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RESEARCH ARTICLE

Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure in elderly patients: A sub-analysis of the STRONG-HF randomized clinical trial

Mattia Arrigo[1]*, Jan Biegus[2], Ayu Asakage[3], Alexandre Mebazaa[3,4], Beth Davison[3,5], Christopher Edwards[6], Marianna Adamo[7], Marianela Barros[6], Jelena Celutkiene[8], Kamilė Čerlinskaitė-Bajorė[8], Ovidiu Chioncel[9], Albertino Damasceno[10], Rafael Diaz[11], Gerasimos Filippatos[12], Etienne Gayat[3,4], Antoine Kimmoun[13,14], Carolyn S.P. Lam[15], Marco Metra[7], Maria Novosadova[6], Matteo Pagnesi[7], Peter S. Pang[16], Piotr Ponikowski[2], Hadiza Saidu[17], Karen Sliwa[18], Koji Takagi[6], Jozine M. Ter Maaten[19], Daniela Tomasoni[7], Adriaan A. Voors[19], Gad Cotter[3,5], and Alain Cohen-Solal[3,20]

[1]Department of Internal Medicine, Stadtspital Zurich, Zurich, Switzerland; [2]Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; [3]Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France; [4]Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France; [5]Heart Initiative, Durham, NC, USA; [6]Momentum Research, Inc., Durham, NC, USA; [7]Cardiology, Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [8]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [9]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine 'Carol Davila', Bucharest, Romania; [10]Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique; [11]Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; [12]National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece; [13]Université de Lorraine, Nancy, France; [14]INSERM, Défaillance Circulatoire Aigue et Chronique; Service de Médecine Intensive et Réanimation Brabois, CHRU de Nancy, Nancy, France; [15]National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore; [16]Department of Emergency Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [17]Department of Medicine, Murtala Muhammed Specialist Hospital/Bayero University Kano, Kano, Nigeria; [18]Cape Heart Institute, Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; [19]University of Groningen, Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands; and [20]Department of Cardiology, APHP Nord, Lariboisière University Hospital, Paris, France

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Aims STRONG-HF examined a high-intensity care (HIC) strategy of rapid up-titration of guideline-directed medical therapy (GDMT) and close follow-up after acute heart failure (AHF) admission. We assess the role of age on efficacy and safety of HIC.

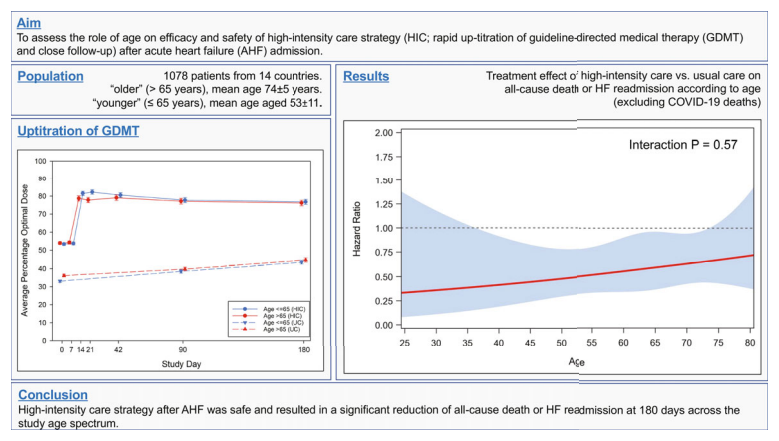
Methods and results Hospitalized AHF patients, not treated with optimal GDMT were randomized to HIC or usual care. The primary endpoint of 180-day death or HF readmission occurred equally in older (>65 years, $n = 493$, 74 ± 5 years) and younger patients (53 ± 11 years, adjusted hazard ratio [aHR] 1.02, 95% confidence interval [CI] 0.73–1.43, $p = 0.89$). Older patients received slightly lower GDMT to day 21, but same doses at day 90 and 180. The effect of HIC on the primary endpoint was numerically higher in younger (aHR 0.51, 95% CI 0.32–0.82) than older patients (aHR 0.73, 95% CI 0.46–1.15, adjusted interaction $p = 0.30$), partially related to COVID-19 deaths. After exclusion of COVID-19 deaths, the effect of HIC was similar in younger (aHR 0.51, 95% CI 0.32–0.82) and older patients (aHR 0.63, 95% CI 0.32–1.02, adjusted interaction $p = 0.56$), with no treatment-by-age interaction (interaction $p = 0.57$). HIC induced

*Corresponding author. Department of Internal Medicine, Stadtspital Zurich, Birmensdorferstrasse 497, 8063 Zürich, Switzerland. Email: mattia.arrigo@uzh.ch

larger improvements in quality of life to day 90 in younger (EQ-VAS adjusted-mean difference 5.51, 95% CI 3.20−7.82) than in older patients (1.77, 95% CI −0.75 to 4.29, interaction $p = 0.032$). HIC was associated with similar rates of adverse events in older and younger patients.

Conclusion High-intensity care after AHF was safe and resulted in a significant reduction of all-cause death or HF readmission at 180 days across the study age spectrum. Older patients have smaller benefits in terms of quality of life.

Graphical Abstract



STRONG-HF showed that a rapid and intensive optimization of guideline-directed medical therapy (GDMT) under close follow-up after an acute heart failure (HF) episode, is feasible, effective, and safe regardless of the patient's age.

Keywords Acute heart failure • Medical therapy • Up-titration • Vulnerable phase • Readmission • High-intensity care • Age • Elderly

Introduction

The initiation, up-titration, and optimization of guideline-directed medical therapy (GDMT) are among the most effective interventions to improve outcomes of patients with acute heart failure (AHF). The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) study was a multinational, open-label, randomized, prospective clinical trial, designed to assess the safety and efficacy of high-intensity care (HIC). HIC consisted of rapid up-titration of treatments before discharge from an AHF admission and during the following weeks compared with usual care (UC).[1,2] The study showed that a HIC strategy consisting of rapid up-titration of GDMT and close follow-up after an AHF admission was feasible, reduced symptoms, improved quality of life and reduced the risk of all-cause death or heart failure (HF) readmission at 180 days compared to UC.[3]

In pre-specified subgroup analyses in STRONG-HF, the benefit of HIC on the primary outcome (180-day HF readmission or all-cause death) was similar in those aged ≤65 versus >65 years and ≤75 versus >75 years.[3] However, in clinical practice, physicians may still be more reluctant to optimize pharmacotherapy in elderly patients due to concerns for side effects (such as hypotension, hyperkalaemia and worsening of renal function) that older, frail, multi-morbid patients may be more prone to, particularly in the early post-discharge phase of AHF. Furthermore, elderly patients themselves may be more interested in benefits in terms of quality of life than survival. The association of age with secondary and safety outcomes in STRONG-HF has not been previously reported. Therefore, the aim of these analyses is to describe the associations of age with outcomes, ability to up-titrate patients quickly to recommended doses of GDMT, the safety of such up-titration, and its effects on outcome and quality of life.

Methods

Study participants and procedures

STRONG-HF was a multinational, open-label, randomized, parallel-group trial designed to assess the efficacy and safety of

an intensive treatment strategy of rapid up-titration of GDMT and close follow-up after an AHF admission compared to UC. The study design has been published elsewhere.[1,2] Briefly, eligible patients, aged 18–85 years, hospitalized for AHF with clinical signs of congestion, elevated circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP), and not treated with full doses of GDMT (beta-blockers; angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB] if intolerant to ACEi, or angiotensin receptor–neprilysin inhibitor [ARNi]; and mineralocorticoid receptor antagonists [MRA]) were randomly assigned (1:1) within 2 days before anticipated hospital discharge to either UC according to local practice or HIC. Patients randomized to HIC were up-titrated to half recommended doses at randomization, were seen at four scheduled outpatient visits over the 2 months after discharge at 1, 2, 3, and 6 weeks and were up-titrated to full recommended doses of GDMT 2 weeks after discharge. Patients in both groups were seen at day 90 after randomization and were contacted at day 180. Doses considered optimal are summarized in online supplementary *Table S3* of the original publication.[3] The study was approved by appropriate competent authorities and ethics committees, and patients provided written informed consent. This study is registered at ClinicalTrials.gov, NCT03412201.

For the purpose of this analysis, the study population was divided by age into two groups: younger (≤65 years) and older patients (>65 years). Because very few patients >75 years old were enrolled ($n = 196$), outcome analyses according to age ≤75 and >75 years are presented in online supplementary *Appendix S1*.

Study outcomes

The primary endpoint of the study was all-cause death or HF readmission at 180 days, considering only the first occurrence of these events per patient. Secondary endpoints were change in quality of life from baseline to day 90 as measured by the EQ-5D visual analogue scale (VAS),[4] all-cause death at 180 days, and all-cause mortality or HF readmission at 90 days.

Safety was assessed through the incidence of treatment-emergent adverse events up to 90 days, and changes in systolic and diastolic blood pressure, heart rate, and body weight and local laboratory results.

Statistical analysis

All efficacy and safety analyses included all patients who were validly randomized in the treatment group to which they were randomly assigned. Continuous variables are presented as mean and standard deviation or as adjusted mean and standard error (SE), as appropriate, and categorical variables as absolute and relative frequencies. NT-proBNP values were log-transformed for analysis. Baseline characteristics were compared between treatment groups using ANOVA for continuous variables, chi-square tests for nominal categorical variables, and the Cochran–Mantel–Haenszel test for general association for ordered categorical variables. Use of oral HF medications relative to optimal doses were compared between age categories across the two treatment groups using the Cochran–Mantel–Haenszel mean score test and differential age differences between treatment groups using a test of the homogeneity of the Mann–Whitney statistic which are derived from the Somers' D statistic and its associated SE. As previously described, because the primary endpoint was changed from 90-day to 180-day death or HF readmission, for 180-day outcomes the results in the cohort of patients enrolled before the change were down-weighted proportional to half the cohort's sample size. Only patients enrolled at sites where the ethics committees approved protocol amendments allowing follow-up of patients to day 180 were included in analyses of 180-day outcomes. Previously published, pre-specified subgroup analyses compared absolute treatment group risk differences, using Kaplan–Meier estimates of cumulative risks of the primary endpoint at 180 days, between subgroups defined as age at screening ≤65 and >65 years, and ≤75 and >75 years. Pre-specified subgroup analyses for the secondary binary endpoints were to be analysed similarly. Because the treatment group hazard ratio (HR) did not differ significantly over time, Cox regression was used to further explore the potential modifying effect of age. Age as a continuous variable was modelled as a restricted cubic spline with three knots. The total number of events and down-weighted, adjusted Kaplan–Meier estimates of cumulative event rates are presented in each treatment group; both unadjusted and adjusted HR and associated 95% confidence intervals (CI) from Cox regression are shown. The pre-specified subgroup analysis of the 90-day change in EQ-VAS employed an ANCOVA model that included effects of treatment group, subgroup, subgroup-by-treatment interaction, and randomization stratification factors (geographic region and left ventricular ejection fraction [LVEF] ≤40% or >40%). Only observed data were used and patients for whom no linguistically validated EQ-5D translation was available were excluded from these analyses. Covariates for further adjustment were selected from variables shown to be prognostic of each outcome in previous studies using backwards selection in the UC group. Because very few patients >75 years old were enrolled ($n = 196$), analyses focused on patients ≤65 and >65 years old. Two-sided $p < 0.05$ was considered to be statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Baseline characteristics and outcome of older patients

During the study period, 1078 patients from 87 hospitals in 14 countries (Argentina, Austria, Bulgaria, Colombia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia) were randomly assigned to HIC ($n = 542$) or UC ($n = 536$).

Older patients (>65 years, $n = 493$, aged 74 ± 5 years) were more frequently women (44% vs. 34%), had more severe HF symptoms, higher LVEF (40 ± 13% vs. 33 ± 11%) and higher proportion of ischaemic aetiology of HF (64% vs. 34%), compared to younger patients (≤65 years, $n = 585$, aged 53 ± 11 years) (all $p < 0.01$) (*Table 1*). Accordingly, older patients displayed a higher prevalence of atherosclerotic cardiovascular disease (i.e. history of acute coronary syndrome, coronary revascularization, and cerebrovascular accident), atrial fibrillation, and other non-cardiovascular comorbidities.

Small differences in vital signs and laboratory parameters were observed at baseline according to age group. Systolic blood pressure was similar in both groups, older patients had lower heart rate (75 ± 10 vs. 82 ± 12 bpm) and haemoglobin levels (133 ± 19 vs. 139 ± 21 g/L) and slightly higher creatinine (110 ± 27 vs. 103 ± 30 μmol/L) and NT-proBNP (geometric mean 3412 vs.

Table 1 Baseline characteristics by age subgroups

Parameter	Age subgroup (years)		*p*-value
	Age ≤65 (*n* = 585)	Age >65 (*n* = 493)	
Demographic characteristics			
Age, years, means (SD)	53.3 (10.60)	74.4 (5.47)	<0.001
Sex, *n* (%)			0.002
Female	201 (34.4)	215 (43.6)	
Male	384 (65.6)	278 (56.4)	
Self-reported race, *n* (%)			<0.001
Black	195 (33.3)	35 (7.1)	
Caucasian	381 (65.1)	451 (91.2)	
Other	9 (1.5)	5 (1.0)	
Geographical region, *n* (%)			<0.001
Europe	364 (62.2)	433 (87.8)	
Non-Europe	221 (37.8)	60 (12.2)	
HF history			
History of HF, *n* (%)	481 (82.2)	435 (88.4)	0.004
NYHA class 1 month before hospital admission, *n* (%)			
I	44 (8.2)	19 (4.1)	0.002
II	177 (33.1)	130 (27.9)	
III	216 (40.4)	199 (42.7)	
IV	97 (18.2)	118 (25.3)	
Ischaemic aetiology, *n* (%)	201 (34.4)	313 (63.9)	<0.001
LVEF, %, mean (SD)	33.4 (11.37)	39.8 (13.0)	<0.001
Implantable cardioverter-defibrillator, *n* (%)	5 (0.9)	4 (0.8)	0.94
Cardiac resynchronization therapy, *n* (%)	2 (0.3)	4 (0.8)	0.30
HF admission in the past year, *n* (%)	140 (23.9)	133 (27.0)	0.24
Number of HF admission in the past year, mean (SD)	0.3 (1.36)	0.4 (0.71)	0.80
NT-proBNP at screening, ng/L, geom. mean (95% CI)	6002 (5734–6283)	6031 (5727–6351)	0.89
Medical history, *n* (%)			
Acute coronary syndrome	123 (21.0)	188 (38.2)	<0.001
Coronary artery bypass surgery	19 (3.2)	40 (8.1)	<0.001
Percutaneous coronary intervention	67 (11.5)	85 (17.3)	0.006
History of atrial fibrillation or atrial flutter	202 (34.5)	294 (59.8)	<0.001
Stroke or transient ischaemic attack	39 (6.7)	60 (12.2)	0.002
Diabetes	141 (24.2)	172 (35.0)	<0.001
Malignancies	9 (1.5)	20 (4.1)	0.011
Psychiatric or neurological disorder	3 (0.5)	17 (3.5)	<0.001
Moderate or severe COPD or asthma	11 (1.9)	16 (3.3)	0.15
Baseline vital signs, mean (SD)			
Systolic blood pressure, mmHg	123.0 (14.44)	122.6 (10.92)	0.64
Pulse, bpm	82.0 (12.16)	74.6 (9.96)	<0.001
Respiratory rate, breaths/min	18.5 (4.24)	17.8 (5.08)	0.018
Baseline laboratory values			
Haemoglobin, g/L, mean (SD)	139.1 (20.56)	133.3 (18.83)	<0.001
White blood cells, 10/L, mean (SD)	7.0 (2.02)	7.0 (2.02)	0.50
Lymphocytes, %, mean (SD)	29.0 (9.78)	25.2 (9.44)	<0.001
Sodium, mmol/L, mean (SD)	139.8 (4.17)	140.7 (4.11)	<0.001
Potassium, mmol/L, mean (SD)	4.2 (0.45)	4.3 (0.44)	0.009
Urea, mmol/L, mean (SD)	7.3 (3.16)	8.9 (3.68)	<0.001
Creatinine, μmol/L, mean (SD)	103.0 (30.00)	110.0 (27.04)	<0.001
Glucose, mmol/L, mean (SD)	6.0 (2.28)	6.5 (2.35)	0.001
NT-proBNP, ng/L, geom. mean (95% CI)	3047 (2898–3205)	3411.6 (3223–3611)	0.003
Oral HF medications taken before randomization, *n* (%)			
ACEi/ARB/ARNi	395 (67.8)	294 (59.9)	0.007
≥50% Optimal dose	132 (22.6)	135 (27.5)	0.067

Table 1 (Continued)

Parameter	Age subgroup (years)		p-value
	Age ≤65 (*n* = 585)	Age >65 (*n* = 493)	
Beta-blockers	181 (31.0)	202 (41.1)	0.001
≥50% Optimal dose	100 (17.2)	130 (26.5)	<0.001
MRA	561 (96.2)	457 (93.1)	0.021
≥50% Optimal dose	558 (95.7)	455 (92.7)	0.032
Loop diuretic	566 (97.1)	463 (94.3)	0.023
Daily dose, mg, mean (SD)	69.1 (49.8)	55.0 (40.5)	<0.001
Oral HF medications taken after randomization, *n* (%)			
ACEi/ARB/ARNi	486 (83.2)	388 (79.0)	0.079
≥50% Optimal dose	308 (52.7)	253 (51.5)	0.69
Beta-blockers	387 (66.3)	352 (71.7)	0.056
≥50% Optimal dose	313 (53.6)	292 (59.5)	0.053
MRA	573 (98.1)	474 (96.5)	0.11
≥50% Optimal dose	572 (97.9)	473 (96.3)	0.11
Loop diuretic	568 (97.3)	468 (95.3)	0.089
Daily dose, mg, mean (SD)	65.7 (49.43)	53.2 (39.57)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

3047 ng/L) (all $p < 0.01$). Before randomization, GDMT, except for beta-blockers, and loop diuretics were more frequently used in younger patients (*Table 1*).

Baseline EQ-VAS was similar in younger and older patients (59.5 ± 15.6 vs. 58.2 ± 14.2 points, $p = 0.15$).

The primary outcome of all-cause death or HF readmission at 180 days occurred in 21.2% of the older patients compared to 17.9% in the younger patients (unadjusted HR 1.21, 95% CI 0.88–1.68, $p = 0.23$). No difference in the hazard of death or HF readmission between older and younger patients was observed after adjustment for blood pressure, ischaemic aetiology, NT-proBNP and oedema (adjusted HR 1.02, 95% CI 0.73–1.43, $p = 0.89$). After exclusion of COVID-19 deaths, the primary outcome of all-cause death or HF readmission at 180 days occurred in 19.7% of the older patients compared to 17.9% in the younger patients (unadjusted HR 1.12, 95% CI 0.80–1.55, $p = 0.51$). No difference in the hazard of death or HF readmission between older and younger patients was observed after adjustment for blood pressure, ischaemic aetiology, NT-proBNP and oedema (adjusted HR 1.01, 95% CI 0.72–1.40, $p = 0.97$).

Notably, a less pronounced change in the secondary outcome of quality of life assessed with the EQ-5D VAS from baseline to 90 days was observed in older patients. With only adjustment for region, LVEF group (≤40%, >40%) and baseline EQ-5D VAS, older patients reported a mean increase of 6.06 ± 0.67 points compared to 11.00 ± 0.67 points in younger patients (adjusted mean difference −4.94, 95% CI −6.79 to −3.10, $p < 0.0001$). After additional adjustment for baseline haemoglobin, creatinine, cholesterol, NT-proBNP, prior hospitalizations, oedema, and New York Heart Association class, the mean difference between older and younger patients remained significant (−3.50, 95% CI −5.37 to −1.63, $p = 0.0003$) in favour of the younger patients.

Treatment of older patients

Before randomization, most patients received half or less of the recommended doses of GDMT. About one third of patients did not receive an ACEi/ARB/ARNi and about two thirds of patients did not receive a beta-blocker. Doses of renin–angiotensin blockers and MRA did not differ according to age groups but older patients received higher doses of beta-blockers (age category $p = 0.0002$). After randomization, a higher proportion of patients received half or more of the recommended doses of GDMT in the HIC compared to UC with no interaction with age (all $p > 0.1$). Doses of ACEi/ARB/ARNi were similar in older patients compared to the younger (age category $p = 0.54$). Doses of beta-blockers were higher in older patients (age category $p = 0.03$) but the difference was more pronounced in the UC group. Doses of MRA were similar across age and treatment groups (*Table 2*).

According to protocol, doses of GDMT were further up-titrated 2 weeks after randomization in the HIC arm, while in the UC group treatment was left at physician's discretion. In the UC arm, doses of GDMT at 90 and 180 days were only slightly higher compared to pre-randomization levels with no difference according to age (*Table 2*). In contrast, more than 80% of patients in the HIC group were treated with half to full optimal doses of all three GDMT classes at 90 and 180 days. A higher proportion of younger patients received full optimal doses of ACEi/ARB/ARNi and beta-blockers at weeks 2 and 3, but this difference was no longer significant at subsequent study visits (*Figure 1* and *Table 2*). The average percentage optimal dose of GDMT at 90 and 180 days

Table 2 Guideline-directed medical therapy dose relative to the optimal dose by visit, treatment arm, and age category

	Immediately after randomization					Week 2				Day 90				
	HIC ($n = 542$)		UC ($n = 536$)		Age category *p*-value	Interaction *p*-value	HIC ($n = 542$)		UC ($n = 536$)		Age category *p*-value	Interaction *p*-value	HIC ($n = 542$)		UC ($n = 536$)		Age category *p*-value	Interaction *p*-value
	≤65	>65	≤65	>65			≤65	>65	≤65	>65			≤65	>65	≤65	>65		
N (data available)	291	250	293	241			283	232					279	226	274	223		
ACEi/ARB/ARNi					0.54	0.022					0.028	0.010					0.60	0.71
None	1.7%	1.2%	31.7%	40.7%			1.1%	1.3%					2.2%	2.7%	25.5%	34.1%		
< ½ full dose	14.8%	26.4%	46.1%	29.5%			9.2%	12.9%					11.8%	13.3%	47.1%	29.6%		
½ - < full dose	83.5%	68.8%	21.8%	29.0%			26.5%	29.7%					30.8%	29.2%	25.2%	34.1%		
≥ Full dose	0	3.6%	0.3%	0.8%			63.3%	56.0%					55.2%	54.9%	2.2%	2.2%		
Beta-blockers					0.028	0.010											0.23	0.45
None	2.4%	1.2%	64.8%	55.6%			2.8%	3.4%					6.1%	3.5%	54.7%	48.4%		
< ½ full dose	11.3%	13.6%	14.0%	11.2%			9.2%	10.8%					11.1%	12.8%	18.6%	14.3%		
½ - < full dose	85.6%	83.6%	20.1%	32.4%			33.2%	39.2%					33.0%	35.0%	22.3%	33.6%		
≥ Full dose	0.7%	1.6%	1.0%	0.8%			54.8%	46.6%					49.8%	48.7%	4.4%	3.6%		
MRA					0.60	0.71											0.06	0.27
None	1.4%	2.0%	2.4%	4.1%			2.1%	4.7%					3.9%	8.8%	5.1%	9.0%		
< ½ full dose	0	0.4%	0.3%	0			0.4%	0					0	0.4%	0.7%	0.9%		
½ - < full dose	60.8%	56.8%	68.3%	61.4%			11.3%	12.5%					11.1%	8.4%	48.5%	42.6%		
≥ Full dose	37.8%	40.8%	29.0%	34.4%			86.2%	82.8%					84.9%	82.3%	45.6%	47.5%		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; HIC, high-intensity care; MRA, mineralocorticoid receptor antagonist; UC, usual care.

Figure 1 Average percentage optimal dose by visit and age category in both treatment arms. The 'average percentage optimal dose' indicates the average of the three guideline-recommended drug classes, expressed as percent of the target dose. HIC, high-intensity care; UC, usual care.

in the HIC group was similar in older and younger patients and was ~77%.

Efficacy and safety of high-intensity care in older patients

The effect of HIC on the primary endpoint was slightly more pronounced in younger patients (adjusted HR 0.51, 95% CI 0.32–0.82) and in older patients (adjusted HR 0.73, 95% CI 0.46–1.15), and the interaction with age was not statistically significant (adjusted interaction $p = 0.30$), however some of this difference was due to deaths due to COVID-19. After exclusion of COVID-19 deaths, the effect of HIC on the primary endpoint was similar in younger patients (adjusted HR 0.51, 95% CI 0.32–0.82) and in older patients (adjusted HR 0.63, 95% CI 0.32–1.02; adjusted interaction $p = 0.56$). *Table 3*, *Figure 2*, and online supplementary *Figure S2* depict the cumulative risk for all-cause death and HF readmission during the 180-day follow-up according to age and treatment group. *Figure 3* shows the effect of HIC on the primary endpoint across the spectrum of age. No significant interaction with age was found for the effect of HIC on 180-day all-cause mortality, which remained non-significant in both age groups (*Table 3*). The effect of HIC on improvement in quality of life from baseline to day 90 was larger in younger (EQ-VAS adjusted mean difference 5.51 [95% CI 3.20–7.82] points) than in older (1.77 [95% CI −0.75 to 4.29] points) patients (interaction $p = 0.032$; *Table 3*).

Proportions of patients randomized to HIC who had adverse events (including bradycardia, hypotension, acute kidney injury and hyperkalaemia) were similar by age and did not vary significantly by age group (37% vs. 29% in younger, and 46% vs. 30% in older patients, interaction $p = 0.25$; *Table 4* and online supplementary *Table S1*). Although numerically there were more adverse events in the elderly, the difference between HIC and UC arms was

Table 3 Primary and selected secondary endpoints according to age and treatment arm

Endpoint	Age ≤65 ($n = 585$)				Age >65 ($n = 493$)				*p*-value (treatment-by-age interaction)	
	HIC	UC	Unadjusted treatment effect	Adjusted treatment effect	HIC	UC	Unadjusted treatment effect	Adjusted treatment effect	Unadjusted	Adjusted
Day 90 analyses	291	294			251	242				
Day 180 analyses	278	280			228	222				
All-cause death or heart failure readmission by day 180[a]	34 (12.8%)	59 (23.1%)	0.52 (0.32, 0.82)	0.51 (0.32, 0.82)	40 (18.3%)	50 (24.0%)	0.75 (0.47, 1.19)	0.73 (0.46, 1.15)	0.26	0.30
All-cause death or heart failure readmission by day 180 (excluding COVID-19 deaths)[a]	34 (12.8%)	59 (23.1%)	0.51 (0.32, 0.82)	0.51 (0.32, 0.82)	35 (15.9%)	49 (23.4%)	0.65 (0.40, 1.06)	0.63 (0.38, 1.02)	0.50	0.56
All-cause death by day 180[b]	16 (6.2%)	23 (8.8%)	0.67 (0.33, 1.37)	0.67 (0.33, 1.36)	23 (11.4%)	25 (11.8%)	0.99 (0.53, 1.83)	0.91 (0.48, 1.69)	0.43	0.53
All-cause death by day 180 (excluding COVID-19 deaths)[b]	15 (5.8%)	23 (8.8%)	0.62 (0.30, 1.29)	0.61 (0.29, 1.27)	18 (8.8%)	24 (11.3%)	0.78 (0.40, 1.52)	0.71 (0.36, 1.41)	0.66	0.77
EQ-VAS change from baseline to visit 7[c]	13.16 (1.08)	8.04 (1.12)	5.12 (2.76, 7.48)	5.51 (3.20, 7.82)	8.13 (1.11)	6.59 (1.11)	1.54 (−1.03, 4.12)	1.77 (−0.75, 4.29)	0.045	0.032

HIC, high-intensity care; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; UC, usual care; VAS, visual analogue scale.
[a]Adjusted for baseline diastolic blood pressure, ischaemic aetiology, oedema, and baseline NT-proBNP using Cox regression.
[b]Adjusted for baseline creatinine, baseline haemoglobin, baseline urea, and baseline NT-proBNP using Cox regression.
[c]All analyses adjusted for baseline EQ-VAS, region, and LVEF group (≤40%/>40%) using ANCOVA. Additional adjustment for baseline haemoglobin, baseline creatinine, baseline cholesterol, baseline NT-proBNP, hospitalized for heart failure in prior year, oedema, and NYHA classification.

similar with age. Notably, hypotension occurred in about 5% of patients in the HIC group with no difference according to age. Acute kidney injury and hyperkalaemia were similar in both treatment arms (HIC and UC) irrespective of age. Rates of serious adverse events were similar across the groups (14% vs. 17% in younger, and 19% vs. 17% in older patients, interaction $p = 0.26$; online supplementary *Tables S2* and *S3*). Patients of the HIC group underwent additional safety visits 1 week after randomization and 1 week after the second up-titration of GDMT. Few reductions in GDMT occurred during these visits, regardless of the age group, indicating good tolerance of the administered doses.

Discussion

This analysis of STRONG-HF demonstrates that rapid and intensive optimization of beta-blockers, ACEi/ARB/ARNi and MRA, performed in the early post-discharge phase after an AHF episode and under close follow-up and monitoring, is effective and safe regardless of the patient's age. Moreover, the percentage of patients who achieved optimal GDMT doses was similar in younger and older patients, indicating that GDMT up-titration is feasible and safe in older patients with scheduled follow-up (*Graphical Abstract*). Traditionally, age is often considered an obstacle to intensifying GDMT due to the potential for higher risk of side effects, but the current analysis challenges this assertion.[5]

In the STRONG-HF study, age was related to some differences in baseline characteristics, in particular in respect to HF phenotype, underlying cause, and comorbidities. This finding is in line with previous AHF studies showing that although age was an independent predictor of outcome, it has a weak prognostic association for post-discharge outcomes, except in very old patients.[6,7] Although the primary outcome of death or HF readmission to day 180 was not different between younger and older patients, improvement in quality of life to day 90 was more pronounced in younger patients.

These data are in line with previous studies indicating that older patients have worse quality of life both in chronic and acute HF[8,9] and a lower likelihood of improvement under treatment with GDMT.[8,10] Age, baseline quality of life, duration of HF, and the burden of comorbidities, in particular obesity, chronic pulmonary disease, anxiety, and depression were related to worse quality of life and reduced recovery after AHF.[10,11]

Use of GDMT at the time of enrolment (~2 days before discharge from an AHF admission) was similarly sparse in both younger and older patients, except for beta-blockers that were more frequently used by older individuals. Although the low utilization of GDMT in the current study before enrolment was part of the inclusion criteria for the study, registry data published previously have shown that in various regions of the world, prescription of and adherence to GDMT is significantly lower in older patients with AHF.[12–17]

There is a common assumption that older age identifies a vulnerable population of patients.[18] Further, these patients may be even more susceptible in the early post-discharge phase. Taken together, older patients are commonly viewed as riskier candidates for rapid intensification of GDMT pharmacotherapy. In the

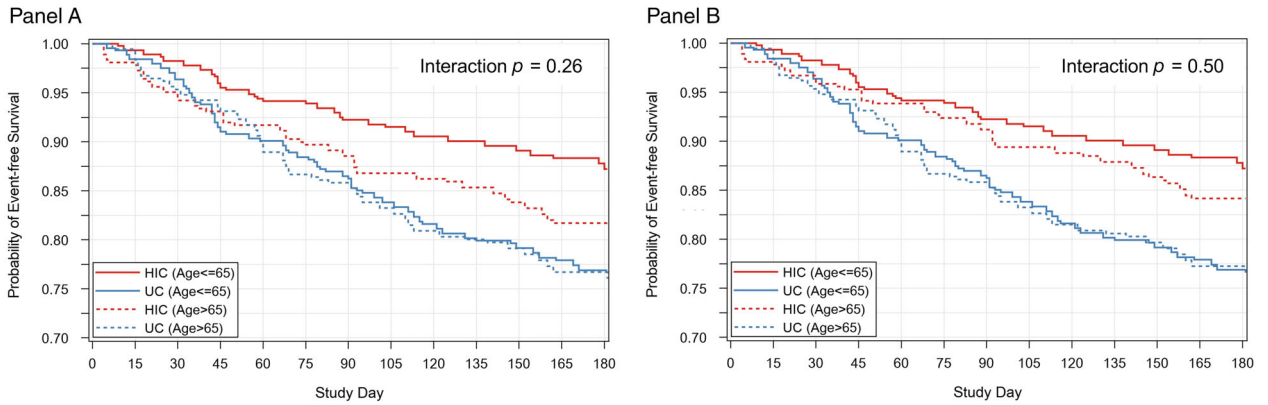


Figure 2 Unadjusted Kaplan–Meier curves for the primary endpoint (all-cause death or heart failure readmission) through day 180 by age category (≤65/>65 years) and treatment. (*A*) Results including all deaths as events. (*B*) Results after exclusion of COVID-19 deaths as events. HIC, high-intensity care; UC, usual care.

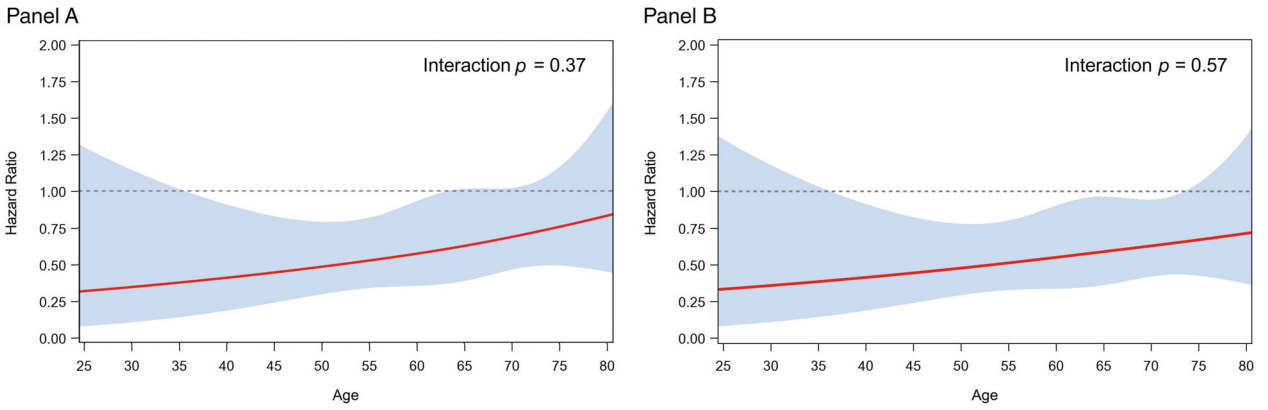


Figure 3 Treatment effect of high-intensity care versus usual care on the primary endpoint (all-cause death or heart failure readmission) through day 180 according to age. (*A*) Results including all deaths as events. (*B*) Results after exclusion of COVID-19 deaths as events. The red line indicates the hazard ratio, the blue surface the 95% confidence interval.

STRONG-HF trial, however, this assumption was disabused. Our results show that the effect of rapid intensification of GDMT is slightly more pronounced in younger patient, however the STRONG-HF study was conducted during the COVID-19 pandemic and the primary endpoint was all-cause death and HF readmissions. We have pre-specified in the analyses a first sensitivity analysis excluding COVID-19 deaths. Since most COVID-19 deaths occurred in older patients, when excluding those from the endpoint (i.e. examining only HF readmission and all-cause death excluding COVID-19 related deaths) the difference in the efficacy between older and younger patients become very small (interaction $p = 0.57$). There may be several reasons for the difference between the common assumption that older patients would respond less well to rapid up-titration of GDMT and the findings of STRONG-HF.

First, patients in the HIC arm were not only rapidly up-titrated, but also closely monitored during the early phase, mitigating safety concerns. Second, the mean age of the older group was 74 ± 5 years and the percentage of patients older than 75 years old was smaller than in registries, which urges caution in data extrapolation to octogenarians and older individuals.[7] Third, the sub-group analyses of other recently published trials that tested the initiation of HF therapies during or just after the AHF episodes (such as AFFIRM-AHF, EMPULSE, SOLOIST-WHF, VICTORIA, and PIONEER-HF), also did not show significant interaction with age, which further confirms the safety of such interventions.[19–23] These data are in line with the analyses from the large trials performed in chronic HF showing consistent beneficial effects of ACEi,[24] ARB,[25] ARNi,[26] beta-blockers,[27] MRA,[28] and sodium–glucose cotransporter 2 inhibitors[29,30] in elderly patients, which support current recommendations for GDMT irrespectively of age. It should be highlighted that in the STRONG-HF trial the adverse events were more often observed in the HIC arm when compared to UC, but there was no difference in the rate of those events between older

Table 4 Selected treatment-emergent adverse events by age group and treatment arm

	Age ≤65		Age >65		Treatment-by-age interaction *p*-value
	HIC (*n* = 291)	UC (*n* = 294)	HIC (*n* = 251)	UC (*n* = 242)	
Cardiac disorders	52 (17.9)	53 (18.0)	47 (18.7)	43 (17.8)	0.81
Bradycardia	1 (0.3)	0	3 (1.2)	2 (0.8)	0.66
Metabolism and nutrition disorders	12 (4.1)	1 (0.3)	13 (5.2)	2 (0.8)	0.61
Hyperkalaemia	9 (3.1)	0	9 (3.6)	0	0.98
Renal and urinary disorders	11 (3.8)	2 (0.7)	9 (3.6)	0	0.39
Acute kidney injury	1 (0.3)	0	2 (0.8)	0	0.84
Renal impairment	10 (3.4)	1 (0.3)	4 (1.6)	0	0.91
Vascular disorders	15 (5.2)	6 (2.0)	20 (8.0)	3 (1.2)	0.22
Hypotension	13 (4.5)	2 (0.7)	14 (5.6)	0	0.30
Orthostatic hypotension	2 (0.7)	0	1 (0.4)	0	0.80

Values are given as *n* (%).
HIC, high-intensity care; UC, usual care.

and younger patients. Importantly, serious adverse events were not more common in patients who were up-titrated quickly to maximally tolerated GDMT doses in the HIC arm.

Finally, our analysis showed consistency regarding efficacy of the HIC strategy across the age spectrum, at least in the explored range. There was a numerically smaller benefit with HIC as compared to UC in older patients; however, this difference was small and did not reach statistical significance. Similarly, when age was considered as a continuous variable, treatment effect of HIC did not differ significantly across ages. Our results are consistent with previous observational studies showing the beneficial effects on outcomes of pre-discharge prescription of GDMT across different ages. The propensity score-matched analysis from the global GREAT Network showed consistently reduced 90-day mortality in AHF patients discharged on beta-blockers, ACEi/ARB or a combination thereof, across the whole age spectrum.[31] Similar data were shown from Australian and Korean registries of elderly AHF patients showing better outcomes in patients discharged on GDMT.[16,32,33] Of note, results were consistent even beyond 80 years of age.

Limitations

This analysis has several limitations. The numbers of patients in the subgroups are small and therefore some observed numerical differences might be non-significant due to insufficient statistical power. Second, the study population was younger than other contemporary AHF studies because of the international design of STRONG-HF with AHF patients from three continents.[34–36] Hence, less than 20% of patients were older than 75 years and patients with age >85 years were not included in the trial, which impairs the ability to draw conclusions for very old patients. In very old patients, the impact of frailty and the burden of non-cardiovascular comorbidities might substantially determine the clinical course after AHF hospitalization, reducing the proportion of HF-related compared to non-HF-related hospitalizations and scaling down the benefits of GDMT.[37,38]

Conclusion

Rapid up-titration of GDMT and close follow-up after an AHF admission was both safe and effective, reducing all-cause death or HF readmission at 180 days across the included age spectrum. However, rapid up-titration of GDMT after an AHF admission was associated with a smaller improvement of quality of life in older patients.

Supplementary Information

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

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