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Safety Indicators in Patients Receiving High-intensity Care After Hospital Admission for Acute Heart Failure: The STRONG-HF Trial

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ABSTRACT

Background: Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) demonstrated the safety and efficacy of rapid up-titration of guideline-directed medical therapy (GDMT) with high-intensity care (HIC) compared with usual care in patients hospitalized for acute heart failure (HF). In the HIC group, the following safety indicators were used to guide up-titration: estimated glomerular filtration rate of <30 mL/min/1.73 m^2, serum potassium of >5.0 mmol/L, systolic blood pressure (SBP) of <95 mmHg, heart rate of <55 bpm, and N-terminal pro-B-type natriuretic peptide concentration of >10% higher than predischarge values.

Methods and Results: We examined the impact of protocol-specified safety indicators on achieved dose of GDMT and clinical outcomes. Three hundred thirteen of the 542 patients in the HIC arm (57.7%) met ≥1 safety indicator at

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any follow-up visit 1−6 weeks after discharge. As compared with those without, patients meeting ≥1 safety indicator had more severe HF symptoms, lower SBP, and higher heart rate at baseline and achieved a lower average percentage of GDMT optimal doses (mean difference vs the HIC arm patients not reaching any safety indicator, −11.0% [95% confidence interval [CI] −13.6 to −8.4%], $P < .001$). The primary end point of 180-day all-cause death or HF readmission occurred in 15.0% of patients with any safety indicator vs 14.2% of those without (adjusted hazard ratio 0.84, 95% CI 0.48−1.46, $P = .540$). None of each of the safety indicators, considered alone, was significantly associated with the primary end point, but an SBP of <95 mm Hg was associated with a trend toward increased 180-day all-cause mortality (adjusted hazard ratio 2.68, 95% CI 0.94−7.64, $P = .065$) and estimated glomerular filtration rate decreased to <30 mL/min/1.73 m^2 with more HF readmissions (adjusted hazard ratio 3.60, 95% CI 1.22−10.60, $P = .0203$). The occurrence of a safety indicator was associated with a smaller 90-day improvement in the EURO-QoL 5-Dimension visual analog scale (adjusted mean difference −3.32 points, 95% CI −5.97 to −0.66, $P = .015$).

Conclusions: Among patients with acute HF enrolled in STRONG-HF in the HIC arm, the occurrence of any safety indicator was associated with the administration of slightly lower GDMT doses and less improvement in quality of life, but with no significant increase in the primary outcome of 180-day HF readmission or death when appropriately addressed according to the study protocol. (*J Cardiac Fail 2024;30:525−537*)

Keywords: Safety indicators, guideline-directed medical therapy, acute heart failure, hypotension, hyperkalemia, STRONG-HF.

Acute heart failure (HF) is associated with a high risk of postdischarge readmissions and death.[1−5] Despite the higher risk of postdischarge events, hospitalization for HF offers the opportunity to initiate or up-titrate guideline-directed medical therapy (GDMT).[6−12] Indeed, although GDMT improves outcome and quality of life of patients with HF, it remains largely underused.[13−15] Patient factors (eg, older age, comorbidities, intolerance or contraindications, instability during hospitalization) and physician factors (eg, clinical inertia) have been suggested as potential reasons for suboptimal dosing of HF therapies during hospitalization.[16−23]

The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial demonstrated that a high-intensity care (HIC) strategy of rapid GDMT up-titration and close follow-up can decrease the risk of 180-day HF readmission or all-cause death in patients recently hospitalized for acute HF, compared with usual care (UC).[24,25] Patients assigned to HIC were followed according to a set of prespecified specific safety indicators, which guided changes in treatment at each follow-up visit.[24,16]

We analyzed in this study the incidence and the impact of the safety indicators on treatment and outcome of the patients assigned to the HIC arm.

Methods

Study Design

The design and main results of the STRONG-HF trial have been previously reported.[24−26] Briefly, this multicenter, open-label, randomized trial compared a HIC strategy with early up-titration of renin angiotensin system (RAS) inhibitors (angiotensin-converting enzyme [ACE] inhibitors, or angiotensin receptor blockers [ARBs] in patients intolerant to ACE inhibitors, or angiotensin receptor-neprilysin inhibitors [ARNIs]), β-blockers, and mineralocorticoid receptor antagonists [MRAs], vs UC, among 1078 patients admitted to hospital for acute HF and not treated with full doses of GDMT. Included patients were hemodynamically stable, had any left ventricular ejection fraction (LVEF) and high N-terminal pro-B-type natriuretic peptide (NT-proBNP) values at screening (>2500 pg/mL). Screening (visit 1) was performed within 72 hours after admission. One to 2 days before discharge, patients underwent further assessment (visit 2, before randomization). At that time, all inclusion and exclusion criteria should have been met and, in addition, to ensure that the patient was still at high risk, NT-proBNP had to be >1500 pg/mL, but with a decrease of >10% compared with screening. To ensure safety of up-titration of GDMT, all measures of systolic blood pressure (SBP), heart rate, and serum potassium within 24 h should have been ≥100 mm Hg, ≥60 bpm, and ≤5.0 mEq/L (mmol/L), respectively. Baseline parameters corresponded to those measured at randomization (visit 2).

In the HIC arm, β-blockers, ACE inhibitors/ARBs/ARNi, and MRA were rapidly up-titrated to 50% of optimal doses before discharge and to 100% of optimal doses within 2 weeks after discharge. At each of the following visits, GDMT up-titration was encouraged in the patients not on maximally tolerated doses of ACE inhibitors/ARBs/ARNi or β-blockers and without any safety criteria (as discussed elsewhere in this article). Patients were assessed by the study team at 1, 2, 3, and 6 weeks after discharge and an additional safety visit was done 1 week after any up-titration to assess safety and tolerability.[24] Clinical

examination and laboratory assessments including NT-proBNP, sodium and potassium plasma concentrations, and kidney function, were repeated at each visit. Patients in the UC group were followed according to local practice until a study visit performed, conducted for patients in both groups, at day 90 after randomization (visit 7).

All randomized patients were contacted at day 180 to assess the occurrence of rehospitalizations and death (visit 8). The study's primary end point was the composite of all-cause death or first HF rehospitalization at day 180. Other end points included 180-day all-cause death, 180-day HF readmission, and change in the EURO-QoL 5-Dimension (EQ-5D) visual analogue scale (VAS) score from baseline to day 90.[27]

The study was approved by appropriate competent authorities and all sites obtained approval from ethics committees. All patients provided written informed consent. The study is registered at ClinicalTrials.gov, NCT03412201.

Protocol Guidance According to Safety Indicators

According to study protocol, patients assigned to HIC were prescribed GDMT at ≥50% optimal doses within 2 days before anticipated hospital discharge with up-titration to full optimal doses at 2 weeks after randomization and/or in the following visits when up-titration was not completed and no safety indicator was met. GDMT up-titration was delayed according to the following prespecified safety indicators:

- No up-titration of ACE inhibitors/ARBs/ARNi and/or MRAs if SBP was <95 mm Hg and/or serum potassium was >5.0 mmol/L and/or estimated glomerular filtration rate (eGFR) was <30 mL/min/1.73 m^2;
- No up-titration of β-blockers if heart rate was <55 bpm and/or SBP was <95 mm Hg; and
- Consideration of no up-titration of β-blockers and increase in diuretic dose if NT-proBNP concentrations were >10% higher than the predischarge level.[24]

In addition, investigators were asked to increase the diuretic dose as needed if clinical signs of congestion were present and to decrease the diuretics dose if eGFR was <30 mL/min/1.73 m^2 without signs of congestion.

Stratifications and Definitions

As per protocol, safety indicators were the following: eGFR of <30 mL/min/1.73 m^2, serum potassium of >5.0 mmol/L, SBP of <95 mm Hg, heart rate of <55 bpm, and NT-proBNP level >10% higher than the predischarge level. Because patients in the UC group were not evaluated by the study team between randomization and day 90, only patients randomized to the HIC strategy were included in the present analysis and were stratified into 2 groups based on the occurrence of any of the safety indicators at any follow-up visit at weeks 1, 2, 3, or 6. Baseline characteristics are presented stratified by these 2 groups. Clinical outcomes as well as the average percentage of achieved GDMT doses were compared between each separate safety indicator. Although not prespecified as a safety indicator, we also explored the impact of worsening renal function (WRF), defined as a decrease in the eGFR of ≥15% from baseline.

The current analysis was not prespecified in the study protocol.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, adjusted mean and associated standard error, or as geometric mean and 95% confidence interval (CI) for log-transformed variables; categorical variables are presented as number and percentage. Comparisons of baseline characteristics among groups were performed by analysis of variance for continuous variables, using log-transformed values for skewed continuous variables, χ^2 test for categorical variables, and Cochran–Mantel–Haenszel nonzero correlation for ordinal categorical variables. Comparisons of binary variables with observed cell counts of <5 were made using Monte Carlo estimation of exact χ^2 *P* values.

Primary and other end points through 180 days were restricted to patients enrolled at sites where the ethics committee approved the amended protocol allowing follow-up of patients through day 180, and in the cohort of patients enrolled before the primary end point was changed from 90 to 180 days, the results were down-weighted proportional to one-half its sample size. Cox proportional hazards regression models were used to evaluate the impact of safety indicators on the study end points.[28,29] Each safety indicator, or the occurrence of any indicator, was considered as a time-dependent covariate in a separate model. The covariate took the value "no" until the visit at which the safety indicator occurred, after which the covariate took the value "yes." Baseline covariates for adjustment were selected using backward selection in the UC group from factors shown to be prognostic of the outcomes in previous studies; $P < .10$ across 10 multiple imputation datasets was the criterion for staying. Covariates finally selected for the primary end point were diastolic blood pressure, baseline NT-proBNP, ischemic aetiology, and oedema. Results are described as hazard ratio (HR) and 95% CI.

Groups were compared with respect to the change in EQ-VAS using ANCOVA adjusted for baseline value and randomization stratification factors (LVEF of ≤40% vs LVEF of >40% and geographic region) and using observed values. Patients from Mozambique, where no linguistically validated EQ-5D was available, were excluded from the analyses. Adjusted results impute missing covariate values with results averaged across 10 multiple imputation datasets.

The dose of medication in each of the 3 medication classes (RAS inhibitors, β-blockers, and MRAs) relative to the optimal doses (see Supplemental Table 3 in the primary publication[24]) was computed for each patient; the average of these percentages was also computed. The trajectory of the percentage optimal dose over time is presented for each medication class and for the average across the 3 medication classes by groups of patients with or without safety indicators. Differences in the percentage optimal doses between the safety indicator groups were compared using mixed models for repeated measures.

Two-sided *P* values of <.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Incidence and Distribution of Safety Indicators

Among the 542 patients randomized to the HIC arm, 313 (57.7%) met ≥1 safety indicator at any visit, 3−6 (Fig. 1). Specifically, 28 patients (5.2%) had an eGFR of <30 mL/min/1.73 m^2, 51 (9.4%) had an SBP of <95 mm Hg, 46 (8.5%) had a heart rate of <55 bpm, and 149 (27.5%) had a serum potassium of >5.0 mmol/L. An increase in NT-proBNP concentration of >10% at any postdischarge follow-up visit, compared with randomization values, was observed in 223 patients (41.1%).

Table 1 shows the concomitant occurrence of multiple safety indicators in the same patients. A large proportion of patients with an eGFR of <30 mL/min/1.73 m^2 at any visit also had a serum potassium of >5.0 mmol/L or an increase in NT-proBNP of >10% from predischarge values (42.9% and 57.1%, respectively) at any visit. Among patients with an SBP of <95 mm Hg, 17 patients (33.3%) also had an increase in NT-proBNP of >10% at any visit.

Decline in eGFR of ≥15%

Although not a predefined safety indicator, 181 patients (33.4%) experienced WRF with a decrease in the eGFR of ≥15% from baseline (Table 1). Approximately 90% of patients who reached an eGFR of <30 mL/min/1.73 m^2 also had a decline in eGFR of ≥15% from baseline. More than one-third of patients with an SBP of <95 mm Hg as well as of those with an increase in NT-proBNP of >10% had a decrease in the eGFR of ≥15%. Patients who had a eGFR decrease of ≥15% where less up-titrated on GDMT.[30]

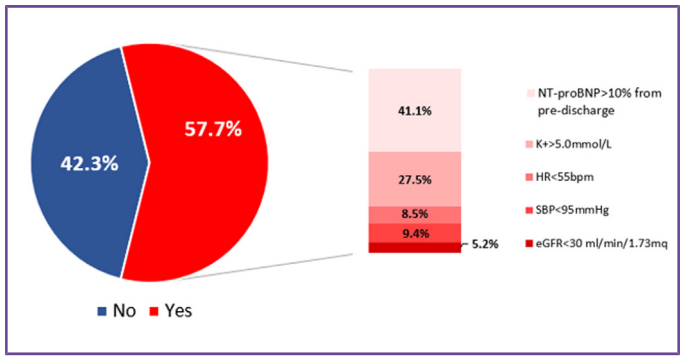

Fig. 1. Distribution of safety indicators in the high-intensity care group. eGFR, estimated glomerular filtration rate; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

Baseline Characteristics by Safety Indicators

Baseline characteristics of patients who met ≥1 safety indicator at any visit 3−6 are shown in Table 2. The mean age, distribution of sex, race/ethnicity, and geography were similar between those with and without a safety indicator. Patients who met any safety indicator were less likely to have a history of HF but more frequently presented with acute coronary syndrome, displayed more severe HF symptoms, higher New York Heart Association functional class 1 month before hospital admission and had a lower SBP and a higher heart rate at baseline, as compared with those without safety indicators. NT-proBNP levels were similar between the 2 groups at screening, but lower at prerandomization assessment among those meeting safety indicators. Additionally, patients with safety indicators had higher hemoglobin and lower cholesterol levels. There were no differences in mean LVEF. Oral HF medications at visit 2 (before randomization) were equally administered.

Table 1 Cross-tabulation of Safety Indicators at Any Visit 3−6 Week 1 through Week 6 in the High-intensity Care Group

	eGFR <30 mL/min/1.73 m^2	SBP < 95mm Hg	Heart Rate <55 bpm	K^+ > 5.0 mmol/L	NT-proBNP >10% Predischarge Value	eGFR Decrease of ≥15%*
eGFR < 30 mL/min/1.73 m^2 (*n* = 28)	–	2 (7)	5 (18)	12 (43)	16 (57)	25 (29)
SBP <95 mm Hg (*n* = 51)	2 (4)	–	6 (12)	10 (20)	17 (33)	18 (35)
Heart rate <55 bpm (*n* = 46)	5 (11)	6 (13)	–	11 (24)	12 (26)	9 (20)
K^+ >5.0 mmol/L (*n* = 149)	12 (8)	10 (7)	11 (7)	–	72 (48)	48 (32)
NT-proBNP >10% from before discharge (*n* = 223)	16 (7)	17 (8)	12 (5)	72 (32)	–	87 (37)
Any safety indicator (*n* = 313)	28 (9)	51 (16)	46 (15)	149 (48)	223 (71)	181 (58)
eGFR decrease ≥15% (*n* = 181)	25 (14)	18 (10)	9 (5)	48 (27)	87 (48)	–

eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
Values are number (%).
*We explored the incidence of a decrease in eGFR of ≥15% from baseline, but it was not included among safety indicators (as per protocol).

Table 2 Baseline Characteristics by Any Safety Indicator Met at Any Visit 3−6 Week 1 to Week 6 in the High Intensity Care Group

Parameter	No (*n* =229)	Yes (*n* =313)	*P* Value
Age, years	62.60 ± 13.78	63.20 ± 13.22	.6234
Sex			
Female	92 (40.2)	124 (39.6)	.8957
Male	137 (59.8)	189 (60.4)	
Self-reported race			
Black	55 (24.0)	60 (19.2)	. 2588
Caucasian	173 (75.5)	245 (78.3)	
Native American	0	1 (0.3)	
Other	1 (0.4)	6 (1.9)	
Pacific Islander	0	1 (0.3)	
Geographical region			
Europe	164 (71.6)	234 (74.8)	.4129
Non-Europe	65 (28.4)	79 (25.2)	
History of atrial fibrillation or atrial flutter or present at screening	92 (40.2)	137 (43.8)	.4026
Medical history			
Stroke or transient ischemic attack	20 (8.7)	36 (11.5)	.2900
Severe liver disease	1 (0.5)	2 (0.8)	.9999
Psychiatric or neurological disorder	3 (1.3)	5 (1.6)	.9999
Malignancies	5 (2.2)	13 (4.2)	.2038
Diabetes	63 (27.6)	89 (28.4)	.8374
Diabetes control method			
Insulin	20 (8.8)	30 (9.6)	.7472
Diet	37 (16.2)	65 (20.8)	.1826
Oral antidiabetic agents	46 (20.2)	64 (20.4)	.9382
Pulmonary embolism	4 (1.7)	9 (2.9)	.5751
Acute coronary syndrome	57 (24.9)	109 (34.8)	.0132
Coronary artery bypass surgery	9 (3.9)	18 (5.8)	.3359
Percutaneous transluminal coronary intervention	32 (14.0)	48 (15.3)	.6589
Angina Canadian Cardiovascular Society class 2 or higher	28 (12.2)	46 (14.7)	.4000
Moderate or severe chronic obstructive pulmonary disease or asthma	5 (2.2)	9 (2.9)	.6159
Cardiac resynchronization therapy	1 (0.4)	2 (0.6)	.9999
Automatic internal cardiac defibrillator	2 (0.9)	1 (0.3)	.5692
Heart failure history			
History of heart failure	205 (89.5)	260 (83.1)	.0335
NYHA functional class 1 month before hospital admission			
1	11 (5.0)	18 (6.2)	.0117
2	67 (30.7)	80 (27.6)	
3	113 (51.8)	103 (35.5)	
4	27 (12.4)	89 (30.7)	
Ischemic etiology	104 (45.6)	156 (49.8)	.3313
LVEF, %	36.90 ± 12.78	36.50 ± 12.42	.6986
LVEF category			
LVEF ≤40%	157 (68.6)	208 (66.5)	.6057
LVEF >40%	72 (31.4)	105 (33.5)	
Hospitalized for heart failure in the past year	64 (27.9)	76 (24.3)	.3354
No. of heart failure hospitalizations in the past year	0.40 ± 0.69	0.30 ± 0.68	.4603
History of atrial fibrillation or atrial flutter	96 (41.9)	142 (45.4)	.4246
Type of atrial fibrillation or atrial flutter			
Paroxysmal	26 (28.3)	31 (21.8)	.1873
Permanent	53 (57.6)	84 (59.2)	
Persistent	13 (14.1)	27 (19.0)	
Baseline vital signs			
Systolic blood pressure at baseline, mm Hg	125.2 ± 14.17	122.1 ± 12.49	.0078
Pulse, beats/min	77.1 ± 11.16	79.5 ± 12.12	.0170
Respiratory rate, breaths/min	18.0 ± 2.58	18.0 ± 2.32)	.9984
Local Laboratory			
Hemoglobin, g/L	134.10 ± 18.52	137.9± 21.40	.0318
Lymphocytes, %	26.50 ± 10.59	27.70 ± 9.42	.1661
White blood cells, 10^9/L	6.90 ± 1.96	6.90 ± 1.95	.6741
Glucose, mmol/L	6.10 ± 2.34	6.30 ± 2.56	.5166
Creatinine, μmol/L	105.40 ± 23.67	107.10 ± 33.76	.5163
Potassium, mmol/L	4.20 ± 0.43	4.30 ± 0.47	.0010

(*Continued*)

Table 2. (*Continued*)

Parameter	No (*n* =229)	Yes (*n* =313)	*P* Value
Sodium, mmol/L	140.00 ± 3.77	140.30 ± 4.22	.4321
Urea, mmol/L	7.80 ± 2.91	8.30 ± 4.01	.1185
ALT, U/L	32.90 ± 67.31	29.40 ± 29.52	.4286
Total bilirubin, μmol/L	17.30 ± 13.52	17.80 ± 10.83	.6721
Total cholesterol, mmol/L	4.40 ± 1.10	4.10 ± 1.07	.0024
NT-proBNP at screening, ng/L	6309.3 (5846.7−6808.4)	6015.8 (5643.5−6412.6)	.3443
NT-proBNP, ng/L	3653.6 (3360.3−3972.6)	2996.6 (2795.8−3211.8)	.0003
Oral heart failure medications taken at visit 2 (before randomization)			
ACE inhibitors/ARBs/ARN inhibitors	148 (65.2)	206 (65.8)	.8817
ß-Blockers	77 (33.9)	106 (33.9)	.9894
Mineralocorticoid receptor antagonists	217 (95.6)	291 (93.0)	.2025
Loop diuretic	219 (96.5)	301 (96.2)	.8508

Values reported are mean ± standard deviation or geometric mean (95% confidence interval) for continuous variables and number (%) for categorical variables. A patient may be classified under >1 diabetes control method.

ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARBs, angiotensin receptor blockers, ARNI angiotensin receptor neprilysin; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Changes in HF Medication Doses According to Safety Indicators

Changes in medication doses in response to each safety indicator at each visit are reported in Fig. 2. Appropriate changes in GDMT were observed at each visit when safety indicators were met (Supplemental Table 1). The occurrence of an SBP of <95 mm Hg was significantly associated with a decrease in RAS inhibitor, MRA, or β-blocker doses at visits 3, 5, and 6 and with a lower probability of up-titration at visit 4 (when doses were to be up-titrated to 100% optimal doses). Both an eGFR of <30 mL/min/1.73 m^2 and a serum potassium of >5.0 mmol/L were associated with higher rates of decrease or no changes in RAS inhibitor and MRA doses at visits 3, 5, and 6 and with a lower rate of up-titration at visit 4. At each visit, patients with an increase in NT-proBNP of >10% greater than predischarge received higher doses of diuretics.

Fig. 3A shows the trajectory of the average percentage of GDMT optimal dose during follow-up in patients who did or did not meet any safety indicator at visits 3−6. Patients with any safety indicator, compared with those without, achieved a lower percentage of GDMT optimal doses (mean difference −11.0%, 95% CI −13.6% to −8.4%, $P < .001$). This difference was already evident at visit 4 occurring at week 2, when 100% of recommended doses should have been reached per protocol, with achieved average GDMT doses of 74.8% vs 89.0% in patients with vs without any safety indicator. The difference between the 2 groups was then more pronounced at visit 6 (73.2% vs 90.4%) and was maintained for the entire follow-up (until visit 8, day 180) (71.5% vs 84.5%) (Fig. 3A). Doses of each of the 3 classes of GDMT (RAS inhibitors, β-blockers, and MRAs) were significantly lower in patients with any safety indicator (Figs. 3B−3D).

The trajectories of the average percentage of GDMT optimal doses over time stratified by each safety indicator separately are reported in Supplemental Figs. 1.1−1.5. Patients with an eGFR of <30 mL/min/1.73 m^2 vs those without, received lower doses of RAS inhibitors and MRA (Supplemental Fig. 1.1). An SBP of <95 mm Hg was associated with the greatest difference in GDMT doses (mean difference −18.5%, 95% CI −22.9% to −14.1%, $P < .001$ as compared with patients without an SBP of <95 mm Hg). The average percentage of GDMT optimal doses were significantly different also among patients with vs without heart rate of <55 bpm, serum potassium of >5.0 mmol/L, and an increase in NT-proBNP of >10% (all $P < .001$) (Supplemental Figs. 1.3−1.5).

Clinical Outcomes by Safety Indicators

The primary end point of 180-day HF readmission or all-cause death occurred in 43 patients (15.0%) with any safety indicator vs 31 patients (14.2%) without (time-dependent covariate adjusted HR 0.84, 95% CI 0.48−1.46, $P = .54$). All-cause mortality through 180 days occurred in 16 patients (5.6%) with and 23 (10.5%) without any safety indicator and was also not significantly different (adjusted HR 0.66 95% CI 0.32−1.39, $P = .28$). HF readmission occurred in 36 patients (12.5%) with and 11 (5.0%) without a safety indicator and was also not significantly different (adjusted HR 1.63 95% CI 0.77−3.47, $P = .20$) (Table 3).

With respect to the impact of each safety indicator, considered alone, on outcomes, no single safety indicator was significantly associated with the primary end point or rates of 180-day mortality. An SBP of <95 mm Hg was associated with a trend toward increased mortality (adjusted HR 2.68, 95% CI 0.94−7.64, $P = .065$). An eGFR of <30 mL/min/1.73 m^2 was associated with an increased risk of 180-day HF readmission (adjusted HR 3.60, 95% CI 1.22−10.60, $P = .020$) (Table 3).

Although patients with and without a safety indicator had a mean increase in EQ-5D VAS scores from randomization to day 90, smaller improvements were observed in patients with vs without safety indicators (adjusted mean

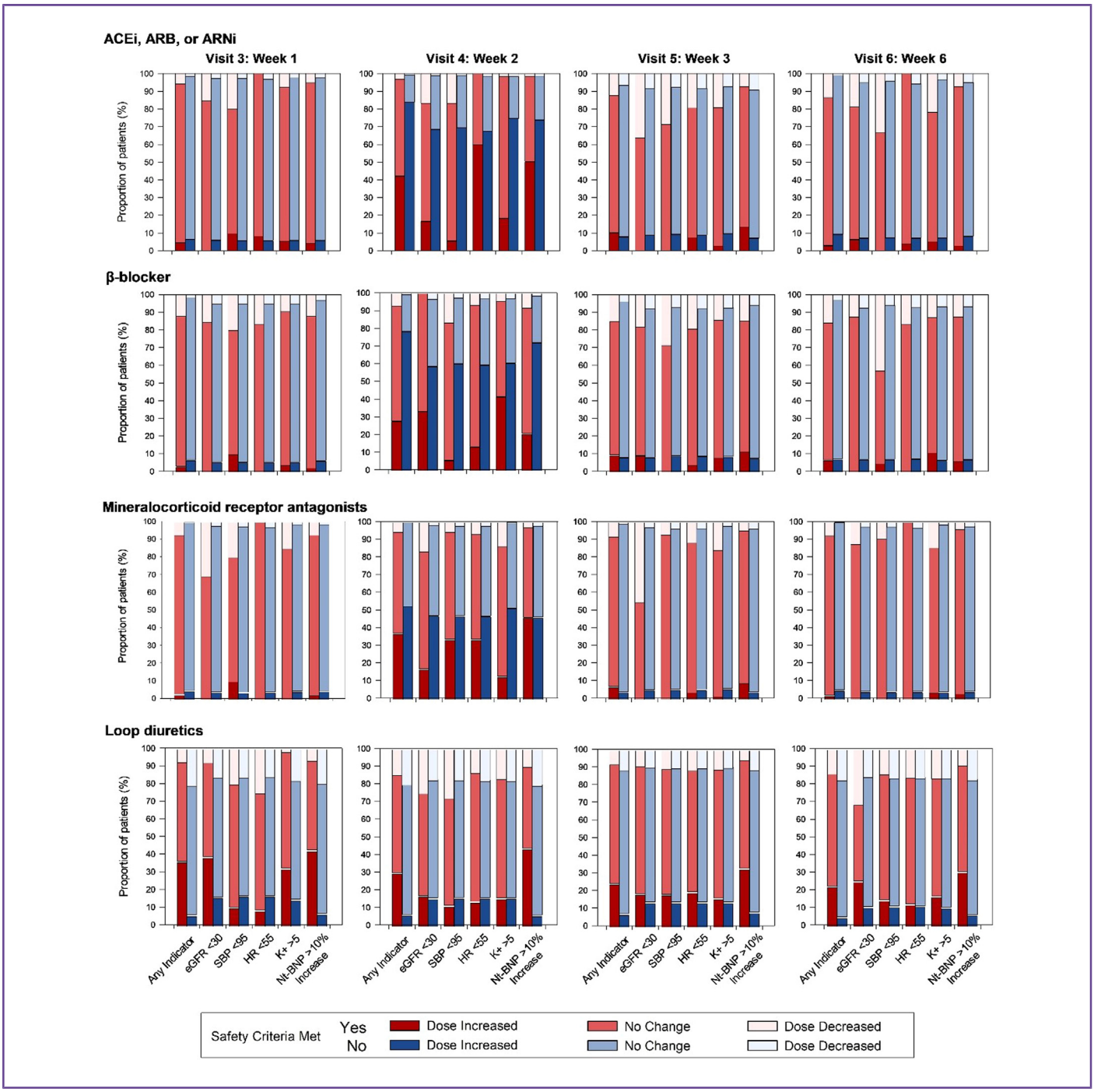

Fig. 2. Stacked bar chart of medication changes by visit and whether safety indicator criteria met. ACEi/ARBs/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor; other abbreviations as in Fig. 1.

difference −3.32 points, 95% CI −5.97 to −0.66, $P = .015$) (Table 4).

Discussion

The key findings of this secondary analysis from STRONG-HF are the following: (1) more than one-half of the patients randomized to HIC met ≥1 safety indicator at any follow-up visit, between 1 and 6 weeks after discharge; (2) patients meeting any safety indicator had more severe HF at baseline; (3) as per protocol, the average percentage of GDMT optimal doses was 11% lower in patients with ≥1 safety indicator compared with those without, but higher than in the UC arm; (4) the occurrence of any safety indicator, when addressed by GDMT dose adjustment, was not associated with a greater risk of the combined primary end point of 180-day HF readmission or death despite the more severe HF at baseline, even if the lack of statistical power could not be excluded as a possible cause of such

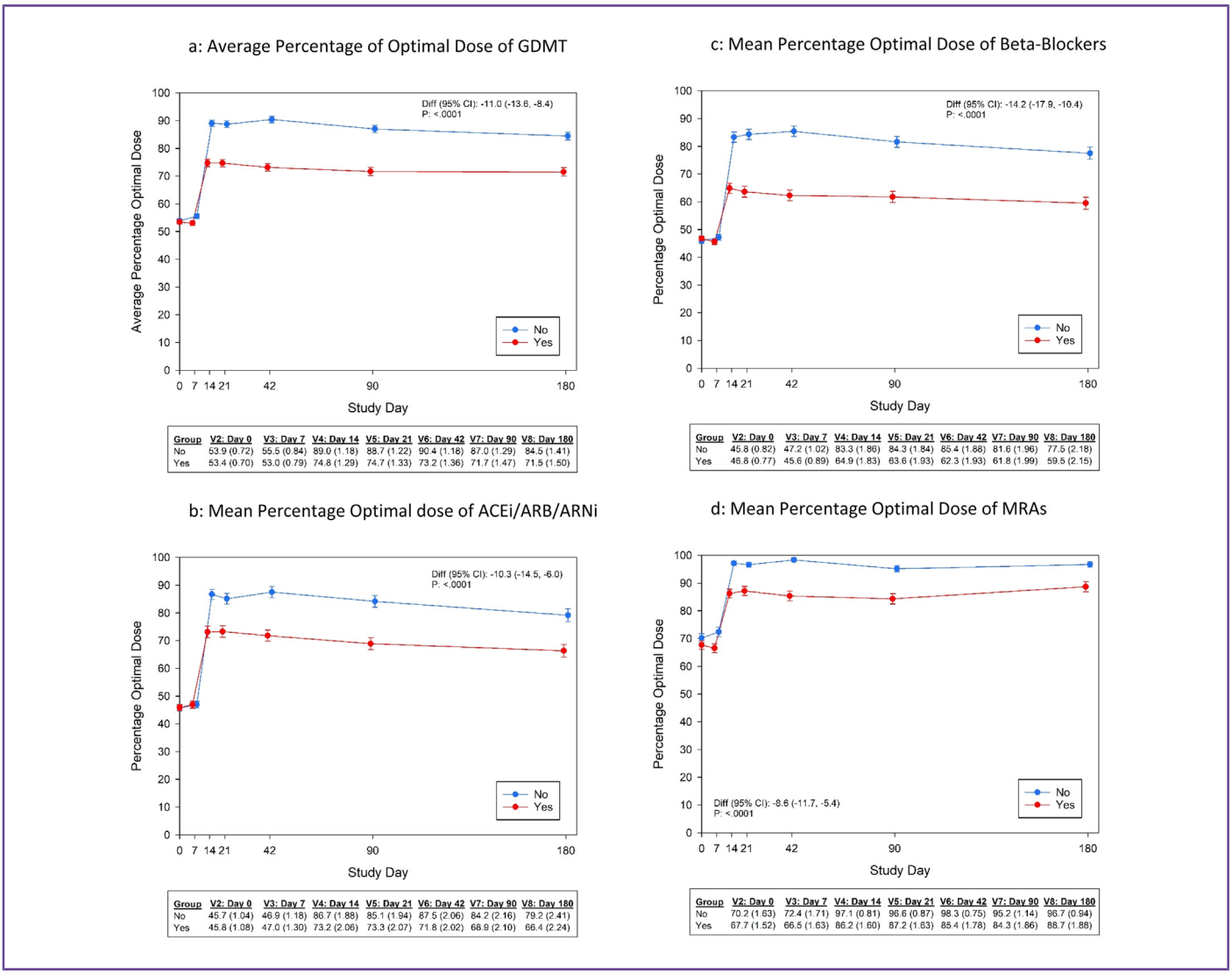

Fig. 3. Mean percentage of optimal dose of GDMT in patients with and without any safety indicator.
GDMT, guideline directed medical therapy; MRAs, mineralocorticoid receptor antagonists; other abbreviation as in Fig. 2.

results (Graphical Abstract); and (5) despite the lack of an impact on the composite primary outcome, the occurrence of an eGFR of <30 mL/min/m^2 and an SBP of <95 mm Hg were associated with an increased risk of 180-days HF rehospitalizations ($P = .02$) and with a tendency to an increased mortality ($P = .065$), respectively.

Incidence of Safety Indicators and Characteristics of Patients Meeting Safety Indicators

STRONG-HF is the first study that assessed the feasibility of rapid and simultaneous up-titration of GDMT after an episode of acute HF, through frequent follow-up visits with both clinical and laboratory assessments. Frequent patient reassessment with protocol-driven changes in GDMT based on safety indicators likely contributed to the success of this treatment strategy. Thus, although more than one-half of the patients met ≥1 safety indicator at any follow-up visit, their prognosis at 180 days was similar to that of the patients who did not meet such indicators and, overall, patients receiving HIC had better outcomes than those on UC.[25]

Among safety indicators, an increase in NT-proBNP values of >10% and serum potassium levels of >5 mmol/L were the most frequent, whereas an SBP of <95 mm Hg, heart rate of <55 bpm, and eGFR of <30 mL/min/1.73 m^2 were met in <10% of patients. These findings may seem to be in contrast with data showing that hypotension, bradycardia, and kidney dysfunction are the major causes of GDMT under-prescription and under-dosing.[13–15,18,23] These differences may be ascribed to differences in the patients enrolled in previous registries, compared with those in STRONG-HF, as shown by the older age, lower SBP, LVEF, and eGFR, consistent with more advanced HF, of the patients in these registries, compared with the patients enrolled in the present trial. Second, our data also show the persistent role of clinical inertia as a major

Table 3 Clinical Outcomes by Safety Indicators as Time-dependent Covariates

	Any Indicator	eGFR <30 mL/min/1.73 m^2	SBP<95 mm Hg	Heart Rate <55 bpm	K^+ >5.0 mmol/L	NT-proBNP >10% Increase
180-Day HF readmission or death						
Unadjusted HR (95% CI), *P* value	0.97 (0.57–1.66), .9164	2.62 (1.00–6.86), .0508	1.13 (0.43–2.97), .8028	0.19 (0.03–1.39), .1024	0.97 (0.53–1.79), .9220	0.97 (0.56–1.67), .9047
Adjusted HR[a] (95% CI), *P* value	0.84 (0.48–1.46), .5396	2.06 (0.77–5.53), .1504	1.38 (0.51–3.71), .5262	0.19 (0.03–1.41), .1052	0.90 (0.49–1.66), .7322	0.83 (0.46–1.48), .5238
180-Day all-cause death						
Unadjusted HR (95% CI), *P* value	0.57 (0.28–1.19), .1371	2.37 (0.65–8.68), .1913	2.21 (0.81–6.05), .1226	0.17 (0.01–2.91), .2211[d]	0.59 (0.23–1.50), .2676	0.51 (0.22–1.16), .1066
Adjusted HR[c] (95% CI), *P* value	0.66 (0.32–1.39), .2796	1.60 (0.36–7.13), .5380	2.68 (0.94–7.64), .0653	0.21 (0.01–3.51), .2796[b]	0.60 (0.23–1.55), .2899	0.65 (0.28–1.51), .3170
180-Day HF readmission						
Unadjusted HR (95% CI), *P* value	1.80 (0.87–3.73), .1111	3.91 (1.38–11.1), .0105	0.58 (0.11–3.01), .5202	0.31 (0.04–2.29), .2525	1.46 (0.71–2.98), .3034	1.44 (0.73–2.82), .2893
Adjusted HR[d] (95% CI), *P* value	1.63 (0.77–3.47), .2005	3.60 (1.22–10.60), .0203	0.59 (0.11–3.13), .5370	0.36 (0.05–2.67), .3181	1.42 (0.69–2.91), .3377	1.35 (0.65–2.78), .4230

CI, confidence interval; HF, heart failure; HR, hazard ratio; other abbreviations as in Table 1.
HRs are relative to not having the indicator.
[a]Adjusted for baseline diastolic blood pressure, baseline NT-proBNP, ischemic etiology, and edema.
[b]Firth correction applied due to no events occurring in patients meeting the criterion causing infinite maximum likelihood estimates
[c]Adjusted for baseline creatinine, baseline hemoglobin, baseline urea, and baseline NT-proBNP.
[d]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline left ventricular ejection fraction, and edema.

cause of patients' under-treatment and the impact that a HIC program may have.[14,15,17,20,31,32]

Patients who met any safety indicator had worse HF symptoms (eg, New York Heart Association functional class), lower SBP, and higher heart rate, consistent with more severe hemodynamic impairment and HF. These patients were less likely to tolerate GDMT also in previous studies.[19,33–36] Our results, therefore, confirm the role of HF severity as a major cause of suboptimal GDMT dosing also in patients treated with a HIC regimen. The average dose of GDMT, relative to the optimal dose, was of 71.5% in the patients who met the safety indicators, only 11% lower than in the patients who did not meet safety indicators in the HIC arm, and much larger than the 44% target dose of the UC group. Consistently, overall outcome of the patients receiving HIC was better than in UC and safety indicators were not associated with increased mortality or HF readmissions rate.

Prognostic Impact of Single Safety Indicators

The analysis of the prognostic impact of the single safety indicators showed that neither of them was associated with an increased rate of the combined primary end point, consistent with the efficacy of the HIC program. However, the rate of HF rehospitalizations was approximately 3-fold higher in the patients who had developed an eGFR of <30 mL/min/1.73 m^2 and all-cause mortality tended to be higher in patients who had developed hypotension, defined as an SBP of <95 mm Hg. Although given the large number of statistical tests performed these results could have been the play of chance,[37] these results are

Table 4 Change in EQ-VAS from Baseline to Day 90 by Any Safety Indicator Met at Any Visit 3–6: Week 1 to Week 6 High-intensity Care Subjects Only

	Any Safety Indicator Met			
EQ-VAS	Yes	No	LS Mean Difference (95% CI)	*P* Value
Baseline, mean (SD)	60.4 (15.83)	57.1 (13.84)		
Day 90, mean (SD)	68.7 (15.60)	71.0 (13.45)		
Change from baseline to day 90				
Partially adjusted LS mean (SE)[a]	9.94 (1.20)	12.99 (1.24)	−3.05 (−5.60, to −0.50)	.0191
Fully adjusted LS mean (SE)[b]	9.99 (1.25)	12.88 (1.27)	−2.89 (−5.55 to −0.23)	.0332

[a]Adjusted for baseline EQ-VAS, region, and LVEF group (≤40/>40).
[b]Additionally adjusted for baseline hemoglobin, baseline creatinine, baseline cholesterol, baseline NT-proBNP, hospitalized for heart failure in prior year, edema, and New York Heart Association functional classification.EQ, EuroQoL; SD, standard deviation; LS, least squares; SE, standard error; VAS, Visual analogue scale; other abbreviation as in Table 2.

consistent with the prognostic role of these events in the patients with HF.[6,16,33,35,38] The negative impact on outcome of kidney dysfunction and hypotension is likely mediated by their untoward effects as well as by the withdrawal and/or down-titration of GDMT that often follows their occurrence in clinical practice.[6,13,14,16,33,35,38,39,34] Both these untoward consequences were likely mitigated by the HIC regimen used in STRONG-HF. However, the lack of collection of data regarding safety indicators in the UC arm precludes any conclusion regarding the efficacy of HIC on the impact of safety indicators.

Observation of a heart rate of <55 bpm in the STRONG-HF trial led to less up-titration of β-blockers. However, it could also be considered as a surrogate parameter for the achievement of adequate β-blockade, with a potential protective role.[40] Consistently, achievement of a low heart rate was not associated with poorer outcome although it hindered titration of β-blockers.

Hyperkaliemia was a frequent cause of discontinuation of GDMT, namely MRA, as repeatedly shown in the literature.[13,18,21,41,42] However, the strategy of frequent follow-up visits used in HIC arm allowed a slower titration with the administration of lower doses, although with maintenance of MRA treatment in most of the patients with no untoward relation between these safety indicators and the risk of death or HF readmissions. Administration of new potassium lowering agent may also be considered in these patients[1,43,44] although these medications were not available in most of the cases at the time of the trial.

An increase in NT-proBNP levels of >10% than predischarge values was highly prevalent. This result is expected in the immediate postdischarge "vulnerable phase," a particularly high-risk period for clinical events, namely, worsening hemodynamics and worsening HF.[11] Few studies investigated the trajectories of NT-proBNP after discharge. In a post hoc analysis of the Aliskiren Trial in Acute Heart Failure Outcomes (ASTRONAUT), among patients hospitalized for worsening chronic HF, increasing NT-proBNP from baseline to the 1-month follow-up was independently predictive of increased cardiovascular mortality or HF hospitalizations.[45] Data in patients hospitalized for HF also show the negative prognostic role of an increase in NTproBNP plasma concentrations during hospitalization.[46] When appropriately addressed as per protocol, namely, with the adjustment of diuretic dose, the increase in NT-proBNP concentrations was not associated with worse outcomes. This finding is also consistent with the beneficial effects of GDMT that was slowly but progressively titrated, even in the patients with an early NTproBNP increase.[47]

An increase in serum creatinine, traditionally defined as WRF occurred in one-third of patients in the HIC group and it was frequently associated with an increase in NT-proBNP levels. WRF may, however, occur as a transient result of better decongestion and/or initiation of RAS inhibitors and be not associated with poorer outcomes.[38,48–50] WRF, defined as a decrease in the eGFR of ≥15% from baseline, was not included among safety indicators and did not require GDMT doses adjustment in STRONG-HF. Despite a large body of evidence suggesting the transient nature of WRF, even up to a 30% increase in eGFR, and particular benefit of RAS inhibitors in patients with lower eGFR,[48–50] many investigators chose to not up-titrate patients who had small drops in eGFR during rapid up-titration.[30] This issue should be emphasized when implementing the results of STRONG-HF in the postacute HF care.

Overall, these data provide important reassurance to physicians who may be reluctant to prescribe and up-titrate medications likely to cause hypotension, bradycardia, hyperkaliemia or WRF, even if they are known to be beneficial. ACE inhibitors/ARBs/ARNi and/or MRAs up-titration should be delayed when the SBP is <95 mm Hg and/or serum potassium is >5.0 mmol/L and/or eGFR is <30 mL/min/1.73 m^2. No up-titration of β-blockers is advised if heart rate is <55 bpm and/or SBP is <95 mm Hg. Furthermore, no up-titration of β-blockers and increase in diuretic dose should be considered if NT-proBNP concentrations are >10% higher than the predischarge level. Finally, the adjustment of diuretic doses based on the evaluation of congestion and renal function is advised.[12,24]

Limitations

There are several inherent limitations to this analysis, in addition to those already mentioned in the main STRONG-HF study. Given that we performed subgroup analyses, statistical power is limited because the study was not specifically powered for these analyses. As stated elsewhere in this article, safety indicators were assessed only in the HIC group. Thus, our data do not allow the evaluation of either the impact of HIC on the occurrence of safety indicators or the role of HIC to decrease their impact on outcomes. However, our analysis highlights the overall efficacy of HIC in the patients enrolled in STRONG-HF. By censoring deaths in the analysis of HF readmission, we assume that the deaths are "noninformative," that is, that these patients would have had the same risk of a HF readmission if they had not died as those patients that we observed. Given the multiple statistical tests performed without control of the overall error rate, caution should be exercised when interpreting statistically significant associations. Finally, we were only able to describe associations, and causality cannot be proven.

Conclusions

Among patients with acute HF enrolled in the STRONG-HF trial and randomized to the HIC strategy, more than one-half presented safety indicators during follow-up. The occurrence of any safety indicator was associated with the

achievement of slightly lower percentage of GDMT optimal doses over time though with a similar effect on 180-day HF readmission or death. Hypotension and poor kidney function were the only safety indicators associated with a trend toward worse outcomes. The occurrence of safety indicators was associated with smaller benefits in quality of life.

Lay Summary

More than one-half of the patients randomized to high-intensity care (HIC) arm in the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial met ≥1 safety indicator; thus, their frequent assessment during the rapid up-titration of guideline-directed medical therapy (GDMT) is strongly recommended.

Patients meeting any safety indicator had more severe HF at baseline and, as per protocol, reached a slightly lower average percentage of GDMT optimal doses, but did not experience an increase in the risk of the primary end point, compared with those without safety indicators in the HIC arm.

Rapid and simultaneous up-titration of GDMT is safe and feasible, provided that safety indicators are frequently assessed and guide the up-titration itself.

Declaration of Competing Interest

None

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cardfail.2023.09.002.

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