Implications of Perceived Dyspnea and Global Well-Being Measured by Visual Assessment Scales During Treatment for Acute Decompensated Heart Failure

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Symptomatic improvement through decongestive therapy is a cornerstone for treatment of acute decompensated heart failure (ADHF). Visual analog scales (VAS) are instruments that can capture patients' perceptions of dyspnea (DVAS) or global well-being (GVAS). However, the clinical implications of these instruments and their changes over time during treatment for ADHF need further clarification. DVAS and GVAS were collected in 657 patients randomized in the DOSE-AHF and ROSE-AHF trials. To determine factors associated with symptom change, multivariable predictors of changes in DVAS and GVAS over 72 hours were determined. In addition, time-to-event analyses determined the association between these assessments and post-discharge clinical outcomes. The median baseline DVAS and GVAS scores were 54 (interquartile range 35 to 76) and 50 (30 to 66), respectively. These scores increased from baseline to 72 hours (ΔDVAS 16 [0 to 35] and ΔGVAS 19 [2 to 37]). Although changes in both scales were associated with their baseline values, 72-hour change in NT-proBNP was associated with each scale in multivariable analysis. However, there were additional variables associated with 72-hour change in GVAS including 72-hour change in creatinine, implantable cardioverter-defibrillator presence, baseline loop diuretic dose, and 72-hour total loop diuretic dose. There were no consistent associations between DVAS or GVAS and clinical composite outcomes at 60 days. In conclusion, DVAS and GVAS may be related to different clinical factors during treatment for ADHF and VAS scores were not consistently associated with clinical outcomes in ADHF. These findings inform the utility of the DVAS and GVAS instruments as measurements of symptom change for future ADHF clinical trials and registries. **(Am J Cardiol 2019;124:402−408)**

Despite adequate decongestion, life-limiting dyspnea and reductions in global well-being frequently persist for patients with ADHF.[1,2] In an era of increasing patient-centered care, dyspnea and global well-being are important therapeutic targets for patients and improvement of dyspnea has been associated with more favorable thirty-day outcomes.[3] There are several instruments used to quantify dyspnea and patient global well-being in heart failure. One such instrument is the visual analog scale (VAS). VAS assessments allow for precise continuous measurements of patient-reported symptoms and have been collected as clinical end points to determine therapeutic efficacy in clinical trials for ADHF.[2,4,5] We hypothesized that symptomatic improvement in patient-reported dyspnea and global well-being as measured by VAS may be associated with factors beyond net fluid loss. We analyzed data from the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF) and the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) datasets to determine variables associated with symptomatic improvement as measured by the dyspnea visual analog scale (DVAS) and global well-being visual analog scale (GVAS) during treatment for ADHF. As a secondary aim we also sought to determine the prognostic implications of DVAS and GVAS measurements.

Methods

The DOSE-AHF and ROSE-AHF trials were conducted within the National Heart, Lung, and Blood Institute National Institute of Health-sponsored Heart Failure Clinical Research Network. All patients provided written consent for their respective studies and the protocols were approved by the institutional review board at each site. This study complies with the Declaration of Helsinki. This manuscript was prepared using research materials obtained from the National Institutes of Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center via an approved proposal.

The DOSE-AHF and ROSE-AHF study designs have both been previously described.[2,6] Briefly, the DOSE-AHF trial evaluated the effectiveness of diuretic dosing strategies. In DOSE-AHF, 308 patients were enrolled during a hospitalization for ADHF with at least 1 clinical symptom (dyspnea, orthopnea, or edema) and clinical sign of heart

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failure (rales, ascites, peripheral edema, or pulmonary vascular congestion on chest radiography).[2] Participants were randomized in a 2 × 2 factorial design to a continuous infusion (n = 152), intermittent 12-hour dosing (n = 156), high-dose (n = 157), and low-dose (n = 151) intravenous loop diuretics.[2] Patients requiring intravenous vasodilators, intravenous inotropes, a systolic blood pressure of less than 90 mm Hg or a serum creatinine level greater than 3.0 mg/dl were excluded.[2]

The ROSE-AHF study enrolled 360 patients with renal dysfunction (glomerular filtration rate of 15 to 60 ml/min/1.73 m^2) during hospitalization for ADHF with at least 1 clinical symptom (dyspnea, orthopnea, or edema) and 1 physical finding of heart failure (rales, edema, ascites, or pulmonary vascular congestion on chest radiography).[6] Patients were randomized in a double-blinded placebo-controlled fashion to dopamine 2 μg/kg/min (n = 122), nesiritide 0.005 μg/kg/min (n = 119), or placebo (n = 119) and standard care for 72 hours.[6] Exclusion criteria included need for dialysis or ultrafiltration, a systolic blood pressure of less than 90 mm Hg, intravenous vasodilators, and intravenous inotropes.[6]

Both dyspnea and global well-being were serially assessed by 2 VAS instruments: DVAS and GVAS as part of the DOSE-AHF and ROSE-AHF protocols. These assessments were conducted by study personnel at the study sites. Participants with baseline DVAS and GVAS measurements were included in this analysis (n = 657). The analyses were only conducted on a complete-case basis and missingness was assumed to be at random. In order to harmonize these 2 studies, we analyzed VAS scores at baseline, 24, 48, and 72 hours.[2,6] The composite 60-day outcomes were death, all-cause hospitalization, and unscheduled emergency room visits and death or heart failure hospitalization for DOSE-AHF and ROSE-AHF, respectively.

Continuous variables were presented as median and interquartile range, and categorical variables were presented as a number and percentage. Tertiles were generated for baseline DVAS and GVAS scores. Mixed effects models assuming unequal variance were constructed to determine the association between baseline VAS tertiles and serial 24-hour VAS assessments from baseline through 72 hours. Two backwards-elimination linear regression algorithms (p entry 0.05 and p retention 0.1) with 200 bootstrap replications determined the multivariable predictors of 72-hour changes in DVAS and GVAS, respectively. There were 36 candidate variables which included trial assignment, clinical characteristics, demographics, laboratory values, and markers of treatment response and cardiorenal response during 72 hours (Supplementary Appendix Table 1). If needed, variables were transformed accordingly. Spearman correlation coefficients tested the correlations between categorical and continuous variables.

Because DOSE-AHF and ROSE-AHF collected different 60-day composite outcomes, time-to-event analyses were separated by trial. The cumulative incidence of each composite end point was determined by the Kaplan-Meier method and differences in failure curves according to trial-specific baseline VAS tertiles were compared by the log-rank test. Cox proportional hazards models tested the associations for trial-specific baseline VAS and 72-hour VAS changes for the trial-specific 60-day composite end points. Multivariable models were adjusted for the baseline VAS value and additionally adjusted for variables in 2 sequential models: Model 1 included age and gender, and Model 2 included the variables in Model 1 and race, blood urea nitrogen, jugular venous pressure >12 cm, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use. The proportional hazards assumption was validated if there were no trends with time for the scaled Schoenfeld residuals. Two-side p values <0.05 were considered statistically significant. All analyses were performed with the use of Stata software, version 15.1 (StataCorp, College Station, Texas).

Results

In the study cohort, there were 657 patients with available VAS data. For DVAS, the median baseline score was 54 (30 to 66) with a median 72-hour change of 16 (0 to 35). For GVAS, the median baseline score was 50 (30 to 66) with a median 72-hour change of 19 (2 to 37). The 72-hour changes in DVAS and GVAS were modestly correlated (Spearman rho 0.49, p <0.001).

The baseline characteristics and their correlations to 72-hour change in DVAS and GVAS are shown in Table 1. The 72-hour change DVAS was negatively correlated with age, baseline DVAS and GVAS, jugular venous pressure >12 cm, blood urea nitrogen, creatinine, and angiotensin-converting enzyme inhibitor use. The 72-hour change in GVAS was negatively correlated with age, baseline DVAS and GVAS, and angiotensin-converting enzyme inhibitor use. Interestingly, neither 72-hour changes in DVAS nor 72-hour changes in GVAS were correlated with left ventricular ejection fraction or baseline NT-proBNP.

Baseline DVAS scores were divided into tertiles with serial reassessment at 24, 48, and 72 hours (Figure 1). The baseline DVAS tertile was significantly associated with serial DVAS measurements (p <0.001) and the slope of DVAS over time (p <0.001). Baseline GVAS scores were divided into tertiles with serial reassessment at 24, 48, and 72 hours (Figure 1). The baseline GVAS tertile was also significantly associated with serial GVAS measurements (p <0.001) and the slope of GVAS over time (p <0.001).

Only 2 of the 36 candidate variables (Supplemental Table 1) that were entered into the backwards selection algorithm for 72-hour change in DVAS were retained in the final model. These included baseline DVAS score and 72-hour change in NT-proBNP (Table 2). Interestingly, the other 34 variables, including 72-hour change in weight (a surrogate for net fluid loss), were not associated with 72-hour change in DVAS. In contrast, 6 of 36 candidate variables that were entered into the backwards selection algorithm for 72-hour change in GVAS were retained in the final model. These included baseline GVAS, 72-hour change in NT-proBNP, 72-hour change in creatinine, implantable cardioverter-defibrillator presence, baseline loop diuretic dose, and 72-hour total loop diuretic dose (Table 2). Similar to DVAS, 72-hour change in weight was not associated with 72-hour change in GVAS.

Table 1
Baseline characteristics and their correlation with change in dyspnea and global well-being visual analog scale assessments from baseline to 72 hours

Variable	Baseline	Spearman's rho for 72-hour change in DVAS	p Value	Spearman's rho for 72-hour change in GVAS	p Value
Age (years)	69 (60-78)	−0.147	0.001	−0.142	0.001
Male	482 (74%)	0.026	0.550	0.000	1.000
White	482 (74%)	−0.136	0.001	−0.044	0.303
Dyspnea visual analog scale	54 (35-76)	−0.629	<0.001	−0.2264	<0.001
Global well-being visual analog scale	50 (30-66)	−0.259	<0.001	−0.584	<0.001
Chronic obstructive pulmonary disorder	167 (26%)	−0.018	0.675	−0.030	0.491
Ever smoker	223 (34%)	0.083	0.053	0.013	0.765
Gout	184 (28%)	−0.033	0.441	−0.021	0.627
Hyperlipidemia	482 (74%)	0.026	0.539	0.012	0.773
Implantable cardioverter-defibrillator	270 (41%)	−0.080	0.062	−0.059	0.168
Stroke	65 (10%)	−0.004	0.933	−0.011	0.790
Left ventricular ejection fraction (%)	30 (20-50)	−0.060	0.166	−0.031	0.471
Jugular venous pressure >12 cm	448 (69%)	−0.085	0.046	−0.077	0.071
Peripheral edema	484 (74%)	−0.049	0.250	−0.014	0.753
Rales	555 (85%)	0.018	0.679	−0.036	0.401
Albumin (g/dl)	3.5 (3.1-3.9)	−0.074	0.151	−0.023	0.652
Blood urea nitrogen (mg/dl)	34 (24-50)	−0.172	<0.001	−0.056	0.195
Creatinine (mg/dl)	1.55 (1.20-1.93)	−0.169	<0.001	−0.063	0.145
N-terminal pro-brain natriuretic peptide (pg/ml)	4653 (2371-10120)	−0.058	0.180	−0.033	0.445
Red blood cell distribution width (%)	16 (15-18)	−0.056	0.197	−0.060	0.168
Sodium (mmol/L)	139 (136-141)	−0.035	0.418	−0.016	0.712
Angiotensin-converting enzyme inhibitor	257 (39%)	0.095	0.026	0.144	0.001
Angiotensin receptor blocker	117 (18%)	−0.013	0.762	−0.063	0.140
Antidepressant	158 (24%)	−0.056	0.191	0.026	0.542
Beta-blocker	545 (83%)	0.022	0.607	0.038	0.370
Digoxin	174 (27%)	−0.010	0.812	0.038	0.377
Furosemide dose (mg)	120 (80-160)	0.025	0.571	0.018	0.677
Hydralazine	118 (18%)	0.005	0.902	−0.044	0.308
Mineralocorticoid receptor antagonist	188 (29%)	−0.034	0.433	−0.016	0.704
Nitrates	179 (27%)	−0.016	0.703	−0.036	0.400

Baseline values are presented as median (twenty-fifth to seventy-fifth percentile) for continuous variables and number (%) for categorical variables.

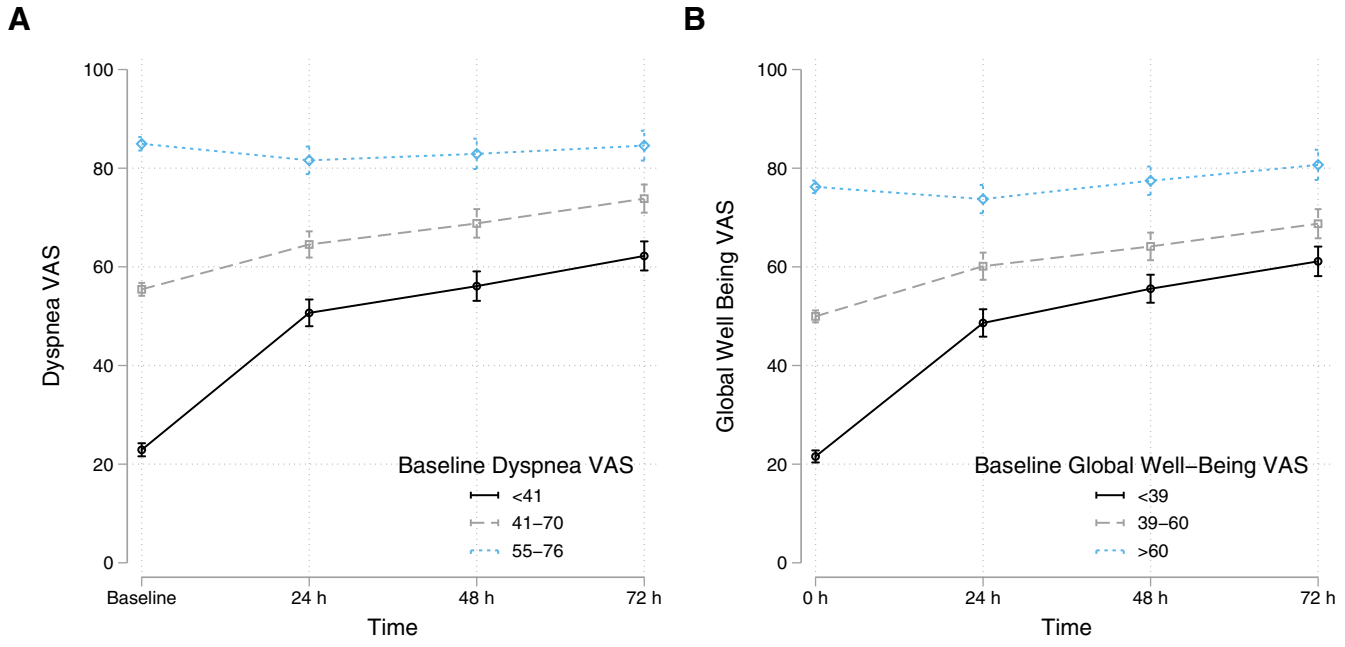

Figure 1. Relationship of serial DVAS and GVAS assessments by baseline level over 72 hours. Serial values of DVAS *(A)* and GVAS *(B)* by baseline tertile over 72 hours. VAS = visual analog scale.

Table 2
Multivariable predictors of changes in VAS scores from baseline to 72 hours

Visual assessment instrument	Predictors	Beta*	p Value
Δ 72-hour DVAS	Baseline DVAS score	−0.63 per 10 baseline DVAS units	<0.001
	Δ 72-hour NT-proBNP	−0.23 per 20% change	<0.001
Δ 72-hour GVAS	Baseline GVAS	−0.65 per 10 baseline GVAS units	0.001
	Δ 72-hour creatinine	−1.0 per mg/dL	0.001
	ICD presence	−0.8 per ICD	0.001
	Δ 72-hour NT-proBNP	−0.22 per 20% change	0.001
	Baseline loop diuretic dose	−0.44 per doubling 40 mg furosemide equivalents	0.001
	72-hour total loop diuretic	0.6 per doubling of 40 mg furosemide equivalent	0.002

Abbreviations: DVAS = dyspnea visual analog scale; GVAS = global well-being visual analog scale; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-brain natriuretic peptide; VAS = visual analog scale.
* Represents a 10-unit change in Δ 72-hour DVAS or GVAS per the displayed change in predictor.

For the study cohort, there were 129 events for death, hospitalization or emergency room visits by 60 days for DOSE-AHF (0.01 events/day, 95% confidence interval [CI] 0.009 to 0.012) and 81 events for death or heart failure hospitalization by 60 days for ROSE-AHF (0.004 events/day, 95% CI 0.0036 to 0.006). Kaplan-Meier estimates for the cumulative incidence of the DOSE-AHF composite end point according to trial-specific baseline DVAS and GVAS tertiles were not different (p >0.6 for both; Figure 2). Similarly, Kaplan-Meier estimates for the cumulative incidence of the ROSE-AHF composite end point according to trial-specific baseline DVAS and GVAS tertiles were also not different (p >0.2 for both; Figure 2).

The results of the Cox proportional hazards models testing the association between baseline DVAS, baseline GVAS, 72-hour changes in DVAS and GVAS, and 60-day composite outcomes for DOSE-AHF and ROSE-AHF are shown in Table 3 and 4, respectively. Neither baseline DVAS, baseline GVAS, 72-hour change in DVAS, or 72-hour change in GVAS were associated with the DOSE-AHF composite clinical end points (p >0.05 for all). Although there was no association between baseline DVAS, baseline GVAS or 72-hour change in DVAS, and the ROSE-AHF composite end point, the 72-hour change in GVAS was associated with the ROSE-AHF composite end point. In both unadjusted and adjusted analysis, baseline higher baseline GVAS (per 10-unit increase) was associated with a ∼16% lower risk in the ROSE-AHF composite end point (hazard ratio 0.84, 95% CI 0.76 to 0.94, p <0.001).

Discussion

Several key observations from this analysis clarify our interpretation and the clinical utility of DVAS and GVAS assessments during treatment for ADHF. First, patients with lower baseline DVAS and GVAS scores are more likely to have increases in VAS scores than patients with higher baseline DVAS and GVAS. This observation may arise in part from regression to the mean or a ceiling effect (top tertile) and floor effect (bottom tertile), but remains insightful for the clinical application of VAS in ADHF. Second, multivariable predictors of 72-hour changes in VAS included the baseline VAS score and 72-hour change in NT-proBNP; however, there were additional multivariable predictors of 72-hour changes in GVAS supporting the hypothesis that different factors influence global well-being. Third, changes in DVAS and GVAS within 72 hours were not consistently associated with adverse clinical outcomes at 60 days.

Assessments of patient-derived outcomes are common clinical end points in trials assessing the efficacy of therapies for ADHF. The VAS instrument allows for an easily administered, low cost, precise, and serial symptom assessment. In particular, VAS is used to track symptom assessments for dyspnea and global well-being in ADHF clinical trials.[4,7]

Our findings are consistent with previous observations from the Measures of Disease Severity in Acute Heart Failure, Recombinant Human Relaxin-2 for Treatment of Acute Heart Failure, and Ularitide Global Evaluation in ADHF studies[4,8,9] that the majority of patients admitted for ADHF have improvements of DVAS and GVAS within the first 24 hours of treatment.[1,4] Mebazaa et al evaluated 524 patients with contemporary treatment for ADHF that were enrolled within 1 hour of presentation and had serial symptom assessments at baseline and 6 hours.[8] Like our present results, patients with more baseline dyspnea by VAS or Likert scales had the largest magnitude of improvement within a few hours of treatment.[8] There may be some similarity to DVAS since the largest magnitude of GVAS increase may occur within the first 24 hours.[10] Our study extends these previous observations suggesting that changes in GVAS may parallel those to DVAS during treatment for ADHF. However, despite contemporary treatment for ADHF, many patients experience persistent symptoms regardless of baseline VAS, with minimal changes in DVAS or GVAS, suggesting that treatment for ADHF translates to a partial symptomatic resolution.[9,11]

Changes in NT-proBNP levels were associated with changes in DVAS and GVAS; however, these associations were independent of weight loss during treatment for ADHF. It is well established that acute changes in NT-proBNP are associated with increased cardiac myocyte wall stress and dyspnea during presentations for ADHF,[12,13] but changes in natriuretic peptide levels have not been consistently associated with measurements of decongestion.[14] Results from previous studies demonstrated inconsistent associations between changes in dyspnea and other signs of congestion such as jugular venous pressure,

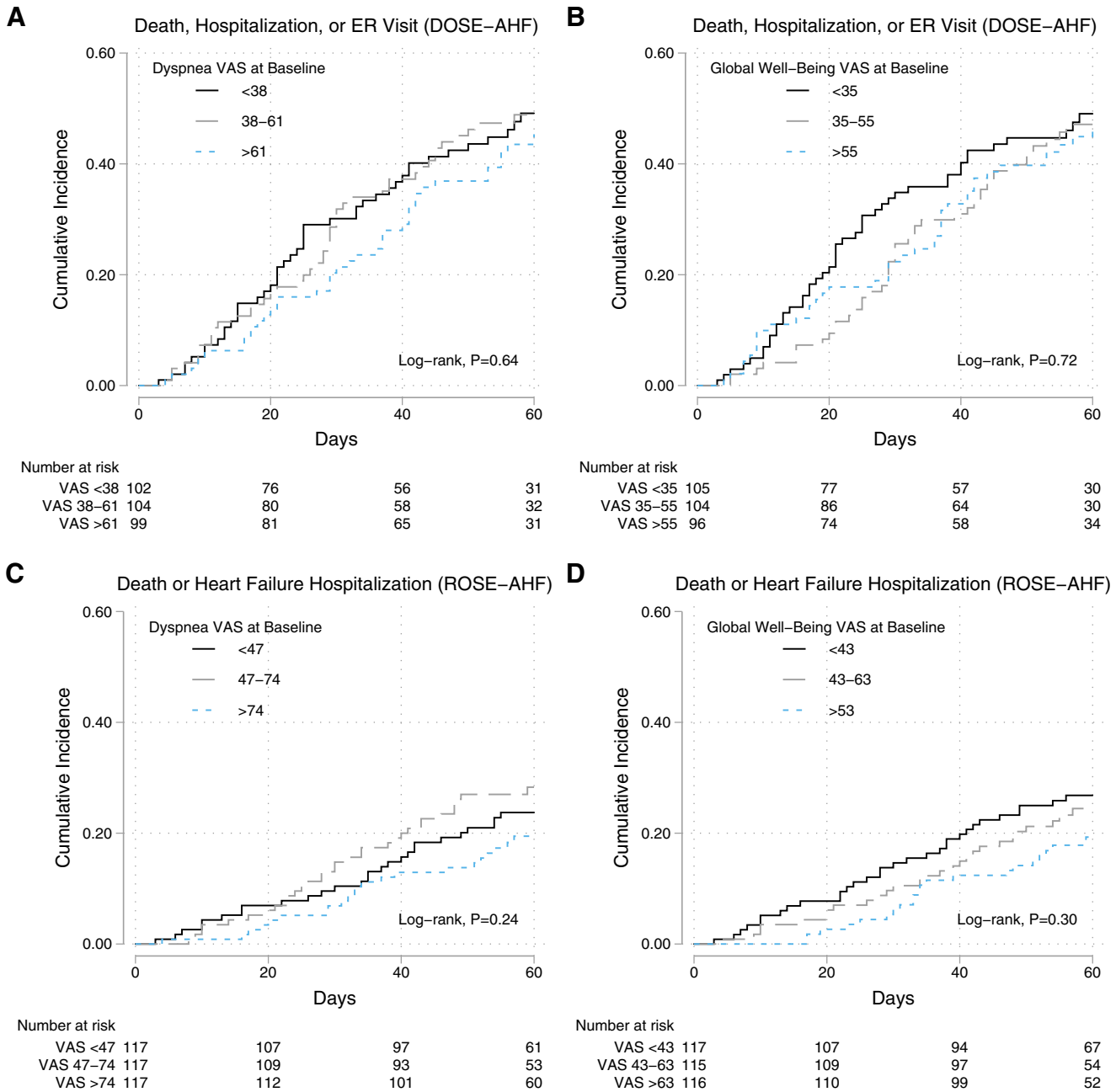

Figure 2. Kaplan-Meier estimates of 60-day clinical outcomes according to baseline DVAS and GVAS. Sixty-day cumulative incidence of death, hospitalization or emergency room visit in DOSE-AHF by baseline dyspnea *(A)* and global well-being VAS tertile *(B)*, respectively. Sixty-day cumulative incidence of death or heart failure hospitalization in ROSE-AHF by baseline dyspnea *(C)* and global well-being VAS tertile *(D)*, respectively. DOSE-AHF = diuretic optimization strategies evaluation in acute heart failure; ROSE-AHF = renal optimization strategies evaluation in acute heart failure; VAS = visual analog scale.

presence of rales, or weight changes.[9,15] Unlike changes in DVAS, changes in GVAS were associated with clinical factors such as disease severity (implantable cardioverter defibrillator presence) and cardiorenal characteristics (creatinine, loop diuretics dose, and 72-hour loop diuretics dose). This observation suggests that perceived global well-being may be reliant on different factors from dyspnea and that global well-being may be more reflective of cardiorenal co-morbidity.

Improvement in patient-symptom perception has not been consistently associated with parallel improvement in clinical outcomes.[2,16,17] Results from the Pre-Relaxin-2 for Treatment of Acute Heart Failure study cohort suggested an association between 5-day DVAS area under the curve and all-cause mortality at 30 and 60 days; however, symptomatic improvement within 24 hours by DVAS did not appear to be associated with clinical outcomes at 30, 60, or 180 days.[9] Findings from a post hoc analysis of the

Table 3
Cox proportional hazard models for the association of DVAS and GVAS with the cumulative incidence of death, hospitalization or ER visit within 60 days in DOSE-AHF

Exposure of interest	Model*	Incidence	HR**	95% CI	p Value
Baseline DVAS	Unadjusted	n/N = 129/305	0.97	0.91-1.03	0.35
	Model 1	n/N = 129/305	0.97	0.91-1.04	0.37
	Model 2	n/N = 129/305	0.97	0.91-1.03	0.28
Baseline GVAS	Unadjusted	n/N = 129/305	0.97	0.90-1.04	0.40
	Model 1	n/N = 129/305	0.97	0.90-1.05	0.43
	Model 2	n/N = 129/305	0.97	0.90-1.04	0.40
Δ 72-hour DVAS	Unadjusted	n/N = 113/233	0.94	0.86-1.02	0.14
	Model 1	n/N = 113/233	0.94	0.87-1.03	0.19
	Model 2	n/N = 113/233	0.96	0.88-1.05	0.37
Δ 72-hour GVAS	Unadjusted	n/N = 112/233	0.99	0.91-1.08	0.82
	Model 1	n/N = 112/233	0.99	0.91-1.08	0.90
	Model 2	n/N = 112/233	1.00	0.92-1.09	0.95

Abbreviations: DVAS = dyspnea visual analog scale; GVAS = global well-being visual analog scale.
* Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, race, blood urea nitrogen, jugular venous pressure >12 cm and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use. All models for where the exposure of interest is a change from baseline are additionally adjusted for the baseline value.
** HR are per 10-unit increase in VAS scale.

Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure study suggested that baseline GVAS scores were associated with 30-day all-cause death or heart failure hospitalization, but not 30-day cardiac death or cardiac rehospitalization, and there was no association between GVAS and 180-day all-cause mortality.[10] Our results add to the inconsistent findings of cohort and instrument-specific associations with clinical outcomes and highlight the prognostic uncertainty of VAS instruments. These observations may suggest that early short-term changes in DVAS (<72 hours) may not be consistent markers of long-term risk; however, a reduction of symptoms by VAS does not come at the expense of worse clinical outcomes.

This study has several limitations inherent to its design. This post hoc analysis combined the DOSE-AHF and ROSE-AHF datasets, and the findings are limited to the outcomes and follow-up data provided. We cannot exclude selection bias for trial participation. However, both studies enrolled patients with ADHF that are characteristic of contemporary ADHF populations. These studies were not prospectively designed to evaluate the prognostic implications of DVAS and GVAS. Still, these findings stem from 2 well-defined cohorts enrolled in detailed clinical trial assessment protocols and provide incremental data on DVAS and DVAS scoring for patients with ADHF.

In conclusion, our findings suggest that the changes in patient-perceived dyspnea and global well-being during ADHF may be related to factors beyond changes in congestion. Patients admitted with ADHF with lower baseline DVAS and GVAS scores are more likely to have higher DVAS and GVAS scores by 72 hours. Although changes in NT-proBNP were independently associated with changes in DVAS and GVAS, other factors may contribute to changes in GVAS. Despite increases in both VAS measurements

Table 4
Cox proportional hazard models for the association of DVAS and GVAS with the cumulative incidence of death, or heart failure hospitalization within 60 days in ROSE-AHF

Exposure of interest	Model*	Incidence	HR**	95% CI	p Value
Baseline DVAS	Unadjusted	n/N = 81/351	0.98	0.90-1.06	0.59
	Model 1	n/N = 81/351	0.98	0.90-1.07	0.64
	Model 2	n/N = 80/349	0.95	0.87-1.04	0.24
Baseline GVAS	Unadjusted	n/N = 79/348	0.93	0.85-1.02	0.15
	Model 1	n/N = 79/348	0.93	0.85-1.03	0.16
	Model 2	n/N = 78/346	0.92	0.83-1.01	0.08
Δ 72-hour DVAS	Unadjusted	n/N = 75/321	0.94	0.84-1.06	0.33
	Model 1	n/N = 75/321	0.95	0.84-1.06	0.36
	Model 2	n/N = 74/319	0.93	0.83-1.05	0.23
Δ 72-hour GVAS	Unadjusted	n/N = 74/316	0.86	0.77-0.95	0.003
	Model 1	n/N = 74/316	0.86	0.77-0.95	0.004
	Model 2	n/N = 73/314	0.84	0.76-0.94	0.001

Abbreviations: DVAS = dyspnea visual analog scale; GVAS = global well-being visual analog scale.
* Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, race, blood urea nitrogen, jugular venous pressure >12 cm and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use. All models for where the exposure of interest is a change from baseline are additionally adjusted for the baseline value.
** HRs are per 10-unit increase in VAS scale.

during treatment for ADHF, neither VAS score was consistently associated with 60-day clinical outcomes. Importantly, a reduction of symptoms by VAS was not associated with worsened 60-day clinical outcomes.

Disclosures

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Supplementary materials

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