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RESEARCH ARTICLE

Non-cardiac comorbidities and intensive up-titration of oral treatment in patients recently hospitalized for heart failure: Insights from the STRONG-HF trial

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Aims To assess the potential interaction between non-cardiac comorbidities (NCCs) and the efficacy and safety of high-intensity care (HIC) versus usual care (UC) in the STRONG-HF trial, including stable patients with improved but still elevated natriuretic peptides.

Methods and results In the trial, eight NCCs were reported: anaemia, diabetes, renal dysfunction, severe liver disease, chronic obstructive pulmonary disease/asthma, stroke/transient ischaemic attack, psychiatric/neurological disorders, and malignancies. Patients were classified by NCC number (0, 1, 2 and ≥3). The treatment effect of HIC versus UC on the primary endpoint, 180-day death or heart failure (HF) rehospitalization, was compared by NCC number and by each individual comorbidity. Among the 1078 patients, the prevalence of 0, 1, 2 and ≥3 NCCs was 24.3%, 39.8%, 24.5% and 11.4%, respectively. Achievement of full doses of HF therapies at 90 and 180 days in the HIC was similar irrespective of NCC number. In HIC, the primary endpoint occurred in 10.0%, 16.6%, 13.6% and 26.2%, in those with 0, 1, 2 and ≥3 NCCs, respectively, as compared to 19.1%, 25.4%, 23.3% and 26.2% in UC (interaction-$p = 0.80$). The treatment benefit of HIC versus UC on the primary endpoint did not differ significantly by each individual comorbidity. There was no significant treatment interaction by NCC number in quality-of-life improvement ($p = 0.98$) or the incidence of serious adverse events ($p = 0.11$).

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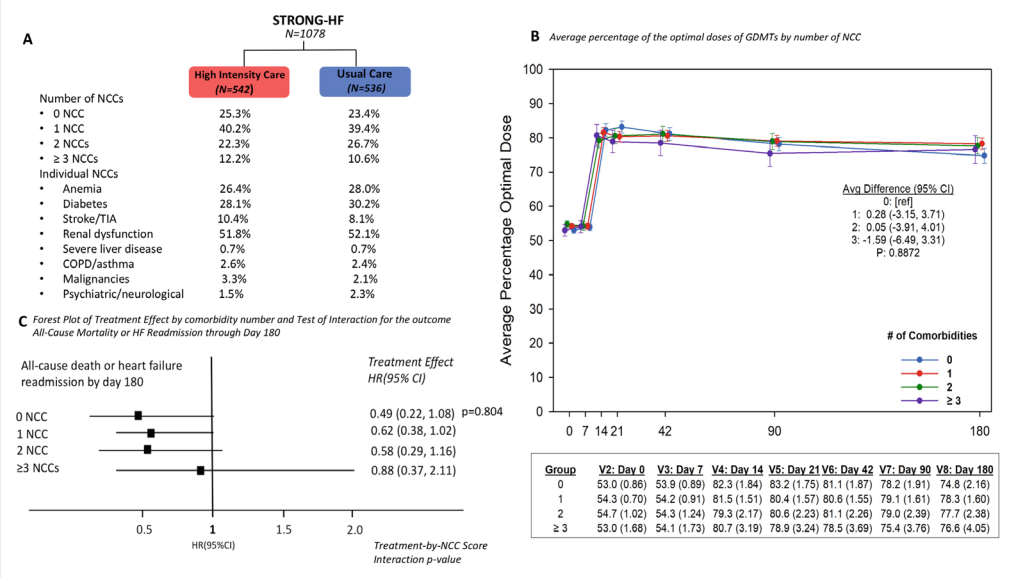
Conclusions In the STRONG-HF trial, NCCs neither limited the rapid up-titration of HF therapies, nor attenuated the benefit of HIC on the primary endpoint. In the context of a clinical trial, the benefit–risk ratio favours the rapid up-titration of HF therapies even in patients with multiple NCCs.

Graphical Abstract



The impact of non-cardiac comorbidities (NNCs) on rapid up-titration of guideline-directed medical therapies (GDMTs) and interactions between NNCs and treatment effect of high-intensity care (HIC) versus usual care (UC) on the primary endpoint. Proportion of patients with 0, 1, 2 and ≥3 NCCs and the prevalence of each individual comorbidity (*A*). Average percentage of the optimal doses of GDMTs by number of NCCs (*B*). Treatment effect by number of NCCs (*C*), with test of interaction for the outcome. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; TIA, transient ischaemic attack.

Keywords Acute heart failure • Comorbidities • Heart failure therapies

Introduction

Acute heart failure (AHF) is associated with high mortality and rehospitalization rates and despite many clinical trials conducted to date in these patients, the rates of adverse outcomes remain very high.[1] Clinical severity during hospitalization and the post-discharge course is the result of the interaction between an acute precipitant and a patient's underlying cardiac and overall medical condition, including non-cardiac comorbidities (NCCs).[2] Impairment of multiple organ systems in heart failure (HF) patients with multiple NCCs may synergistically increase vulnerability to destabilization leading to hospitalization and risk for progressive mortality.[3]

Data from observational studies demonstrated that in both chronic[4,5] and acute HF[6,7] comorbidities are common and are associated with increased mortality and morbidity risk. Particularly, in patients with AHF a higher comorbidity burden was associated with increased complexity of clinical management, more residual congestion and suboptimal guideline-directed medical therapies (GDMTs) at discharge.[6]

The STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-ProBNP Testing, of Heart Failure Therapies) trial demonstrated that a high-intensity care (HIC) treatment strategy, characterized by rapid up-titration 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 (UC).[8] This strategy was both safe and effective regardless of age,[9] sex,[10] left ventricular ejection fraction (LVEF)[11] or baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[12]

In clinical trial settings, there are relatively limited data to describe the impact of comorbidities on optimization of HF medical therapies and relationship between comorbidity burden and

post-discharge clinical outcomes. Therefore, the objective of the current analysis was to assess the potential interaction between NCCs, in terms of overall burden and each individual comorbidity, and the feasibility, efficacy and safety of HIC versus UC in the STRONG-HF trial.

Methods

Study design

The design and main results of STRONG-HF have been previously described.[8,13,14]

Briefly, the STRONG-HF trial was an international, multicentre, open-label, randomized trial designed to compare the safety and efficacy of a HIC strategy comprising early up-titration of oral HF medications including beta-blockers (BB), a renin–angiotensin system inhibitor (RASi), such as angiotensin-converting enzyme inhibitors (ACEi) (or angiotensin receptor blockers [ARB] in case of intolerance of ACEi) or angiotensin receptor–neprilysin inhibitors (ARNi), and mineralocorticoid receptor antagonists (MRA), versus UC in 1078 patients admitted to hospital for AHF. The study, registered at ClinicalTrials.gov (NCT03412201), was approved by appropriate competent authorities and all sites obtained approval from ethics committees. All patients provided written informed consent.

Patient population

Inclusion criteria in the STRONG-HF trial were age from 18 to 85 years; admission for AHF within 72 h before screening; haemodynamic stability with any LVEF; a high NT-proBNP value at screening (>2500 pg/ml) with a >10% decrease in value between screening and randomization that remained >1500 pg/ml; and the absence of treatment with optimal doses of oral HF therapies at 1 week prior to admission, at screening, and just prior to randomization which occurred within 2 days before anticipated hospital discharge. To be eligible, patients had been prescribed either (i) half dose or less than half-dose of the optimal dose of RASi, no BB, and half dose or less than half-dose of the optimal dose of MRA, or (ii) no RASi, half dose or less than half-dose of the optimal dose of BB, and half dose or less than half-dose of the optimal dose of MRA. Eligible patients were randomized 1:1 within strata defined by LVEF (≤40% or >40%) and country as previously described.[8]

Intervention

Patients assigned to HIC had physical examination to measure vital signs and assess congestion, and laboratory assessments including NT-proBNP at follow-up visits at 1, 2, 3, and 6 weeks and 90 days after randomization. In the HIC group, BB, RASi and MRA were up-titrated to half the optimal doses at randomization and to full optimal doses at week 2, guided by NT-proBNP, serum potassium, and estimated glomerular filtration rate (eGFR) levels, and systolic blood pressure. If a delay in the up-titration was needed, a safety visit including all assessments was required 1 week after any up-titration. Patients assigned to UC were followed up after discharge according to the local practice and were seen again by the study team at day 90 after randomization. Patients in both groups were contacted at day 180 to assess the occurrence of pre-specified outcomes of interest, rehospitalizations and death, and current prescriptions of oral HF medications.

Study endpoints

Outcomes included the composite of first HF rehospitalization or all-cause death through day 180 (the study primary endpoint), 180-day all-cause death (a secondary endpoint of the study), and first HF readmission through day 180. The change in EQ-5D visual analogue scale (VAS) score from baseline to day 90 (a secondary endpoint of the study) was also examined.

Stratifications and definitions

In the STRONG-HF trial, eight NCCs were reported at baseline: anaemia, diabetes, renal dysfunction, severe liver disease, chronic obstructive pulmonary disease (COPD)/asthma, stroke/transient ischaemic attack (TIA), psychiatric or neurological disorders, and malignancies (online supplementary *Table S1*). Patients were classified by the number of NCCs (0, 1, 2 and ≥3). The treatment effect of HIC versus UC on the primary endpoint was compared by number of NCCs and by each individual comorbidity.

Statistical analysis

Continuous variables are presented as mean and standard deviation or for skewed variables as geometric mean (95% confidence interval [CI]) and frequencies and percentages for categorical variables. NT-proBNP values were log-transformed for analysis.

Patients were classified in four groups by number of NCC (0, 1, 2 and ≥3). A test of trend across the NCC groups in baseline characteristics was performed using the Cochran–Armitage trend test for binary variables, the Jonckheere's trend test for continuous variables, and the Cochran–Mantel–Haenszel test of non-zero correlation for ordinal or general association test for categorical variables.

For patients from the HIC group, to explore the time course of up-titration of oral HF medications, the percentage dose of each medication in each of three classes (RASI, BB, and MRA) relative to the drug's optimal dose (online supplementary *Table S3* in the original publication) Ref 8 was calculated and then averaged across the three medication classes. The trajectory of this average percentage optimal dose over time is presented by the number of NCCs and by the presence or absence of each of the eight comorbidities separately. The percentage of optimal dose in each of the three individual medication classes was also examined by NCC number and each individual NCC. Comparisons were made using mixed models for repeated measures with either the number of NCCs or individual NCC, visit, and NCC-by-visit interaction included in the model. The average difference over the follow-up, 95% CI, and associated *p*-value is provided for the comparison of those with versus those without each individual NCC; for NCC number, those with no NCCs serve as the reference group.

Outcomes to 180 days were examined using unadjusted and adjusted Cox regression models, and the interaction between treatment and NCC number (or presence of each individual NCC) was assessed. Analyses were restricted to 1008 patients enrolled at sites where the ethics committee approved the amended protocol allowing follow-up of patients through day 180, and results in a cohort of 380 patients enrolled prior to an amendment where the primary endpoint was changed from 90 to 180 days were down-weighted proportionally to half its sample size, as previously described.[8]

Kaplan–Meier plots are provided for selected endpoints, and the number of events, weighted Kaplan–Meier estimate of 180-day cumulative risk, and associated hazard ratio (HR) and 95% CI are presented. A sensitivity analysis was also conducted on the primary endpoint in which deaths due to COVID-19 were censored at the time of death in subjects who had not experienced a prior HF rehospitalization. Change in EQ-VAS was analysed using an ANCOVA model adjusted for baseline EQ-VAS, geographic region, and baseline LVEF ≤40%/>40% with the treatment effect represented by the least square (LS)-mean difference and associated 95% CI. Analyses of the change in EQ-5D VAS were restricted to countries where a linguistically validated translation was available (i.e. subjects from Mozambique were excluded).

Similar to other STRONG-HF sub-analyses,[9,10] variables used for covariate adjustment were selected from those most highly associated with each endpoint in the UC group of STRONG-HF using backwards selection in the Cox regression model.

We examined whether the safety profile differed across NCC number between treatments by assessing the treatment-by-NCC number interaction for adverse events and serious adverse events through day 90. The interaction *p*-value was derived from a logistic regression model with NCC number, treatment, and NCC number-by-treatment interaction. Firth's correction was used when the occurrence of an event was <5 in any cell.

Two-sided *p*-values <0.05 were considered to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among the 1078 patients randomized, the prevalence of 0, 1, 2 and ≥3 NCCs was 24.3%, 39.8%, 24.5% and 11.4%, respectively, and the most common NCCs were renal dysfunction (52.0%), diabetes (29.1%), anaemia (27.2%) and history of stroke/TIA (9.2%) (*Graphical Abstract*). A proportion of 67.8% STRONG-HF patients had LVEF <40% and 32.2% had LVEF >40%. The prevalence of each NCC was higher in patients with LVEF >40%, and fewer patients with LVEF >40% had no NCCs (14% vs. 29%) (online supplementary *Figure S1*).

Baseline characteristics

Patients with more NCCs were significantly older, more commonly female and Caucasians, had a higher LVEF and were more likely to have a HF diagnosis or a history of HF hospitalization in the last year (*Table 1*). Also, they were more likely to have history of atrial fibrillation or flutter or acute coronary syndrome when compared with those with lower NCC number. Ischaemic aetiology as well as history of percutaneous coronary intervention and coronary artery bypass graft were more common in the group of patients with more NCCs. Systolic blood pressure was higher and heart rate lower in patients with many NCCs.

When patients were stratified by number of NCCs, significant differences in laboratory parameters were reported. Creatinine, urea and glucose increased gradually with number of NCCs, while haemoglobin and eGFR decreased. NT-pro-BNP levels increased with each NCC stratum.

At visit 2 (pre-randomization), proportions of patients taking BBs, ACEis/ARBs/ARNi and loop diuretics did not differ significantly by number of NCCs.

Oral heart failure therapy up-titration

Overall, achievement of full doses of GDMTs at 90 and 180 days in the HIC group was similar irrespective of number of NCCs (*Graphical Abstract*) or each comorbidity assessed separately. Also, for each medication classes, the average percentage optimal dose of RASi and MRAs at 90 and 180 days were similar irrespective of number of NCCs (*Figure 1*). For BB, patients with ≥3 NCCs had lower percentage of optimal dose at 90 days, but at 180 days there were no differences by number of NCCs. The impact of each individual comorbidity on the average percentage of optimal dose of GDMTs are presented in *Figure 2*, while 180-day trajectories of the average optimal dose of the medication classes (BBs, RASi and MRAs) separately by the individual comorbidities are presented in online supplementary *Figure S2*. Except stroke/TIA (where percentage of optimal dose of BBs was lower), COPD (where percentage of optimal dose of MRAs was lower), and diabetes (where percentage of optimal dose of ACEi/ARB/ARNi was higher), no significant interaction was noted between individual comorbidities and up-titration of the three therapeutic classes.

In addition, when baseline indicators of NCCs were considered as continuous variables, no significant interaction was detected between baseline eGFR, plasma haemoglobin and serum bilirubin and achieved percentage of optimal dose at 90 days (online supplementary *Figure S3*).

Clinical outcomes

Kaplan–Meier curves for the primary endpoint, 180-day all-cause mortality or HF readmission, by number of NCCs is presented in *Figure 3* and online supplementary *Figure S4*. Rates of the primary endpoint and the treatment effects between HIC and UC arms for each category of NCC score (*Table 2*) show no significant interaction (interaction $p = 0.80$ and $p = 0.95$ in unadjusted and adjusted models, respectively) between treatment effect and number of NCCs, with the effect favouring patients in the HIC group compared to UC across all NCC scores. In sensitivity analysis, excluding COVID-19 deaths, treatment effect by NCC number, has lower HRs and narrow CI margins, and a trend to better treatment effect was observed in patients with 2 and ≥3 NCCs (*Table 2*). Similarly, for 180-day all-cause mortality (*Figure 4* and and online supplementary *Figure S5*), the interaction between NCC number and treatment effect was non-significant (interaction $p = 0.79$).

When considering each individual comorbidity, the treatment benefit of HIC versus UC on the primary endpoint did not differ significantly by any of individual comorbidity (*Figure 5*).

The EQ-VAS improved less from baseline to 90 days with increasing number of NCCs in both treatment groups. However, the adjusted treatment effect of HIC compared to UC was similar

Table 1 Baseline characteristics by number of non-cardiac comorbidities

Parameter	Number of non-cardiac comorbidities				*p*-value for trend*
	0 (*n* = 262)	1 (*n* = 429)	2 (*n* = 264)	≥3 (*n* = 123)	
Age, years	54.7 (14.91)	63.0 (13.12)	68.1 (10.10)	69.4 (9.21)	<0.0001
Male sex, *n* (%)	176 (67.2%)	267 (62.2%)	144 (54.5%)	74 (60.7%)	0.0203
Self-reported race, *n* (%)					<0.0001
Black	102 (38.9%)	103 (24.1%)	20 (7.6%)	5 (4.1%)	
Caucasian/White	157 (59.9%)	322 (75.2%)	240 (90.9%)	113 (92.6%)	
Native American	0	0	1 (0.4%)	0	
Other	3 (1.1%)	2 (0.5%)	3 (1.1%)	4 (3.3%)	
Pacific Islander	0	1 (0.2%)	0	0	
Geographical region, *n* (%)					<0.0001
Europe	146 (55.7%)	305 (71.1%)	232 (87.9%)	113 (92.6%)	
Non-Europe	116 (44.3%)	124 (28.9%)	32 (12.1%)	9 (7.4%)	
NT-proBNP at screening, ng/L, geom. mean (95% CI)	5756.3 (5383.5–6155.0)	6032.9 (5722.4–6360.2)	6058.6 (5637.5–6511.3)	6444.3 (5766.2–7202.2)	0.2633
History of atrial fibrillation/flutter or present at screening, *n* (%)	86 (32.8%)	192 (44.8%)	135 (51.1%)	69 (56.6%)	<0.0001
Medical history					
Pulmonary embolism	2 (0.8%)	10 (2.3%)	3 (1.1%)	4 (3.3%)	0.2708
Acute coronary syndrome	41 (15.6%)	116 (27.0%)	96 (36.4%)	58 (47.5%)	<0.0001
Coronary artery bypass surgery	8 (3.1%)	24 (5.6%)	15 (5.7%)	12 (9.8%)	0.0126
Percutaneous transluminal coronary intervention	19 (7.3%)	53 (12.4%)	47 (17.8%)	33 (27.0%)	<0.0001
Angina Canadian Cardiovascular Society class 2 or higher	16 (6.1%)	44 (10.3%)	40 (15.2%)	25 (20.5%)	<0.0001
Cardiac resynchronization therapy	0	1 (0.2%)	5 (1.9%)	0	0.1309
Automatic internal cardiac defibrillator	1 (0.4%)	5 (1.2%)	2 (0.8%)	1 (0.8%)	0.8603
History of HF	206 (78.6%)	363 (84.6%)	232 (87.9%)	115 (94.3%)	<0.0001
NYHA class 1 month before hospital admission, *n* (%)					0.0143
I	21 (9.0%)	26 (6.5%)	11 (4.4%)	5 (4.2%)	
II	73 (31.2%)	127 (32.0%)	78 (31.3%)	29 (24.2%)	
III	93 (39.7%)	164 (41.3%)	101 (40.6%)	57 (47.5%)	
IV	47 (20.1%)	80 (20.2%)	59 (23.7%)	29 (24.2%)	
Ischaemic etiology, *n* (%)	75 (28.6%)	187 (43.7%)	159 (60.5%)	93 (76.2%)	<0.0001
LVEF, %	33.7 (11.92)	35.6 (12.37)	39.2 (13.51)	38.0 (10.58)	<0.0001
LVEF category, *n* (%)					<0.0001
≤40%	215 (82.1%)	299 (69.7%)	141 (53.4%)	76 (62.3%)	
>40%	47 (17.9%)	130 (30.3%)	123 (46.6%)	46 (37.7%)	
Hospitalixed for HF in the past year?, *n* (%)	51 (19.5%)	103 (24.0%)	75 (28.4%)	44 (36.1%)	0.0002
Number of HF hospitalizations in the past year, *n* (%)	0.2 (0.53)	0.4 (1.57)	0.4 (0.67)	0.5 (0.81)	0.0001
History of atrial fibrillation/flutter, *n* (%)	87 (33.2%)	197 (45.9%)	138 (52.3%)	74 (60.7%)	<0.0001
Type of atrial fibrillation/flutter, *n* (%)					0.2356
Paroxysmal	19 (21.6%)	45 (23.1%)	31 (23.0%)	22 (30.6%)	
Permanent	50 (56.8%)	113 (57.9%)	89 (65.9%)	41 (56.9%)	
Persistent	19 (21.6%)	37 (19.0%)	15 (11.1%)	9 (12.5%)	

Table 1 (Continued)

Parameter	Number of non-cardiac comorbidities				*p*-value for trend*
	0 (*n* = 262)	1 (*n* = 429)	2 (*n* = 264)	≥3 (*n* = 122)	
Baseline vital signs					
Systolic blood pressure, mmHg	121.9 (13.97)	123.0 (13.30)	123.5 (11.49)	122.8 (12.41)	0.0334
Pulse, bpm	82.7 (11.85)	79.5 (12.30)	75.5 (10.20)	73.7 (9.41)	<0.0001
Respiratory rate, breaths/min	18.2 (3.07)	18.2 (4.03)	18.3 (7.17)	17.8 (1.70)	0.1382
Local laboratory					
Haemoglobin, g/L	146.0 (15.41)	138.1 (19.21)	131.3 (19.73)	121.4 (19.91)	<0.0001
Lymphocytes, %	29.5 (10.01)	27.8 (9.69)	26.1 (9.68)	22.7 (8.17)	<0.0001
White blood cells, 10^9/L	6.7 (1.96)	6.9 (2.02)	7.1 (2.09)	7.5 (1.91)	0.0002
Glucose, mmol/L	5.3 (1.17)	6.0 (2.18)	7.0 (2.59)	7.4 (2.97)	<0.0001
Creatinine, µmol/L	88.4 (14.84)	104.8 (26.05)	119.3 (33.22)	120.9 (29.36)	<0.0001
Potassium, mmol/L	4.2 (0.47)	4.2 (0.45)	4.3 (0.43)	4.4 (0.41)	0.0024
Sodium, mmol/L	139.8 (4.15)	140.2 (4.05)	140.7 (3.94)	140.2 (4.97)	0.0014
Urea, mmol/L	6.1 (1.86)	7.7 (2.93)	9.4 (4.02)	10.5 (4.26)	<0.0001
ALT, U/l	28.8 (28.32)	28.9 (28.81)	29.5 (46.96)	36.1 (86.50)	0.2879
Total bilirubin, µmol/L	18.0 (12.51)	17.2 (9.72)	17.1 (11.24)	16.6 (13.75)	0.1627
Total cholesterol, mmol/L	4.4 (0.99)	4.3 (1.12)	4.1 (1.12)	3.7 (1.06)	<0.0001
NT-proBNP, ng/L, geom. mean (95% CI)	2840.3 (2649.5–3044.9)	3196.5 (3010.6–3393.8)	3408.6 (3146.2–3693.0)	3708.2 (3294.7–4173.5)	<0.0001
eGFR, ml/min/1.73 m^2	79.7 (19.06)	63.2 (19.93)	50.4 (14.75)	49.4 (13.59)	<0.0001
Oral HF medications taken at visit 2: pre-randomization, *n* (%)					
ACEi/ARBs/ARNi	184 (70.8%)	267 (62.4%)	158 (59.8%)	80 (65.6%)	0.0903
Beta-blockers	76 (29.2%)	157 (36.7%)	107 (40.5%)	43 (35.2%)	0.0536
MRAs	249 (95.8%)	407 (95.1%)	251 (95.1%)	111 (91.0%)	0.1071
Loop diuretic	250 (96.2%)	411 (96.0%)	251 (95.1%)	117 (95.9%)	0.6734

Values are given as mean ± standard deviation, unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, Left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

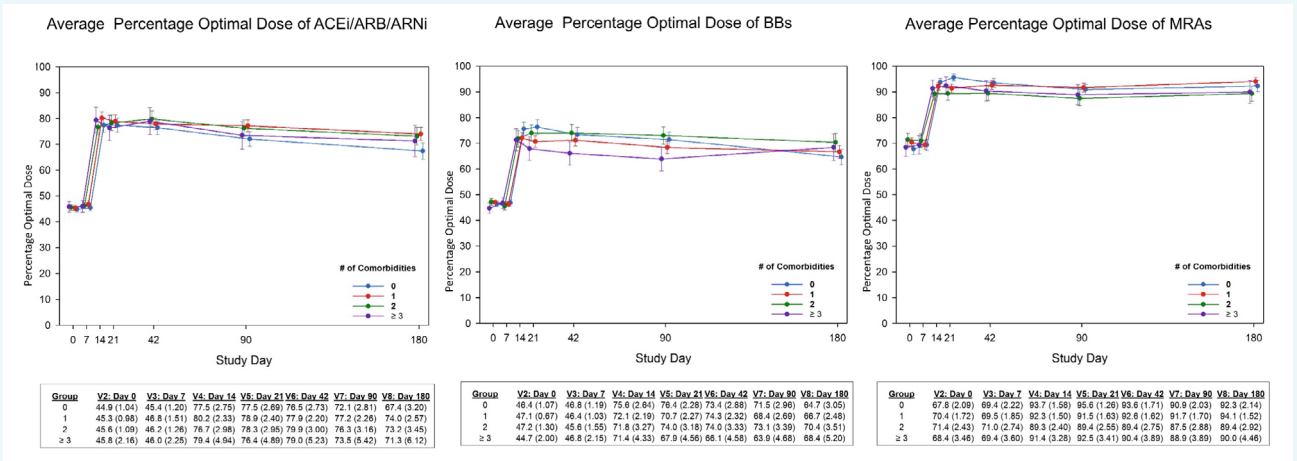


Figure 1 Average percentage of optimal dose by number of non-cardiac comorbidities for each heart failure therapeutic classes: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors (ACEi/ARB/ARNi), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA).

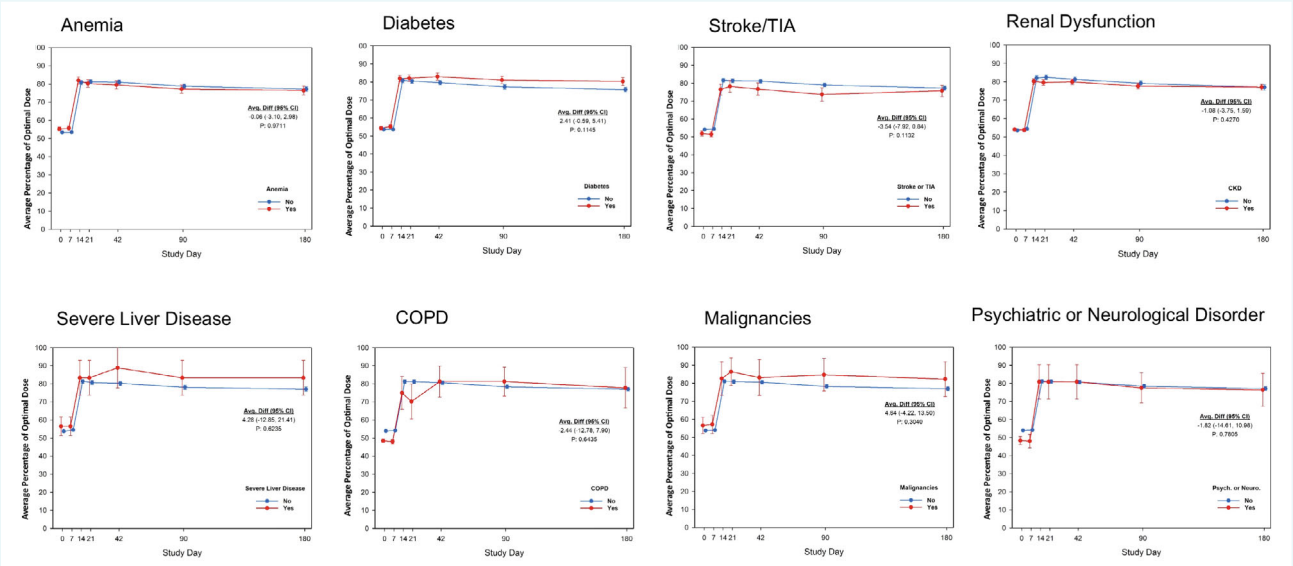


Figure 2 Average percentage of optimal dose by each individual comorbidity. CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

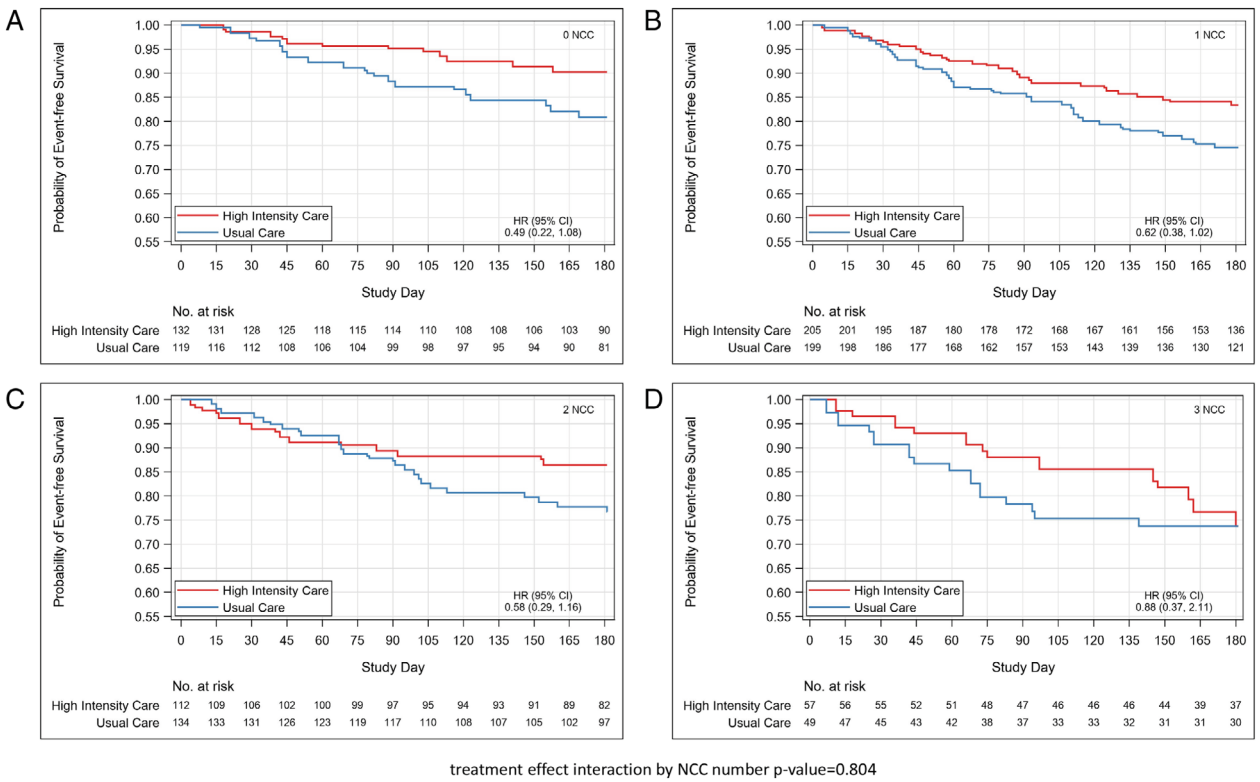


Figure 3 Unadjusted Kaplan–Meier curves for the primary endpoint (180-day all-cause death or heart failure readmission) by number of non-cardiac comorbidities (NCC): (*A*) 0 NCC; (*B*) 1 NCC; (*C*) 2 NCCs; and (*D*) ≥3 NCCs. CI, confidence interval; HR, hazard ratio.

Table 2 Primary, secondary and exploratory endpoints in patients with 0, 1, 2 and ≥3 non-cardiac comorbidities

Outcome	High-intensity care	Usual care	Unadjusted		Adjusted	
			Treatment effect (95% CI)	Treatment-by-NCC score interaction *p*-value	Treatment effect (95% CI)	Treatment-by-NCC score interaction *p*-value
Primary endpoint						
All-cause death or HF readmission by day 180[a]						
0 NCC	12 (10.0%)	21 (19.1%)	0.49 (0.22–1.08)	0.8045	0.51 (0.23, 1.12)	0.9489
1 NCC	33 (16.6%)	47 (25.4%)	0.62 (0.38, 1.02)		0.62 (0.38, 1.01)	
2 NCCs	15 (13.6%)	28 (23.3%)	0.58 (0.29, 1.16)		0.59 (0.29, 1.17)	
≥3 NCCs	14 (26.2%)	13 (26.2%)	0.88 (0.37, 2.11)		0.72 (0.30, 1.75)	
Secondary endpoints						
All-cause death by day 180[b]						
0 NCC	8 (6.9%)	9 (7.3%)	0.90 (0.30, 2.68)	0.8007	0.93 (0.31, 2.75)	0.7852
1 NCC	15 (7.7%)	20 (10.8%)	0.69 (0.33, 1.42)		0.73 (0.35, 1.52)	
2 NCCs	11 (10.8%)	11 (9.6%)	1.18 (0.49, 2.87)		1.02 (0.41, 2.50)	
≥3 NCCs	5 (11.4%)	8 (15.3%)	0.67 (0.19, 2.34)		0.47 (0.13, 1.70)	
EQ-5D VAS change from baseline to visit 7[c]						
0 NCC	13.09 (1.42)	9.92 (1.51)	3.17 (−0.50, 6.83)	0.9648	4.09 (0.52, 7.66)	0.9881
1 NCC	11.07 (1.15)	7.14 (1.17)	3.93 (1.21, 6.64)		3.54 (0.91, 6.18)	
2 NCCs	9.71 (1.45)	6.86 (1.40)	2.85 (−0.64, 6.35)		3.61 (0.20, 7.03)	
≥3 NCCs	6.17 (1.96)	2.33 (2.04)	3.84 (−1.38, 9.07)		4.41 (−0.67, 9.50)	
Exploratory endpoints						
HF readmission by day 180[d]						
0 NCC	7 (5.1%)	15 (15.6%)	0.32 (0.12, 0.90)	0.3440	0.33 (0.12, 0.91)	0.4318
1 NCC	23 (11.8%)	32 (18.4%)	0.64 (0.35, 1.15)		0.64 (0.35, 1.16)	
2 NCCs	7 (5.4%)	20 (17.2%)	0.30 (0.11, 0.86)		0.30 (0.11, 0.85)	
≥3 NCCs	10 (18.4%)	7 (16.3%)	0.92 (0.31, 2.74)		0.75 (0.25, 2.26)	
Sensitivity analyses						
All-cause death or HF readmission by day 180 (excluding COVID deaths)[a]						
0 NCC	12 (10.0%)	21 (19.1%)	0.49 (0.22, 1.08)	0.8866	0.50 (0.23, 1.12)	0.9542
1 NCC	32 (16.1%)	46 (24.8%)	0.62 (0.37, 1.01)		0.61 (0.37, 1.00)	
2 NCCs	13 (11.6%)	28 (23.3%)	0.48 (0.23, 1.01)		0.49 (0.23, 1.02)	
≥3 NCCs	12 (22.4%)	13 (26.2%)	0.71 (0.28, 1.79)		0.59 (0.23, 1.51)	

Data presented as *n* (Kaplan–Meier %) or LS-mean (standard error). Unadjusted treatment effects are the LS-mean difference between treatment groups (for change in EQ-5D) and hazard ratio for the other endpoints. Results for patients in cohort 1 were down-weighted for day 180 analyses.
CI, confidence interval; HF, heart failure; LS, least squares; LVEF, left ventricular ejection fraction; NCC, non-cardiac comorbidity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VAS, visual analogue scale.
[a]Adjusted for baseline diastolic blood pressure, ischaemic heart disease, oedema severity, and NT-proBNP.
[b]Adjusted for baseline creatinine, haemoglobin, urea, and NT-proBNP.
[c]LS-mean change and LS-Mean difference from an ANCOVA model with baseline EQ-VAS, region, baseline LVEF (≤40/>40%), treatment, NCC score, and treatment-by-NCC score interaction. Subjects from Mozambique were excluded from these analyses because of the unavailability of a linguistically validated translation of the EQ-5D VAS in that country. Additional adjustment for age, haemoglobin, creatinine, cholesterol, NT-proBNP, hospitalization for HF in the previous year, oedema severity, and NYHA class.
[d]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF, and oedema.

irrespective of number of comorbidities at baseline (interaction $p = 0.99$) (*Table 2*).

Safety

The incidence of serious adverse events increased with number of NCCs, and for those with ≥3 NCCs was nominally higher in HIC than UC, but without significant interaction between treatment strategy and NCC number (interaction $p = 0.11$) (*Table 3*). Also, there was no significant treatment-by-NCC number interaction in the incidence of any adverse events (interaction $p = 0.28$) (online supplementary *Table S2*).

The most common adverse events were cardiac related (99 in HIC vs. 96 in UC), but again without significant interaction by comorbidity score (interaction $p = 0.72$). Of note, bradycardia and complete atrio-ventricular block events were rare (5 in HIC vs. 3 in UC). Decreased eGFR and hyperkalaemia occurred in 2 (<1%) and 18 (3%) patients from HIC, respectively. HIC patients had additional safety visits at 1 week after randomization and 1 week after the second up-titration of GDMT. Few reductions in

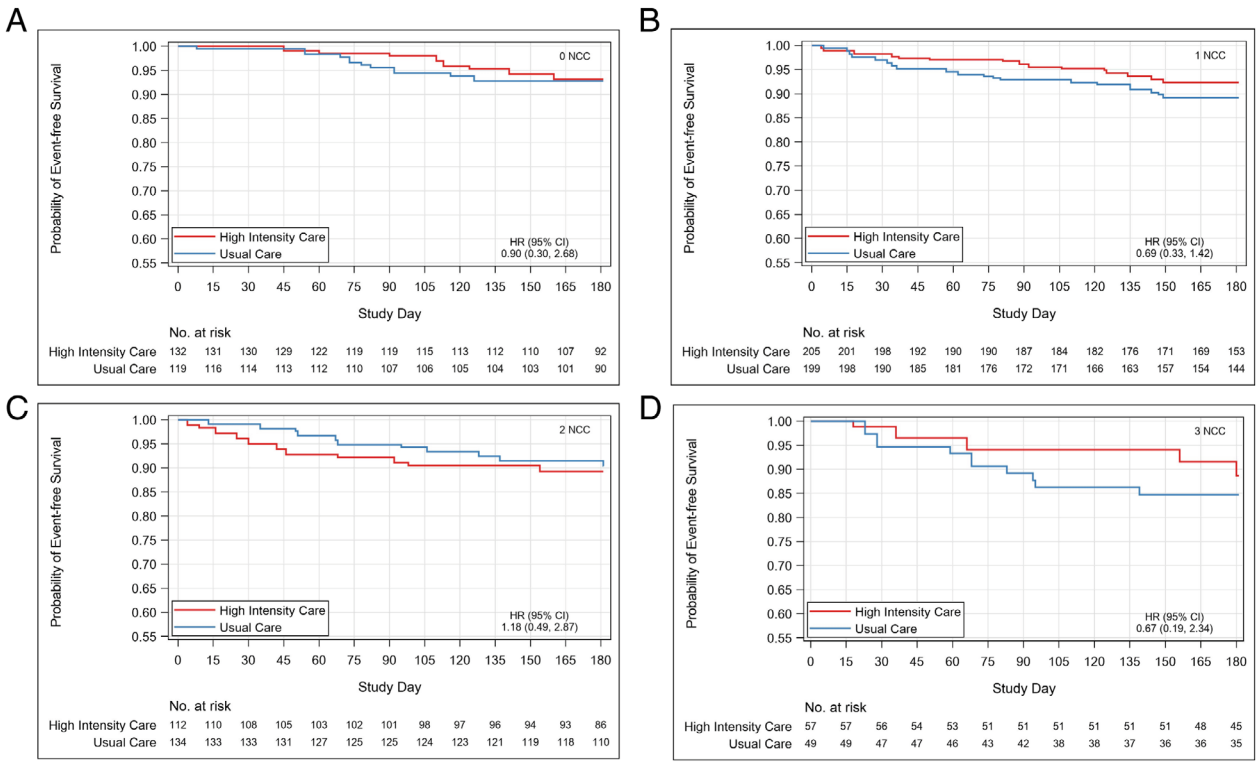


Figure 4 Unadjusted Kaplan–Meier curves for 180-day all-cause mortality by number of non-cardiac comorbidities (NCC): (*A*) 0 NCC; (*B*) 1 NCC; (*C*) 2 NCCs; and (*D*) ≥3 NCCs. CI, confidence interval; HR, hazard ratio.

GDMTs occurred during these visits, regardless of the NCC group, indicating good tolerance of the administered doses.

Discussion

This analysis of STRONG-HF demonstrates that rapid and intensive optimization of BBs, RASi and MRAs, performed in the early post-discharge phase after an AHF episode and under close follow-up and monitoring, is effective regardless of the number of NCCs or each individual comorbidity. In addition, the percentage of patients who achieved optimal GDMT doses by day 90 and 180 was similar irrespective of number and type of NCC, indicating that GDMT up-titration is feasible and safe in patients with scheduled follow-up. For quality-of life improvements, the benefits of the HIC strategy in terms of higher mean change from baseline to day 90 in EQ-5D VAS were consistent with no significant interaction between the treatment strategy and NCC number.

In the STRONG-HF trial, the proportion of patients with ≥3 NCCs was lower than in the ASCEND-HF trial (11.4% vs. 35.7%) but ASCEND-HF collected a higher number of diverse NCCs (including smoker status and alcohol history) and enrolled an older population.[7] Similar to other studies,[6,7] STRONG-HF patients with LVEF >40% had higher number of NCCs, and diabetes, anaemia and renal dysfunction were the most frequently reported NCCs, a common finding for all three studies.

The impact of multiple comorbidities on the beneficial prognostic effect of GDMT has not been fully elucidated in clinical trials. NCCs could plausibly alter the biological response to a trial therapy and/or the risk–benefit balance, resulting in the occurrence of side effects.

However, in a propensity-matched score analysis from the GREAT registry, HF therapies at discharge were associated with a consistent reduction in mortality in patients with recent AHF, regardless of LVEF or the presence of comorbidities.[15] Furthermore, in two other AHF registries, GDMT was consistently beneficial regardless of the comorbidity burden.[16,17]

Notably, in STRONG-HF rapid up-titration of oral HF medications and close follow-up reduced post-discharge outcomes irrespective of the number of NCCs and the benefits of this strategy persist with no interaction between treatment strategy and NCC number. Although GDMT was consistently beneficial regardless of the NCC number, the association between GDMT and reduced risk of adverse events tended to weaken with increasing comorbidity burden. However, in sensitivity analysis, excluding COVID-19 death, lower HRs with narrow margins of 95% CIs were reported, suggesting a trend to better treatment effect irrespective of number of NCCs. This is probably the consequence of the

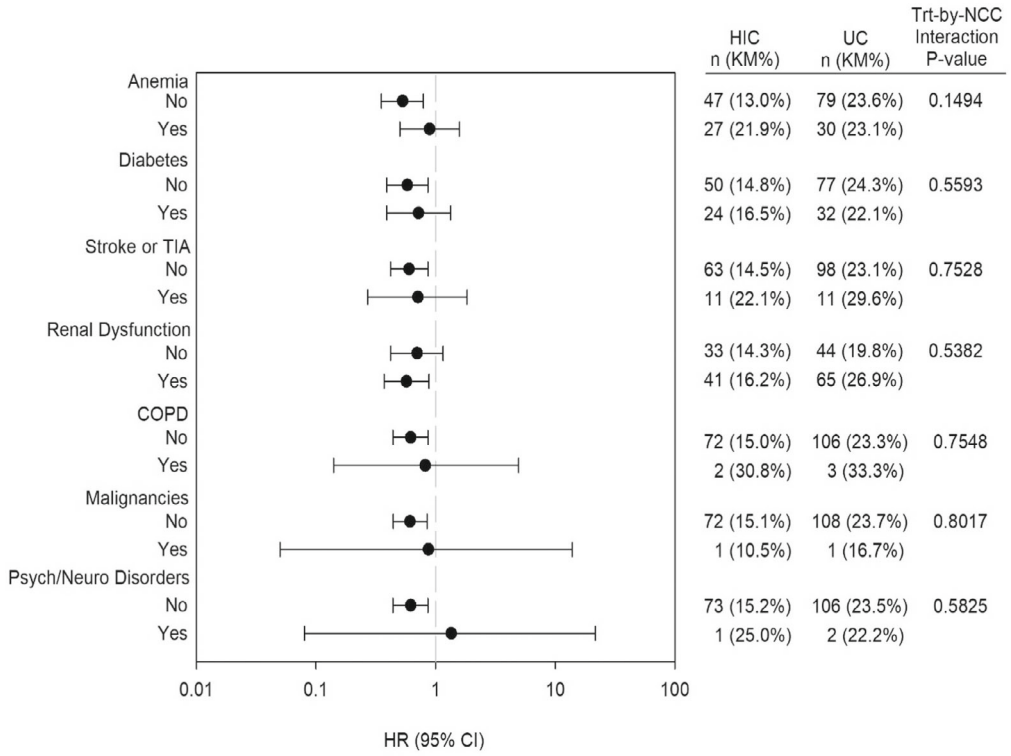


Figure 5 Forest plot of treatment effect by individual components of comorbidities score and test of interaction for the outcome of all-cause mortality or heart failure readmission through day 180. COPD, chronic obstructive pulmonary disease; HIC, high-intensity care; KM, Kaplan–Meier; NCC, non-cardiac comorbidity; TIA, transient ischaemic attack; UC, usual care.

fact that patients with more comorbidities had more COVID-19 deaths, which are not directly impacted by the HIC strategy. Although, it did not reach statistical significance, potentially due to the small sample size of the study, this finding represents an important signal in favour of HIC benefit on the cardiovascular component of the primary endpoint and explaining gradual decrease of treatment effect with number of NCCs. Also, the benefit of HIC on the primary endpoint was consistent for all eight individual NCCs, with no interaction between treatment effect and each NCC assessed individually.

The results of the current analysis are in line with numerous HF studies showing the clinical benefits of renin–angiotensin–aldosterone system inhibition in diverse stages of kidney disease[18–21] or diabetic status.[22] Although asthma and COPD are associated with a lower likelihood of being prescribed a BB and being prescribed the target dose,[23] multiple studies and meta-analyses found that BBs improve survival in these patients without significant worsening of respiratory symptoms.[24–27] Also, robust evidence shows that BBs improved mortality and decreased all-cause hospitalization, regardless of diabetic status.[28,29]

While comorbidities may impact eligibility for particular therapies, it is important to optimize medical therapy as early as possible to reduce clinical risk. GDMTs improve prognosis soon after initiation[30–33] and delays in initiating treatment are inevitably accompanied by high rate of death and HF hospitalization, emphasizing the need for rapid initiation and up-titration of GDMTs. Also, deferring in-hospital initiation and up-titration of GDMT leads to delay or even deprivation of life-saving therapies. Multiple real-world studies show that failure to discharge eligible patients on GDMT significantly increases the chance that therapies will never be started or started with considerable delay and with suboptimal dose regimens.[34–36]

This fact documents furthermore that the HF admission and early weeks post-discharge are, for a relevant number of patients, a concrete opportunity to optimize their background therapy. Although physicians managing HF patients cite comorbidity burden as a ‘reason’ for not applying standard therapies, in the STRONG-HF trial the effects of HIC were beneficial irrespective of number of NCCs or each individual NCC, and application of the rapid up-titration strategy coupled with high-intensity follow-up reduced post-discharge outcomes.

We acknowledge that the STRONG-HF study population was younger than in other contemporary AHF studies. The impact of NCC burden might substantially determine the clinical course after AHF hospitalization in elderly patients, reducing the proportion of cardiovascular events compared to non-cardiovascular events, probably diminishing the benefits of GDMTs.

Although patients with multiple NCCs are traditionally perceived as riskier candidates for rapid intensification of GDMTs, the results of the current analysis show feasibility of the up-titration

Table 3 Treatment emergent serious adverse events by system organ class and preferred term by number of non-cardiac comorbidities and treatment

System Organ Class / Preferred Term	0 NCC		1 NCC		2 NCCs		≥3 NCCs		Interaction p-value
	High-intensity care (*n* = 137)	Usual care (*n* = 125)	High-intensity care (*n* = 218)	Usual care (*n* = 211)	High-intensity care (*n* = 121)	Usual care (*n* = 143)	High-intensity care (*n* = 66)	Usual care (*n* = 57)	
Any serious adverse event	15 (10.9%)	18 (14.4%)	32 (14.7%)	38 (18.0%)	22 (18.2%)	25 (17.5%)	19 (28.8%)	11 (19.6%)	0.1068
Cardiac disorders	9 (6.6%)	11 (8.8%)	21 (9.6%)	22 (10.4%)	9 (7.4%)	17 (11.9%)	9 (13.6%)	9 (16.1%)	0.9157
Gastrointestinal disorders	0	0	0	0	2 (1.7%)	0	1 (1.5%)	0	
General disorders and administration site conditions	1 (0.7%)	3 (2.4%)	3 (1.4%)	7 (3.3%)	1 (0.8%)	1 (0.7%)	0	0	0.5580
Hepatobiliary disorders	0	0	0	0	1 (0.8%)	0	1 (1.5%)	0	
Infections and infestations	2 (1.5%)	2 (1.6%)	6 (2.8%)	6 (2.8%)	5 (4.1%)	3 (2.1%)	6 (9.1%)	0	0.0525
Metabolism and nutrition disorders	0	0	0	1 (0.5%)	0	0	1 (1.5%)	0	
Nervous system disorders	1 (0.7%)	2 (1.6%)	2 (0.9%)	2 (0.9%)	2 (1.7%)	0	0	0	0.2071
Renal and urinary disorders	0	0	1 (0.5%)	1 (0.5%)	2 (1.7%)	1 (0.7%)	2 (3.0%)	0	0.3640
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.9%)	1 (0.5%)	1 (0.8%)	1 (0.7%)	1 (1.5%)	2 (3.6%)	
Surgical and medical procedures	0	0	1 (0.5%)	0	1 (0.8%)	0	0	0	
Vascular disorders	1 (0.7%)	2 (1.6%)	0	0	0	0	1 (1.5%)	0	

Including serious adverse events with onset date equal to or greater than date of randomization through 90 days post-randomization.
NCC, non-cardiac comorbidity.

process regardless of number of NCCs. Even if with distinct up-titration trajectories during follow-up visits, the 180-day uptake of BBs, RASi and MRAs was not impacted by number of NCCs and, notably, was similar by each type of NCC. The adherence to the study protocol, with high-intensity follow-up visits that guided the up-titration process contributed to these results. To note, these findings occurred in the context of the eligibility criteria of the STRONG-HF trial (excluding hypotensive patients and those with severe comorbidities that prevent up-titration), and future implementation studies in real-world settings are needed to evaluate the external generalizability of the STRONG-HF study protocol.

One important finding of the current analysis is that treatment effect of HIC compared to UC on 90-day change in quality of life did not differ by number of NCCs with no interaction between treatment strategy and NCC number. This is clinically relevant in a HF multimorbid population and demonstrates that the HIC strategy is associated with improvement in quality of life even in patients with multiple NCCs.

Finally, in STRONG-HF, rapid up-titration was coupled with a high-intensity follow-up, minimizing adverse effects potentially related to older age or associated comorbidities. The lack of increase of severe adverse events in the HIC group was achieved by meticulous adherence to the study protocol during follow-up visits, that set clear rules of up-titration guided by several safety indicators, including systolic blood pressure, NT-proBNP, serum potassium, and eGFR levels.

Limitations

Our results must be interpreted in the particular context of the clinical trial settings, both with respect to its inclusion criteria and follow-up strategy used in the HIC arm. The set of NCCs was obtained from medical history and collected in the context of the clinical trial settings to ensure the study eligibility. Severity of comorbidities was not collected, and we are not able to account for the relative severity of comorbidities in the outcomes we examined. However, we acknowledge that mild or moderate levels of the identified NCCs were included in this study. Thus, the STRONG-HF comorbidities may vary in the number, extent and severity as compared with a 'real-world' population, limiting generalizability of the results.

The treatment effect on quality of life should be interpreted with caution because the study was open-label, existing the possibility that patients from the HIC group might have been biased to report greater improvements if they knew they were in the HIC group.

Tests of subgroup-by-treatment interactions may have a limited statistical power in this study owing to small sample sizes and a corresponding small number of events in the subgroups.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are now recommended as first-line therapy for patients with HF and their early initiation has beneficial effects also in patients with AHF. STRONG-HF was initiated prior this current evidence and recommendations for SGLT2 inhibitors. Thus, these drugs were not included in the study design.

Conclusions

In the STRONG-HF trial, enrolling stable patients with improved but still elevated natriuretic peptide, rapid up-titration of HF medications and close follow-up reduced 180-day mortality or HF rehospitalization irrespective of the number of NCCs or each NCC assessed individually. There was no significant treatment-by-NCC number interaction in quality-of-life improvement. Higher proportions of patients with multiple NCCs had serious adverse events, but the benefit–risk ratio favours the rapid up-titration of HF therapies even in patients with multiple NCCs.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: none declared.

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