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ORIGINAL RESEARCH

HEART FAILURE

Rapid Uptitration of Guideline-Directed Medical Therapies in Acute Heart Failure With and Without Atrial Fibrillation

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ABSTRACT

BACKGROUND Rapid uptitration of guideline-directed medical therapy (GDMT) before and after discharge in hospitalized heart failure (HF) patients is feasible, is safe, and improves outcomes; whether this is also true in patients with coexistent atrial fibrillation/flutter (AF/AFL) is not known.

OBJECTIVES This study sought to investigate whether rapid GDMT uptitration before and after discharge for HF is feasible, safe and beneficial in patients with and without AF/AFL.

METHODS In this secondary analysis of the STRONG-HF (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial, GDMT uptitration and patient outcomes were analyzed by AF/AFL status and type (permanent, persistent, paroxysmal).

RESULTS Among 1,078 patients enrolled in STRONG-HF, 496 (46%) had a history of AF, including 238 assigned to high-intensity care (HIC) and 258 to usual care (UC), and 581 did not have a history of AF/AFL, including 304 assigned to HIC and 277 to UC. By day 90, the average percent optimal dose of neurohormonal inhibitors achieved in the HIC arm was similar in patients with and without AF/AFL, reaching approximately 80% of the optimal dose (average absolute difference between AF/AFL and non-AF/AFL groups: −0.81%; 95% CI: −3.51 to 1.89). All-cause death or HF readmission by day 180 occurred less frequently in the HIC than the UC arm, both in patients with and without AF (adjusted HR: 0.75 [95% CI: 0.48-1.19] in AF vs adjusted HR: 0.50 [95% CI: 0.31-0.79] in non-AF/AFL patients; *P* for interaction = 0.2107). Adverse event rates were similar in patients with and without AF/AFL. AF/AFL type did not affect either uptitration or patient outcomes.

CONCLUSIONS Nearly half of acute HF patients have AF/AFL history. Rapid GDMT uptitration before and early after discharge is feasible, is safe, and may improve outcomes regardless of AF presence or type. (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies [STRONG-HF]; NCT03412201) (JACC Heart Fail. 2024;12:1845-1858) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

GDMT = guideline-directed medical therapy

HF = heart failure

HIC = high-intensity care

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

RASI = renin-angiotensin-aldosterone system inhibitor

UC = usual care

Atrial fibrillation or flutter (AF/AFL) and heart failure (HF) are closely interrelated, increasing the incidence and worsening the severity of each other.[1,2] In acute HF, AF/AFL may be a trigger of patients' decompensation and further complicates their clinical course and management.[1]

Guideline-directed medical therapies (GDMTs) improve clinical outcomes for HF patients, including those with AF/AFL.[3] Nevertheless, the optimal management of acute HF patients with AF/AFL and the challenges posed by the initiation and uptitration of GDMT in this setting have not been sufficiently addressed.

In STRONG-HF (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies), initiation and rapid uptitration of GDMT was feasible and safe in hospitalized HF patients before and soon after discharge and led to improved clinical outcomes.[4] In the present secondary analysis of this trial, we hypothesized that the coexistence of AF/AFL does not impair the feasibility, safety, and benefits of initiation and rapid uptitration of GDMT in acute HF patients being discharged from the hospital.

METHODS

The STRONG-HF trial was a multinational, multicenter, open-label, randomized, parallel-group study designed to assess the safety and efficacy of rapid uptitration of GDMT on morbidity and mortality when initiated during and uptitrated early after hospitalization for acute HF. The design, methods, and main results of the study have been described in detail elsewhere.[4] In brief, the study enrolled patients aged 18 to 85 years who were admitted to the hospital within 72 hours before screening, with clinical signs of congestion and elevated N-terminal pro-B-type natriuretic concentrations, and who had not been treated with optimal doses of oral HF therapies. There were no inclusion criteria based on left ventricular ejection fraction (LVEF). Patients with a clear intolerance to high doses of GDMT were excluded. Randomization was stratified by LVEF and country; patients were randomized in a 1:1 fashion to either the high-intensity care (HIC) uptitration group or the usual care (UC) group. Treatment allocation could not be blinded because of the nature of the study. In the HIC group, patients were uptitrated at randomization to half optimal doses and at 2 weeks to full doses of 3 classes of medications: renin-angiotensin system inhibitors (RASIs) (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor neprilysin inhibitors), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). The UC group followed the usual local practice. HIC patients had scheduled outpatient visits at 1, 2, 3, and 6 weeks postdischarge, whereas both HIC and UC patients were seen at day 90 and contacted by telephone at day 180 to assess vital status, occurrence of any rehospitalization, and current prescriptions of oral HF medications. The primary cause of death and reason for readmission were based on investigators' reports and were not adjudicated. The study was approved by appropriate competent authorities and ethics committees before enrollment. All patients provided written informed consent. To ensure participants' safety, an independent Data and Safety Monitoring Board was established. The trial was registered at ClinicalTrials.gov (NCT03412201).

In the present analysis, AF/AFL was defined as any history of electrocardiographic evidence of AF or AFL. The type of AF/AFL was classified as either

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics by History of AF/AFL

	AF/AFL (n = 496)	No AF/AFL (n = 581)	*P* Value[a]
Age, y	68.0 ± 10.19	58.7 ± 14.61	<0.0001
Sex			
Female	167 (33.7)	249 (42.9)	0.0020
Male	329 (66.3)	332 (57.1)	
Self-reported race			
Black	10 (2.0)	220 (37.9)	<0.0001
White	481 (97.2)	351 (60.4)	
Native American	0	1 (0.2)	
Other	4 (0.8)	8 (1.4)	
Pacific Islander	0	1 (0.2)	
Geographic region			
Europe	473 (95.4)	323 (55.6)	<0.0001
Non-Europe	23 (4.6)	258 (44.4)	
NT-proBNP at screening, ng/L	6,079.5 (5,771.8-6,403.5)	5,961.3 (5,696.2-6,238.7)	0.5750
Medical history			
Stroke or transient ischemic attack	51 (10.3)	48 (8.3)	0.2601
Severe liver disease	5 (1.3)	1 (0.2)	0.0912
Psychiatric or neurologic disorder	14 (2.8)	6 (1.0)	0.0310
Malignancies	18 (3.6)	11 (1.9)	0.0811
Diabetes	165 (33.4)	148 (25.5)	0.0046
Pulmonary embolism	10 (2.0)	9 (1.5)	0.5617
Acute coronary syndrome	161 (32.5)	150 (25.8)	0.0165
Coronary artery bypass surgery	33 (6.7)	26 (4.5)	0.1155
Percutaneous transluminal coronary intervention	79 (16.0)	73 (12.6)	0.1110
Moderate or severe chronic obstructive pulmonary disease or asthma	16 (3.2)	11 (1.9)	0.1632
Sustained ventricular arrhythmia (with syncopal episodes in past 3 mo)	1 (0.2)	0	0.4605
Cardiac resynchronization therapy	4 (0.8)	2 (0.3)	0.4226
Automatic internal cardiac defibrillator	7 (1.4)	2 (0.3)	0.0891
Anemia	121 (24.4)	172 (29.6)	0.0555
HF history			
History of HF	440 (88.7)	476 (81.9)	0.0019
NYHA functional class 1 mo before hospital admission			
I	17 (3.7)	46 (8.6)	<0.0001
II	119 (25.7)	188 (35.0)	
III	192 (41.5)	223 (41.5)	
IV	135 (29.2)	80 (14.9)	
Ischemic etiology	283 (57.2)	231 (39.8)	<0.0001
LVEF, %	37.6 ± 12.58	35.2 ± 12.37	0.0011
LVEF category			
≤40%	301 (60.7)	430 (74.0)	<0.0001
>40%	195 (39.3)	151 (26.0)	
Hospitalized for HF in the past year	160 (32.3)	113 (19.4)	<0.0001
Number of HF hospitalizations in the past year	0.4 ± 0.73	0.3 ± 1.35	0.0371
Baseline vital signs			
Systolic blood pressure at baseline, mm Hg	121.6 ± 10.64	123.9 ± 14.55	0.0026
Pulse, beats/min	76.9 ± 10.63	80.2 ± 12.52	<0.0001

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permanent, paroxysmal (episodes of <7 days), or persistent (episodes of longer than 7 days). Patients' characteristics at baseline were compared between patients with and without AF/AFL. In addition, the titration of GDMT, including RASI, beta-blockers, and MRA by days 90 and 180; the changes in vital signs and laboratory measurements by day 90; and the rates of all-cause death or HF readmission by day 180 were analyzed by treatment arm (HIC vs UC) and AF/AFL status. The same analyses were further

TABLE 1 Continued

	AF/AFL (n = 496)	No AF/AFL (n = 581)	*P* Value[a]
Local laboratory values			
Hemoglobin, g/L	139.2 ± 21.08	134.2 ± 18.72	<0.0001
White blood cells, 10^3/L	7.2 ± 2.17	6.8 ± 1.86	0.0004
Creatinine, μmol/L	110.0 ± 26.26	103.0 ± 30.61	<0.0001
Potassium, mmol/L	4.3 ± 0.43	4.2 ± 0.45	<0.0001
Sodium, mmol/L	141.0 ± 4.27	139.6 ± 3.97	<0.0001
Urea, mmol/L	8.6 ± 3.54	7.6 ± 3.40	<0.0001
NT-proBNP, ng/L	3,336.7 (3,149.7-3,534.9)	3,103.4 (2,952.2-3,262.3)	0.0609
Oral HF medications taken at visit 2 prerandomization			
ACEIs/ARBs/ARNIs	275 (55.7)	414 (71.4)	<0.0001
Beta-blockers	223 (45.1)	160 (27.6)	<0.0001
MRAs	472 (95.5)	546 (94.1)	0.3007
Loop diuretic agents	473 (95.7)	556 (95.9)	0.9266

Values are mean ± SD, n (%), or geometric mean (95% CI). [a]The chi-square test or Fisher exact test was used for dichotomous and categorical variables, Student's *t*-test for continuous variables, and Cochran-Mantel-Haenszel mean score difference for ordinal variables. Skewed variables were log-transformed, and results are presented as the geometric mean (95% CI) with comparison based on log-transformed value.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARN = angiotensin receptor neprilysin inhibitor; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NTproBNP = N-terminal pro–B-type natriuretic peptide.

performed by AF/AFL types (paroxysmal, persistent, permanent).

STATISTICAL ANALYSIS. Analyses include all randomized patients, excluding those patients randomized in error. Unless otherwise stated, continuous variables are reported as mean ± SD, and categorical variables as absolute and relative frequencies. Log transformations were applied to skewed variables for analysis, with results presented as geometric mean and associated 95% CI.

Baseline characteristic differences between individuals with and without a history of AF/AFL were examined using the Student's *t*-test for continuous variables, chi-square test or Fisher exact test for dichotomous and categorical variables, and the Cochran-Mantel-Haenszel test of general association for ordered categorical variables. Comparisons of characteristics based on AF/AFL type (permanent, persistent, and paroxysmal) among those with a history of AF/AFL used an analysis of variance *F*-test for continuous variables.

Interactions between history of AF/AFL and treatment for baseline characteristics were explored using an analysis of covariance model containing history of AF/AFL, treatment, and the AF/AFL-by-treatment interaction. Logistic models incorporating AF/AFL, treatment, and AF/AFL-by-treatment interaction were used for dichotomous variables. Firth's correction was applied when the possibility of quasi-complete separation was detected in the model. For ordinal variables, a test of the homogeneity of the Mann-Whitney statistic, derived from the Somers's *D* statistic and associated SE, was used. Similar methods were used for examining interactions between type of AF/AFL and treatment in those patients with a history of AF/AFL.

Because the primary endpoint of death or HF readmission was changed after the trial began from 90 to 180 days, 180-day endpoint results involved a proportional down-weighting based on half the sample size of the prechange cohort. Analyses of the 180-day outcomes were confined to patients from sites where the Ethics Committee approved the protocol amendment permitting collection of follow-up data to day 180.

To assess the impact of treatment on time-to-event outcomes in patients with and without a history of AF/AFL, Cox regression models were used. These models were further used to explore if there was a significant interaction of the treatment effect among the AF/AFL groups. The total number of events, down-weighted Kaplan-Meier estimates, both unadjusted and adjusted HRs, and their associated 95% CIs are presented. Kaplan-Meier plots illustrating survival probability for the primary endpoint by history of AF/AFL and treatment are provided. Covariates for adjustment were selected based on their prognostic significance from previous studies and were chosen using backward selection within the UC group.

Changes in vital signs and laboratory data were examined using analysis of covariance models with terms for history of AF/AFL, treatment, baseline value, and the AF/AFL-by-treatment interaction.

TABLE 2 Baseline Characteristics by History of AF/AFL and Treatment

	AF/AFL (n = 496)		No AF/AFL (n = 581)		
	HIC (n = 238)	UC (n = 258)	HIC (n = 304)	UC (n = 277)	Interaction *P* Value
Age, y	68.0 ± 10.23	68.0 ± 10.18	59.0 ± 14.32	58.3 ± 14.94	0.7054
Sex					0.3855
Female	86 (36.1)	81 (31.4)	130 (42.8)	119 (43.0)	
Male	152 (63.9)	177 (68.6)	174 (57.2)	158 (57.0)	
Self-reported race					0.3577
Black	7 (2.9)	3 (1.2)	108 (35.5)	112 (40.4)	
White	228 (95.8)	253 (98.4)	190 (62.5)	161 (58.1)	
Native American	0	0	1 (0.3)	0	
Other	3 (1.3)	1 (0.4)	4 (1.3)	4 (1.4)	
Pacific Islander	0	0	1 (0.3)	0	
Geographic region					0.1419
Europe	224 (94.1)	249 (96.5)	174 (57.2)	149 (53.8)	
Non-Europe	14 (5.9)	9 (3.5)	130 (42.8)	128 (46.2)	
NT-proBNP at screening, ng/L	6,201.0 (5,743.3-6,695.1)	5,969.5 (5,560.9-6,408.0)	6,089.3 (5,715.0-6,488.1)	5,823.9 (5,454.4-6,218.4)	0.9501
Medical history					
Stroke or transient ischemic attack	27 (11.3)	24 (9.3)	29 (9.6)	19 (6.9)	0.7474
Severe liver disease	2 (1.1)	3 (1.5)	1 (0.4)	0	0.4692
Psychiatric or neurologic disorder	7 (2.9)	7 (2.7)	1 (0.3)	5 (1.8)	0.1409
Malignancies	9 (3.8)	9 (3.5)	9 (3.0)	2 (0.7)	0.1429
Diabetes	72 (30.4)	93 (36.2)	80 (26.3)	68 (24.6)	0.1955
Pulmonary embolism	8 (3.4)	2 (0.8)	5 (1.6)	4 (1.4)	0.1924
Acute coronary syndrome	85 (35.7)	76 (29.5)	81 (26.6)	69 (24.9)	0.4711
Coronary artery bypass surgery	17 (7.1)	16 (6.2)	10 (3.3)	16 (5.8)	0.1787
Percutaneous transluminal coronary intervention	40 (16.8)	39 (15.2)	40 (13.2)	33 (11.9)	0.9816
Moderate or severe chronic obstructive pulmonary disease or asthma	7 (2.9)	9 (3.5)	7 (2.3)	4 (1.4)	0.4233
Cardiac resynchronization therapy	2 (0.8)	2 (0.8)	1 (0.3)	1 (0.4)	0.9199
Automatic internal cardiac defibrillator	2 (0.8)	5 (1.9)	1 (0.3)	1 (0.4)	0.6475
Anemia	55 (23.1)	66 (25.6)	88 (28.9)	84 (30.3)	0.8059
HF history					
History of HF	215 (90.3)	225 (87.2)	250 (82.2)	226 (81.6)	0.4500
NYHA functional class 1 month before hospital admission					0.8729
I	10 (4.4)	7 (3.0)	19 (6.8)	27 (10.5)	
II	52 (22.7)	67 (28.6)	95 (34.1)	93 (36.0)	
III	95 (41.5)	97 (41.5)	121 (43.4)	102 (39.5)	
IV	72 (31.4)	63 (26.9)	44 (15.8)	36 (14.0)	
Ischemic etiology	136 (57.1)	147 (57.2)	124 (40.9)	107 (38.6)	0.6933
LVEF, %	38.3 ± 12.75	37.0 ± 12.40	35.4 ± 12.2	34.9 ± 12.47	0.5920
LVEF category					0.7601
≤40%	141 (59.2)	160 (62.0)	224 (73.7)	206 (74.4)	
>40%	97 (40.8)	98 (38.0)	80 (26.3)	71 (25.6)	
Hospitalized for HF in the past year	86 (36.1)	74 (28.7)	54 (17.8)	59 (21.3)	0.0467
Number of HF hospitalizations in the past year	0.5 ± 0.77	0.4 ± 0.69	0.2 ± 0.58	0.3 ± 1.86	0.1238
Baseline vital signs					
Systolic blood pressure at baseline, mm Hg	121.2 ± 10.69	121.9 ± 10.61	125.2 ± 14.82	122.6 ± 14.15	0.0352
Pulse, beats/min	76.7 ± 10.87	77.1 ± 10.42	79.9 ± 12.28	80.4 ± 12.79	0.8933
Respiratory rate, breaths/min	17.8 ± 2.03	18.3 ± 8.19	18.2 ± 2.69	18.3 ± 3.17	0.4126

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TABLE 2 Continued

	AF/AFL (n = 496)		No AF/AFL (n = 581)		
	HIC (n = 238)	UC (n = 258)	HIC (n = 304)	UC (n = 277)	Interaction *P* Value
Local laboratory values					
Hemoglobin, g/L	138.7 ± 21.29	139.6 ± 20.93	134.5 ± 19.33	133.8 ± 18.05	0.4983
White blood cells, 10^3/L	7.0 ± 1.88	7.5 ± 2.38	6.9 ± 2.01	6.7 ± 1.68	0.0082
Creatinine, μmol/L	110.8 ± 26.35	109.2 ± 26.21	103.0 ± 32.04	103.1 ± 29.03	0.6343
Potassium, mmol/L	4.4 ± 0.43	4.3 ± 0.44	4.2 ± 0.46	4.2 ± 0.44	0.6566
Sodium, mmol/L	140.7 ± 4.07	141.2 ± 4.44	139.7 ± 3.96	139.5 ± 3.99	0.0960
Urea, mmol/L	8.7 ± 3.47	8.4 ± 3.60	7.7 ± 3.62	7.5 ± 3.15	0.8480
NT-proBNP, ng/L	3,437.0 (3,155.9-3,743.0)	3,246.9 (3,001.6-3,512.2)	3,125.1 (2,916.3-3,348.9)	3,079.7 (2,864.0-3,311.7)	0.5416
Oral HF medications taken at visit 2 prerandomization					
ACEIs/ARBs/ARNIs	136 (57.6)	139 (53.9)	218 (71.7)	196 (71.0)	0.6476
Beta-blockers	103 (43.6)	120 (46.5)	80 (26.3)	80 (29.0)	0.9463
MRAs	223 (94.5)	249 (96.5)	285 (93.8)	261 (94.6)	0.5621
Loop diuretic agents	228 (96.6)	245 (95.0)	292 (96.1)	264 (95.7)	0.6139

Values are mean ± SD, n (%), or geometric mean (95% CI).
HIC = high-intensity care; UC = usual care; other abbreviations as in Table 1.

The adjusted ratio of geometric means is presented for log-transformed variables, representing the ratio of the postbaseline value over the baseline value, and the corresponding treatment effect represents the ratio of these ratios between the treatment groups.

The percentage of optimal dose was calculated for each of the 3 medication classes (RASI, beta-blockers,

TABLE 3 Clinical Outcomes by History of AF/AFL

		Unadjusted		Adjusted	
Endpoint	n/N (KM%)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death or HF readmission by day 180[a]			0.1707		0.7017
AF/AFL	93/462 (21.2)	1.25 (0.91-1.72)		1.07 (0.77-1.48)	
No AF/AFL	90/545 (17.9)	Ref.		Ref.	
All-cause death or HF readmission (excluding COVID deaths) by day 180[a]			0.2375		0.7807
AF/AFL	89/462 (20.2)	1.22 (0.88-1.69)		1.05 (0.75-1.47)	
No AF/AFL	88/545 (17.4)	Ref.		Ref.	
All-cause death by day 180[b]			0.6608		0.4223
AF/AFL	41/462 (9.7)	1.11 (0.70-1.76)		1.22 (0.75-1.99)	
No AF/AFL	46/545 (9.1)	Ref.		Ref.	
All-cause death by day 180 (excluding COVID deaths)[b]			0.7990		0.4778
AF/AFL	37/462 (8.6)	1.07 (0.65-1.73)		1.20 (0.72-2.01)	
No AF/AFL	43/545 (8.4)	Ref.		Ref.	
HF readmission by day 180[c]			0.1705		0.3297
AF/AFL	63/462 (15.0)	1.32 (0.89-1.96)		1.24 (0.81-1.89)	
No AF/AFL	58/545 (11.9)	Ref.		Ref.	
	LS Mean (SE)	LS Mean Difference (95% CI)	*P* Value	LS Mean Difference (95% CI)	*P* Value
EQ-VAS change from baseline to visit 7[d]			0.8391		0.2464
AF/AFL	9.19 (1.00)	0.20 (−1.76 to 2.17)		1.17 (−0.81 to 3.15)	
No AF/AFL	8.98 (0.86)	Ref.		Ref.	

Results are restricted to subjects at sites where patients were followed for 180 days. Results for patients in cohort 1 are down-weighted proportional to half of the sample size. n/N (Kaplan-Meier estimates) are presented. HRs are from the Cox proportional hazards model. Subjects from Mozambique were excluded from EQ-VAS analyses. [a]Adjusted for baseline diastolic blood pressure, baseline NT-proBNP, ischemic etiology, and edema. [b]Adjusted for baseline creatinine, baseline hemoglobin, baseline urea, and baseline NT-proBNP. [c]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF, and edema. [d]Adjusted for baseline hemoglobin, baseline creatinine, baseline cholesterol, baseline NT-proBNP, hospitalization for heart failure in prior year, edema, NYHA functional class, region, LVEF group (≤40/>40), and baseline EQ-VAS.
EQ-VAS = Euroqol Visual Analogue Scale; KM = Kaplan-Meier; LS = least-square; Ref. = Reference; other abbreviations as in Table 1.

TABLE 4 Changes From Baseline in Vital Signs and Laboratory Data to Day 90 by History of AF/AFL and Treatment

	AF/AFL (n = 496)		No AF/AFL (n = 581)		
	HIC (n = 238)	UC (n = 258)	HIC (n = 304)	UC (n = 277)	Interaction *P* Value
Vital signs					
Systolic blood pressure, mm Hg					
Baseline	121.20 ± 10.69	121.90 ± 10.61	125.19 ± 14.82	122.57 ± 14.15	
Day 90	117.93 ± 13.99	123.72 ± 15.11	119.76 ± 17.24	123.79 ± 15.49	
Adjusted mean change,[a] LS mean (SE)	−4.40 (1.00)	1.24 (0.96)	−4.19 (0.88)	0.94 (0.92)	
LS mean difference (95% CI)	−5.63 (−8.34 to −2.92)	Ref.	−5.13 (−7.63 to −2.63)	Ref.	0.7886
Diastolic blood pressure, mm Hg					
Baseline	75.04 ± 8.23	73.94 ± 7.30	77.96 ± 11.39	77.66 ± 9.51	
Day 90	72.37 ± 9.18	74.63 ± 9.97	75.32 ± 11.11	77.10 ± 10.18	
Adjusted mean change,[a] LS mean (SE)	−3.43 (0.64)	−0.58 (0.62)	−1.85 (0.56)	0.16 (0.59)	
LS mean difference (95% CI)	−2.85 (−4.59 to −1.11)	Ref.	−2.00 (−3.60 to −0.41)	Ref.	0.4817
Heart rate, beats/min					
Baseline	76.71 ± 10.87	77.07 ± 10.42	79.89 ± 12.28	80.43 ± 12.79	
Day 90	72.53 ± 15.27	77.50 ± 13.34	70.38 ± 11.52	77.12 ± 11.92	
Adjusted mean change,[a] LS mean (SE)	−5.16 (0.83)	−0.42 (0.79)	−8.57 (0.72)	−2.05 (0.76)	
LS mean difference (95% CI)	−4.74 (−6.98 to −2.50)	Ref.	−6.51 (−8.57 to −4.46)	Ref.	0.2536
Respiratory rate, breaths/min					
Baseline	17.76 ± 2.03	18.33 ± 8.19	18.23 ± 2.69	18.33 ± 3.17	
Day 90	17.37 ± 2.26	17.59 ± 2.21	17.08 ± 2.52	17.88 ± 2.91	
Adjusted mean change,[a] LS mean (SE)	−0.71 (0.17)	−0.59 (0.16)	−1.05 (0.14)	−0.30 (0.15)	
LS mean difference (95% CI)	−0.12 (−0.57 to 0.33)	Ref.	−0.76 (−1.17 to −0.34)	Ref.	0.0404
Weight, kg					
Baseline	76.05 ± 20.57	75.60 ± 20.70	87.33 ± 18.34	88.09 ± 18.40	
Day 90	74.97 ± 21.06	75.72 ± 20.36	87.13 ± 17.68	88.42 ± 17.85	
Adjusted mean change,[a] LS mean (SE)	−1.47 (0.27)	−0.28 (0.29)	−1.11 (0.31)	0.39 (0.30)	
LS mean difference (95% CI)	−1.19 (−1.96 to −0.42)	Ref.	−1.50 (−2.34 to −0.66)	Ref.	0.5937

Continued on the next page

and MRAs), and an average of these 3 percentages was used to derive an average percent optimal dose. Figures depicting the percent optimal dose over time in the HIC group, starting at day 0 (post-randomization), for each medication class individually, as well as the average percent optimal dose of the 3 classes, by treatment and AF/AFL groups are presented with results from a mixed model for repeated measures that included history of AF/AFL, visit, and history of AF/AFL-by-visit interaction.

Adverse events and serious adverse events occurring between randomization and 90 days postrandomization are presented. A 2-sided value of $P < 0.05$ was considered statistically significant. SAS version 9.4 (SAS Institute) was used for all analyses.

RESULTS

Among 1,078 patients enrolled in the study, 496 (46%) had a history of AF/AFL. Patients with AF/AFL were older (mean age: 68 ± 10 years vs 59 ± 15 years; $P < 0.0001$) (Tables 1 and 2) and more frequently male (66.3% vs 57.1%; $P = 0.002$) than those without AF/AFL. Previous history of HF (88.7% vs 81.9%), HF hospitalization in the preceding year (32.3% vs 19.4%; $P < 0.0001$), and ischemic HF etiology (57.2% vs 39.8%; $P < 0.0001$) as well as prevalence of diabetes and psychiatric or neurologic disorders were all more common in patients with AF/AFL. History of stroke or transient ischemic attack was only numerically higher in patients with AF/AFL.

Patients with AF/AFL presented with worse NYHA functional class and lower systolic blood pressure ($P < 0.0001$) as well as numerically higher natriuretic peptide values. These patients also had a higher mean LVEF value (37.6% vs 35.2%; $P = 0.0011$) and belonged more frequently to the mildly reduced or preserved LVEF phenotype than those without AF/AFL. Regarding oral HF medications before randomization, the AF/AFL group had a lower use of RASI and a higher use of beta-blockers compared to the non-AF/AFL group. The use of MRA and loop diuretic agents was similar in the 2 groups. The rate of all-cause death or HF readmission at 180 days was similar in patients with and without AF/AFL

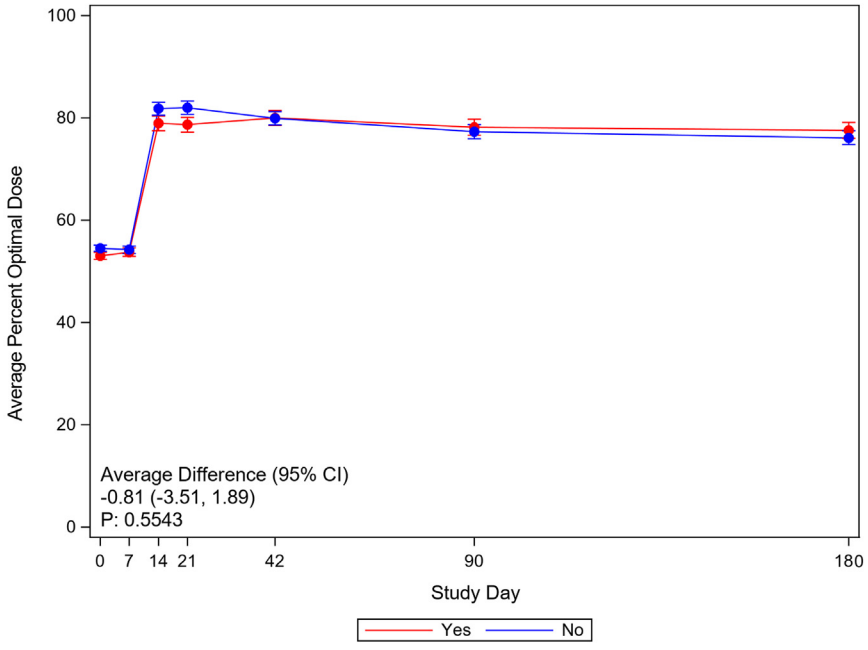
TABLE 4 Continued

	AF/AFL (n = 496)		No AF/AFL (n = 581)		
	HIC (n = 238)	UC (n = 258)	HIC (n = 304)	UC (n = 277)	Interaction *P* Value
Local laboratory values					
Hemoglobin, g/L					
Baseline	138.7 ± 21.29	139.6 ± 20.93	134.5 ± 19.33	133.8 ± 18.05	
Day 90	134.0 ± 17.44	136.9 ± 16.99	130.8 ± 16.88	130.0 ± 17.01	
Adjusted mean change,[a] LS mean (SE)	−3.81 (0.91)	−1.74 (0.87)	−4.90 (0.80)	−5.03 (0.84)	
LS mean difference (95% CI)	−2.07 (−4.53 to 0.38)	Ref.	0.13 (−2.14 to 2.40)	Ref.	0.1969
Glucose, mmol/L					
Baseline	6.30 ± 2.28	6.43 ± 1.91	6.13 ± 2.60	6.12 ± 2.37	
Day 90	6.46 ± 2.48	6.74 ± 2.87	6.24 ± 2.46	5.96 ± 2.38	
Adjusted mean change, LS mean (SE)	0.29 (0.15)	0.45 (0.14)	0.11 (0.13)	−0.14 (0.14)	
LS mean difference (95% CI)	−0.16 (−0.57 to 0.25)	Ref.	0.25 (−0.13 to 0.62)	Ref.	0.1507
Sodium, mmol/L					
Baseline	140.7 ± 4.07	141.2 ± 4.44	139.7 ± 3.96	139.5 ± 3.99	
Day 90	141.2 ± 4.31	141.2 ± 4.22	140.0 ± 4.19	139.4 ± 4.11	
Adjusted mean change,[a] LS mean (SE)	0.61 (0.26)	0.44 (0.25)	−0.09 (0.23)	−0.62 (0.24)	
LS mean difference (95% CI)	0.18 (−0.53 to 0.88)	Ref.	0.54 (−0.11 to 1.19)	Ref.	0.4619
Potassium, mmol/L					
Baseline	4.36 ± 0.43	4.32 ± 0.44	4.21 ± 0.46	4.20 ± 0.44	
Day 90	4.60 ± 0.45	4.51 ± 0.48	4.60 ± 0.49	4.39 ± 0.52	
Adjusted mean change,[a] LS mean (SE)	0.31 (0.03)	0.23 (0.03)	0.34 (0.03)	0.14 (0.03)	
LS mean difference (95% CI)	0.08 (−0.01 to 0.17)	Ref.	0.21 (0.12 to 0.29)	Ref.	0.0434
Urea, mmol/L					
Baseline	8.68 ± 3.47	8.45 ± 3.60	7.67 ± 3.62	7.52 ± 3.15	
Day 90	8.39 ± 3.68	8.20 ± 3.55	7.41 ± 3.90	7.67 ± 4.39	
Adjusted mean change,[a] LS mean (SE)	−0.01 (0.25)	0.11 (0.23)	−0.37 (0.21)	0.00 (0.23)	
LS mean difference (95% CI)	−0.12 (−0.78 to 0.54)	Ref.	−0.38 (−0.99 to 0.23)	Ref.	0.5810
eGFR, mL/min/1.73 m^2					
Baseline	56.91 ± 16.13	58.75 ± 17.06	70.15 ± 23.06	71.51 ± 26.50	
Day 90	56.59 ± 17.87	58.41 ± 17.02	70.31 ± 23.46	71.54 ± 25.11	
Adjusted mean change,[a] LS mean (SE)	−1.88 (1.02)	−1.84 (0.97)	1.60 (0.89)	2.25 (0.94)	
LS mean difference (95% CI)	−0.04 (−2.76 to 2.69)	Ref.	−0.65 (−3.16 to 1.87)	Ref.	0.7480
AST, U/L					
Baseline	28.29 ± 12.28	28.90 ± 15.95	25.15 ± 14.32	24.95 ± 17.87	
Day 90	28.31 ± 42.95	29.42 ± 31.10	22.83 ± 20.62	25.56 ± 33.60)	
Adjusted mean change,[a] LS mean (SE)	0.97 (2.30)	2.15 (2.18)	−3.56 (2.04)	−0.76 (2.14)	
LS mean difference (95% CI)	−1.18 (−7.38 to 5.02)	Ref.	−2.80 (−8.60 to 3.00)	Ref.	0.7083
ALT, U/L					
Baseline	35.28 ± 66.65	31.51 ± 49.07	27.43 ± 28.64	26.20 ± 20.81	
Day 90	24.59 ± 13.88	25.73 ± 25.78	23.30 ± 44.91	23.67 ± 26.34	
Adjusted mean change,[a] LS mean (SE)	−6.25 (2.19)	−4.97 (2.06)	−7.20 (1.95)	−6.91 (2.05)	
LS mean difference (95% CI)	−1.28 (−7.18 to 4.63)	Ref.	−0.29 (−5.84 to 5.26)	Ref.	0.8115
NT-proBNP, pg/mL					
Baseline, geometric mean (95% CI)	3,306.9 (3,032.3-3,606.3)	3,136.4 (2,893.3-3,400.0)	3,097.2 (2,875.9-3,335.6)	3,052.4 (2,828.6-3,293.8)	
Day 90, geometric mean (95% CI)	1,729.3 (1,493.4-2,002.5)	1,854.8 (1,602.4-2,146.9)	1,121.8 (974.0-1,291.9)	1,617.7 (1,397.1-1,873.2)	
Adjusted mean change,[b] LS mean (95% CI)	0.536 (0.462-0.623)	0.591 (0.514-0.680)	0.360 (0.316-0.410)	0.523 (0.456-0.600)	
LS mean difference (95% CI)	0.91 (0.74-1.11)	Ref.	0.69 (0.57-0.83)	Ref.	0.0525

Values are mean ± SD, unless otherwise indicated. The usual care group is used as reference within each type of AF category. [a]Least square mean (SE) and LS mean difference (95% CI) estimated based on an analysis of covariance model with terms for type of AF, treatment, baseline value and type of AF-by-treatment interaction. [b]Analyses for NT-proBNP were on the log scale with the geometric mean (95% CI) shown at each visit; adjusted ratio of geometric means represents the ratio of the postbaseline value over the baseline value from an analysis of covariance model of the log-transformed NT-proBNP with terms for type of AF, treatment, baseline value, and type of AF-by-treatment interaction. The LS mean difference represents the ratio of the ratios in the 2 groups.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR, estimated glomerular filtration rate; other abbreviations as in Tables 1 to 3.

FIGURE 1 Average Optimal Dose of Neurohormonal Inhibitors in the High-Intensity Care Group



Average optimal dose of neurohormonal inhibitors by history of atrial fibrillation/flutter (yes/no) in high-intensity care group.

(adjusted HR for AF/AFL history: 1.07; 95% CI: 0.77-1.48) (**Table 3**).

The baseline characteristics of patients were also analyzed based on the type of AF/AFL (Supplemental Tables 1 and 2). Age, sex distribution, geographical region, and natriuretic peptide levels did not differ among the 3 groups.

By day 90, changes in vital signs and laboratory data were consistent in patients with and without AF/AFL (**Table 4**), including a greater reduction in systolic and diastolic blood pressure, heart rate, body weight, and natriuretic peptide levels in the HIC than in the UC arm. Similar results were obtained in the analyses by AF/AFL type (Supplemental Table 3).

Regarding initiation and uptitration of GDMT, the average percent optimal dose of neurohormonal inhibitors achieved by day 90 in the HIC arm was similar in patients with and without AF/AFL, reaching approximately 80% of the optimal dose (average absolute difference between AF/AFL and non-AF/AFL groups: −0.81%; 95% CI: −3.5 to 1.89) (**Figure 1**). Similar results were obtained for individual drug categories, ie, RASI (~75% of optimal dose), beta-blockers (~70% of optimal dose), and MRA (≈90% of optimal dose) (Supplemental Figures 1 to 3). Further stratification by the type of AF/AFL showed no significant disparities in optimal dose percentages for RASI, beta-blockers, or MRA (Supplemental Figures 4 and 5).

The rate of all-cause death or HF readmission was lower in patients in the HIC than in the UC arm, both in patients with and without AF/AFL (adjusted HR for AF/AFL history: 0.75 [95% CI: 0.48-1.19] in AF/AFL group vs 0.50 [95% CI: 0.31-0.79] in non-AF/AFL group; *P* for interaction = 0.2107) (**Table 5**, **Figure 2**). The same was true for the components of the primary endpoint and for the analysis excluding COVID-19-related deaths. Results were further consistent when analyzed by AF/AFL type (Supplemental Figure 6).

Adverse events were generally more frequent in the HIC than in the UC arm; however, the proportions of patients with adverse events or serious adverse events did not differ by history or type of AF/AFL (Supplemental Tables 4 to 7).

DISCUSSION

The current post hoc analysis of STRONG-HF demonstrates that rapid uptitration of GDMT under close follow-up during and after discharge from an HF

TABLE 5 Clinical Outcomes by History of AF/AFL and Treatment

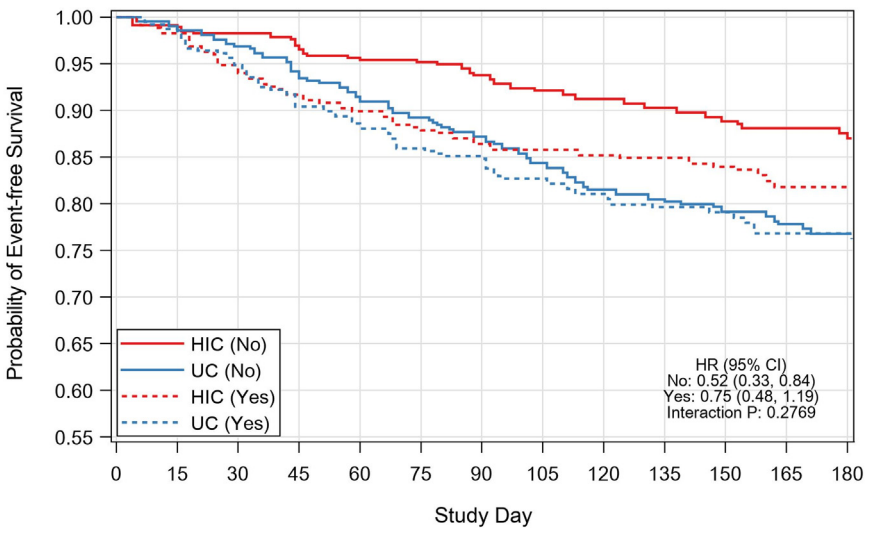
	AF/AFL (n = 493)				No AF/AFL (n = 585)				*P* Value (Treatment by AF/AFL Interaction)	
Endpoint	HIC	UC	Unadjusted Treatment Effect	Adjusted Treatment Effect	HIC	UC	Unadjusted Treatment Effect	Adjusted Treatment Effect	Unadjusted	Adjusted
All-cause death or HF readmission by day 180[a]	40/223 (18.2)	53/239 (23.8)	0.75 (0.48 to 1.19)	0.75 (0.48 to 1.19)	34/283 (13.0)	56/262 (23.2)	0.52 (0.33 to 0.84)	0.50 (0.31 to 0.79)	0.2769	0.2107
All-cause death by day 180[b]	20/223 (9.7)	21/239 (9.7)	1.01 (0.52 to 1.97)	0.98 (0.50 to 1.92)	19/283 (7.7)	27/262 (10.6)	0.70 (0.37 to 1.33)	0.66 (0.34 to 1.26)	0.4365	0.4043
All-cause death or HF readmission by day 180 (excluding COVID deaths)[a]	36/223 (16.2)	53/239 (23.8)	0.65 (0.41 to 1.06)	0.66 (0.41 to 1.06)	33/283 (12.6)	55/262 (22.8)	0.51 (0.32 to 0.83)	0.49 (0.30 to 0.79)	0.4848	0.3953
All-cause death by day 180 (excluding COVID deaths)[b]	16/223 (7.5)	21/239 (9.7)	0.77 (0.37 to 1.58)	0.74 (0.36 to 1.53)	17/283 (6.8)	26/262 (10.1)	0.65 (0.33 to 1.27)	0.61 (0.31 to 1.20)	0.7330	0.6990
HF readmission by day 180[c]	25/223 (11.4)	38/239 (18.1)	0.61 (0.35 to 1.08)	0.58 (0.33 to 1.04)	22/283 (7.8)	36/262 (16.5)	0.46 (0.25 to 0.83)	0.45 (0.25 to 0.82)	0.4807	0.5380
EQ-VAS change from baseline to visit 7[d]	10.36 ± 1.20	8.08 ± 1.16	2.28 (-0.25 to 4.80)	3.09 (0.63 to 5.54)	11.08 ± 1.02	6.42 ± 1.09	4.67 (2.23 to 7.10)	4.51 (2.16 to 6.86)	0.1815	0.4123

Values are n/N (%), mean ± SD, or HR (95% CI). Results are restricted to subjects at sites where patients were followed up for 180 days for day 180 analyses. Results for patients in cohort 1 are down-weighted proportional to half of the sample size. n/N (Kaplan-Meier estimates) are presented. HRs are from the Cox proportional hazards model. Subjects from Mozambique were excluded from EQ-VAS analyses. [a]Adjusted for baseline diastolic blood pressure, baseline NT-proBNP, ischemic etiology, and edema. [b]Adjusted for baseline creatinine, baseline hemoglobin, baseline urea, and baseline NT-proBNP. [c]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF, and edema. [d]Adjusted for baseline hemoglobin, baseline creatinine, baseline cholesterol, baseline NT-proBNP, hospitalization for heart failure in prior year, edema, NYHA functional class, region, LVEF group (≤40/>40), and baseline EQ-VAS.

Abbreviations as in Tables 1 and 2.

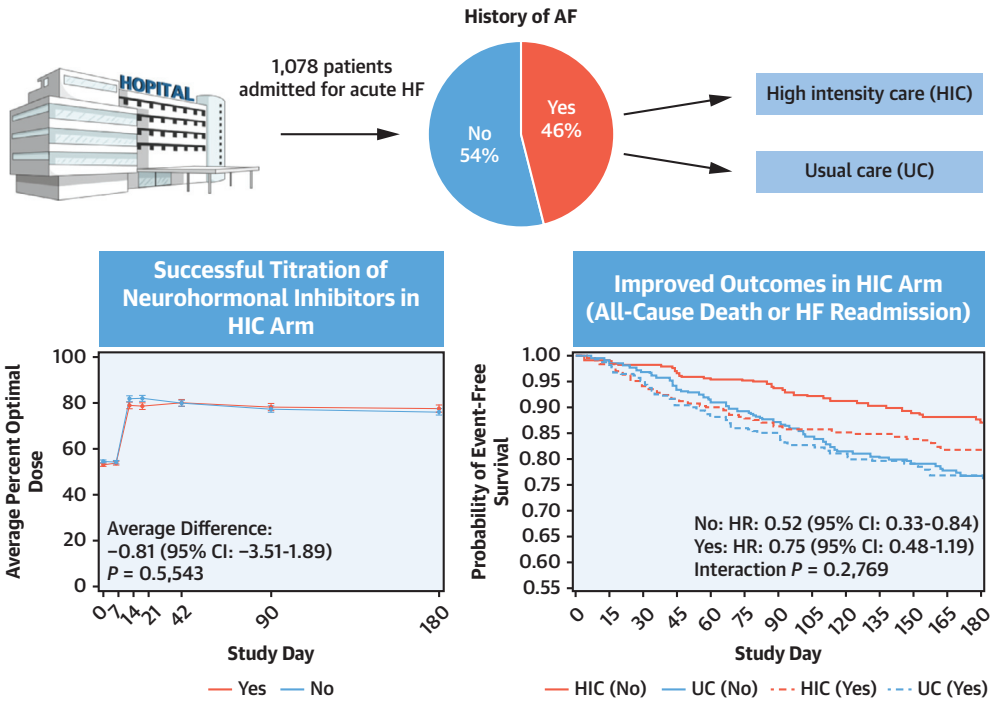
hospital admission is feasible and safe and improves clinical outcomes, regardless of the presence or type of AF/AFL history. The percentage of patients who achieved optimal doses of all neurohormonal inhibitors (RASI, beta-blockers, and MRA) was similar in patients with and without AF/AFL, regardless of the type of AF/AFL, and was further followed by a reduction in all-cause death or HF readmission in the 6-month period after discharge (**Central Illustration**). These results confirm a series of

FIGURE 2 All-Cause Death or HF Readmission



Kaplan-Meier curve for all-cause death or HF readmission to day 180 by history of atrial fibrillation/flutter (yes/no) and treatment. HF = heart failure; HIC = high intensity care; UC = usual care.

CENTRAL ILLUSTRATION **Rapid Uptitration of Neurohormonal Inhibitors in Acute HF With and Without Atrial Fibrillation**



Farmakis D, et al. JACC Heart Fail. 2024;12(11):1845–1858.

Among 1,078 patients admitted for acute HF, 46% had a history of atrial fibrillation or flutter. Rapid uptitration of neurohormonal inhibitors before and after discharge was feasible and improved outcomes (all-cause death or HF readmission) regardless of atrial fibrillation or flutter history. AF = atrial fibrillation; HF = heart failure; No = no history of atrial fibrillation or flutter; Yes = history of atrial fibrillation or flutter.

previous post hoc analyses of STRONG-AF, indicating that the HIC approach suggested by the study is applicable to a broad spectrum of the heterogeneous population of patients hospitalized for HF, regardless of age, sex, LVEF, or the presence of noncardiac comorbidities.[5-8]

AF or AFL affects approximately one-third of patients with HF and reduced LVEF and up to one-half of those with preserved LVEF.[9-11] The prevalence of AF/AFL in HF increases with HF severity, ranging from 4% in NYHA functional class I to nearly 45% to 50% in NYHA functional class IV.[6] Accordingly, in STRONG-HF, patients with AF/AFL more frequently had a previous history of HF, more HF hospitalizations in the preceding year, and worse NYHA functional class than those without AF/AFL. As a result, acute HF patients are expected to have a high prevalence of AF/AFL. Indeed, 46% of patients with acute HF in STRONG-AF had baseline AF/AFL. In a pooled analysis of 3 randomized trials on acute HF, DOSE (Diuretic Optimization Strategies Evaluation), ROSE (Renal Optimization Strategies Evaluation), and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), history of AF/AFL was present in 56% of 750 patients enrolled and was associated with a blunted response to diuretic therapy.[12]

In the present study, patients with AF/AFL were older and had a higher prevalence of diabetes, severe liver disease, and psychiatric or neurologic disorders than those without AF/AFL, findings that are in line with previous epidemiologic studies.[13-17] The older age and the greater burden of comorbidities associated with AF/AFL in HF patients are often considered a barrier to intensifying GDMT because of concerns about safety and tolerability.[8,18,19] However, for this

vulnerable population, our analysis provides evidence to support a rapid initiation and uptitration of GDMT with close follow-up over the usual practice, reducing all-cause death or HF readmission at 180 days across all types of AF/AFL. GDMT seem to be equally safe and effective in patients with HF and AF/AFL compared to those without AF/AFL. Previous studies have documented the safety and efficacy of neurohormonal inhibitors and sodium-glucose cotransporter 2 inhibitors in patients with chronic HF and AF/AFL.[3,20-22] In addition, RASIs have been associated with a lower incidence of AF/AFL in patients with sinus rhythm.[23,24] Therefore, HF patients with AF/AFL should not be deprived of the beneficial effects of GDMT.

A particular case is that of beta-blockers. At the time of enrollment, AF/AFL patients of the STRONG-HF trial were on beta-blockers more frequently compared to the patients without AF/AFL, indicating their wide use as first-line rate control therapy.[25] Beta-blockade is a fundamental therapy for patients with HF and reduced LVEF based on the results of landmark trials having shown that beta-blockers decrease long-term mortality in these patients by approximately 35%.[26] However, in HF with reduced LVEF and AF/AFL, as opposed to those in sinus rhythm, heart rate has not been shown to be a predictor of mortality[27] Thus, any β-blockade-conferred benefit in these patients may be more dependent on additional mechanisms besides heart rate reduction concerning the attenuation of the detrimental sympathetic nervous system effects on myocardium, peripheral vasculature, metabolism, and renal and immune function.[26] In addition, an individual-patient data meta-analysis has questioned the benefit of beta-blockers in patients with HF with reduced LVEF and AF/AFL.[27] Moreover, it is unclear what the optimal heart rate target should be in these patients.[25] Attempts to uptitrate beta-blockers to the maximal tolerated dose may have a harmful effect, as ventricular rates of <70 beats/min have been associated with a worse outcome.[28] Therefore, adherence to a close follow-up regimen, as performed in STRONG-HF, is key for safe implementation in the broader HF population.[29]

Acute HF has long been considered a window of opportunity for treatment optimization. STRONG-HF provided key evidence, supporting the rapid optimization of neurohormonal inhibitors before and soon after discharge, during this particularly vulnerable period, in which HF events are higher.[30] Patients with AF/AFL should not be excluded for such an approach according to the results of the present analysis. Patients tolerated the administered doses of GDMT across all types of the AF/AFL spectrum, and adverse events were observed more often in the high-intensity arm, regardless of the presence of AF/AFL. This emphasizes the importance of the close monitoring of patients during the vulnerable transition period.

STUDY LIMITATIONS. This is a post hoc analysis of data, and thus the results should be treated with caution. Subgroup analyses are subject to well-known limitations, including that the application of findings to individual patients who have multiple characteristics may be challenging. In addition, because the study was stopped early, it may be underpowered to detect interactions. The study's sample size limits the power to detect subgroup differences. In STRONG-HF, an electrocardiogram was not captured at the time of admission or during hospitalization, and therefore, this analysis refers to patients with a history of AF/AFL. In addition, as in other similar secondary analyses on AF/AFL, there is always a possibility of undetected episodes of paroxysmal AF/AFL in patients' history or the development of AF/AFL in the course of the study. It should also be stressed that the main trial excluded patients in whom admission for HF was triggered by a correctable cause, including AF/AFL with rapid ventricular response (>130 beats/min). Therefore, the results of the present analysis may not apply to patients who present with acute HF induced by rapid AF/AFL. These reasons may explain the lack of difference in the rate of all-cause death or HF readmission at 180 days between patients with and without AF/AFL history, in contrast to previous studies in which AF/AFL was associated with an increased risk of adverse long-term outcomes in patients hospitalized for HF, particularly in those with mildly reduced or preserved LVEF.[31]

CONCLUSIONS

AF/AFL affects nearly half of hospitalized HF patients. In these patients, rapid uptitration of GDMT before and early after discharge seems to be feasible and safe and may lead to improved outcomes regardless of the presence or type of AF/AFL.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF/AFL affect roughly half of patients hospitalized with HF, being associated with higher age and greater comorbidity burden. Rapid uptitration of GDMT during and soon after discharge for HF is feasible and safe and improves long-term outcomes, regardless of the presence or type of AF/AFL history.

TRANSLATIONAL OUTLOOK: AF/AFL should not be considered a barrier for initiating and/or titrating GDMT in patients hospitalized for HF before and soon after discharge. Given the high and increasing prevalence of AF/AFL in these patients, future studies should clarify its impact on the outcomes of other therapies used in this setting.

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KEY WORDS atrial fibrillation, guideline-directed medical therapies, heart failure, hospitalization, titration

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