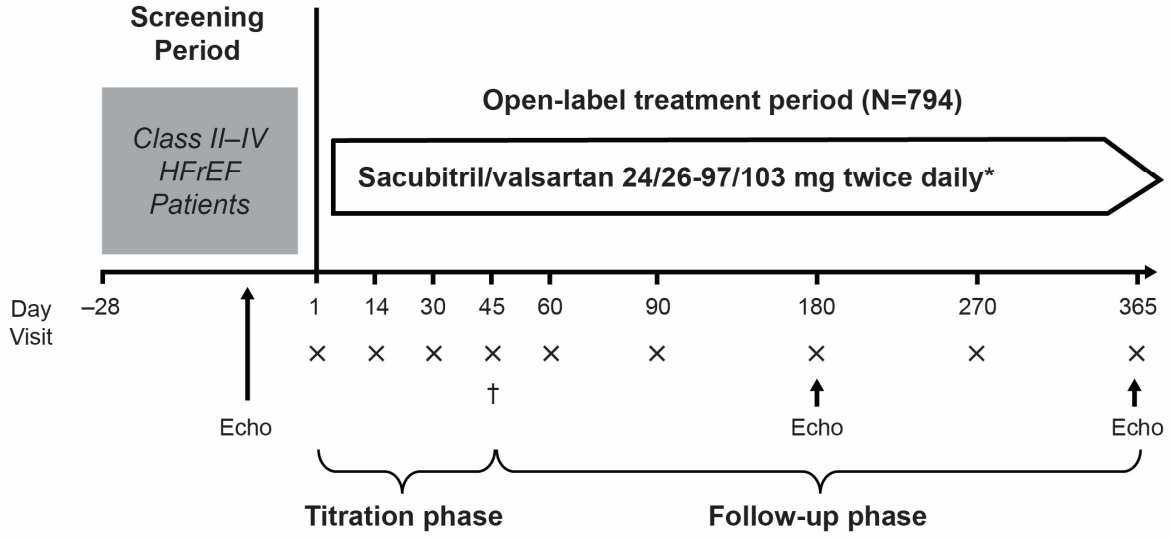
Supplementary Online Content

Januzzi Jr JL, Prescott MF, Butler J, et al; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril/valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. doi:10.1001/jama.201912821

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1: Study procedures during PROVE-HF. Patients were included in the remodeling analyses if their echocardiograms were performed within ± 7 days of the 6 and 12 month follow up visit.

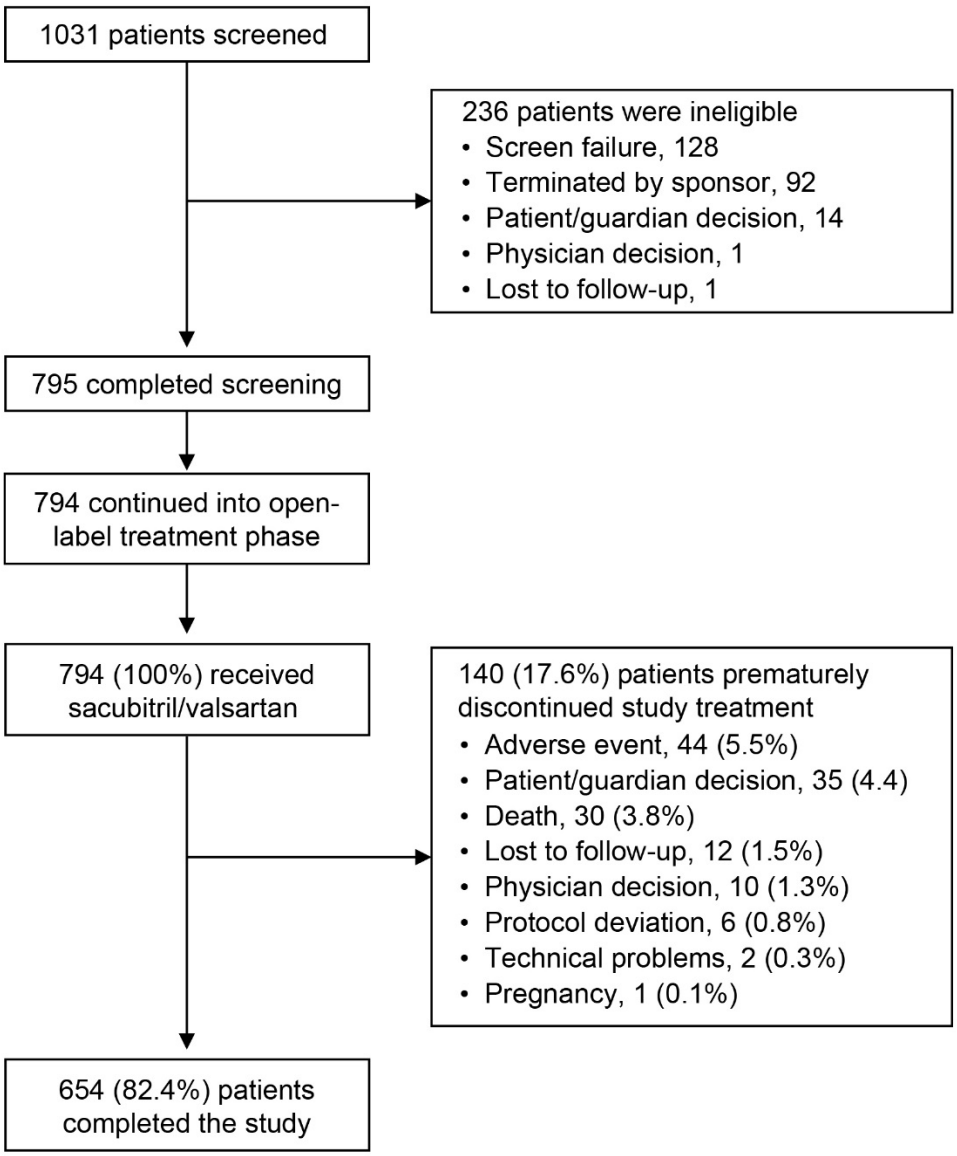


X = Vital status/events (CV death, HF hospitalization, worsening HF), physical examination, blood samples for safety chemistry and biomarkers, urine sampling, HF symptom assessment, KCCQ-23.

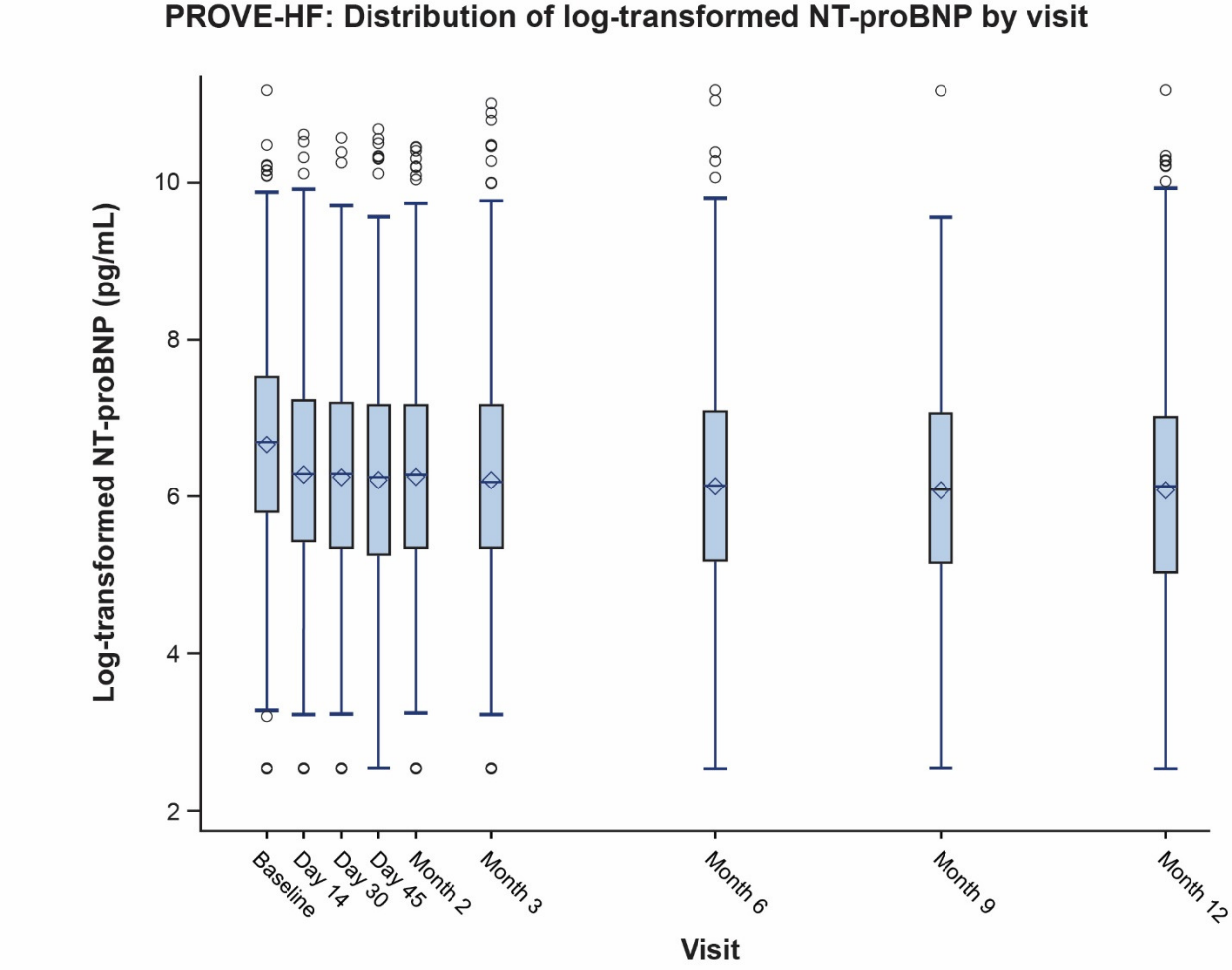
* Standard HF therapy was continued throughout the study with the exception of ACEI/ARB; †At Day 45, KCCQ-23 was not administered.

CV denotes: cardiovascular; HF denotes: heart failure; KCCQ-23 denotes: Kansas City Cardiomyopathy Questionnaire-23.

eFigure 2: Study flow diagram and patient disposition.

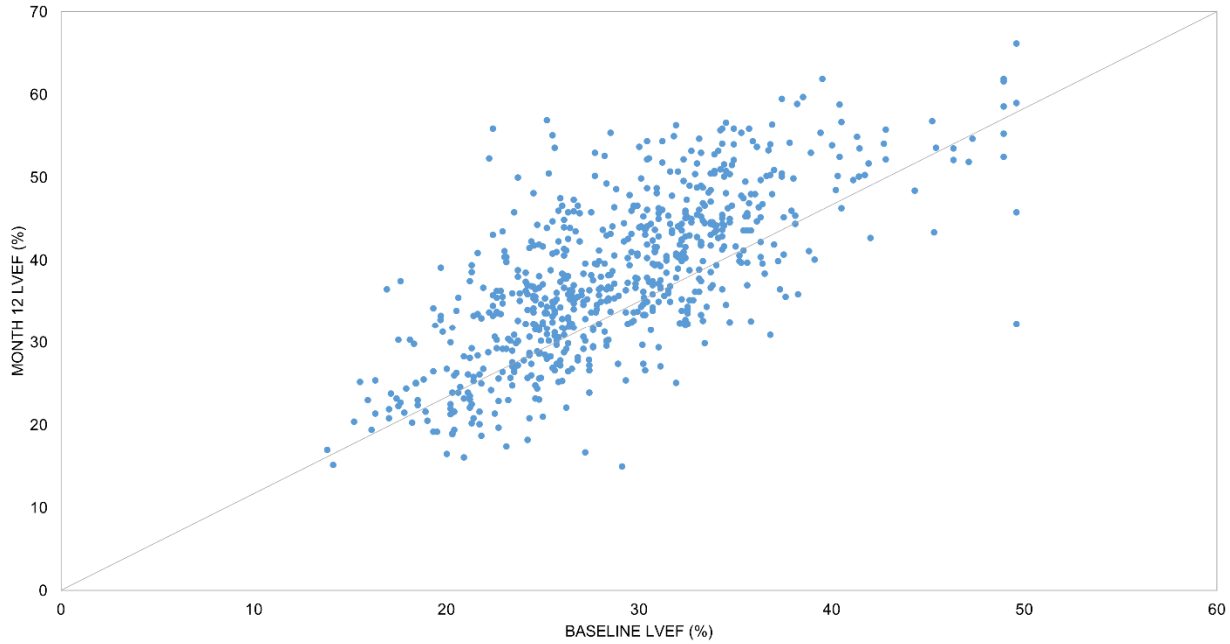


eFigure 3: Boxplots detailing median concentrations of log_2-NT-proBNP across study visits. Boxes indicate 25th-75th percentile concentrations, whiskers identify the 5th and 95th percentiles, and open circles indicate outliers. The line identifies median values while diamonds identify mean values.

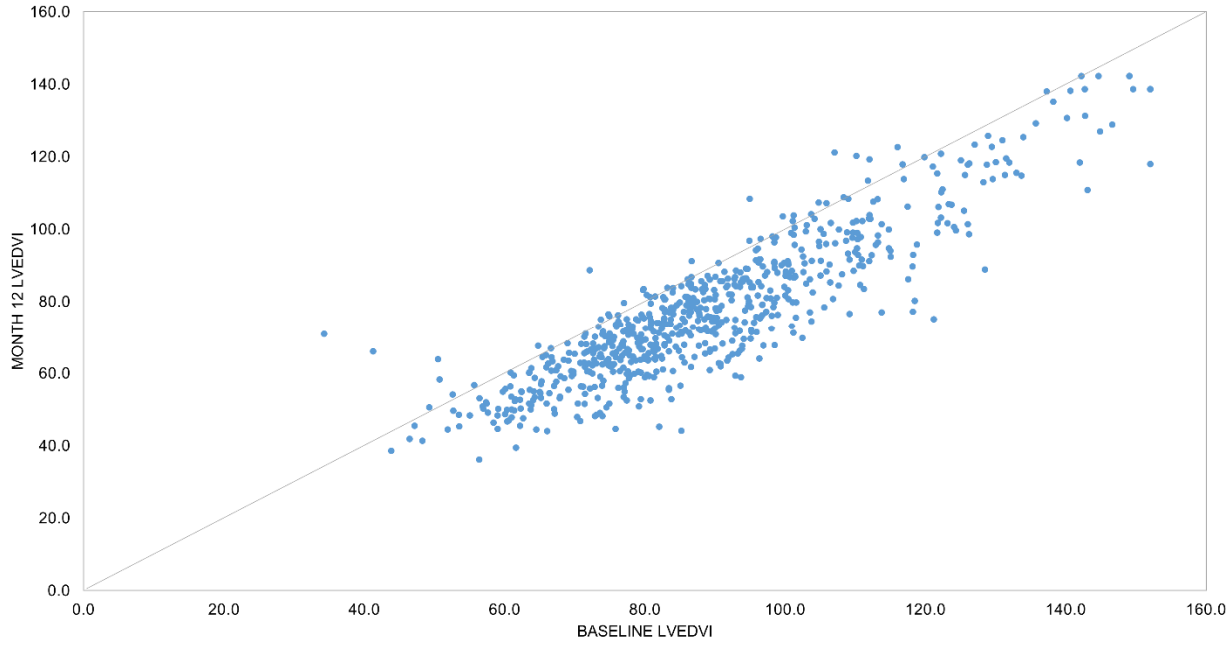


eFigure 4: Scatter plots demonstrating baseline versus 12 month results for A) LVEF, B) LVEDVi, C) LVESVi, D) LAVi, and E) E/E'. Improvement of cardiac performance or volumes was evident with each variable.

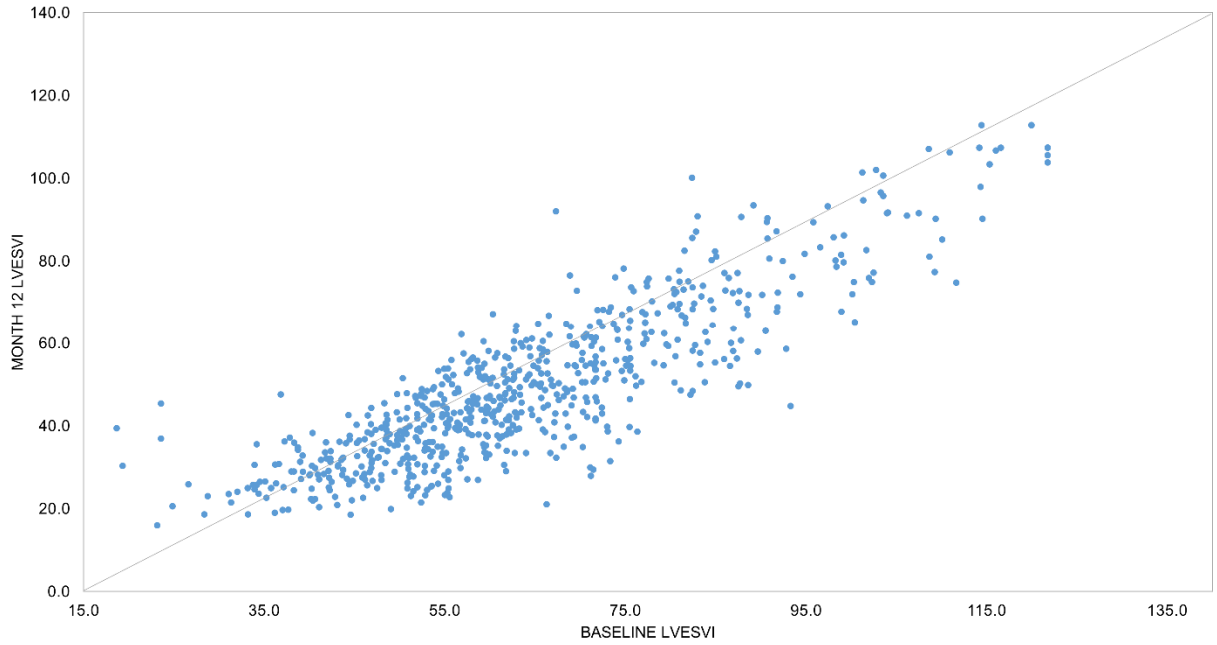
A)



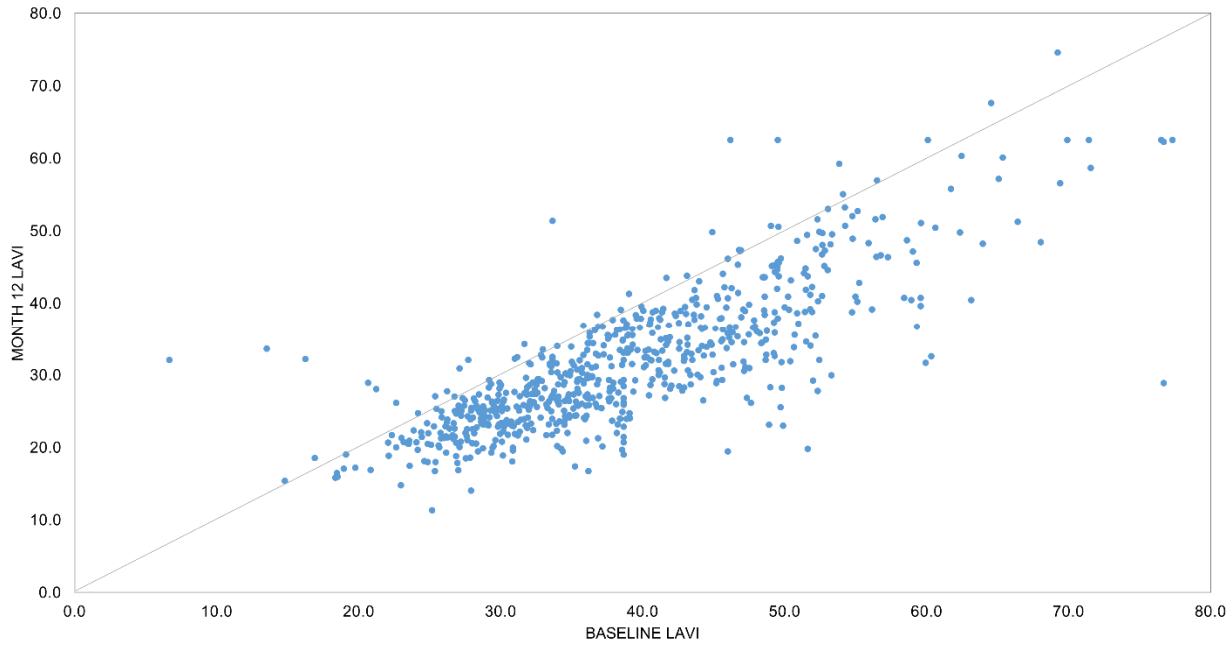
B)



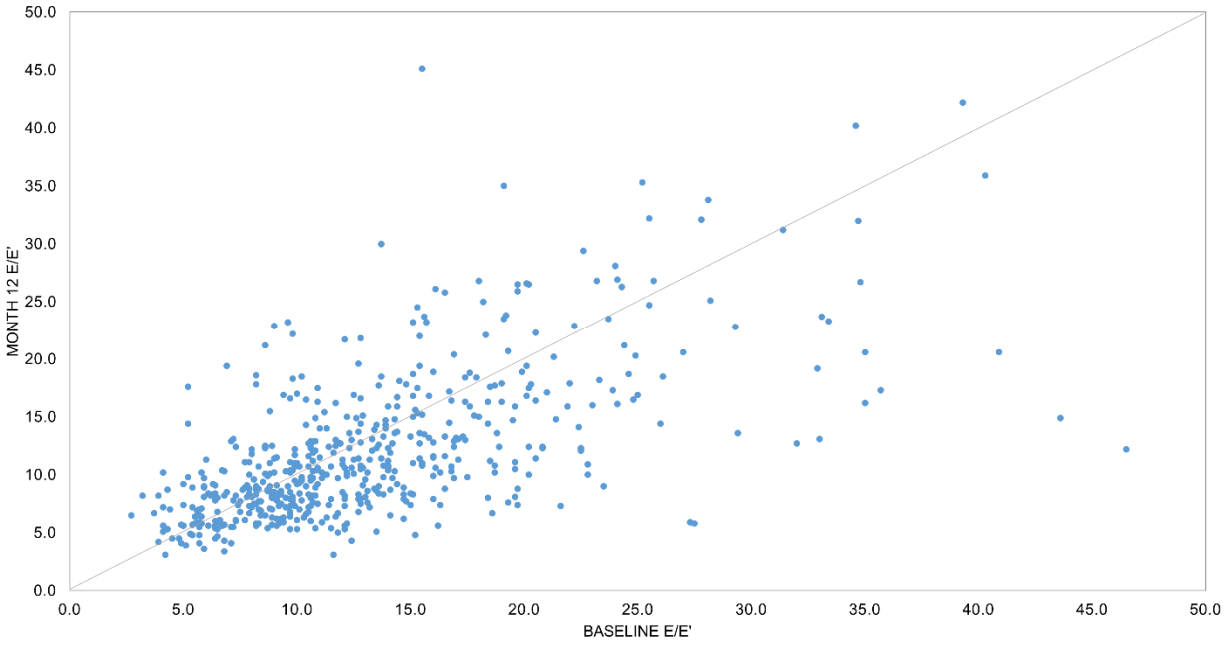
C)



D)



E)



eTable 1: Patient eligibility criteria for PROVE-HF.

Key Inclusion Criteria	Key Exclusion Criteria
• Aged ≥18 years • Patients with HFrEF who are candidates for on-label sacubitril/valsartan treatment per the standard of care • NYHA functional class II, III, or IV • LVEF ≤40% within the preceding 6 months according to any local measurement, and no subsequent documentation of EF >40% ○ For EF measurements expressed as ranges, the average of the range endpoint values should be <40% • Stable dose of loop diuretic for the 2 weeks preceding study start	• History of hypersensitivity/allergy or suspected contraindication to any study-drug component or to drugs of similar chemical classes, including ACEIs, angiotensin receptor blockers, or neprilysin inhibitors • Any angioedema history (drug related or otherwise) • Concomitant use of ACEI therapy, nesiritide, aliskiren, or drugs that may affect absorption of the study medication • Current or previous treatment with sacubitril/valsartan • Inadequate washout of other investigational drugs before study initiation • Enrollment in another clinical trial within 30 days of screening • Potassium >5.2 mEq/L at screening • History of malignancy within 1 year • Pregnancy, lactation, or use of any method of contraception that is not highly effective • Implantation of CRT/D within 6 months of screening visit • Prior heart transplant or left ventricular assist device or intent to implant either

eTable 2: Median (25th, 75th percentile) NT-proBNP concentrations at each study time-point.

Time point	N	Median NT-proBNP (25th, 75th percentile), pg/mL
Baseline	760	816 (332, 1822)
Day 14	754	528 (226, 1378)
Day 30	740	546 (211, 1321)
Day 45	734	514 (192, 1297)
Month 2	721	535 (210, 1299)
Month 3	719	488 (211, 1315)
Month 6	699	473 (179, 1163)
Month 9	659	444 (170, 1153)
Month 12	638	455 (153, 1090)

NT-proBNP denotes: amino-terminal pro-B type natiuretic peptide; pg/mL denotes: picograms per milliliter

eTable 3: Correlations between change in Log_2-NT-proBNP and echocardiographic measurements at 6 months post-enrollment.

Parameter	N	Pearson r (95% CI)	*P* value
NT-proBNP (pg/mL) / LVEF (%)	651	-0.226 (-0.298, -0.152)	<.0001
NT-proBNP (pg/mL) / LVEDVi (mL/m^2)	650	0.164 (0.088, 0.238)	<.0001
NT-proBNP (pg/mL) / LVESVi (mL/m^2)	650	0.233 (0.159, 0.305)	<.0001
NT-proBNP (pg/mL) / LAVi (mL/m^2)	625	0.190 (0.113, 0.264)	<.0001
NT-proBNP (pg/mL) / E/E'	495	0.210 (0.124, 0.292)	<.0001

NT-proBNP denotes: amino-terminal pro-B type natriuretic peptide; pg/mL denotes: picograms per milliliter; LVEF denotes: left ventricular ejection fraction; LVEDVi denotes: left ventricular end-diastolic volume index; mL denotes: milliliter; LAVi denotes: left atrial volume index; E/E' denotes: ratio of early diastolic filling velocity and early diastolic mitral annular velocity.

eTable 4: Echocardiographic results only in those subjects with available data from all three echocardiographic examinations (baseline, 6 months, and 12 months).

Parameter	N	Baseline value, median (25^{th}, 75^{th} percentile)	LS mean change from baseline at 6 months (95% CI)	*P* value	LS mean change from baseline at 12 months (95% CI)	*P* value
LVEF (%)	619	28.4 (24.8, 33.0)	+5.2 (+4.8, +5.6)	<.0001	+9.4 (+8.9, +10.0)	<.0001
LVEDVi (mL/m^2)	618	86.51 (75.42, 98.76)	-6.76 (-7.24, -6.28)	<.0001	-12.39 -13.08, -11.70)	<.0001
LVESVi (mL/m^2)	618	61.06 (51.69, 73.04)	-8.76 (-9.29, -8.23)	<.0001	-15.41 (-16.16, -14.65)	<.0001
LAVi (mL/m^2)	590	36.78 (31.20, 45.61)	-4.36 (-4.76, -3.97)	<.0001	-7.54 (-7.97, -7.11)	<.0001
E/E’	432	11.20 (8.45, 15.60)	-1.32 (-1.77, -0.87)	<.0001	-1.35 (-1.82, -0.88)	<.0001

LS denotes: least-square; LVEF denotes: left ventricular ejection fraction; LVEDVi denotes: left ventricular end-diastolic volume index; mL denotes: milliliter; LAVi denotes: left atrial volume index; E/E’ denotes: ratio of early diastolic filling velocity and early diastolic mitral annular velocity.

eTable 5: Adverse events of interest during the 12 months of PROVE-HF.

Event	N = 794; n, (%)
Hypotension (systolic blood pressure <90 mm mercury)	140 (17.6)
Dizziness	133 (16.8)
Hyperkalemia (potassium > 5.3 milliequivalents/liter)	105 (13.2)
Worsening kidney function*	98 (12.3)
Angioedema	
No treatment or antihistamines only without hospitalization	2 (0.3)
Use of catecholamines or glucocorticoids without hospitalization	0
Hospitalization without airway compromise	0
Airway compromise	0

*Worsening (decrease) in estimated glomerular filtration rate of ≥ 35% from baseline, or an increase in creatinine of ≥ 0.5 mg/dL from baseline and a worsening (decrease) in estimated glomerular filtration rate of ≥ 25% from baseline at a given visit.