AHF phenotypes. Symptom relief is poorly correlated to widely used markers of decongestion efficacy. Additional prospective studies are needed to support the use of the worse symptom score as a novel metric of symptom relief in AHF.

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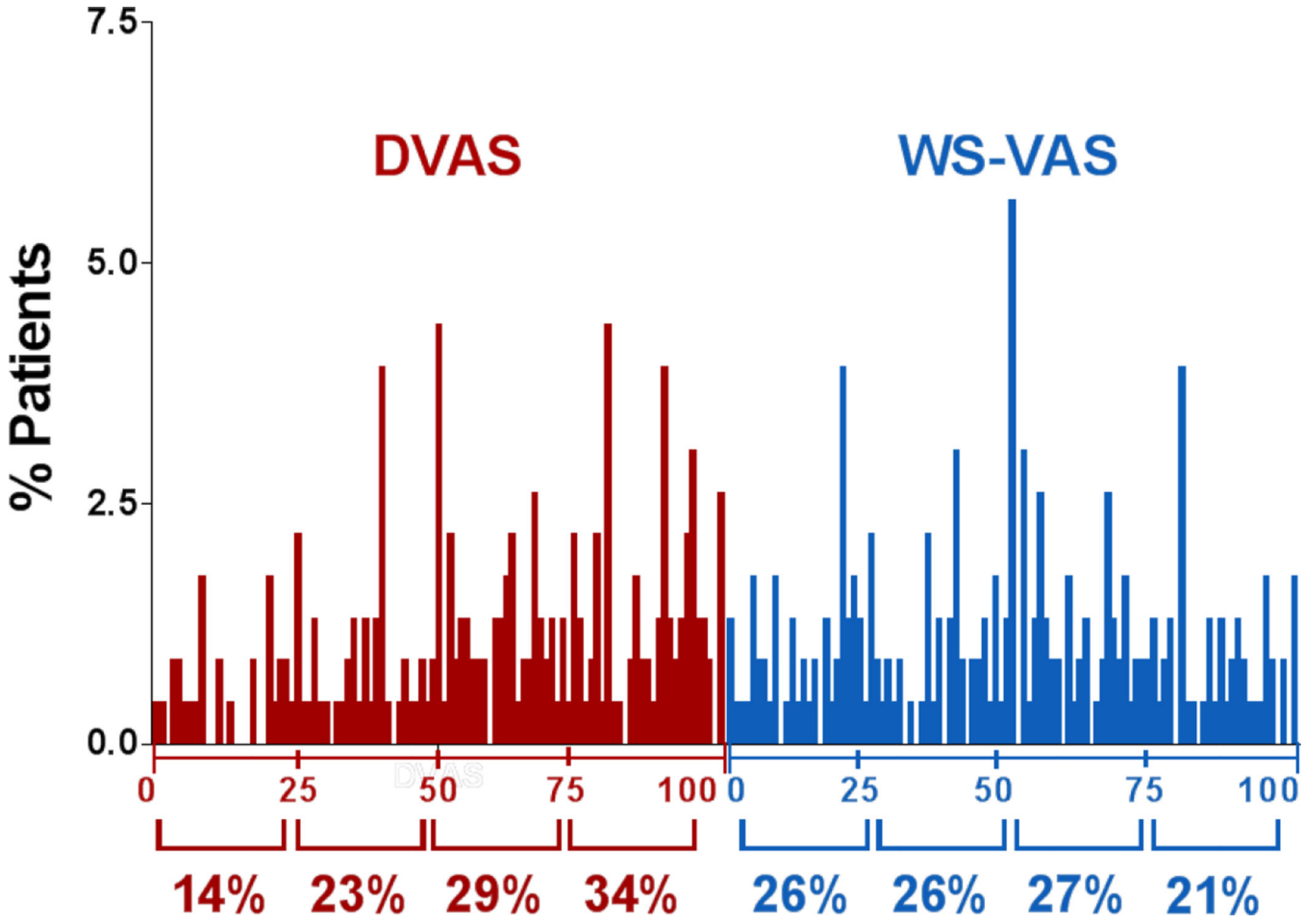

Figure 1. Distribution of symptom scores at enrollment

The frequency distribution of the dyspnea visual analogue scale (DVAS: n= 230), or worst symptom visual analogue scale (WS-VAS; n=230) are shown per quartile of each scale. Patients were more evenly distributed across the range of possible WS-VAS scores compared to DVAS scores.

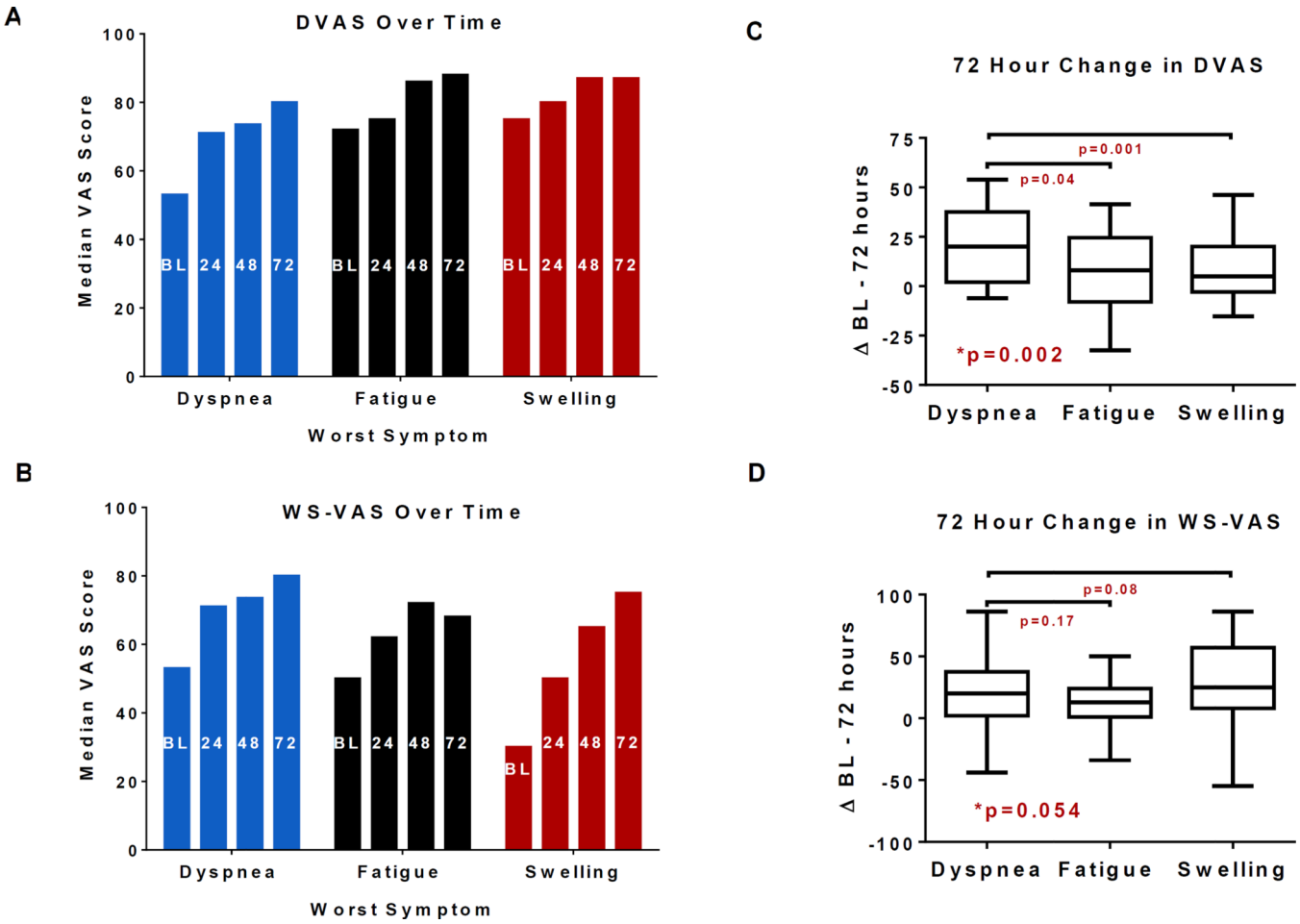

Figure 2. Symptom scores over time

Median dyspnea visual analogue scale (DVAS: A), or worst symptom visual analogue scale (WS-VAS; B) at enrollment (BL) through 72 hours. Both scores increased over time within each WS group ($p<0.0001$ for all). Median (IQR) for changes in DVAS (C) or WS-VAS (D) from BL to 72 hours according to the self-identified worst symptom (dyspnea, fatigue or body swelling); *p: overall Kruskal-Wallis test. The p values for comparison between patients with fatigue or with body swelling versus those with dyspnea (Mann Whitney test) are shown.

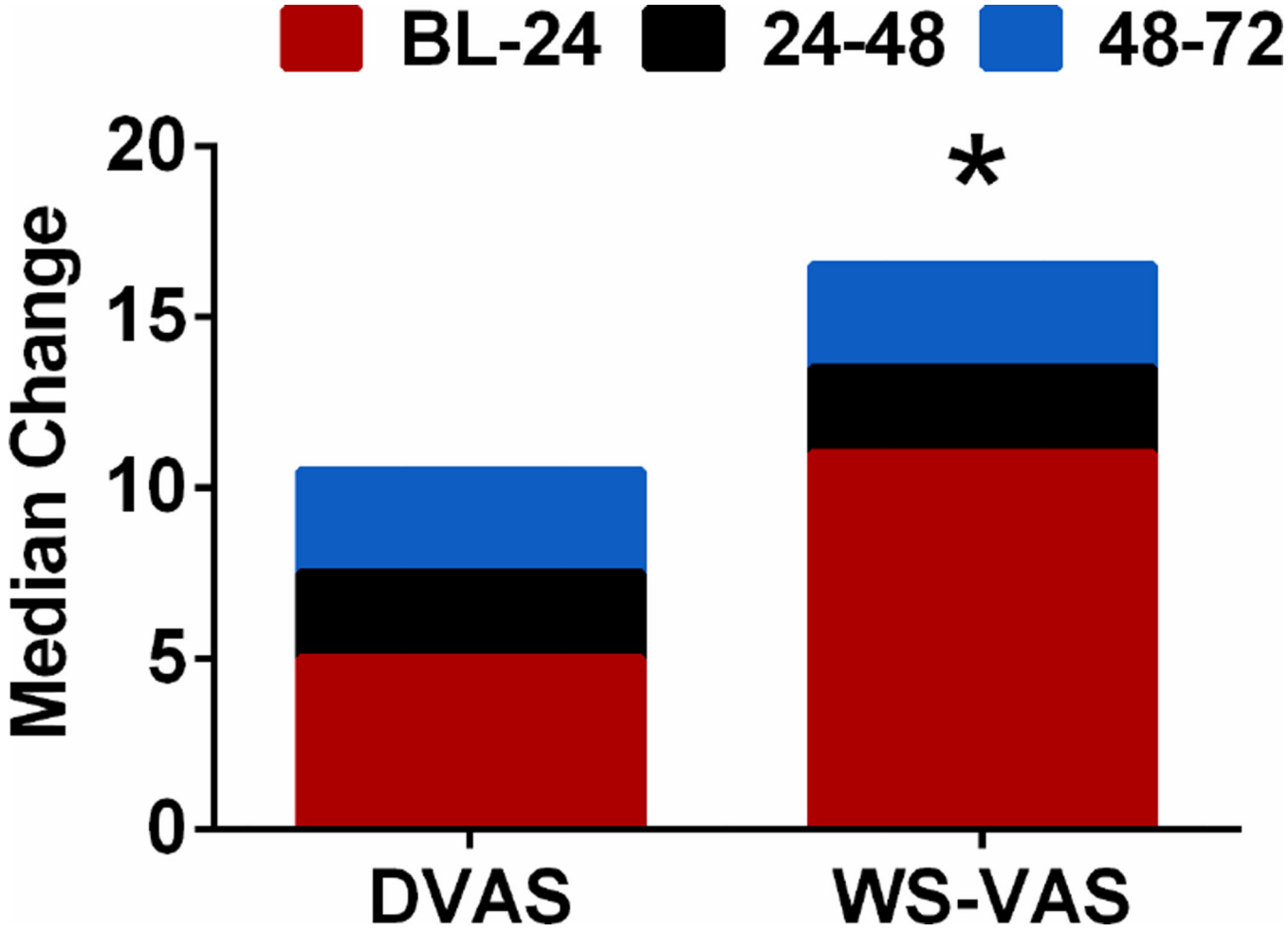

Figure 3. Changes in symptom scores over time

Median change in dyspnea visual analogue scale (DVAS), or worst symptom visual analogue scale (WS-VAS) from BL to 72hrs in 24 hour increments. * $p<0.001$ vs DVAS

Table 1

Baseline characteristics of RED-ROSE cohort versus ROSE cohort

Characteristic	RED-ROSE (N=232)	ROSE (N=360)
Age, years	69 (62–79)	70 (62–79)
Male sex	159 (69%)	264 (73%)
White race	166 (72%)	272 (76%)
HF hospitalization	143 (62%)	240 (67%)
Ejection fraction, %	35 (23–54)	34 (21–53)
Ejection fraction ≥ 50%	76 (33%)	94 (26%)
Hypertension	195 (84%)	298 (83%)
Diabetes	127 (55%)	200 (56%)
Stroke	21 (9%)	31 (9%)
Atrial fibrillation	135 (58%)	215 (60%)
COPD	59 (25%)	95 (26%)
Medications		
Loop diuretic	215 (93%)	340 (94%)
ACE or ARB	112 (48%)	179 (50%)
Hydralazine	52 (22%)	68 (19%)
Nitrates	60 (26%)	90 (25%)
Beta blocker	196 (84%)	300 (83%)
Aldosterone antagonist	68 (29%)	109 (30%)
Digoxin	53 (23%)	89 (25%)
Clinical Examination		
Heart rate (bpm)	74 (66–85)	74 (65–85)
Systolic BP, mmHg	116 (104–129)	114 (103–127)
Body mass index, Kg/m^2	31 (27–37)	31 (27–37)
JVP ≥ 8 cm,	212 (95%)	327 (95%)
Rales	122 (54%)	197 (56%)
Edema ≥ 2+/4+	159 (69%)	251 (70%)
Orthopnea	193 (88%)	307 (90%)
Laboratory data		
Hemoglobin, g/dL	11.5 (10.4–12.8)	11.4 (10.3–12.7)
eGFR, $mL/min/1.73m^2$	45 (33–56)	42 (32–53)
NT Pro-BNP, pg/mL	5055 (2358–10348)	5323 (2420–10797)

Table 2

Baseline Characteristics of RED-ROSE cohort

	WORST REPORTED SYMPTOM			
Characteristic	**All (N=232)**	**Dyspnea (N=141)**	**Fatigue (N=24)**	**Body Swelling (N=67)**
Age, years	69 (62–79)	68 (60–75)	71 (62–82)	72 (62–82)
Male sex	159 (69%)	96 (68%)	17 (71%)	46 (69%)
White race	166 (72%)	98 (70%)	18 (75%)	50 (75%)
HF hospitalization	143 (62%)	93 (67%)	13 (54%) *	37 (55%) *
Ejection fraction, %	35 (23–54)	33 (23–52)	43 (18–55)	38 (23–53)
Ejection fraction ≥ 50%	76 (33%)	42 (30%)	10 (42%)	24 (36%)
Hypertension	195 (84%)	120 (85%)	19 (79%)	56 (84%)
Diabetes	127 (55%)	80 (57%)	14 (58%)	33 (49%)
Stroke	21 (9%)	10 (7%)	4 (17%)	7 (10%)
Atrial fibrillation	135 (58%)	74 (52%)	18 (75%) *	43 (64%)
COPD	59 (25%)	41 (29%)	3 (13%)	15 (22%)
Medications				
Loop diuretic	215 (93%)	128 (91%)	24 (100%)	63 (94%)
ACE or ARB	112 (48%)	74 (52%)	6 (25%) *	32 (48%)
Hydralazine	52 (22%)	30 (21%)	6 (25%)	16 (24%)
Nitrates	60 (26%)	39 (28%)	5 (21%)	16 (24%)
Beta blocker	196 (84%)	120 (85%)	22 (92%)	54 (81%)
Aldosterone antagonist	68 (29%)	44 (31%)	6 (25%)	18 (27%)
Digoxin	53 (23%)	29 (21%)	8 (33%)	16 (24%)
Clinical Examination				
Heart rate (bpm)	74 (66–85)	76 (68–85)	72 (66–81)	71 (63–85)
Systolic BP, mmHg	116 (104–129)	117 (106–127)	114 (106–124)	114 (100–132)
Body mass index, Kg/m^2	31 (27–37)	31 (28–37)	29 (25–37)	31 (27–37)
JVP ≥ 8 cm, (n=224)	212 (95%)	125 (93%)	24 (100%)	63 (97%)
Rales (n=227)	122 (54%)	81 (59%)	12 (52%)	29 (46%) *
Edema ≥ 2+/4+ (n=229)	159 (69%)	89 (64%)	18 (75%)	52 (79%) *
Orthopnea, (n=219)	193 (88%)	126 (95%)	20 (87%) *	47 (75%) *
Laboratory data				
Hemoglobin, g/dL	11.5 (10.4–12.8)	11.8 (10.4–12.9)	11.4 (10.7–12.6)	11.2 (10.3–12.6)
eGFR, $mL/min/1.73m^2$	45 (33–56)	45 (35–57)	48 (33–57)	42 (30–51) *
NT Pro-BNP, pg/mL	5055 (2358–10348)	5109 (2371–9516)	4269 (2223–12402)	5268 (2905–11888)
Baseline Symptom Scores				
Dyspnea VAS	62.5 (40.0–82.0)	54.0 (35.0–75.0)	77.0 (54.0–92.0) *	74.5 (50.0–90.0) *

	WORST REPORTED SYMPTOM			
Characteristic	**All (N=232)**	**Dyspnea (N=141)**	**Fatigue (N=24)**	**Body Swelling (N=67)**
WS-VAS	50.0 (25.0–71.0)	54.0 (35.0–75.0)	52.0 (47.0–80.0)	32.5 (18.0–56.0) *†

Data are number (%) or median (interquartile range).

* p<0.05 vs dyspnea as worse symptom,

† p <0.05 vs fatigue as worst symptom for “Baseline Symptom Scores” analysis only.

Abbreviations:
ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker; BP, Blood Pressure; COPD, Chronic Obstructive Pulmonary Disease; eGFR, Estimated Glomerular Filtration Rate; HF, Heart Failure; JVP, Jugular Venous Pressure; NT Pro-BNP, N-terminal pro-brain natriuretic peptide

Table 3

Association between changes in symptom scores and extent of decongestion.

	Cumulative Urine Volume (BL to 72 Hours)			Weight Change (BL to 72 Hours)			Percent Change in NT-proBNP (BL to 72 Hours)		
	Model R^2	Parameter Estimate (CI) ml	P value	Model R^2	Parameter Estimate (CI) lbs	P value	Model R^2	Parameter Estimate (CI) %	P value
Change DVAS (BL to 72 Hours)	0.04	29 (9 – 50)	0.005	0.02	−0.05 (−0.10 – 0.004)	0.07	0.01	−0.23 (−0.50 − 0.04)	0.10
Change WS-VAS (BL to 72 Hours)	0.02	17 (−3 – 36)	0.09	0.02	−0.04 (−0.09 – 0.01)	0.13	0.02	−0.35 (−0.70 − 0.00)	0.05

Linear regression model adjusts for baseline symptom score value and when appropriate, for baseline value of the congestion marker (weight and NT-proBNP level).