

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

**PARADIGM-HF**

S. Selvaraj et al.

Supplemental Material

## **SUPPLEMENTARY FIGURE LEGEND**

### **Supplementary Figure 1:**

***Title: Timing of Study Visits, Physical Examinations Performed, and Natriuretic Peptide Analysis in PARADIGM-HF***

**Caption:** Timing of study visits, physical examination, and laboratory analysis is shown after the run-in period. Physical examination was performed at each study visit. Natriuretic peptide analysis was only performed in a subpopulation of participants in each study arm at the time of randomization as well as 1 and 8 months after randomization. PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Nepriylsin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in HF.

### **Supplementary Figure 2:**

***Title: Baseline Event Rates for Efficacy Outcomes by Total Number of Signs of Congestion.***

**Caption:** Event rates per 100 person-years and 95% confidence intervals using signs at baseline are shown for each of the four efficacy outcomes by treatment arm (enalapril shown in blue, sacubitril/valsartan shown in red). CV, cardiovascular; HF, heart failure.

**SUPPLEMENTARY TABLE 1. Methodology used to Create Weighted Scoring System for Severity of Congestion**

<b>Physical exam sign</b>	<b>Beta-coefficient (95% CI) for Cardiovascular Death</b>	<b>Beta-coefficient Divided by Common Denominator (0.3)</b>	<b>Weighted Number of Points</b>
Rales (ref = no rales)			
• Basilar only	0.42 (0.25, 0.60)	1.40	1
• >1/3 of lung field	1.27 (0.83, 1.70)	4.23	4
JVD (ref = no JVD)	0.33 (0.17, 0.50)	1.10	1
Edema (ref = no edema)			
• Trace	0.29 (0.07, 0.50)	0.97	1
• Feet and ankles	0.58 (0.41, 0.76)	1.93	2
• Lower legs and thighs	0.85 (0.66, 1.03)	2.77	3
• Sacrum	1.93 (1.03, 2.83)	6.43	6
S3 (ref = no S3)	0.30 (0.12, 0.47)	1.00	1

Ref, reference; CI, confidence interval; JVD, jugular venous distention; S3, third heart sound.

**SUPPLEMENTARY TABLE 2. Baseline Clinical Characteristics by Individual Physical Exam Sign**

	Jugular Venous Distention		Edema		S3 Heart Sound		Rales	
	No (N=7563)	Yes (N=817)	No (N=7187)	Yes (N=1193)	No (N=7584)	Yes (N=796)	No (N=7717)	Yes (N=663)
Jugular venous distention	-	-	553 (7.7 %)	264 (22.1%)	629 (8.3 %)	188 (23.6%)	640 (8.3 %)	177 (26.7%)
Edema	929 (12.3%)	264 (32.3%)	-	-	1044 (13.8%)	149 (18.7%)	916 (11.9%)	277 (41.8%)
S3 heart sound	608 (8.0 %)	188 (23.0%)	647 (9.0 %)	149 (12.5%)	-	-	688 (8.9 %)	108 (16.3%)
Rales	486 (6.4 %)	177 (21.7%)	386 (5.4 %)	277 (23.2%)	555 (7.3 %)	108 (13.6%)	-	-
Age, years	64 ± 11	65 ± 11	63 ± 11	66 ± 11	64 ± 11	62 ± 12	64 ± 11	67 ± 10
Female, n (%)	1632 (21.6%)	199 (24.4%)	1544 (21.5%)	287 (24.1%)	1642 (21.7%)	189 (23.7%)	1659 (21.5%)	172 (25.9%)
White race, n (%)								
White	5024 (66.4%)	509 (62.3%)	4645 (64.6%)	888 (74.4%)	5095 (67.2%)	438 (55.0%)	5000 (64.8%)	533 (80.4%)
Black	365 (4.8 %)	60 (7.3 %)	378 (5.3 %)	47 (3.9 %)	382 (5.0 %)	43 (5.4 %)	402 (5.2 %)	23 (3.5 %)
Asian	1420 (18.8%)	85 (10.4%)	1389 (19.3%)	116 (9.7 %)	1248 (16.5%)	257 (32.3%)	1453 (18.8%)	52 (7.8 %)
Other	754 (10.0%)	163 (20.0%)	775 (10.8%)	142 (11.9%)	859 (11.3%)	58 (7.3 %)	862 (11.2%)	55 (8.3 %)
Region								
North America	557 (7.4 %)	43 (5.3 %)	513 (7.1 %)	87 (7.3 %)	549 (7.2 %)	51 (6.4 %)	573 (7.4 %)	27 (4.1 %)
Latin American	1217 (16.1%)	213 (26.1%)	1249 (17.4%)	181 (15.2%)	1339 (17.7%)	91 (11.4%)	1361 (17.6%)	69 (10.4%)
Western Europe	1896 (25.1%)	149 (18.2%)	1814 (25.2%)	231 (19.4%)	1948 (25.7%)	97 (12.2%)	1952 (25.3%)	93 (14.0%)

Central Europe	2494 (33.0%)	329 (40.3%)	2242 (31.2%)	581 (48.7%)	2527 (33.3%)	296 (37.2%)	2400 (31.1%)	423 (63.8%)
Asia-Pacific	1399 (18.5%)	83 (10.2%)	1369 (19.0%)	113 (9.5 %)	1221 (16.1%)	261 (32.8%)	1431 (18.5%)	51 (7.7 %)
NYHA Class, n (%)								
I	366 (4.8 %)	23 (2.8 %)	375 (5.2 %)	14 (1.2 %)	354 (4.7 %)	35 (4.4 %)	381 (4.9 %)	8 (1.2 %)
II	5473 (72.4%)	440 (53.9%)	5336 (74.2%)	577 (48.4%)	5419 (71.5%)	494 (62.1%)	5660 (73.3%)	253 (38.2%)
III	1690 (22.3%)	328 (40.1%)	1443 (20.1%)	575 (48.2%)	1769 (23.3%)	249 (31.3%)	1629 (21.1%)	389 (58.7%)
IV	34 (0.4 %)	26 (3.2 %)	33 (0.5 %)	27 (2.3 %)	42 (0.6 %)	18 (2.3 %)	47 (0.6 %)	13 (2.0 %)
Diagnosis of heart failure								
<1 year	2279 (30.1%)	238 (29.1%)	2214 (30.8%)	303 (25.4%)	2246 (29.6%)	271 (34.0%)	2348 (30.4%)	169 (25.5%)
1-5 years	2894 (38.3%)	329 (40.3%)	2771 (38.6%)	452 (37.9%)	2904 (38.3%)	319 (40.1%)	2931 (38.0%)	292 (44.0%)
>5 years	2390 (31.6%)	250 (30.6%)	2202 (30.6%)	438 (36.7%)	2434 (32.1%)	206 (25.9%)	2438 (31.6%)	202 (30.5%)
MAGGIC risk score	20.6 ± 5.7	22.0 ± 5.9	20.6 ± 5.6	22.1 ± 5.9	20.7 ± 5.7	21.0 ± 5.8	20.6 ± 5.6	23.0 ± 5.8
Kansas City Cardiomyopathy Questionnaire overall score	74 ± 19	66 ± 22	75 ± 19	61 ± 21	73 ± 19	70 ± 21	74 ± 19	63 ± 19
<b>Physical Characteristics</b>								
Systolic blood pressure, mmHg	121 ± 15	123 ± 15	121 ± 15	125 ± 15	121 ± 15	122 ± 14	121 ± 15	125 ± 14
Diastolic blood pressure, mmHg	73 ± 10	75 ± 10	73 ± 10	75 ± 11	73 ± 10	75 ± 9	73 ± 10	77 ± 9
Heart rate (beats/min)	72 ± 12	74 ± 13	72 ± 12	74 ± 13	72 ± 12	74 ± 12	72 ± 12	75 ± 13
Body mass index (kg/m <sup>2</sup> )	28.2 ±	28.0 ±	27.8 ±	30.1 ±	28.3 ±	27.2 ±	28.1 ±	28.5 ±



Estimated glomerular filtration rate (mL/min/1.78 m <sup>2</sup> )	67.7 ± 20.0	68.3 ± 20.7	68.0 ± 20.0	65.7 ± 20.8	67.5 ± 20.0	69.7 ± 20.9	67.8 ± 20.2	67.0 ± 19.4
Hemoglobin (mg/dL)	13.9 ± 1.6	13.9 ± 1.7	13.9 ± 1.6	13.9 ± 1.7	14.0 ± 1.6	13.7 ± 1.7	13.9 ± 1.6	13.9 ± 1.7
BNP (pg/mL)*	247 [152, 455]	320 [180, 644]	247 [151, 455]	284 [172, 581]	250 [154, 464]	277 [159, 505]	250 [153, 464]	294 [172, 544]
NT-proBNP (pg/mL)*	1572 [870, 3076]	2101 [1109, 4806]	1564 [870, 3095]	1892 [1042, 4269]	1609 [886, 3185]	1639 [878, 3560]	1586 [877, 3142]	1883 [1059, 4282]
<b>Imaging Data</b>								
Ejection fraction (%)	29.5 ± 6.2	29.2 ± 6.2	29.4 ± 6.2	30.1 ± 6.1	29.6 ± 6.2	28.5 ± 6.3	29.4 ± 6.2	30.1 ± 5.9

NYHA, New York Heart Association, BNP, b-type natriuretic peptide; N-terminal pro-B-type natriuretic peptide (NT-proBNP).

\*Presented as median (25<sup>th</sup> – 75<sup>th</sup> percentile) since the variable is right-skewed.

**SUPPLEMENTARY TABLE 3. Baseline Characteristics of Participants by Change in Congestion between Time of Randomization and 4 Month Visit**

	<b>Decrease in Congestion N=1016</b>	<b>No Change in Congestion N=6289</b>	<b>Increase in Congestion N=659</b>	<b>P-value</b>
Jugular venous distention	348 (34.3%)	364 (5.8 %)	43 (6.5 %)	<0.001
Edema	573 (56.4%)	502 (8.0 %)	46 (7.0 %)	<0.001
S3 heart sound	267 (26.3%)	427 (6.8 %)	49 (7.4 %)	<0.001
Rales	333 (32.8%)	248 (3.9 %)	32 (4.9 %)	<0.001
Age, years	65 ± 11	63 ± 11	65 ± 11	<0.001
Female, n (%)	240 (23.6%)	1349 (21.5%)	144 (21.9%)	0.30
Race, n (%)				<0.001
White	688 (67.7%)	4128 (65.6%)	472 (71.6%)	
Black	62 (6.1 %)	298 (4.7 %)	40 (6.1 %)	
Asian	125 (12.3%)	1195 (19.0%)	94 (14.3%)	
Other	141 (13.9%)	668 (10.6%)	53 (8.0 %)	
Region				<0.001
North America	65 (6.4 %)	438 (7.0 %)	68 (10.3%)	
Latin American	205 (20.2%)	1054 (16.8%)	92 (14.0%)	
Western Europe	218 (21.5%)	1552 (24.7%)	187 (28.4%)	
Central Europe	403 (39.7%)	2069 (32.9%)	220 (33.4%)	
Asia-Pacific	125 (12.3%)	1176 (18.7%)	92 (14.0%)	
NYHA Class, n (%)				<0.001
I	35 (3.4 %)	305 (4.8 %)	30 (4.6 %)	
II	565 (55.6%)	4642 (73.8%)	447 (67.8%)	
III	397 (39.1%)	1312 (20.9%)	174 (26.4%)	
IV	19 (1.9 %)	30 (0.5 %)	8 (1.2 %)	
Diagnosis of heart failure				<0.001
<1 year	284 (28.0%)	1945 (30.9%)	161 (24.4%)	
1-5 years	405 (39.9%)	2407 (38.3%)	249 (37.8%)	
>5 years	327 (32.2%)	1937 (30.8%)	249 (37.8%)	
MAGGIC risk score	21.9 ± 5.8	20.4 ± 5.6	21.7 ± 5.6	<0.001
Kansas City Cardiomyopathy Questionnaire overall score	66 ± 20	75 ± 19	70 ± 20	<0.001
<b>Physical Characteristics</b>				
Systolic blood pressure, mmHg	123 ± 15	121 ± 15	121 ± 16	0.002
Diastolic blood pressure, mmHg	75 ± 10	73 ± 10	73 ± 10	<0.001
Heart rate (beats/min)	74 ± 13	72 ± 12	73 ± 12	<0.001
Body mass index (kg/m <sup>2</sup> )	28.5 ± 5.3	28.1 ± 5.5	29.1 ± 6.2	<0.001
<b>Comorbidities, n (%)</b>				
Hypertension	771 (75.9%)	4364 (69.4%)	497 (75.4%)	<0.001
Atrial fibrillation	422 (41.5%)	2234 (35.5%)	278 (42.2%)	<0.001
Diabetes mellitus	363 (35.7%)	2082 (33.1%)	303 (46.0%)	<0.001
Ischemic heart disease	616 (60.6%)	3750 (59.6%)	397 (60.2%)	0.81
Myocardial infarction	435 (42.8%)	2706 (43.0%)	286 (43.4%)	0.97



Heart failure hospitalization	663 (65.3%)	3903 (62.1%)	437 (66.3%)	0.023
Stroke	89 (8.8 %)	520 (8.3 %)	71 (10.8%)	0.09
Current smoker	141 (13.9%)	914 (14.5%)	82 (12.4%)	0.32
<b>Medication and Device Use, n (%)</b>				
Beta-blocker	930 (91.5%)	5885 (93.6%)	603 (91.5%)	0.013
Digitalis	326 (32.1%)	1869 (29.7%)	202 (30.7%)	0.30
Diuretic	878 (86.4%)	4944 (78.6%)	565 (85.7%)	<0.001
Mineralocorticoid antagonist	575 (56.6%)	3504 (55.7%)	357 (54.2%)	0.62
Implantable cardioverter-defibrillator	133 (13.1%)	930 (14.8%)	134 (20.3%)	<0.001
Cardiac resynchronization therapy	64 (6.3 %)	419 (6.7 %)	72 (10.9%)	<0.001
<b>Laboratory Testing</b>				
Estimated glomerular filtration rate (mL/min/1.78 m <sup>2</sup> )	66.4 ± 19.7	68.4 ± 20.2	63.7 ± 18.6	<0.001
Hemoglobin (mg/dL)	13.8 ± 1.7	14.0 ± 1.6	13.9 ± 1.6	0.036
BNP (pg/mL)*	269 [160 , 554]	243 [150 , 443]	277 [161 , 524]	<0.001
NT-proBNP (pg/mL)*	1780 [981 , 3927]	1536 [852 , 2965]	1789 [1026, 4049]	<0.001
<b>Imaging Data</b>				
Ejection fraction (%)	29.3 ± 6.2	29.6 ± 6.1	29.2 ± 6.7	0.19

NYHA, New York Heart Association; BNP, b-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide (NT-proBNP).

\*Presented as median (25<sup>th</sup> – 75<sup>th</sup> percentile) since the variable is right-skewed.

**SUPPLEMENTARY TABLE 4. Baseline Frequency of Common Combinations of Physical Exam Signs\***

<b>Frequency (%)</b>	<b>N</b>	<b>Combination of Signs</b>
70	5,854	No signs
8	675	Edema only
6	475	S3 heart sound only
5	378	Jugular venous distention only
3	255	Rales only
2	171	Edema and rales
1	122	Jugular venous distention and edema
1	94	Jugular venous distention and S3 heart sound

\*Combinations listed if frequency was greater than 1%.

**SUPPLEMENTARY TABLE 5. Number of Events and Person-years per Sign Category by Treatment Arm**

<b>Outcomes</b>	<b>0 Signs</b>	<b>1 Sign</b>	<b>2 Signs</b>	<b>3 Signs</b>	<b>4 Signs</b>
<b>Composite endpoint</b>					
• Number of events (enalapril)	648	284	109	59	17
• Number of events (sacubitril/valsartan)	512	260	91	41	10
• Number of person-years (enalapril)	6275	1615	448	132	19
• Number of person-years (sacubitril/valsartan)	6520	1634	414	141	9
<b>Cardiovascular death</b>					
• Number of events (enalapril)	388	180	78	38	9
• Number of events (sacubitril/valsartan)	310	152	64	28	4
• Number of person-years (enalapril)	6708	1800	524	170	28
• Number of person-years (sacubitril/valsartan)	6850	1792	484	167	12
<b>Heart failure hospitalization</b>					
• Number of events (enalapril)	360	172	69	43	14
• Number of events (sacubitril/valsartan)	283	163	54	30	7
• Number of person-years (enalapril)	6275	1615	448	132	19
• Number of person-years (sacubitril/valsartan)	6520	1634	414	141	9
<b>All cause mortality</b>					
• Number of events (enalapril)	478	213	91	44	9
• Number of events (sacubitril/valsartan)	410	184	79	32	6

(sacubitril/valsartan)					
• Number of person-years (enalapril)	6708	1800	524	170	28
• Number of person-years (sacubitril/valsartan)	6850	1792	484	167	12

**SUPPLEMENTARY TABLE 6. Crude and Adjusted Hazard Ratios for Efficacy Outcomes by Total Number of Physical Exam Signs at Baseline**

<b>Outcomes</b>	<b>HR (95% CI) per Sign Increase</b>	<b>P-value</b>
<b>Composite endpoint</b>		
• Crude model	1.19 (1.13, 1.26)	<0.001
• Adjustment for NT-proBNP	1.12 (1.06, 1.18)	<0.001
<b>Cardiovascular mortality</b>		
• Crude model	1.19 (1.11, 1.27)	<0.001
• Adjustment for NT-proBNP	1.10 (1.03, 1.18)	0.006
<b>Heart failure hospitalization</b>		
• Crude model	1.18 (1.10, 1.27)	<0.001
• Adjustment for NT-proBNP	1.11 (1.04, 1.20)	0.003
<b>All cause mortality</b>		
• Crude model	1.17 (1.10, 1.25)	<0.001
• Adjustment for NT-proBNP	1.10 (1.03, 1.17)	0.004

HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**SUPPLEMENTARY TABLE 7. Subanalysis of Time-updated Signs of Congestion for Efficacy Outcomes among 2066 Participants with Complete Data during Follow-up.**

<b>Outcomes</b>	<b>0 Signs</b>	<b>1 Sign HR (95% CI)</b>	<b>2 Signs HR (95% CI)</b>	<b>3 or 4 Signs HR (95% CI)</b>
<b>Composite endpoint</b>				
• Events/person-years	299/3519	108/770	35/226	20/105
• Crude model	ref	1.65 (1.32, 2.05)	1.80 (1.27, 2.56)	2.21 (1.41, 2.05)
• Adjustment for time-updated NT-pro-BNP	ref	1.37 (1.09, 1.85)	1.28 (0.88, 1.85)	1.65 (1.05, 2.61)
• Adjustment for time-updated NT-pro-BNP and time-updated MAGGIC score	ref	1.33 (1.05, 1.68)	1.22 (0.84, 1.79)	1.61 (1.01, 2.57)
• Adjustment for time-updated NT-pro-BNP, time-updated MAGGIC score, and time-updated NYHA class	ref	1.27 (1.00, 1.61)	1.11 (0.75, 1.63)	1.38 (0.85, 2.23)

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  
 Subanalysis only includes participants with complete NT-proBNP values, MAGGIC score, and NYHA class at randomization, 1 month, and 8 month visits (N=2066).

**SUPPLEMENTARY TABLE 8. Time-updated Crude and Adjusted Hazard Ratios for Efficacy Outcomes by Individual Physical Exam Signs**

<b>Outcomes</b>	<b>Jugular Venous Distention HR (95% CI)</b>	<b>Edema HR (95% CI)</b>	<b>S3 Heart Sound HR (95% CI)</b>	<b>Rales HR (95% CI)</b>
Composite endpoint				
• Crude model	1.34 (1.17, 1.53)	2.07 (1.86, 2.31)	1.40 (1.22, 1.61)	1.87 (1.64, 3.12)
• Adjustment for baseline NT-proBNP	1.22 (1.07, 1.39)	1.97 (1.77, 2.20)	1.44 (1.25, 1.65)	1.76 (1.54, 2.01)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.19 (1.04, 1.35)	1.93 (1.73, 2.15)	1.44 (1.25, 1.65)	1.67 (1.46, 1.91)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.05 (0.92, 1.20)	1.69 (1.51, 1.89)	1.34 (1.16, 1.54)	1.49 (1.30, 1.70)
Cardiovascular mortality				
• Crude model	1.36 (1.16, 1.61)	2.01 (1.75, 2.30)	1.35 (1.15, 1.62)	1.81 (1.53, 2.13)
• Adjustment for baseline NT-proBNP	1.22 (1.04, 1.44)	1.89 (1.65, 2.17)	1.37 (1.15, 1.64)	1.68 (1.43, 1.99)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.17 (1.00, 1.38)	1.83 (1.60, 2.10)	1.37 (1.15, 1.63)	1.59 (1.35, 1.88)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.03 (0.87, 1.22)	1.59 (1.38, 1.83)	1.28 (1.07, 1.53)	1.38 (1.16, 1.63)
HF hospitalization				
• Crude model	1.51 (1.29, 1.78)	2.37 (2.07, 2.71)	1.43 (1.20, 1.71)	2.03 (1.72, 2.39)

• Adjustment for baseline NT-proBNP	1.38 (1.18, 1.63)	2.27 (1.98, 2.61)	1.48 (1.24, 1.76)	1.92 (1.63, 2.27)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.35 (1.15, 1.59)	2.22 (1.94, 2.54)	1.48 (1.24, 1.76)	1.82 (1.55, 2.15)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.16 (0.99, 1.37)	1.89 (1.64, 2.17)	1.33 (1.11, 1.59)	1.60 (1.36, 1.89)
All cause mortality				
• Crude model	1.39 (1.20, 1.61)	1.83 (1.62, 2.08)	1.28 (1.09, 1.51)	1.81 (1.56, 2.11)
• Adjustment for baseline NT-proBNP	1.26 (1.09, 1.46)	1.74 (1.53, 1.97)	1.30 (1.11, 1.53)	1.70 (1.46, 1.98)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	1.20 (1.04, 1.40)	1.68 (1.48, 1.90)	1.29 (1.10, 1.52)	1.60 (1.37, 1.86)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	1.08 (0.93, 1.25)	1.48 (1.30, 1.68)	1.22 (1.03, 1.44)	1.40 (1.20, 1.63)

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.



**SUPPLEMENTARY TABLE 9. Time-updated Adjusted Hazard Ratios for Efficacy Outcomes by Graded Assessment of Physical Examination Signs**

<b>Signs</b>	<b>Weighted Number of Points*</b>	<b>Cardiovascular Mortality HR (95% CI)</b>	<b>Composite Endpoint HR (95% CI)</b>	<b>HF Hospitalization HR (95% CI)</b>	<b>All Cause Mortality HR (95% CI)</b>
<b>Jugular venous distention</b>					
• Present	1	1.02 (0.86, 1.20)	1.05 (0.92, 1.20)	1.17 (0.99, 1.38)	1.06 (0.91, 1.23)
<b>Edema</b>					
• Trace	1	1.12 (0.90, 1.41)	1.18 (1.00, 1.41)	1.22 (0.98, 1.53)	1.07 (0.87, 1.31)
• Feet and ankles	2	1.46 (1.22, 1.74)	1.42 (1.23, 1.64)	1.51 (1.26, 1.81)	1.34 (1.14, 1.57)
• Lower legs and thighs	3	1.79 (1.48, 2.16)	2.18 (1.88, 2.52)	2.57 (2.15, 3.08)	1.66 (1.39, 1.98)
• Sacrum	6	7.58 (3.83, 15.01)	15.85 (7.46, 33.70)	17.37 (7.09, 42.57)	5.84 (2.96, 11.53)
<b>S3 heart sound</b>					
• Present	1	1.29 (1.08, 1.54)	1.32 (1.15, 1.52)	1.30 (1.09, 1.55)	1.23 (1.04, 1.44)
<b>Rales</b>					
• Basilar only	1	1.30 (1.09, 1.56)	1.43 (1.25, 1.65)	1.53 (1.29, 1.82)	1.31 (1.12, 1.54)
• >1/3 of lung field	4	2.02 (1.30, 3.13)	1.91 (1.27, 2.87)	2.08 (1.28, 3.38)	2.41 (1.65, 3.52)
<b>Sign score (per 1 point increase)</b>	-	1.20 (1.16, 1.25)	1.25 (1.22, 1.29)	1.32 (1.27, 1.37)	1.19 (1.15, 1.23)

HF, heart failure; HR, hazard ratio; CI, confidence interval.

All referent arms for individual signs are the absence of the physical examination sign.

Analyses adjusted for baseline NT-proBNP, time-updated Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, time-updated New York Heart Association class, as well as presence of other examination signs.

\*Weighted based upon beta-coefficients for cardiovascular mortality.

**SUPPLEMENTARY TABLE 10. Time-updated, Sensitivity Analysis including Crude and Adjusted Hazard Ratios for Heart Failure Related Outcomes by Total Number of Physical Exam Signs\***

<b>Outcomes</b>	<b>0 Signs</b>	<b>1 Sign HR (95% CI)</b>	<b>2 Signs HR (95% CI)</b>	<b>3 Signs HR (95% CI)</b>	<b>4 Signs HR (95% CI)</b>
<b>Composite endpoint</b>					
• Events/person-years	1205/12780	531/3213	186/838	86/267	15/25
• Crude model	ref	1.74 (1.57, 1.92)	2.33 (1.99, 2.72)	3.42 (2.75, 4.25)	6.18 (3.71, 10.28)
• Adjustment for baseline NT-proBNP	ref	1.65 (1.49, 1.83)	2.10 (1.80, 2.46)	2.91 (2.33, 3.62)	5.47 (3.29, 9.10)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	ref	1.59 (1.43, 1.76)	1.95 (1.67, 2.28)	2.77 (2.22, 3.45)	4.66 (2.80, 7.76)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-updated NYHA class	ref	1.47 (1.33, 1.63)	1.61 (1.37, 1.89)	2.05 (1.63, 2.57)	3.38 (2.02, 5.66)
<b>Heart failure hospitalization</b>					
• Events/person-years	676/12780	333/3213	107/838	62/267	12/25
• Crude model	ref	1.93 (1.70, 2.21)	2.38 (1.94, 2.92)	4.39 (3.39, 5.70)	8.62 (4.87, 15.26)
• Adjustment for baseline NT-proBNP	ref	1.84 (1.62, 2.10)	2.16 (1.76, 2.66)	3.77 (2.90, 4.89)	7.72 (4.36, 13.67)
• Adjustment for baseline NT-proBNP and time-updated MAGGIC score	ref	1.77 (1.55, 2.02)	2.00 (1.63, 2.46)	3.58 (2.75, 4.64)	6.53 (3.68, 11.58)
• Adjustment for baseline NT-proBNP, time-updated MAGGIC score, and time-	ref	1.62 (1.41, 1.85)	1.60 (1.30, 1.98)	2.54 (1.93, 3.34)	4.57 (2.56, 8.14)

updated NYHA class					
--------------------	--	--	--	--	--

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

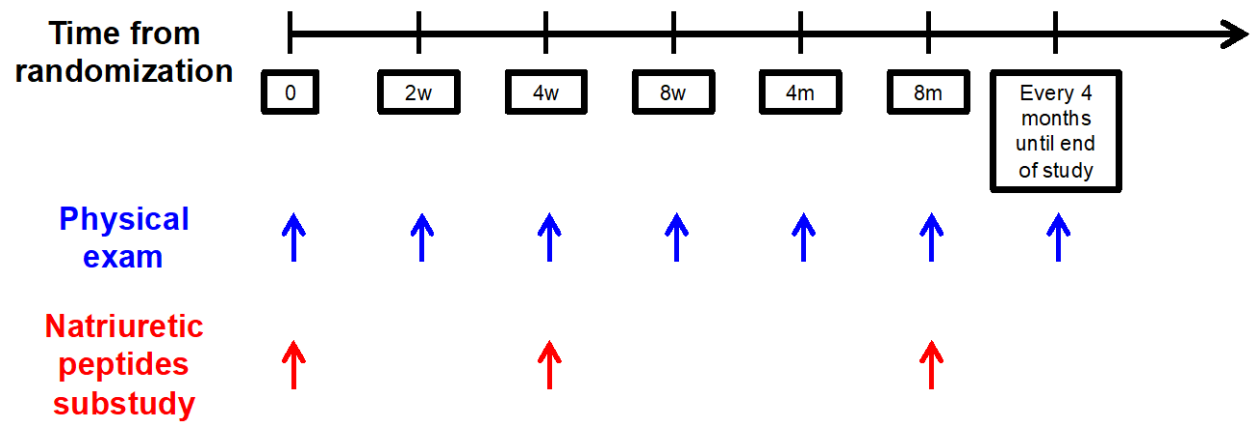
\*Patient censored if hospitalized the same date as a clinic visit.

**SUPPLEMENTARY TABLE 11. Multivariable Predictors (P<0.01) of Change in Number of Physical Exam Signs at 4 Months, Based Upon Characteristics at Time of Randomization**

	<b>Odds Ratio</b>	<b>95% Confidence Interval</b>	<b> Z </b>	<b>P-value</b>
Baseline number of physical exam signs	0.15	0.13, 0.16	39.5	<0.001
Enrollment from Latin America	0.65	0.55, 0.76	5.40	<0.001
Diabetes mellitus	1.28	1.13, 1.44	3.90	<0.001
Body mass index	1.02	1.01, 1.03	3.25	0.001
Log NT-proBNP	1.11	1.04, 1.18	3.24	0.001
Enrollment from Western Europe	0.80	0.70, 0.92	3.06	0.002
Diuretic use	1.23	1.05, 1.43	2.72	0.006

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**SUPPLEMENTARY FIGURE 1.**



## SUPPLEMENTARY FIGURE 2.

