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ORIGINAL INVESTIGATIONS

Uptitrating Treatment After Heart Failure Hospitalization Across the Spectrum of Left Ventricular Ejection Fraction

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ABSTRACT

BACKGROUND Acute heart failure (AHF) is associated with a poor prognosis regardless of left ventricular ejection fraction (LVEF). STRONG-HF showed the efficacy and safety of a strategy of rapid uptitration of oral treatment for heart failure (HF) and close follow-up (high-intensity care), compared with usual care, in patients recently hospitalized for AHF and enrolled independently from their LVEF.

OBJECTIVES In this study, we sought to assess the impact of baseline LVEF on the effects of high-intensity care vs usual care in STRONG-HF.

METHODS The STRONG-HF trial enrolled patients hospitalized for AHF with any LVEF and not treated with full doses of renin-angiotensin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. High-intensity care with uptitration of oral medications was performed independently from LVEF. The primary endpoint was the composite of HF rehospitalization or all-cause death at day 180.

RESULTS Among the 1,078 patients randomized, 731 (68%) had LVEF ≤40% and 347 (32%) had LVEF >40%. The treatment benefit of high-intensity care vs usual care on the primary endpoint was consistent across the whole LVEF spectrum (interaction *P* with LVEF as a continuous variable = 0.372). Mean difference in the EQ-5D visual analog scale change from baseline to day 90 between treatment arms was slightly greater at higher LVEF values, but with no interaction between LVEF as a continuous variable and the treatment strategy (interaction *P* = 0.358). Serious adverse events were also independent from LVEF.

CONCLUSIONS Rapid uptitration of oral medications for HF and close follow-up reduce 180-day death and HF rehospitalization after AHF hospitalization independently from LVEF. (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-ProBNP Testing, of Heart Failure Therapies [STRONG-HF]; NCT03412201)
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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AHF = acute heart failure

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonists

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RAS = renin-angiotensin system

SGLT = sodium-glucose cotransporter

VAS = visual analog scale

Hospitalizations for acute heart failure (AHF) are followed by a high risk of heart failure (HF) rehospitalization and mortality.[1-4] The STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-ProBNP Testing, of Heart Failure Therapies; NCT03412201) trial demonstrated that a high-intensity care treatment strategy characterized by rapid uptitration of oral medications for HF and close follow-up with multiple early ambulatory visits after an admission for AHF improves quality of life and reduces the risk of 180-day all-cause death or HF rehospitalization, compared with usual care, in patients with any left ventricular ejection fraction (LVEF).[5] However, the use of renin-angiotensin system (RAS) modulators (ie, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or angiotensin receptor-neprilysin inhibitors [ARNIs]), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) is best supported by evidence in patients with chronic heart failure with reduced ejection fraction (HFrEF) (LVEF ≤40%).[1,2] Recent data suggest that some benefit can be seen in patients with heart failure with mildly reduced ejection fraction (HFmrEF),[1,2] and no studies have directly addressed the efficacy of those drugs in AHF. Nevertheless, patients with HF and LVEF >40% frequently receive neurohormonal modulators and have comorbidities, such as hypertension, that are established indications for them. Indeed, neurohormonal activation may be present in patients with both preserved and reduced LVEF.[6,7] In the decompensated AHF state, greater neurohormonal activation may occur, related to the episode of decompensation and/or its intravenous treatment, so that treatment with neurohormonal antagonists may have beneficial effects independently from LVEF. Causes of decompensation, clinical characteristics, and hemodynamic measurements are indeed similar in patients with decompensated HF and reduced or preserved LVEF, with congestion as the main pathophysiologic mechanism.[8-11]

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We therefore assessed whether a high-intensity care strategy with rapid uptitration of neurohormonal antagonists and modulators is safe and effective across different LVEF categories in the patients with AHF enrolled in STRONG-HF.

METHODS

STUDY DESIGN. The design and main results of the STRONG-HF trial have been previously reported.[5,12,13] In brief, this international, multicenter, open-label, randomized trial compared a high-intensity care strategy with early uptitration of beta-blockers, ACE inhibitors (or ARBs in patients intolerant to ACE inhibitors), or ARNIs and MRAs vs usual care, in 1,078 patients aged 18 to 85 years admitted to hospital for AHF and not treated with full doses of oral treatments for HF. Included patients were hospitalized within 72 hours before screening for AHF, were hemodynamically stable, and had high N-terminal pro-B-type natriuretic peptide (NT-proBNP) values (>2,500 pg/mL) at screening with a >10% decrease in value between screening and randomization (but still >1,500 pg/mL). Patients with any LVEF were included in the trial. Details on randomization and study procedures have been described.[5] Patients in the usual care group were discharged, followed according to local practice, and seen by the study team at day 90 after randomization. Patients in the high-intensity care group were treated according to an algorithm combining rapid optimization of RAS modulators, beta-blockers, and MRAs and visits at 1, 2, 3, and 6 weeks after randomization, including physical examination to assess congestion and laboratory

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assessments including NT-proBNP, with a subsequent study visit at day 90. Patients in both groups were contacted at day 180 to assess the occurrence of rehospitalizations and death. Additional safety visits were done in case of delayed uptitration.

The study was approved by appropriate competent authorities, and all sites obtained approval from the relevant ethics committees. All patients provided written informed consent.

STUDY ENDPOINTS. The primary endpoint was the composite of first HF rehospitalization or all-cause death at day 180. Secondary endpoints were change in EQ-5D visual analog scale (VAS) from baseline to day 90, 180-day all-cause death, and the composite of first HF rehospitalization or all-cause death at day 90. Additional prespecified exploratory endpoints have already been described.[5] The prespecified safety endpoint was the 90-day incidence of treatment-emergent adverse events, coded with the use of Medical Dictionary for Regulatory Activities (version 21.1) terminology. Changes from baseline in vital signs (blood pressure, heart rate, and body weight) at each visit and changes from baseline in local laboratory results were also used to assess safety.

STATISTICAL ANALYSIS. Prespecified subgroup analyses of the primary and secondary endpoints were conducted according to the randomization stratification factor LVEF ≤40% and >40%. Additional post hoc analyses of exploratory efficacy and safety endpoints were further performed by this subgrouping. Continuous variables are presented as mean ± SD or adjusted mean ± SE as appropriate, and categoric variables as n (%). Skewed variables were log transformed for analysis as appropriate. All efficacy and safety analyses were performed in the full analysis set with the use of treatment as randomized. Endpoints through 180 days were restricted to patients enrolled at sites where the ethics committees approved the amended protocol allowing follow-up of patients through day 180, and down-weighted results in the cohort of patients enrolled before the primary endpoint was changed proportional to one-half of its sample size.

The treatment effects of high-intensity care strategy vs usual care strategy on primary, secondary, exploratory, and safety endpoints were evaluated separately in the LVEF ≤40% and >40% groups. Risk differences, based on unadjusted Kaplan-Meier estimates, are presented for 90- and 180-day clinical outcomes within each subgroup as well as the LVEF subgroup-by-treatment group interaction *P* value. Further details on how these endpoints were analyzed by subgroups have been previously described.[5] Analyses comparing LVEF subgroups, regardless of treatment, and the subgroup-by-treatment interaction was assessed for all parameters. Linear regression models were used to compare LVEF subgroups for continuous baseline characteristics and to assess the subgroup-by-treatment interaction. Chi-square tests were used for comparison of LVEF groups for dichotomous characteristics with the Breslow-Day test to assess the subgroup-by-treatment interaction. Cochran-Mantel-Haenszel tests were used for comparing LVEF subgroups for ordinal variables, and the homogeneity of Mann-Whitney statistics was used to assess the LVEF subgroup-by-treatment group interaction. Comparisons of LVEF subgroups and subgroup-by-treatment interaction for changes in vital signs and laboratory measures were assessed by means of ANCOVA models adjusted for baseline value. In addition, analyses were repeated post hoc comparing patients with baseline LVEF <50% and those with baseline LVEF ≥50%.

Because the HR did not vary significantly over time (treatment-by-time interaction: $P = 0.3891$), the treatment effect on the primary endpoint was modeled as a function of LVEF ≤40% and >40% and, separately, as continuous LVEF, as a restricted cubic spline with 3 knots, using Cox proportional hazards regression. In addition, the treatment effect on the change in EQ-5D VAS from baseline to day 90 was modeled as a function of continuous baseline LVEF, as a restricted cubic spline with 3 knots, using linear regression. LVEF values <10% were truncated at 10% for these analyses.

Two-sided *P* values of <0.05 were considered to be statistically significant. All analyses were performed with the use of SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION. Among the 1,078 patients randomized in the STRONG-HF trial, 731 (68%) were randomized in the LVEF ≤40% stratification factor and 347 (32%) in the LVEF >40% stratification factor. Beyond LVEF strata used at entry, numeric LVEF values within 6 months before screening were reported for 1,075 of the 1,078 enrolled patients and were used for further analyses. As presented in **Table 1**, compared with patients with LVEF >40%, patients with LVEF ≤40% were younger, more likely to be male and Black and slightly, but significantly, less likely to have a history of HF. They were also less likely to have a primary ischemic HF etiology, though with the same prevalence of history of acute coronary syndrome or coronary revascularization, and had a lower prevalence of comorbidities such as atrial fibrillation or

TABLE 1 Baseline Characteristics in Patients With LVEF ≤40% and LVEF >40%

	LVEF ≤40% (n = 731)		LVEF >40% (n = 347)		*P* Value	
	High-Intensity Care (n = 365)	Usual Care (n = 366)	High-Intensity Care (n = 177)	Usual Care (n = 170)	LVEF <40% vs >40%	Treatment-by-LVEF Interaction
Demographic variables						
Age, y	59.9 ± 13.68	60.3 ± 14.34	69.1 ± 10.57	68.8 ± 10.17	<0.0001	0.6718
Male	239 (65.5)	242 (66.1)	87 (49.2)	94 (55.3)	<0.0001	0.4123
Geographic region					<0.0001	0.6135
Europe	246 (67.4)	249 (68.0)	152 (85.9)	150 (88.2)		
Non-Europe	119 (32.6)	117 (32.0)	25 (14.1)	20 (11.8)		
Self-reported race					<0.0001	0.9498
Black	99 (27.1)	100 (27.3)	16 (9.0)	15 (8.9)		
White	261 (71.5)	262 (71.6)	157 (88.7)	152 (90.5)		
Native American	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)		
Other	5 (1.4)	4 (1.1)	2 (1.1)	1 (0.6)		
Pacific Islander	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)		
Heart failure history						
History of heart failure	306 (83.8)	302 (82.5)	159 (89.8)	149 (88.2)	0.0120	0.8486
NYHA functional class 1 mo before hospital admission					0.1016	0.0600
I	23 (6.8)	28 (8.4)	6 (3.5)	6 (3.8)		
II	88 (26.2)	112 (33.5)	59 (34.3)	48 (30.4)		
III	144 (42.9)	130 (38.9)	72 (41.9)	69 (43.7)		
IV	81 (24.1)	64 (19.2)	35 (20.3)	35 (22.2)		
Primary heart failure etiology					0.0011	0.4636
Ischemic	165 (45.3)	159 (43.4)	95 (53.7)	95 (56.5)		
Nonischemic	199 (54.7)	207 (56.6)	82 (46.3)	73 (43.5)		
Hospitalized for heart failure in the past year?	101 (27.7)	95 (26.0)	39 (22.0)	38 (22.5)	0.1083	0.7123
No. of heart failure hospitalizations in the past year	0.3 ± 0.64	0.4 ± 1.68	0.3 ± 0.77	0.3 ± 0.55	0.3162	0.4271

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flutter, previous stroke or transient ischemic attack, diabetes, malignancies, psychiatric or neurologic disorders. They had lower systolic blood pressure and higher NT-proBNP levels both at screening and at baseline. The other parameters, including the distribution of New York Heart Association functional classes 1 month before admission and history of HF hospitalization in the past year, were not different between the LVEF ≤40% and >40% groups.

Just before randomization, patients with LVEF ≤40% were slightly less likely to be treated with beta-blockers and more likely to be treated with MRAs and loop diuretics, whereas the proportion of patients treated with ACE inhibitors/ARBs/ARNIs was not different between the LVEF ≤40% and >40% groups.

A relatively small proportion of patients had LVEF ≥50% at baseline: 163 (15%) of the 1,075 patients analyzed. Characteristics similar to those obtained with an LVEF 40% cutoff were observed when patients with LVEF <50% were compared with those with LVEF ≥50% (Supplemental Table 1).

ORAL THERAPY UPTITRATION AND CHANGES IN VITAL SIGNS AND LABORATORY MEASURES. As previously reported[5] and shown in Supplemental Figure 1, uptitration to higher doses of HF oral treatments at day 90 was achieved more frequently in patients randomized to high-intensity care compared with those randomized to usual care, and this occurred to a similar extent in both LVEF ≤40% and >40% groups (interaction *P* value = 0.561 for ACE inhibitors/ARBs/ARNIs; interaction *P* value = 0.864 for beta-blockers; interaction *P* value = 0.933 for MRAs; see Supplemental Table 5 in Mebazaa et al[5]). By day 90, the proportions of patients on full doses of all 3 classes (ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs) were 36.4% (184 of 505) in the high-intensity care group vs 0.4% (2 of 497) in the usual care group. No differences were found when patients were subdivided by LVEF. By day 90, the proportions of patients randomized to high-intensity care who were uptitrated to full doses of all 3 drug classes were 36.2% (122 of 337) in the LVEF ≤40% group and 36.9% (62 of 168) in the LVEF >40% group, whereas these proportions were 0.6% (2 of 341) in the LVEF ≤40% group and 0.0% (0 of 156) in the LVEF >40% group for patients randomized to usual care (interaction *P* value = 0.974). Mean total daily dose of oral loop diuretics at day 90 was lower in the high-intensity care group both in patients with LVEF ≤40% (54.8 mg furosemide equivalents in the high-intensity care group vs 63.4 mg furosemide

TABLE 1 Continued

	LVEF ≤40% (n = 731)		LVEF >40% (n = 347)		*P* Value	
	High-Intensity Care (n = 365)	Usual Care (n = 366)	High-Intensity Care (n = 177)	Usual Care (n = 170)	LVEF <40% vs >40%	Treatment-by-LVEF Interaction
Comorbidities						
History of acute coronary syndrome	113 (31.0)	104 (28.4)	53 (29.9)	41 (24.3)	0.3946	0.5686
Previous coronary artery bypass surgery	17 (4.7)	19 (5.2)	10 (5.6)	13 (7.7)	0.2414	0.6872
Previous percutaneous transluminal coronary intervention	54 (14.8)	52 (14.2)	26 (14.7)	20 (11.8)	0.5897	-
Angina Canadian Cardiovascular Society class 2 or higher	40 (11.0)	26 (7.1)	34 (19.3)	25 (14.9)	0.0001	0.6797
History of atrial fibrillation or atrial flutter	141 (38.6)	160 (43.7)	97 (54.8)	98 (58.0)	<0.0001	0.7603
Type of atrial fibrillation or atrial flutter					0.2290	0.1611
Paroxysmal	39 (28.5)	39 (24.4)	18 (18.6)	21 (21.9)		
Permanent	74 (54.0)	101 (63.1)	63 (64.9)	55 (57.3)		
Persistent	24 (17.5)	20 (12.5)	16 (16.5)	20 (20.8)		
History of atrial fibrillation or atrial flutter or presence at screening	134 (36.7)	157 (42.9)	95 (53.7)	97 (57.1)	<0.0001	0.6456
Sustained ventricular arrhythmia (with syncopal episodes in past 3 mo)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.4913	-
Stroke or transient ischemic attack	34 (9.3)	23 (6.3)	22 (12.4)	20 (11.9)	0.0208	0.3791
Pulmonary embolism	10 (2.7)	4 (1.1)	3 (1.7)	2 (1.2)	0.5842	0.5998
Severe liver disease	3 (1.0)	0 (0.0)	0 (0.0)	3 (2.2)	0.3152	0.0135
Psychiatric or neurologic disorder	3 (0.8)	4 (1.1)	5 (2.8)	8 (4.8)	0.0015	0.7911
Malignancies	5 (1.4)	8 (2.2)	13 (7.4)	3 (1.8)	0.0067	0.0188
Diabetes	96 (26.3)	101 (27.7)	56 (31.8)	60 (35.5)	0.0262	0.7453
Diabetes control method						
Insulin	32 (8.8)	19 (5.2)	18 (10.2)	13 (7.7)	0.2516	0.6145
Diet only	62 (17.0)	60 (16.5)	40 (22.7)	40 (23.7)	0.0115	0.7832
Oral antidiabetic agents	69 (18.9)	77 (21.1)	41 (23.3)	47 (27.8)	0.0411	0.7446
Moderate or severe chronic obstructive pulmonary disease or asthma	6 (1.6)	8 (2.2)	8 (4.5)	5 (3.0)	0.0710	0.3566
Clinical and laboratory parameters						
Systolic blood pressure at baseline, mm Hg	122.6 ± 14.19	121.4 ± 12.74	125.1 ± 11.09	124.1 ± 12.00	0.0019	0.9298
Systolic blood pressure category					<0.0001	0.9151
≤Median	199 (54.5)	207 (56.6)	68 (38.4)	69 (41.1)		
>Median	166 (45.5)	159 (43.4)	109 (61.6)	99 (58.9)		
Heart rate at baseline, beats/min	79.8 ± 12.07	80.3 ± 12.43	75.8 ± 10.69	75.5 ± 9.63	<0.0001	0.6268
Weight at baseline, kg	80.2 ± 21.25	80.6 ± 21.26	82.8 ± 18.41	83.8 ± 18.87	0.0299	0.8440
NT-proBNP at screening, ng/L	7,893.7 ± 5,439.97	7,178.4 ± 4,626.41	6,107.4 ± 3,634.95	6,323.5 ± 3,535.71	<0.0001	0.1236
NT-proBNP at baseline, ng/L	4,492.5 ± 4,135.04	4,095.0 ± 3,480.48	3,349.8 ± 2,293.37	3,568.1 ± 2,507.59	0.0002	0.1704
Treatment before randomization						
ACE inhibitors/ARB/ARNI	246 (67.6)	236 (64.5)	108 (61.4)	99 (58.9)	0.0620	0.8919
Beta-blocker	110 (30.2)	133 (36.3)	73 (41.5)	67 (39.9)	0.0180	0.2052
MRA	347 (95.3)	353 (96.4)	161 (91.5)	157 (93.5)	0.0177	0.9994
Loop diuretic	357 (98.1)	356 (97.3)	163 (92.6)	153 (91.1)	<0.0001	0.8098
Cardiac resynchronization therapy	3 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)	0.0910	-
Automatic internal cardiac defibrillator	3 (0.8)	5 (1.4)	0 (0.0)	1 (0.6)	0.1752	0.4433

Values are mean ± SD or n (%). *P* values for comparison between the LVEF ≤40% and LVEF >40% groups (combining the two treatment arms) and *P* values for the treatment × LVEF group interaction are reported.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

equivalents in the usual care group) and in those with LVEF >40% (48.8 mg furosemide equivalents in the high-intensity care group vs 50.7 mg furosemide equivalents in the usual care group; interaction $P = 0.284$).

Similar findings were observed comparing uptitration of oral treatments for HF according to high-intensity vs usual care strategy in patients with LVEF <50% and those with LVEF ≥50% (Supplemental Table 2).

TABLE 2 Changes in Vital Signs and Laboratory Measures in Patients With LVEF ≤40% and LVEF >40%

	LVEF ≤40% (n = 731)		LVEF >40% (n = 347)		*P* Value	
	High-Intensity Care (n = 365)	Usual Care (n = 366)	High-Intensity Care (n = 177)	Usual Care (n = 170)	LVEF <40% vs >40%	Treatment-by-LVEF Interaction
Vital signs						
Systolic blood pressure, mm Hg						
Baseline	122.6 ± 14.19	121.4 ± 12.74	125.1 ± 11.09	124.1 ± 12.00		
Day 90	118.6 ± 17.21	122.4 ± 14.83	119.6 ± 13.04	126.6 ± 15.91		
Adjusted mean change	−3.5 (1.01)	0.88 (1.03)	−4.5 (1.31)	2.90 (1.35)	0.5971	0.1344
Diastolic blood pressure, mm Hg						
Baseline	76.9 ± 10.97	75.9 ± 9.28	76.3 ± 8.47	75.9 ± 7.34		
Day 90	74.3 ± 11.03	75.5 ± 10.14	73.6 ± 9.09	76.7 ± 10.14		
Adjusted mean change	−2.3 (0.65)	−0.52 (0.66)	−2.7 (0.84)	0.69 (0.87)	0.5559	0.1944
Heart rate, beats/min						
Baseline	79.8 ± 12.07	80.3 ± 12.43	75.8 ± 10.69	75.5 ± 9.63		
Day 90	71.8 ± 14.02	78.1 ± 13.10	70.3 ± 11.70	75.6 ± 11.32		
Adjusted mean change	−7.8 (0.85)	−1.7 (0.86)	−7.6 (1.09)	−2.3 (1.13)	0.8141	0.6212
Respiratory rate, breaths/min						
Baseline	18.4 ± 2.43	18.7 ± 6.48	17.3 ± 2.30	17.5 ± 5.20		
Day 90	17.4 ± 2.56	18.0 ± 2.62	16.8 ± 2.05	17.3 ± 2.47		
Adjusted mean change	−1.9 (0.16)	−1.5 (0.16)	−2.4 (0.20)	−2.0 (0.21)	0.0041	0.9606
Weight, kg						
Baseline	80.2 ± 21.25	80.6 ± 21.26	82.8 ± 18.41	83.8 ± 18.87		
Day 90	79.2 ± 21.54	81.0 ± 20.75	82.3 ± 18.32	83.7 ± 18.85		
Adjusted mean change	−1.9 (0.31)	−0.31 (0.32)	−1.5 (0.40)	−0.67 (0.42)	0.9628	0.2153

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Changes from baseline to day 90 in vital signs and laboratory measurements did not differ significantly between patients with LVEF ≤40% vs >40% (**Table 2**). Greater reductions in systolic blood pressure, heart rate, body weight, and NT-proBNP were observed in patients randomized to high-intensity care compared with those randomized to usual care, in both LVEF ≤40% and >40% groups.

Similar findings were observed when comparing changes from baseline to day 90 in vital signs and laboratory measurements according to high-intensity vs usual care strategy in patients with LVEF <50% and ≥50% (Supplemental Table 3), except for a more pronounced reduction in systolic blood pressure in patients with LVEF ≥50% randomized to high-intensity care (interaction $P = 0.048$).

CLINICAL OUTCOMES. Compared with usual care, high-intensity care led to an absolute risk reduction of 8.1% (95% CI: 2.9%-13.2%; $P = 0.0021$) of the primary composite endpoint at 180 days in the overall study population enrolled in STRONG-HF.[5] Among the patients with LVEF ≤40%, the primary endpoint occurred in 57 (17.4%) of 346 patients in the high-intensity care group and in 74 (23.7%) of 346 patients in the usual care group (risk difference: 6.3%; 95% CI: −0.2% to 12.9%). Among the patients with LVEF >40%, the primary composite endpoint occurred in 17 (10.7%) of 160 patients in the high-intensity care group and in 35 (23.3%) of 156 patients in the usual care group (risk difference: 12.5%; 95% CI: 3.7%-21.3%). No significant interaction was observed between LVEF ≤40% vs >40% and high-intensity vs usual care regarding the primary endpoint (interaction *P* value = 0.268) (**Table 3**). As presented in Supplemental Table 4, this finding was confirmed when evaluating women (interaction *P* value = 0.397) and men (interaction *P* value = 0.460) separately. Rates of the primary endpoint and risk differences between treatment arms for each 5% category of LVEF are shown in Supplemental Figure 2. Kaplan-Meier curves for the primary endpoint in the LVEF ≤40% and >40% groups are shown in **Figure 1**. The HR for high-intensity care vs usual care on the primary endpoint estimated from Cox proportional hazards regression was 0.62 (95% CI: 0.45-0.86; $P = 0.0042$) overall and was consistently below 1.00 across the whole LVEF spectrum (**Central Illustration**), with no significant interaction between LVEF, considered as a continuous variable, and the treatment strategy (interaction $P = 0.372$).

The mean change from baseline to day 90 in EQ-5D VAS was larger in patients randomized to

TABLE 2 Continued

	LVEF ≤40% (n = 731)		LVEF >40% (n = 347)		*P* Value	
	High-Intensity Care (n = 365)	Usual Care (n = 366)	High-Intensity Care (n = 177)	Usual Care (n = 170)	LVEF <40% vs >40%	Treatment-by-LVEF Interaction
Local laboratory tests						
Hemoglobin, g/L						
Baseline	137.3 ± 20.19	137.7 ± 19.75	134.4 ± 20.45	134.3 ± 19.40		
Day 90	132.5 ± 17.69	133.6 ± 17.31	131.6 ± 16.17	132.8 ± 17.46		
Adjusted mean change	−4.6 (0.92)	−3.9 (0.93)	−5.4 (1.19)	−3.9 (1.23)	0.6229	0.6591
White blood cells, 10^9/L						
Baseline	6.8 ± 1.98	7.1 ± 2.11	7.1 ± 1.89	7.1 ± 2.03		
Day 90	6.8 ± 1.85	7.0 ± 2.15	7.1 ± 1.71	7.0 ± 1.85		
Adjusted mean change	−0.02 (0.12)	0.12 (0.12)	−0.03 (0.15)	−0.09 (0.16)	0.3577	0.3635
Lymphocytes, %						
Baseline	27.3 ± 10.24	27.6 ± 9.77	27.1 ± 9.32	26.4 ± 9.42		
Day 90	28.4 ± 9.05	27.9 ± 9.42	27.3 ± 7.96	26.6 ± 8.64		
Adjusted mean change	0.95 (0.56)	0.32 (0.56)	0.74 (0.71)	0.20 (0.73)	0.7614	0.9337
Glucose, mmol/L						
Baseline	6.0 ± 2.15	6.2 ± 2.16	6.5 ± 2.99	6.5 ± 2.16		
Day 90	6.1 ± 2.27	6.2 ± 2.57	6.7 ± 2.80	6.6 ± 2.83		
Adjusted mean change	0.06 (0.15)	0.11 (0.15)	0.20 (0.20)	−0.01 (0.20)	0.9360	0.3885
Sodium, mmol/L						
Baseline	140.0 ± 4.05	140.3 ± 4.34	140.4 ± 3.99	140.2 ± 4.24		
Day 90	140.4 ± 4.37	140.1 ± 4.42	140.7 ± 4.09	140.5 ± 3.86		
Adjusted mean change	−0.54 (0.26)	−1.0 (0.26)	−0.92 (0.34)	−0.94 (0.35)	0.5778	0.3644
Potassium, mmol/L						
Baseline	4.3 ± 0.46	4.2 ± 0.44	4.3 ± 0.44	4.3 ± 0.43		
Day 90	4.6 ± 0.48	4.4 ± 0.51	4.6 ± 0.46	4.5 ± 0.50		
Adjusted mean change	0.36 (0.03)	0.19 (0.03)	0.28 (0.04)	0.17 (0.04)	0.1484	0.3411
Urea, mmol/L						
Baseline	7.8 ± 3.45	7.8 ± 3.24	8.7 ± 3.80	8.3 ± 3.71		
Day 90	7.7 ± 3.87	7.8 ± 4.12	8.1 ± 3.76	8.2 ± 3.73		
Adjusted mean change	0.16 (0.25)	0.38 (0.25)	0.02 (0.32)	0.37 (0.33)	0.7664	0.7848
eGFR, mL/min/1.73 m^2						
Baseline	65.0 ± 20.02	66.2 ± 23.58	55.6 ± 18.18	56.4 ± 17.74		
Day 90	65.7 ± 22.00	65.7 ± 22.66	55.0 ± 18.72	57.2 ± 18.24		
Adjusted mean change	2.75 (1.06)	2.54 (1.07)	−0.04 (1.36)	1.05 (1.40)	0.0448	0.5264
Uric acid, μmol/L						
Baseline	444.0 ± 123.10	451.0 ± 130.22	424.0 ± 128.26	429.7 ± 117.93		
Day 90	402.4 ± 105.98	416.6 ± 117.01	394.0 ± 99.10	391.8 ± 91.66		
Adjusted mean change	−68 (8.79)	−50 (8.87)	−55 (10.7)	−58 (11.6)	0.7933	0.2054
AST, U/L						
Baseline	27.3 ± 14.01	27.3 ± 18.51	24.9 ± 12.35	25.8 ± 13.44		
Day 90	26.3 ± 38.78	28.6 ± 38.04	23.1 ± 11.46	25.1 ± 13.34		
Adjusted mean change	−2.7 (2.64)	−0.48 (2.66)	−6.8 (3.35)	−5.0 (3.34)	0.0682	0.9432
ALT, U/L						
Baseline	32.7 ± 48.46	28.3 ± 25.78	27.1 ± 50.96	29.7 ± 54.52		
Day 90	24.9 ± 41.74	24.9 ± 30.36	21.8 ± 11.20	24.3 ± 12.24		
Adjusted mean change	−7.8 (2.51)	−8.0 (2.55)	−12 (3.20)	−9.8 (3.19)	0.1742	0.5792
Total bilirubin, μmol/L						
Baseline	18.2 ± 12.51	17.5 ± 10.55	16.4 ± 10.74	15.8 ± 10.62		
Day 90	14.2 ± 8.43	16.2 ± 12.39	14.4 ± 9.84	14.5 ± 10.00		
Adjusted mean change	−4.8 (0.83)	−2.5 (0.83)	−4.6 (1.03)	−4.2 (1.04)	0.3294	0.1560

Continued on the next page

high-intensity care vs usual care in both the LVEF ≤40% group (mean difference: 2.49; 95% CI: 0.34-4.64) and the LVEF >40% group (mean difference: 5.46; 95% CI: 2.45-8.47; interaction $P = 0.115$). Mean difference in the EQ-5D VAS change between treatment arms slightly increased at higher LVEF values (Figure 2), but with no significant interaction between LVEF as a continuous variable and the

TABLE 2 Continued

	LVEF ≤40% (n = 731)		LVEF >40% (n = 347)		*P* Value	
	High-Intensity Care (n = 365)	Usual Care (n = 366)	High-Intensity Care (n = 177)	Usual Care (n = 170)	LVEF <40% vs >40%	Treatment-by-LVEF Interaction
Total cholesterol, mmol/L						
Baseline	4.1 ± 1.05	4.2 ± 1.11	4.3 ± 1.18	4.2 ± 1.09		
Day 90	4.4 ± 1.03	4.5 ± 1.21	4.4 ± 1.08	4.3 ± 1.11		
Adjusted mean change	0.21 (0.09)	0.24 (0.09)	0.15 (0.11)	0.09 (0.12)	0.1600	0.5651
NT-proBNP, pg/mL						
Baseline	3,470.9 (3,238.8-3,719.7)	3,263.2 (3,056.3-3,484.1)	2,860.4 ± (2,639.5-3,099.7)	2,945.3 ± (2,688.7-3,226.3)		
Day 90	1,347.0 (1,183.0-1,533.7)	1,702.5 (1,492.2-1,942.5)	1,375.3 (1,156.8-1,635.0	1,788.8 (1,520.7-2,104.2)		
Adjusted ratio of geometric mean	0.426	0.549	0.445	0.580	0.5254	0.9526

Values are mean ± SD or adjusted mean change (standard error), unless otherwise indicated. *P* value for comparison between the LVEF ≤40% and LVEF >40% groups (combining the two treatment arms) and *P* value for the treatment × LVEF group interaction are reported.

ALT = alanine transaminase; AST = aspartate transaminase; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

treatment strategy (interaction $P = 0.358$). Mean changes in EQ-5D VAS and mean differences between treatment arms for each 5% category LVEF are shown in Supplemental Figure 3.

Results for other secondary endpoints and exploratory endpoints in patients with LVEF ≤40% and those with LVEF >40% are presented in **Table 3**. A larger treatment effect of high-intensity vs usual care was observed among patients with LVEF >40%, compared with those with LVEF ≤40%, regarding all-cause death at day 180 (interaction *P* value = 0.021) and cardiovascular death at day 180 (interaction $P = 0.033$). However, this finding was not confirmed for 180-day all-cause death after excluding COVID-19 deaths, and treatment-by-LVEF interaction was not significant for HF rehospitalization at day 90 and at day 180.

Similar findings were observed for primary, secondary and exploratory endpoints according to high-intensity vs usual care strategy in patients with LVEF <50% and those with LVEF ≥50%, although with no significant treatment-by-LVEF interaction regarding all-cause and cardiovascular mortality at day 180 (Supplemental Table 5, Supplemental Figure 4).

ADVERSE EVENTS. The incidence of treatment-emergent adverse events in patients with LVEF ≤40% and those with LVEF >40% is reported in Supplemental Table 6. Among the patients with LVEF ≤40%, adverse events up to day 90 were observed in 148 (40.5%) of 365 patients in the high-intensity care group and in 102 (27.9%) of 366 patients in the usual care group. Among the patients with LVEF >40%, adverse events up to day 90 were observed in 75 (42.4%) of 177 patients in the high-intensity care group and in 56 (32.9%) of 170 patients in the usual care group. No significant interaction was observed between LVEF ≤40% vs >40% and high-intensity vs usual care regarding the incidence of adverse events (interaction $P = 0.547$ for any adverse event). Of note, bradycardias occurred in fewer than 1.5% of patients, regardless of LVEF and treatment arm (high-intensity vs usual care). The incidence of serious adverse events was similar between the high-intensity care and usual care groups in patients with LVEF ≤40% and those with LVEF >40% (interaction $P = 0.524$ for any serious adverse event) (Supplemental Table 7).

DISCUSSION

This prespecified analysis of STRONG-HF shows that, in patients hospitalized for AHF, rapid uptitration of oral HF therapies can be safely performed within a few weeks after discharge and is associated with a reduced risk of death or HF readmission at 180 days and improved quality of life, independently from LVEF (**Central Illustration**). A high-intensity care strategy characterized by rapid uptitration of oral treatment for HF to recommended doses and frequent visits comprising clinical and laboratory assessments, including NT-proBNP, was beneficial in both patients with LVEF ≤40% (ie, HFrEF) and those with LVEF >40% (ie, HFmrEF or heart failure with preserved ejection fraction [HFpEF]). Despite some expected differences between the LVEF ≤40% and >40% groups in terms of baseline characteristics, with higher NT-proBNP values and lower systolic blood pressure in the former and more elderly with comorbidities in the latter, patients randomized to

TABLE 3 Primary, Secondary, and Exploratory Endpoints in Patients With LVEF ≤40% and LVEF >40%

	LVEF ≤40% (n = 731)			LVEF >40% (n = 347)			*P* Value
	High-Intensity Care	Usual Care	Unadjusted Treatment Effect	High-Intensity Care	Usual Care	Unadjusted Treatment Effect	Treatment-by-LVEF Interaction
Day 90 analyses	365	366		177	170		
Day 180 analyses	346	346		160	156		
Primary endpoint							
All-cause death or HF readmission by day 180	57 (17.4)	74 (23.7)	6.3% (−0.2% to 12.9%)	17 (10.7)	35 (23.3)	12.5% (3.7%-21.3%)	0.2684
Secondary endpoints							
Change from baseline to day 90 in EQ-5D VAS	10.77 (0.97)	8.29 (0.98)	2.49 (0.34-4.64)	11.54 (1.23)	6.08 (1.27)	5.46 (2.45-8.47)	0.1150
All-cause death by day 180	33 (11.0)	31 (9.6)	−1.4% (−6.4%-3.5%)	6 (3.5)	17 (11.4)	7.9% (1.8%-14.0%)	0.0208
All-cause death or HF readmission by day 90	38 (10.7)	49 (13.8)	3.1% (−1.7% to 7.9%)	17 (9.8)	23 (13.8)	4.0% (−2.8% to 10.9%)	0.8374
Exploratory endpoints							
Cardiovascular death by day 180	28 (9.2)	29 (9.2)	-0.02% (−4.8% to 4.8%)	4 (2.0)	15 (9.8)	7.9% (2.4%-13.4%)	0.0329
Cardiovascular death by day 90	14 (3.9)	18 (5.1)	1.1% (−1.9% to 4.2%)	3 (1.7)	10 (6.0)	4.3% (0.2%-8.4%)	0.2218
All-cause death by day 90	18 (5.1)	19 (5.3)	0.3% (−3.0% to 3.5%)	5 (2.9)	11 (6.6)	3.7% (−0.8% to 8.3%)	0.2234
HF readmission by day 180	35 (10.1)	51 (17.9)	7.8% (2.1% to 13.5%)	12 (7.8)	23 (16.2)	8.4% (0.6%-16.2%)	0.9025
HF readmission by day 90	24 (6.9)	33 (9.6)	2.7% (−1.3% to 6.8%)	12 (7.1)	15 (9.2)	2.1% (−3.8% to 8.0%)	0.8570
All-cause death by day 180, excluding COVID-19 deaths	28 (9.2)	31 (9.6)	0.3% (−4.5% to 5.1%)	5 (2.7)	16 (10.6)	7.8% (2.0%-13.6%)	0.0502

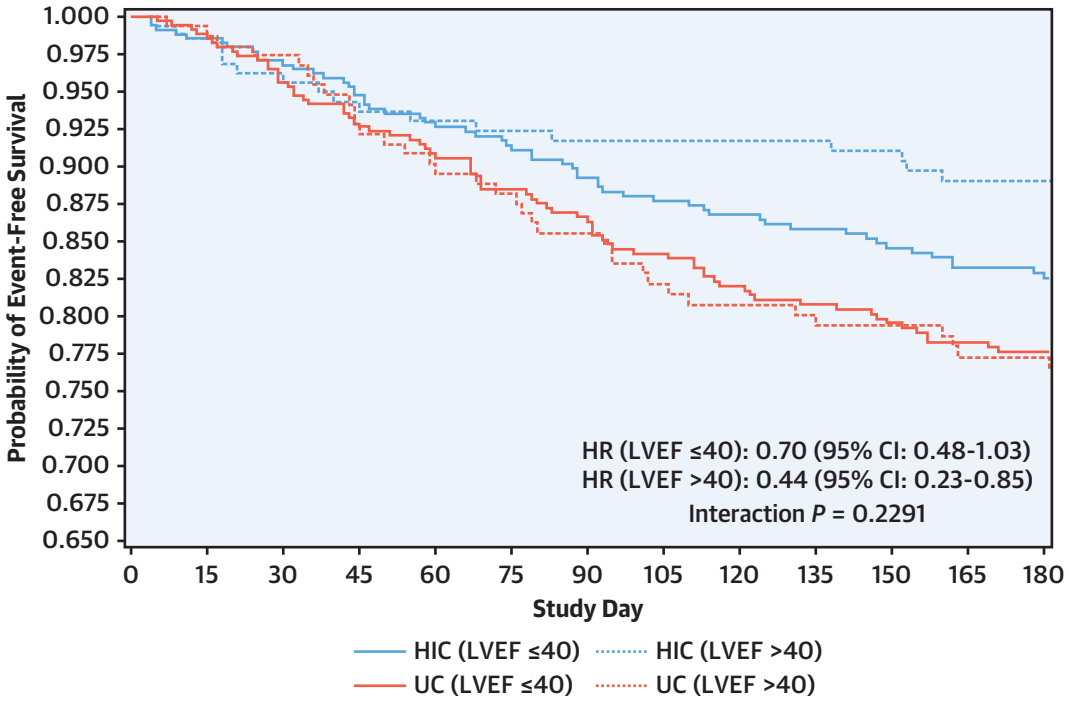
Values are n, n (Kaplan-Meier %), or mean (standard error) for change in EQ-5D VAS. Unadjusted treatment effects are the mean difference between treatment groups (for change in EQ-5D VAS) and the risk difference between treatment groups (for all other endpoints). *P* value for the treatment × LVEF group interaction is reported.

HF = heart failure; LVEF = left ventricular ejection fraction; VAS = visual analog scale.

high-intensity care achieved similar uptitration of oral treatment in both groups. Almost all patients with either LVEF ≤40% or LVEF >40% received ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs if assigned to the high-intensity care strategy, including at least one-half of patients receiving full recommended doses of therapies by day 90 in both LVEF groups. Consequently, patients with both LVEF ≤40% and LVEF >40% randomized to high-intensity care had lower systolic blood pressure, heart rate, body weight, and NT-proBNP at day 90 compared with those randomized to usual care, despite lower doses of loop diuretics. The benefits of the high-intensity care strategy in terms of reduced risk of all-cause death or HF rehospitalization at day 180 (primary endpoint) and higher mean change from baseline to day 90 in EQ-5D VAS were consistent in patients with LVEF ≤40% and >40%. No significant interaction was observed between the treatment strategy and LVEF as a continuous variable regarding these endpoints. Although a numerically larger treatment effect of high-intensity vs usual care was observed in patients with LVEF >40%, compared with those with LVEF ≤40%, regarding all-cause and cardiovascular mortality at day 180, it must be noticed that the number of deaths was low, this finding was not confirmed after excluding COVID-19 deaths, multiple statistical tests were performed, and there was no treatment-by-LVEF interaction on HF rehospitalization. Of note, there were no differences in the prevalence of adverse events and their prevalence between high-intensity care and usual care, including those feared to be more prevalent in patients with higher LVEF when treated with high doses of medications, such as bradycardia. Serious adverse events were similar between treatment arms in both LVEF ≤40% and >40% groups. Similar findings were also found when comparing patients with LVEF <50% and ≥50%, although the number of patients with LVEF ≥50% was relatively low. The lack of increase in certain adverse effects in patients with high LVEF and the lack of increase of severe adverse events in the high-intensity care group was achieved by meticulous adherence to the study protocol that set clear rules of when and where medications should not be further uptitrated, or downtitrated,[5] during close follow-up in the first 6 weeks after discharge.

Previous studies have demonstrated that a relevant proportion of patients admitted to hospital for AHF have HFmrEF (LVEF 41%-49%) or HFpEF (LVEF ≥50%) and that the risk of clinical events at short-term and long-term follow-up after discharge is substantial.[3,4,14-18] In a recent analysis of the large European Society of Cardiology-Heart Failure Association EURObservational Research Programme HF Long-Term Registry including 5,951 patients hospitalized for AHF, all-cause death or first HF rehospitalization at 12 months occurred in 27%, 29%, and

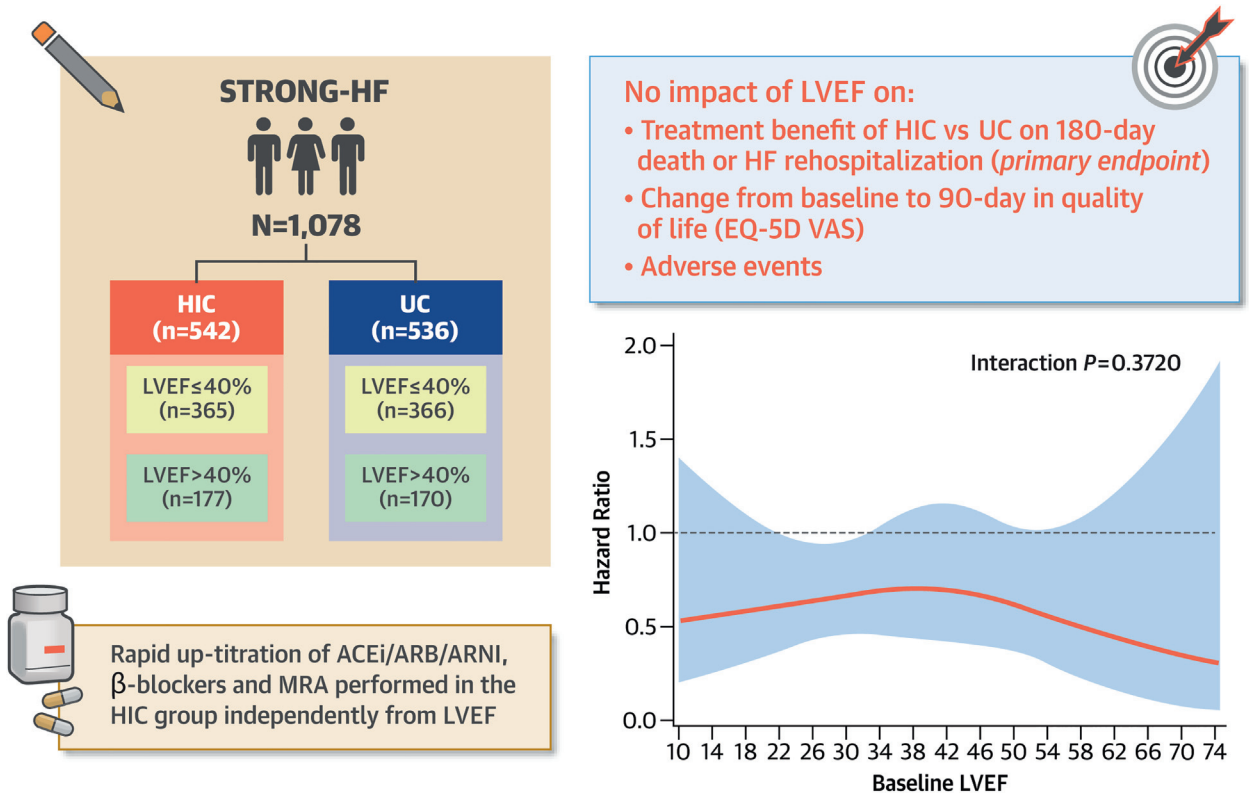
FIGURE 1 Kaplan-Meier Curves for the Primary Endpoint



Kaplan-Meier estimates of cumulative event-free survival for the composite of all-cause mortality or heart failure rehospitalization according to high-intensity care (HIC) or usual care (UC) strategy in patients with left ventricular ejection fraction (LVEF) ≤40% and >40%, from randomization up to day 180. HRs with 95% CIs for HIC vs UC in patients with LVEF ≤40% and ≥40%, along with interaction *P* value derived from Cox regression models, are also reported.

39% of the patients with HFpEF, HFmrEF, and HFrEF, respectively.[4] However, based on available evidence from randomized trials in outpatients with chronic HF, treatment with ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs is now strongly recommended only for patients with HFrEF and may be considered also for patients with HFmrEF, whereas it is not specifically indicated for patients with HFpEF.[1,2] Our analysis of STRONG-HF shows that, in the specific setting of patients who have been hospitalized for AHF, rapid uptitration of ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs within a few weeks after discharge is safe and effective across the entire LVEF spectrum. These findings are in line with previous evidence from nonrandomized studies,[18,19] and meta-regression in AHF[20] and may be explained by heightened neurohormonal activation related to the recent AHF episode or its intravenous treatment, regardless of LVEF and favoring the beneficial effects of neurohormonal modulators.[8-11] It cannot be excluded that neurohormonal antagonists offer mid- or long-term protection in the presence of cardiovascular comorbidities, such as hypertension and ischemic heart disease, commonly associated with HFpEF. Finally, in STRONG-HF, rapid uptitration strategy was coupled with a high-intensity follow-up, minimizing adverse effects potentially related to older age or associated comorbidities. Although in a recent real-world cohort of AHF patients with mean age of 83 years, treatment with neurohormonal antagonists, particularly beta-blockers and MRAs, did not seem to reduce cardiovascular outcomes in HFpEF patients; this represented a retrospective analysis not accounting for postdischarge follow-up visits.[21] Nevertheless, the relatively low proportion of patients with LVEF >40% (347 of 1,078, 32%) and especially of patients with LVEF ≥50% (163 of 1,075, 15%) in our study may have underpowered the analyses in these subgroups and does not allow drawing of definitive conclusions on the efficacy of uptitration of oral treatment in HFpEF. Of note, although previous data showed benefit from neurohormonal modulators, namely ARNIs, in women with higher LVEF than men,[22] we did not

CENTRAL ILLUSTRATION **Left Ventricular Ejection Fraction and Medical Therapy Uptitration in STRONG-HF**



Pagnesi M, et al. J Am Coll Cardiol. 2023;81(22):2131–2144.

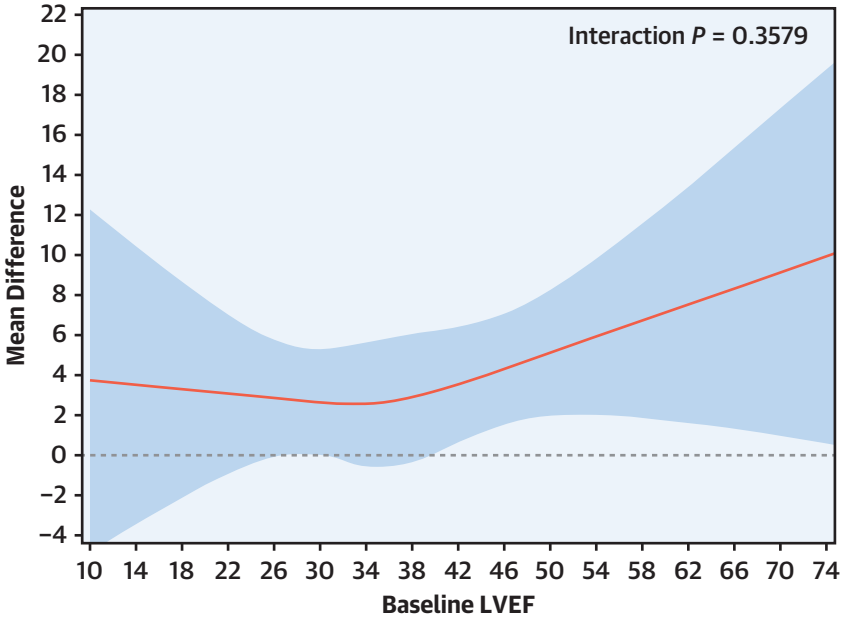
Among the 1,078 patients with acute heart failure (HF) enrolled in the STRONG-HF trial, 713 (68%) had left ventricular ejection fraction (LVEF) ≤40% and 347 (32%) had LVEF >40%. A high-intensity care (HIC) strategy characterized by rapid uptitration of oral medications for HF (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs] or angiotensin receptor-neprilysin inhibitors [ARNIs], beta-blockers, and mineralocorticoid receptor antagonists [MRAs]) and close follow-up, compared with a usual care (UC) strategy, resulted in a reduction of all-cause death or HF rehospitalization at day 180 independently from LVEF (**lower right panel:** treatment effect on the primary endpoint according to baseline LVEF modeled as a restricted cubic spline with 3 knots). Similarly, no interaction between LVEF and treatment strategy was observed for EQ-5D visual analog scale (VAS) change from baseline to day 90.

observe a significant interaction between the treatment strategy and LVEF ≤40% vs >40% in both women and men.

Four previous randomized trials failed to demonstrate the effectiveness of intense management with additional early follow-up visits (without prespecified treatment uptitration) after hospitalization for AHF,[23-26] suggesting that intense follow-up alone without rapid uptitration of oral HF therapies does not have an impact on clinical outcomes. Two of those trials did not report data according to LVEF,[24,25] and one of them was focused on HFrEF.[26] Of note, in the ECAD-HF (Early Care After Discharge of Heart Failure Patients) trial, the neutral effect of the intensive follow-up strategy was confirmed in both LVEF ≤40% and >40% groups (interaction $P = 0.77$ for the primary endpoint).[23] This finding further suggests that beyond early follow-up visits alone, the benefits associated with the high-intensity care strategy in our study was driven by rapid and safe uptitration of oral treatment in both patients with LVEF ≤40% and patients with LVEF >40%.

STRONG-HF tested a strategy of rapid uptitration of ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs; sodium-glucose cotransporter (SGLT) inhibitors were not indicated when the trial was designed.[12] Only 10% and 5% of the patients in the high-intensity care and usual care groups, respectively, were receiving SGLT2 inhibitors in this trial.[5] Two recent prospective randomized trials, SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular

FIGURE 2 Mean Difference Between Treatment Groups in the EQ-5D VAS Change



Mean difference between high-intensity care vs usual care estimated from linear regression on the EQ-5D visual analog scale (VAS) change from baseline to day 90 (secondary endpoint) according to baseline left ventricular ejection fraction (LVEF) modeled as a restricted cubic spline with 3 knots. The *P* value for interaction between LVEF and treatment strategy on the EQ-5D VAS change is also reported.

Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) and EMPULSE (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized) showed beneficial effects of the SGLT inhibitors sotagliflozin and empagliflozin in patients recently hospitalized for acute HF, independently from their LVEF.[27,28] Accordingly, an analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial, enrolling patients with HF and LVEF >40%, showed a similar reduction in the risk of worsening HF or cardiovascular death in patients with and without recent HF hospitalization.[29] Thus, randomized controlled trials support the indication for SGLT inhibitors in patients with AHF independently from LVEF. STRONG-HF suggests a similar indication for ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs in patients discharged from an admission for AHF independently from LVEF. Of note, these neurohormonal agents were also concurrently administered to the majority of patients in the SGLT inhibitors trials, although not tested prospectively.[27-29] In aggregate, the benefits of rapid uptitration of ACE inhibitors/ARBs/ARNIs, beta-blockers, and MRAs and close follow-up after AHF regardless of LVEF, demonstrated by the present study, can be considered complementary to that of SGLT inhibitors.[30]

STUDY LIMITATIONS. Beyond the already described limitations of the overall STRONG-HF study,[5] there are some limitations that are specific to the present analysis. First, although the subgroup analysis in patients with LVEF ≤40% vs >40% was prespecified for the primary and secondary endpoints, the other comparisons were post hoc analyses, including the assessment of LVEF <50% vs ≥50% subgroups and the analysis of LVEF as a continuous variable. Second, subgroup analyses may have a limited statistical power in this study owing to limited sample sizes and numbers of events in the subgroups. For example, although we recognize the controversy of beta-blockade in HFpEF,[31] subgroup analyses according to specific beta-blocker uptitration and presence of chronotropic incompetence was not feasible. Furthermore, the most recent LVEF value measured within 6 months before screening, including during the index hospitalization for AHF, was recorded in STRONG-HF, so results may have been different in case of LVEF assessment only during screening or before randomization. Finally, quantification of LVEF

was performed at local study sites and was therefore investigator rather than core laboratory reported.

CONCLUSIONS

Among patients with AHF enrolled in STRONG-HF, rapid uptitration of oral treatment for HF during hospitalization and early after discharge, performed under close follow-up and monitoring, is safe and results in a reduction of death or HF rehospitalization and an improvement in quality of life, independently from LVEF. A high-intensity care strategy may therefore be beneficial in AHF across the entire LVEF spectrum, including patients with HFrEF, HFmrEF, and HFpEF. Future studies are needed to confirm these findings and further explore the implications of rapid uptitration of oral treatment in HF patients with different LVEF values.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with acute heart failure, rapid uptitration of oral therapies during and early after hospitalization, performed under close follow-up, is beneficial for patients with reduced, mildly reduced, or preserved left ventricular ejection fraction.

TRANSLATIONAL OUTLOOK: The mechanisms by which patients benefit from rapid uptitration of neurohormonal antagonists and modulators independently from left ventricular ejection fraction require further investigation.

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KEY WORDS acute heart failure, ejection fraction, heart failure, medical therapy, randomized trial

APPENDIX For supplemental tables and figures, please see the online version of this paper.