Prognostic Implications of Congestion on Physical Examination among Contemporary Patients with Heart Failure and Reduced Ejection Fraction: PARADIGM-HF

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ABSTRACT (word count=350)

Background: The contemporary prognostic value of the physical examination, beyond traditional risk factors including natriuretic peptides (NPs), risk scores, and symptoms, in heart failure with reduced ejection fraction (HFrEF) is unknown. We sought to determine the association between physical signs of congestion at baseline and during study follow up with quality of life (QoL) and clinical outcomes and to assess the treatment effects of sacubitril/valsartan on congestion.

Methods: We analyzed participants from PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in HF) with an available physical examination at baseline. We examined the association of the number of signs of congestion (jugular venous distention, edema, rales, and S3) with the primary outcome (cardiovascular death or HF hospitalization), its individual components, and all-cause mortality using time-updated, multivariable-adjusted Cox regression. We further evaluated whether sacubitril/valsartan reduced congestion during follow-up, and whether improvement in congestion is related to changes in clinical outcomes and QoL, assessed by Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-OSS).

Results: Among 8380 participants, 0, 1, 2, and 3+ signs of congestion were present in 70%, 21%, 7%, and 2%. Patients with baseline congestion were older, more often female, had higher Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk scores and lower KCCQ-OSS ($p<0.05$). After adjusting for baseline NPs, time-updated MAGGIC score, and time-updated New York Heart Association class, increasing time-updated congestion was associated with all outcomes ($p<0.001$). Sacubitril/valsartan reduced the risk of the primary outcome irrespective of

clinical signs of congestion at baseline (p=0.16 for interaction), and treatment with the drug improved congestion to a greater extent than enalapril (p=0.011). Each 1-sign reduction was independently associated with a 5.1 (95%CI: 4.7-5.5) point improvement in KCCQ-OSS. Change in congestion strongly predicted outcomes even after adjusting for baseline congestion (p<0.001).

Conclusions: In HFrEF, the physical exam continues to provide significant, independent prognostic value even beyond symptoms, NPs, and MAGGIC risk score. Sacubitril/valsartan improved congestion to a greater extent than enalapril. Reducing congestion in the outpatient setting is independently associated with improved QoL and reduced cardiovascular events, including mortality.

Clinical Trials Registration Information: ClinicalTrials.gov identifier: NCT01035255 (https://clinicaltrials.gov/ct2/show/NCT01035255)

Keywords: heart failure with reduced ejection fraction; physical exam; sacubitril/valsartan; congestion

CLINICAL PERSPECTIVES

What is New?

- In a contemporary, time-updated analysis of patients with heart failure with reduced ejection fraction, the number of physical exam signs was strongly predictive of clinical outcomes even after adjusting for several confounding variables including baseline natriuretic peptides, time-updated Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, and time-updated New York Heart Association Class.
- The effect of sacubitril/valsartan relative to enalapril in reducing cardiovascular outcomes was consistent across the baseline physical exam and improved congestion over enalapril.
- Change in the physical exam strongly related to patient-assessed quality of life and, further, was prognostic for future events over baseline physical exam.

What are the Clinical Implications?

- Our findings reinforce the significant, ongoing clinical relevance of the physical exam in HF, reducing congestion as assessed by serial physical exams (which was independently associated with improved quality of life and reduced risk for adverse cardiovascular events), and the notion that measuring NPs does not substitute for a comprehensive physical exam for risk stratification.

NON-STANDARD ABBREVIATIONS AND ACRONYMS

Confidence interval (CI)

Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT)

Hazard ratio (HR)

Heart failure with reduced ejection fraction (HFrEF)

Jugular venous distention (JVD)

Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)

N-terminal pro-B-type natriuretic peptide (NT-proBNP)

New York Heart Association (NYHA)

Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF)

Studies of Left Ventricular Dysfunction (SOLVD)

Third heart sound (S3)

Valsartan Heart Failure Trial (Val-HEFT)

INTRODUCTION

With advancements in biochemical, imaging, and invasive hemodynamic assessments of patients with heart failure (HF), there is growing concern regarding the lack of clinician interest and expertise in performing the cardiovascular physical examination in the contemporary era.[1-3] An analysis of trainees showed poor proficiency in numerous domains of cardiac auscultation,[4] and the physical examination has been considered by some to be a vanishing art.[3] Previous studies, however, have demonstrated the value of information provided by the physical examination. An analysis of Studies of Left Ventricular Dysfunction (SOLVD) showed that jugular venous distention (JVD) and a third heart sound (S3) were independently associated with progression of HF.[5] Similarly, the Valsartan Heart Failure Trial (Val-HEFT) showed the value of the number of physical exam signs in the stratification of risk.[6]

Despite these available data, several questions remain regarding the relevance of the physical exam in HF. First, with the significant evolution of disease-modifying treatments and declining risk for adverse events,[7, 8] the clinical and prognostic value of the physical exam in the contemporary era is uncertain. Second, the independent and incremental value of the physical exam beyond symptoms, validated risk scores, and HF biomarkers (e.g. natriuretic peptides (NPs)) is unclear. Third, the relation of changes in the physical exam with changes in quality of life and prognosis have not been well characterized. Fourth, previous analyses of the physical exam in HF have generally focused on the relationship between baseline exam and outcomes,[5, 6, 9] but since congestion can change significantly within patients throughout their clinical trajectory, a time-updated analysis might be more informative. Finally, it is unknown whether sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, improves congestion over enalapril in HF with reduced ejection fraction (HFrEF).

We analyzed the clinical and prognostic significance of signs of congestion in the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in HF) trial. We subsequently evaluated the influence of sacubitril/valsartan on the physical exam, and whether improvements in the physical exam were associated with improved quality of life and prognosis in patients with HFrEF treated in the modern era.

METHODS

PARADIGM-HF study design and objectives

Study data are confidential and cannot be shared according to the terms of the contracts of the study. Therefore, the data, analytic methods, and study materials will not be made available to other researchers. The design of PARADIGM-HF has been described in detail previously.[10] Briefly, HF patients at least 18 years of age with New York Heart Association (NYHA) class II, III, or IV functional capacity and left ventricular EF <=40%. Additionally, patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg/mL (or an N-terminal pro-BNP [NT-proBNP] level ≥600 pg/mL) or, if they had been hospitalized for heart failure within the previous 12 months, a BNP of at least 100 pg/mL (or an NT-proBNP ≥400 pg/mL). Patients already taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were eligible if they were taking a daily dose equivalent to enalapril 10 mg and were on stable dose of beta-blocker for a minimum of 4 weeks. Key exclusion criteria included symptomatic hypotension, systolic blood pressure <100 mm Hg at screening, estimated glomerular filtration rate <30 mL/min 1.73 m^2, history of angioedema, or potassium >5.2 mmol/L. Eligible patients were entered (in a single blinded fashion) into a run-in

phase where they took enalapril 10 mg twice daily for 2 weeks followed by sacubitril/valsartan 100 mg twice daily initially followed by 200 mg twice daily for a 4- to 6-week period. Patients without significant intolerances to either drug were randomized in 1:1 ratio to either enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily in a double-blinded fashion. The study was approved by an institutional review committee and informed consent was obtained.

Physical exam and natriuretic peptide data collection

The presence of jugular venous distention (JVD), S3 heart sound, rales, and edema were assessed throughout the trial, including at screening, randomization, and at each study visit follow-up.[10] Physical exams were performed by clinically trained study personnel authorized to perform physical exams based on local regulations. For our analysis, we considered the randomization visit, as opposed to the screening visit, the baseline visit since event adjudication began at the time of randomization and quality of life scoring was also performed at this visit. Per the study protocol, the presence of JVD and S3 were assessed in a "yes" or "no" format. Edema was graded as "absent", "trace", "feet and ankles", "lower legs and thighs", and "sacrum". Rales were graded as "absent", "basilar only", or ">1/3 of lung field". For the main analysis, we dichotomized edema as present if edema was graded at least to the level of the feet and ankles, and absent otherwise; rales where similarly dichotomized as 'present' (either "basilar only" or ">1/3 of lung field) or 'absent'. We also performed a complementary analysis that analyzed signs using the original graded format (for rales and edema). We excluded participants with incomplete data on the physical exam (N=19) at the randomization visit.

After run-in, NT pro-BNP measurements were analyzed in a subpopulation of participants: at the time of randomization (n=1044 in the sacubitril/valsartan arm and n=1029 in

the enalapril arm), 1 month after randomization (n=995 in the sacubitril/valsartan arm and n=1003 in the enalapril arm), and 8 months after randomization (n=915 in the sacubitril/valsartan arm and n=903 in the enalapril arm).[11] **Supplementary Figure 1** provides a diagram of the relationship of study visits to physical examinations performed and NP laboratory analysis.

Study outcomes

The primary outcome of PARADIGM-HF was a composite of death from cardiovascular cause or a first hospitalization for HF.[12] We also assessed several trial secondary outcomes, including the time to death from any cause and the change from baseline to 4 months in the Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF). KCCQ was administered in 38 of the 46 countries, excluding countries without validated versions of the instrument.[13] Adjudication of all clinical outcomes was carried out in a blinded fashion by a clinical-end-points committee according to prespecified criteria.

Statistical analysis

Baseline characteristics are summarized by the total number of signs (0, 1, 2, and 3-4) and by individual signs (edema, rales, S3, and JVD) using mean and standard deviation for normally distributed variables and median [25^{th}-75^{th} percentile] if non-normally distributed. Categorical variables are presented as counts and percentages. The values of NPs were right-skewed and therefore required log transformation to approximate a normal distribution for analysis as a continuous variable. ANOVA and chi-squared tests were performed, with p-values shown for trend using linear regression for continuous, normally distributed variables and the

method of Cuzick for non-parametric testing of continuous variables.[14] We used chi-squared trend tests for categorical variables.

The association between the number of signs and individual signs with the efficacy outcomes was assessed using time-updated crude and multivariable-adjusted Cox regression. We analyzed the physical exam as a categorical, time-updated variable since this model yielded the lowest Akaike Information Criteria for cardiovascular death relative to models using the baseline physical exam or modeling the signs of congestion as a continuous variable. In addition, we modeled the physical exam as a time-updated variable since the physical exam can change over time, mirroring clinical practice.[15] Multivariable models were adjusted for baseline covariates including 1) baseline NT-proBNP, 2) baseline NT-proBNP and time-updated Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, and 3) baseline NT-proBNP, time-updated MAGGIC risk score, and time-updated NYHA class. The MAGGIC risk score was originally derived from a large analysis of patients enrolled in clinical trials and cohort studies to predict mortality.[16] We have previously validated its use to predict study outcomes in PARADIGM-HF.[17] Given the available data collected, we time-updated the following components of the MAGGIC risk score: age, systolic blood pressure, body mass index, creatinine, NYHA class, and HF first diagnosed >18 months ago, with missing covariates at follow-up visits carried forward from the last available. An interaction analysis by time-updated obesity (body mass index > 30 kg/m^2) as well as body mass index (continuous variable) with time-updated signs of congestion was performed since obesity may hinder the clinician's ability to assess congestion and influence NP measurements. In addition, we analyzed signs in a graded fashion (as rales and edema were dichotomized for the main analysis), using the absence of the individual sign as the referent arm. A sign score was constructed based upon relative weighting

of the beta-coefficients for cardiovascular mortality, as similarly done in other studies (**Supplementary Table 1**).[16]

Because NT-proBNP is only available at 3 time points (**Supplementary Figure 1**), we provided a subanalysis of participants with complete NT-proBNP values, MAGGIC risk score, and NYHA class at these time points. We performed a time-updated analysis at these time points for signs of congestion and the primary outcome, adjusting for time-updated NT-proBNP, MAGGIC score, and NYHA class.

Since the physical exam might inform a physician's decision to hospitalize patients, and therefore inflate the relationship between signs of congestion and HF-related outcomes, we performed a sensitivity analysis. For the primary endpoint (which includes HF hospitalization) and HF hospitalization, we censored participants at the time of hospitalization for those hospitalized for HF on the same date as a clinic visit (N=169).

To assess the treatment effect of sacubitril/valsartan relative to enalapril on congestion, we compared the percent of patients with any congestion (versus no congestion) between study arms over the course of follow-up using binary repeated measures logistic regression. We next determined the relationship between the change in signs of congestion with change in KCCQ-OSS at the 4-month visit. Post-randomization changes from baseline were compared using linear regression, controlling for treatment allocation and baseline physical exam as independent variables. We further controlled for clinical covariates that were independently associated with change in the number of physical exam signs from baseline to the 4-month visit using backward stepwise ordinal logistic regression at a significance level of 0.01. Finally, to determine whether reducing the number of signs of congestion was associated with improved prognosis, we simultaneously entered both the baseline and change in signs of congestion (during study follow-

up) into models assessing the relationship with the efficacy outcomes. Analyses were performed using STATA version 12, and a two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Of the initial study population of 8399 participants in the Americas, we excluded 19 participants with incomplete physical exam data at baseline. **Table 1** lists the baseline characteristics of the study population, stratified by number of signs of congestion at baseline: 5854 (70%) had no signs, 1783 (21%) had 1 sign, 563 (7%) had 2 signs, and 180 (2%) had 3-4 signs. By individual signs of congestion: 9.7% had JVD, 14.2% had edema, 9.5% had an S3, and 7.9% had rales. Overall cohort characteristics were similar to those presented in the main analysis.[12] Patients with more congestive signs were older, more often female, had more advanced NYHA class, had higher MAGGIC risk scores and lower KCCQ-OSS, and more frequently had hypertension, diabetes mellitus, and atrial fibrillation, ($p<0.05$ for all comparisons). They were also more likely to take diuretics, less likely to take beta-blockers or have devices, and had higher NP levels ($p<0.05$ for all comparisons).

Supplementary Table 2 shows clinical characteristics by presence of individual signs of congestion (JVD, edema, S3, and rales), demonstrating similar trends as observed in **Table 1**. Likewise, characteristics of participants by change in the physical exam between the baseline and 4 month visit are shown in **Supplementary Table 3**. Patients who decongested, for example, had shorter duration of HF, higher blood pressure, and higher heart rate. **Supplementary Table 4** shows the frequency of the most common combination of signs of congestion. Among the 30% of participants with any congestion, the majority only exhibited one sign of congestion. At least

two signs were observed in a minority of all patients in the trial at baseline: 2.0% had edema and rales, 1.5% had JVD and edema, and 1.3% had JVD and an S3.

Association of physical exam signs and adverse cardiovascular outcomes during follow-up

At any point during follow-up, 2980 (36%), 2935 (35%), 1547 (18%), 734 (9%), and 184 (2%) had a maximum of 0, 1, 2, 3, and 4 signs, respectively. **Figure 1** shows incidence rates per 100 person-years for each of the 4 study outcomes (primary endpoint, HF hospitalization, cardiovascular death, and all-cause mortality) by trial randomization arm using time-updated analysis. The number of events and person-years per sign category in each randomization arm are shown in **Supplementary Table 5**. Of note, participants can contribute person-years to more than one category as they increase or decrease in the number of signs of congestion during their clinical trajectory. There was a significant, graded relationship between number of signs of congestion and incidence rates for each outcome. A complementary figure is presented as **Supplementary Figure 2** using baseline, instead of time-updated, signs of congestion.

Table 2 shows time-updated, crude and multivariable-adjusted hazard ratios (HR) for the study outcomes, stratified by signs of congestion, with 0 signs designated as the referent group. On univariable analysis, using no signs of congestion as the referent group, increasing number of signs was associated with an increased risk for all outcomes. Adjusting for baseline NT-proBNP, time-updated MAGGIC risk score, and time-updated NYHA class generally diminished the strength of these relationships but remained statistically significant. For example, the HRs for the primary endpoint for 1, 2, 3, and 4 signs of congestion (versus 0 signs) were 1.48, 1.74, 2.35, and 5.96, respectively after these multivariable adjustments ($p<0.001$ for all sign groups versus no congestion). Neither obesity nor body mass index modified the relationship between the number

of signs with the primary outcome in fully adjusted models (p-interaction >0.40 for both comparisons). We also analyzed the association between baseline signs and adverse outcomes in **Supplementary Table 6**. This showed weaker, though significant relationships with increasing baseline congestion and adverse events than with the time-updated analysis. Adjustment for NT-proBNP further attenuated, but did not eliminate, these associations.

We performed a subanalysis of 2066 participants with complete data for NT-proBNP values, MAGGIC risk score, and NYHA class at 3 study visits (**Supplementary Table 7**). After adjusting for time-updated NT-proBNP and MAGGIC risk score, increasing congestion was generally associated with an increased risk for the primary outcome. There was further attenuation of the statistical significance after adjusting for time-updated NYHA class in this limited subanalysis.

Supplementary Table 8 demonstrates through time-updated analysis that presence of each individual sign of congestion was associated with an increased risk for all events on univariable and multivariable analysis. Though JVD was associated with all outcomes after adjusting for NT-proBNP and MAGGIC risk score, it was no longer associated with the study endpoints after adjusting for NYHA class.

In a complementary analysis, we assessed the prognostic value of signs using the original graded format in the trial protocol instead of dichotomizing rales and edema (**Supplementary Table 9**). In fully adjusted models, increasing severity of congestion was generally associated with a graded and increased risk for all study outcomes. We also created a congestion point score by weighting severity of congestion in relation to cardiovascular mortality. Each 1-point increase in congestion score equated to 25% increase in risk for the primary endpoint [HR 1.25, 95% confidence interval (CI) 1.22-1.29].

Since clinicians may partially base their decision to hospitalize patients on the number of signs of congestion, we performed a sensitivity analysis (**Supplementary Table 10)**. Even after censoring those hospitalized for HF the same date as a clinic visit (N=169), there were still significant, strong, and graded relationships between number of signs of congestion and risk for the primary endpoint and HF hospitalization. The HRs for the primary endpoint for 1, 2, 3, and 4 signs of congestion (versus 0 signs) were 1.47, 1.61, 2.05, and 3.38, respectively after multivariable adjustments ($p<0.001$ for all comparisons).

Effect of sacubitril/valsartan on congestion

Sacubitril/valsartan reduced the risk for the primary outcome regardless of the baseline physical exam modeled, as a continuous variable ($p=0.16$ for interaction). **Figure 2** shows the percent of participants with any congestion during follow-up by treatment arm. Sacubitril/valsartan improved clinical congestion relative to enalapril during study follow-up ($p=0.011$).

Relationship of change in physical exam to quality of life and outcomes

We performed an analysis of participants attending the 4-month visit with available physical exam (N=7967). The relationship between change in the physical exam and change in quality of life (assessed using the KCCQ-OSS) is shown in **Table 3**. Each disappearance of a sign of congestion was associated with a 5.1 (95% CI: 4.5, 5.7) increase in KCCQ-OSS, indicating improvement in quality of life. Multivariable adjustment for covariates associated with the change in the physical examination identified in **Supplementary Table 11** yielded similar results. Findings were similar when analyzed by each physical exam sign.

We subsequently sought to understand whether the risk of adverse events is mutable by changing congestion. **Table 4** shows that change in number of signs of congestion was a strong predictor even after adjusting for baseline signs of congestion. For example, the HR (95% CI) for the primary endpoint per sign increase in congestion was 2.00 (1.89, 2.13) after adjusting for the number of baseline signs of congestion.

DISCUSSION

In a large study of congestion on physical examination in outpatients with HFrEF, we demonstrated that the number of physical examination signs of congestion was strongly predictive of clinical outcomes even after adjusting for baseline NT-proBNP, time-updated MAGGIC risk score, and time-updated NYHA class. In a subanalysis of 2066 individuals with complete NP data available, increasing congestion was associated with the primary outcome even after adjusting for time-updated NT-proBNP and MAGGIC risk score. Moreover, the effect of sacubitril/valsartan relative to enalapril was consistent across the baseline physical exam and improved congestion over enalapril. Change in the physical exam strongly related to patient-assessed quality of life and, further, was prognostic for future events even after adjusting baseline physical exam. Our findings reinforce the ongoing clinical relevance of the physical exam in HF, reducing congestion as assessed by serial physical exams (which was independently associated with improved quality of life and reduced risk for adverse cardiovascular events), and the notion that measuring NPs does not substitute for a comprehensive exam for risk stratification.

NPs have emerged as markers of volume status and prognosis in HF. Even in the absence of clinical congestion, the presence of elevated NPs portends a poor prognosis (a condition

referred to as "hemodynamic congestion").[18] PARADIGM-HF required elevated NPs as a study entry criterion. Thus, in our study, everyone without clinical congestion had "hemodynamic congestion", with a corresponding median (25^{th}-75^{th} percentile) NT-pro BNP of 1529 (852, 2969)) pg/mL. Thus, enthusiasm for NP-based algorithms to guide diuresis and HF therapy has recently accrued. However, the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial) failed to demonstrate improved clinical outcomes with such an approach[19] and actually resulted in increased costs with similar impact on quality of life.[20] Our results show that congestion is associated with worse outcomes even after adjusting for NPs. Wireless pulmonary artery hemodynamic monitoring is effective to guide decongestion and reduce hospitalizations, but enthusiasm for widespread implementation is tempered by cost, need for central monitoring capabilities, and infrequent, but potentially serious, risks related to implantation.[21, 22] Treating HF patients based upon the physical exam, rather than biomarker data, is important not just to improve outcomes, but also symptoms. While intuitive, there is a paucity of data in chronic HF that quantifies this association. We show that each reduction in sign of congestion was associated with a 5-point increase in KCCQ-OSS. For perspective, a 5-point improvement in KCCQ-OSS has been associated with a 10% reduction in cardiovascular mortality or hospitalization, and some have considered a 5-point increase to indicate a clinically significant improvement in QoL.[23-25]

In PARADIGM-HF, edema was the most common sign of congestion followed by JVD. The frequencies observed here are largely consistent with other trials in HFrEF.[6, 9, 26] Observational studies and clinical registries of the physical exam have varied in the frequency of signs of congestion, which may reflect differences in patient population selected.[27, 28] Inpatient data on the prognostic value of congestion at admission and discharge have generally been

concordant with our findings,[29, 30] and though not frequently accomplished by discharge, relief of congestion has been associated with improved outcomes.[31, 32] Outpatient analyses of congestion in HFrEF, where most clinical care occurs, are less frequent.[5, 6, 9] These studies, while important, did not adjust for NPs and only analyzed the baseline physical exam, which may inaccurately quantify risk since clinical congestion can change significantly within patients over time. Indeed, we showed that baseline signs of congestion was a relatively weak predictor of adverse events, reflecting the fact that a "snapshot" of congestion at one time point does not strongly relate to longer term future risk, as risk appears to be mutable by change in congestion. We further demonstrated that time-updated change in physical exam signs during follow-up was strongly predictive of clinical outcomes even after adjusting for baseline signs, which therefore underscores the need to keep patients decongested to improve prognosis.

Detection of clinical congestion can be challenging, crude, and operator-dependent.[29, 33, 34] While no sign has perfect predictive value, signs of congestion in aggregate are useful to understanding the hemodynamic status and can inform treatment decisions. The number of signs was significantly more predictive than using any individual sign (or models just assessing 1+ signs versus 0 signs), which emphasizes the importance of a thorough physical exam. Further, the physical exam may be challenging in obese individuals, a population also in whom NP levels may be "leftward shifted". However, we found no effect modification by obesity or body mass index on the predictive value of clinical congestion.

Sacubitril/valsartan reduced the number of signs of congestion over time compared with enalapril. The modest observed improvement in congestion may be related to 1) greater increase in diuretic use in the enalapril arm over time;[35] 2) survivorship bias, whereby the sickest patient may not have presented later in follow-up, as more deaths occurred in the enalapril arm; 3)

assessment of congestive signs at randomization, which occurred after sequential run-in phases with enalapril and sacubitril/valsartan that may have attenuated differences between arms.

Strengths of our study include the large sample size, population receiving contemporary HF management, time-updated analysis of the physical exam with numerous follow-up visits, assessment of quality of life using a validated instrument, and event adjudication. In addition, we adjusted for several strong predictors of prognosis, such as NT-proBNP, MAGGIC risk score, and NYHA class.

Limitations

Our analysis has some possible limitations. Performance of the physical exam by the study investigators was not standardized. In addition, signs may have considerable interobserver variability, and confirmatory methods were not employed. However, our analysis is reflective of clinical practice and therefore increases generalizability of our findings. Next, signs of congestion may influence a physician's decision to hospitalize patients and therefore might explain the relationship between the physical exam and HF hospitalization. However, our results were relatively similar in a sensitivity analysis censoring patients who were hospitalized the same date as a clinic visit. In addition, signs of congestion powerfully predicted other outcomes that would be unaffected by a physician's knowledge of the physical exam, including cardiovascular death and all-cause mortality. Finally, historical features might influence a clinician's evaluation of the physical examination. However, our results were robust even after adjusting for symptoms as reflected by NYHA class.

In summary, in the largest study to date of the physical exam in HF, signs of congestion independently predicted adverse events even after adjusting for NPs, MAGGIC risk score, and

NYHA class. Improvement in the physical exam was associated with improved quality of life and prognosis. The effect of sacubitril/valsartan relative to enalapril was consistent across the baseline physical exam, and sacubitril/valsartan improved congestion over enalapril. The physical exam, a highly utilized and readily available assessment in HF, continues to have strong utility in the contemporary era of HFrEF treatment.

DISCLOSURES

Dr. Claggett is a consultant for Gilead, AO Biome, and Boehringer Ingelheim. Dr. McMurray is an employee of Glasgow University, and Glasgow University has been paid by Novartis for his participation in a number of trials, including PARADIGM-HF and lectures, advisory boards, and other meetings related to PARADIGM-HF and sacubitril/valsartan. Dr. Jhund is a consultant for and has received speaker and advisory board fees from Novartis. Drs. Lefkowitz, Prescott, and Shi are employees of and own stock in Novartis Pharmaceuticals. Dr. Rouleau is a consultant for Novartis, Bayer, and AstraZeneca. Drs. Swedberg and Zile are consultants for Novartis. Dr. Packer is a consultant for Amgen, AstraZeneca, Bayer Boehringer Ingelheim, Cardiorentis, Saiichi Sankyo, Gilead, NovoNordisk, Novartis, Relypsa, Sanofi, Teva, Takeda, and ZS Pharma. Dr. Desai has received consulting fees and research support from Novartis, as well as consulting fees from AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Corvidia, DalCor Pharma, Relypsa, and Signature Medical. Affiliation: Baylor University Medical Center, Dallas TX and Imperial College, London, UK. Dr. Packer has consulted for Abbvie, Akcea, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, NovoNordisk, Sanofi, Synthetic Biologics, and Theravance. Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541), and serves on advisory boards for AstraZeneca, Bayer AG, and Baxter Healthcare. Dr. Solomon has received research grants from and is a consultant for Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Elder A, Japp A, Verghese A. How valuable is physical examination of the cardiovascular system? *BMJ*. 2016;354:i3309.
2. Nohria A, Stevenson LW. Observation is never obsolete. *JACC Heart Fail*. 2014;2:32-34.
3. Bank I, Vliegen HW, Bruschke AV. The 200th anniversary of the stethoscope: Can this low-tech device survive in the high-tech 21st century? *Eur Heart J*. 2016;37:3536-3543.
4. Mangione S, Nieman LZ. Cardiac auscultatory skills of internal medicine and family practice trainees. A comparison of diagnostic proficiency. *JAMA*. 1997;278:717-722.
5. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med*. 2001;345:574-581.
6. Wong M, Staszewsky L, Carretta E, Barlera S, Latini R, Chiang YT, Glazer RD, Cohn JN. Signs and symptoms in chronic heart failure: Relevance of clinical trial results to point of care-data from val-heft. *Eur J Heart Fail*. 2006;8:502-508.
7. Shen L, Jhund PS, McMurray JJV. Declining risk of sudden death in heart failure. *N Engl J Med*. 2017;377:1794-1795.
8. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344-350.
9. Caldentey G, Khairy P, Roy D, Leduc H, Talajic M, Racine N, White M, O'Meara E, Guertin MC, Rouleau JL, Ducharme A. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: Insights from the af-chf trial (atrial fibrillation and chronic heart failure). *JACC Heart Fail*. 2014;2:15-23.
10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR, Committees P-H, Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: Rationale for and design of the prospective comparison of arni with acei to determine impact on global mortality and morbidity in heart failure trial (paradigm-hf). *Eur J Heart Fail*. 2013;15:1062-1073.
11. Myhre PL, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. B-type natriuretic peptide during treatment with sacubitril/valsartan: The paradigm-hf trial. *J Am Coll Cardiol*. 2019;73:1264-1272.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
13. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-related quality of life outcomes in paradigm-hf. *Circ Heart Fail*. 2017;10(8).
14. Cuzick J. A wilcoxon-type test for trend. *Stat Med*. 1985;4:87-90.
15. Selvaraj S, Claggett B, Shah SJ, Anand IS, Rouleau JL, Desai AS, Lewis EF, Vaduganathan M, Wang SY, Pitt B, Sweitzer NK, Pfeffer MA, Solomon SD. Utility of the cardiovascular physical examination and impact of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12:e006125.

16. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart F. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *Eur Heart J*. 2013;34:1404-1413.
17. Simpson J, Jhund PS, Silva Cardoso J, Martinez F, Mosterd A, Ramires F, Rizkala AR, Senni M, Squire I, Gong J, Lefkowitz MP, Shi VC, Desai AS, Rouleau JL, Swedberg K, Zile MR, McMurray JJV, Packer M, Solomon SD, Investigators P-H, Committees. Comparing lcz696 with enalapril according to baseline risk using the maggic and emphasis-hf risk scores: An analysis of mortality and morbidity in paradigm-hf. *J Am Coll Cardiol*. 2015;66:2059-2071.
18. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G, European Society of C, European Society of Intensive Care M. Assessing and grading congestion in acute heart failure: A scientific statement from the acute heart failure committee of the heart failure association of the european society of cardiology and endorsed by the european society of intensive care medicine. *Eur J Heart Fail*. 2010;12:423-433.
19. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Jr., Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA*. 2017;318:713-720.
20. Mark DB, Cowper PA, Anstrom KJ, Sheng S, Daniels MR, Knight JD, Baloch KN, Davidson-Ray L, Fiuzat M, Januzzi JL, Jr., Whellan DJ, Pina IL, Ezekowitz JA, Adams KF, Cooper LS, O'Connor CM, Felker GM. Economic and quality-of-life outcomes of natriuretic peptide-guided therapy for heart failure. *J Am Coll Cardiol*. 2018;72:2551-2562.
21. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, Group CTS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *Lancet*. 2011;377:658-666.
22. Vaduganathan M, DeFilippis EM, Fonarow GC, Butler J, Mehra MR. Postmarketing adverse events related to the cardiomems hf system. *JAMA Cardiol*. 2017;2:1277-1279.
23. Kelkar AA, Spertus J, Pang P, Pierson RF, Cody RJ, Pina IL, Hernandez A, Butler J. Utility of patient-reported outcome instruments in heart failure. *JACC Heart Fail*. 2016;4:165-175.
24. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, Spertus JA. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation*. 2007;115:1975-1981.
25. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS, Cardiovascular Outcomes Research C. Monitoring clinical changes in patients with heart failure: A comparison of methods. *Am Heart J*. 2005;150:707-715.
26. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-HC. Baseline characteristics

and treatment of patients in prospective comparison of arni with acei to determine impact on global mortality and morbidity in heart failure trial (paradigm-hf). *Eur J Heart Fail*. 2014;16:817-825.
27. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation*. 2011;124:2865-2873.
28. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;261:884-888.
29. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A. Value of clinician assessment of hemodynamics in advanced heart failure: The escape trial. *Circ Heart Fail*. 2008;1:170-177.
30. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol*. 2003;41:1797-1804.
31. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Jr., Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, Investigators ET. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: Findings from the everest trial. *Eur Heart J*. 2013;34:835-843.
32. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW. Relief and recurrence of congestion during and after hospitalization for acute heart failure: Insights from diuretic optimization strategy evaluation in acute decompensated heart failure (dose-ahf) and cardiorenal rescue study in acute decompensated heart failure (caress-hf). *Circ Heart Fail*. 2015;8:741-748
33. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail*. 2018;6:543-551.
34. From AM, Lam CS, Pitta SR, Kumar PV, Balbissi KA, Booker JD, Singh IM, Sorajja P, Reeder GS, Borlaug BA. Bedside assessment of cardiac hemodynamics: The impact of noninvasive testing and examiner experience. *Am J Med*. 2011;124:1051-1057.
35. Vardeny O, Claggett B, Kachadourian J, Desai AS, Packer M, Rouleau J, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: The paradigm-hf trial. *Eur J Heart Fail*. 2019;21:337-341.

FIGURE LEGENDS

Figure 1:

***Title*: Time-Updated Event Rates for Efficacy Outcomes by Total Number of Signs of Congestion.**

Caption: Event rates using time-updated analysis per 100 person-years and 95% confidence intervals are shown for each of the four efficacy outcomes by treatment arm (enalapril shown in blue, sacubitril/valsartan shown in red). Participants can contribute person-years to more than one category as they increase or decrease in the number of signs of congestion during their clinical trajectory. The number of events and person-years in each sign category is presented in Supplementary Table 5. CV, cardiovascular; HF, heart failure.

Figure 2:

***Title:* Percent of Patients with Any Congestion During Follow-up by Randomization Arm.**

Caption: Sacubitril/valsartan (red) reduced the frequency of patients with any congestion relative to enalapril (blue) during follow-up. Error bars denote 95% confidence intervals. The number of participants at each study visit by randomization arm is shown in the bottom table. P-value shown for binary repeated measures logistic regression.

TABLE 1. Baseline Clinical Characteristics by Number of Physical Exam Signs

	0 Signs N=5854	1 Sign N=1783	2 Signs N=563	3-4 Signs N=180	P-value*
Jugular venous distention	-	378 (21.2%)	269 (47.8%)	170 (94.4%)	<0.001
Edema	-	675 (37.9%)	366 (65.0%)	152 (84.4%)	<0.001
S3 heart sound	-	475 (26.6%)	217 (38.5%)	104 (57.8%)	<0.001
Rales	-	255 (14.3%)	274 (48.7%)	134 (74.4%)	<0.001
Age, years	63 ± 11	64 ± 12	66 ± 11	65 ± 10	< 0.001
Female, n (%)	1219 (20.8%)	436 (24.5%)	124 (22.0%)	52 (28.9%)	0.001
Race, n (%)					0.042
White	3856 (65.9%)	1131 (63.4%)	411 (73.0%)	135 (75.0%)	
Black	303 (5.2 %)	86 (4.8 %)	25 (4.4 %)	11 (6.1 %)	
Asian	1085 (18.5%)	343 (19.2%)	66 (11.7%)	11 (6.1 %)	
Other	610 (10.4%)	223 (12.5%)	61 (10.8%)	23 (12.8%)	
Region					<0.001
North America	438 (7.5 %)	124 (7.0 %)	31 (5.5 %)	7 (3.9 %)	
Latin American	1016 (17.4%)	298 (16.7%)	94 (16.7%)	22 (12.2%)	
Western Europe	1582 (27.0%)	375 (21.0%)	70 (12.4%)	18 (10.0%)	
Central Europe	1757 (30.0%)	640 (35.9%)	303 (53.8%)	123 (68.3%)	
Asia-Pacific	1061 (18.1%)	346 (19.4%)	65 (11.5%)	10 (5.6 %)	
NYHA Class, n (%)					<0.001
I	315 (5.4 %)	68 (3.8 %)	6 (1.1 %)	0 (0.0 %)	
II	4515 (77.1%)	1090 (61.1%)	253 (44.9%)	55 (30.6%)	
III	1007 (17.2%)	610 (34.2%)	286 (50.8%)	115 (63.9%)	
IV	17 (0.3 %)	15 (0.8 %)	18 (3.2 %)	10 (5.6 %)	
Diagnosis of heart failure					0.21
<1 year	1782 (30.4%)	543 (30.5%)	144	48 (26.7%)	

			(25.6%)		
1-5 years	2230 (38.1%)	680 (38.1%)	235 (41.7%)	78 (43.3%)	
>5 years	1842 (31.5%)	560 (31.4%)	184 (32.7%)	54 (30.0%)	
MAGGIC risk score	20.3 ± 5.6	21.5 ± 5.8	22.6 ± 5.8	22.2 ± 6.2	< 0.001
Kansas City Cardiomyopathy Questionnaire overall score	76 ± 18	69 ± 20	62 ± 21	57 ± 21	< 0.001
Physical Characteristics					
Systolic blood pressure, mmHg	121 ± 15	122 ± 15	124 ± 14	127 ± 15	< 0.001
Diastolic blood pressure, mmHg	73 ± 10	74 ± 10	76 ± 9	78 ± 10	< 0.001
Heart rate (beats/min)	72 ± 12	73 ± 12	75 ± 13	78 ± 14	< 0.001
Body mass index (kg/m^2)	28.0 ± 5.4	28.6 ± 6.0	28.4 ± 5.7	29.3 ± 5.2	< 0.001
Comorbidities, n (%)					
Hypertension	4067 (69.5%)	1285 (72.1%)	425 (75.5%)	152 (84.4%)	<0.001
Atrial fibrillation	2044 (34.9%)	700 (39.3%)	264 (46.9%)	75 (41.7%)	<0.001
Diabetes mellitus	1961 (33.5%)	662 (37.1%)	207 (36.8%)	72 (40.0%)	0.002
Ischemic heart disease	3507 (59.9%)	1065 (59.7%)	342 (60.7%)	108 (60.0%)	0.85
Myocardial infarction	2538 (43.4%)	771 (43.2%)	244 (43.3%)	71 (39.4%)	0.54
Heart failure hospitalization	3627 (62.0%)	1121 (62.9%)	392 (69.6%)	123 (68.3%)	<0.001
Stroke	520 (8.9 %)	141 (7.9 %)	53 (9.4 %)	10 (5.6 %)	0.25
Current smoker	875 (14.9%)	248 (13.9%)	59 (10.5%)	23 (12.8%)	0.008
Medication and Device Use, n (%)					

Beta-blocker	5480 (93.6%)	1630 (91.4%)	519 (92.2%)	165 (91.7%)	0.007
Digitalis	1679 (28.7%)	603 (33.8%)	201 (35.7%)	54 (30.0%)	<0.001
Diuretic	4530 (77.4%)	1526 (85.6%)	503 (89.3%)	167 (92.8%)	<0.001
Mineralocorticoid antagonist	3243 (55.4%)	998 (56.0%)	327 (58.1%)	93 (51.7%)	0.70
Implantable cardioverter-defibrillator	940 (16.1%)	233 (13.1%)	58 (10.3%)	10 (5.6 %)	<0.001
Cardiac resynchronization therapy	426 (7.3 %)	109 (6.1 %)	33 (5.9 %)	5 (2.8 %)	0.005
Laboratory Testing					
Estimated glomerular filtration rate (mL/min/1.78 m^2)	68.0 ± 19.9	66.8 ± 20.8	67.2 ± 19.9	70.1 ± 21.3	0.47
Hemoglobin (mg/dL)	14.0 ± 1.6	13.8 ± 1.7	13.9 ± 1.7	14.1 ± 1.8	0.006
BNP (pg/mL) †	242 [149, 442]	274 [163, 523]	297 [176, 587]	363 [185, 710]	<0.001
NT-pro-BNP (pg/mL) †	1529 [852, 2969]	1785 [978, 3785]	1909 [1020, 4138]	2181 [1156, 5538]	<0.001
Imaging Data					
Ejection fraction (%)	29.5 ± 6.2	29.3 ± 6.2	29.7 ± 6.1	30.1 ± 6.1	0.51

NYHA, New York Heart Association; BNP, b-type natriuretic peptide.
*P-value shown for trend.
†Presented as median (25^{th} – 75^{th} percentile) since the variable is right-skewed.

TABLE 2. Crude and Adjusted Hazard Ratios using Time-updated Signs of Congestion for Efficacy Outcomes by Total Number of Physical Exam Signs

Outcomes	1 Sign vs. 0 Signs HR (95% CI)	2 Signs vs. 0 Signs HR (95% CI)	3 Signs vs. 0 Signs HR (95% CI)	4 Signs vs. 0 Signs HR (95% CI)
Composite endpoint				
• Crude model	1.77 (1.59, 1.96)	2.61 (2.24, 3.03)	4.22 (3.45, 5.16)	11.88 (8.17, 17.29)
• Adjustment for baseline NT-proBNP	1.68 (2.03, 2.74)	2.36 (2.03, 2.74)	3.60 (2.94, 4.40)	10.53 (7.24, 15.33)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.62 (1.46, 1.80)	2.20 (1.89, 2.55)	3.43 (2.80, 4.20)	9.03 (6.20, 13.16)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.48 (1.34, 1.65)	1.74 (1.49, 2.03)	2.35 (1.90, 2.90)	5.96 (4.06, 8.74)
Cardiovascular mortality				
• Crude model	1.76 (1.54, 2.01)	2.89 (2.41, 3.45)	3.82 (2.95, 4.93)	7.45 (4.46, 12.42)
• Adjustment for baseline NT-proBNP	1.65 (1.45, 1.89)	2.56 (2.14, 3.06)	3.16 (2.44, 4.08)	5.62 (3.36, 9.39)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.57 (1.38, 1.80)	2.33 (1.95, 2.79)	2.95 (2.28, 3.82)	4.71 (2.82, 7.88_
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.43 (1.25, 1.64)	1.82 (1.51, 2.20)	1.99 (1.52, 2.61)	2.60 (1.53, 4.42)
Heart failure hospitalization				
• Crude model	2.00 (1.75, 2.29)	2.89 (2.38, 3.51)	5.84 (4.61, 7.39)	18.99 (12.73, 28.33)
• Adjustment for baseline NT-	1.91 (1.67, 2.18)	2.64 (2.17, 3.20)	5.03 (3.97, 6.37)	17.04 (11.42, 25.44)

proBNP				
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.84 (1.61, 2.10)	2.45 (2.02, 2.98)	4.79 (3.78, 6.07)	14.55 (21.76)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.64 (1.43, 1.88)	1.84 (1.50, 2.25)	3.00 (2.34, 3.86)	8.82 (5.84, 13.31)
All cause mortality				
• Crude model	1.61 (1.43, 1.82)	2.76 (2.35, 3.24)	3.50 (2.76, 4.42)	6.63 (4.10, 10.72)
• Adjustment for baseline NT-proBNP	1.52 (1.35, 1.72)	2.47 (2.10, 2.91)	2.95 (2.33, 3.74)	5.16 (3.19, 8.35)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.44 (1.28, 1.63)	2.23 (1.90, 2.63)	2.75 (2.17, 3.48)	4.27 (2.64, 6.92)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.32 (1.17, 1.49)	1.78 (1.51, 2.12)	1.92 (1.50, 2.47)	2.53 (1.54, 4.15)

HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association

TABLE 3. Relationship between Reducing Signs of Congestion and Quality of Life from Baseline to the 4-Month Visit.

	Change in KCCQ-OSS per Reduction in Sign of Congestion Minimally-adjusted Model Beta-coefficient (95% CI)*	P-value	Change in KCCQ-OSS per Reduction in Sign of Congestion Fully-adjusted Model Beta-coefficient (95% CI)* †	P-value
Change per decrease in number of physical exam signs	5.1 (4.5, 5.7)	<0.001	4.9 (4.3, 5.5)	<0.001
Edema	7.8 (6.7, 8.9)	<0.001	7.4 (6.3, 8.5)	<0.001
S3	3.2 (1.5, 5.0)	<0.001	3.0 (1.3, 4.8)	0.001
Jugular venous distention	7.3 (5.8, 8.7)	<0.001	6.9 (5.5, 8.4)	<0.001
Rales	7.0 (5.5, 8.4)	<0.001	6.7 (5.3, 8.1)	<0.001

CI, confidence interval; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

*Expressed per decrease in, or absence of, physical exam sign. All analyses controlled for randomization arm and baseline physical exam.

†Additionally adjusted for enrollment from Latin America, diabetes mellitus, enrollment from Western Europe, body mass index, log NT-proBNP, and diuretic use.

TABLE 4. Prognostic Value of Baseline Signs and Change in Signs

Outcomes	Baseline Number of Signs HR (95% CI)*	P-value	Change in Number of Signs HR (95% CI) †‡	P-value
Composite endpoint	1.47 (1.39, 1.55)	<0.001	2.00 (1.89, 2.13)	<0.001
Cardiovascular mortality	1.45 (1.35, 1.56)	<0.001	1.85 (1.72, 1.99)	<0.001
HF hospitalization	1.50 (1.40, 1.61)	<0.001	2.31 (2.15, 2.49)	<0.001
All cause mortality	1.42 (1.33, 1.51)	<0.001	1.78 (1.66, 1.90)	<0.001

HF, heart failure; CI, confidence interval.
*Adjusted for change in number of signs
†Adjusted for baseline number of signs
‡Change in number of signs is time-updated at each visit from baseline signs