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ORIGINAL ARTICLE

Socio-economic status and the effect of guideline-directed medical therapy in the STRONG-HF study

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Abstract

Aims Acute heart failure (AHF) impacts millions globally, with outcomes varying based on socio-economic status (SES).

Methods SES measured by annual household income, years of education and medical insurance coverage. Each patient's income and education level relative to the median or mean, respectively, in the country was calculated, and categorized into tertiles (0, 1 or 2 from lowest to highest). SES scores (0–5) were computed as the sum of these levels plus insurance coverage (0 = *no* or 1 = *yes*). Patients' baseline characteristics, outcomes (HF readmission, death and their composite) and the effect of high-intensity care (HIC) vs. usual care (UC) were examined by SES scores 0–2, 3 and 4–5.

Results Lower SES patients, who were younger, predominantly female, Black and non-European, had fewer comorbidities such as atrial fibrillation, diabetes and ischaemic heart disease and exhibited milder HF, indicated by a lower NYHA class, lower creatinine and higher cholesterol before discharge. Despite having milder HF and less comorbidities, after adjusting for baseline characteristics, patients with higher SES had numerically better outcomes, though differences were not statistically significant. 180-day hazard ratios (HRs) for HF readmission or death were 0.75 (95% CI 0.48–1.16) for SES scores of 3 and 0.85 (95% CI 0.58–1.23) for scores of 4–5, compared to 0–2. Higher SES patients had numerically better treatment effect from HIC, with HRs of 0.69 for SES 0–2, 0.72 for SES 3 and 0.50 for SES 4–5.

Conclusions In this post hoc analysis of the STRONG-HF study, lower SES was associated with milder acute HF but similar 180-day outcomes. Higher SES patients benefitted more from HIC.

Keywords Socio-economic status; Acute heart failure; Guideline-directed medical therapy

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Introduction

The incidence of heart failure (HF) is higher in patients with indicators of lower socio-economic status (SES).[1–3] In those who develop HF, the incidence of adverse outcomes such as death and hospital admission are also higher in patients with low SES across the globe.[4–6] This was also shown in patients admitted with acute heart failure (AHF) although the associations were not consistent showing more impact of low SES on longer-term than on shorter-term outcomes,[7,8] while some found the association limited to race and marital status.[9] The reasons for this association are not universally agreed upon. While some showed less HF care in patients with lower SES,[3,10] this was not confirmed by others.[7,11] In a recent analysis, Spanish investigators have found that lower SES was associated with long-term adverse outcomes after an AHF admission,[11] but the positive impact of an integrated care intervention was independent of SES score. In the current post hoc analysis, we have investigated the impact of SES variables on the outcomes and treatment effect of rapid up-titration of guideline-directed medical therapy (GDMT) in the STRONG-HF study.

Methods

Study design

The STRONG-HF trial was a multinational, multicentre, open-label, randomized, parallel-group study that between May 2018 and September 2022 enrolled 1078 patients hospitalized for AHF. Patients were randomized within 2 days prior to anticipated discharge in a 1:1 ratio to either high-intensity care (HIC) or usual care (UC). Patients in both groups had a follow-up visit 90 days after randomization and a follow-up phone contact at 180 days. HIC comprised early and rapid up-titration of neurohormonal blockade (beta-blockers [BB]; renin angiotensin system inhibitors [RASi]; and mineralocorticoid receptor antagonists [MRA]) under strict safety supervision through additional post-discharge ambulatory follow-up visits 1, 2, 3 and 6 weeks after discharge. UC followed local practice. The study design and main results have been previously published,[12–14] showing that HIC was safe and effective in reducing 180-day HF readmission or death compared with UC.

The study recruited patients aged 18–85 years old admitted to the hospital due to a clinical diagnosis of AHF, who had high natriuretic peptides at admission that had decreased but were still elevated prior to discharge and who were not previously treated by ideal GDMT therapy. These patients were screened for the study within 72 h of admission and randomized shortly before discharge to HIC vs. UC.

Study procedures

Patients allocated to the HIC arm were titrated to half of the optimal doses of GDMT at randomization and to full optimal doses at Week 2. Patients who were assigned to the UC group were monitored and managed based on the standard procedures followed in their local healthcare practices. Patients in both groups were seen by the study team on Day 90 and were contacted by telephone at 180 days. Patients completed the EQ-5D-5L, a quality-of-life questionnaire,[15] at randomization and Day 90. In addition to rating their health on five dimensions, patients reported their overall health on a visual analogue scale (VAS) from 0 = *the worst health you can imagine* to 100 = *the best health you can imagine*.

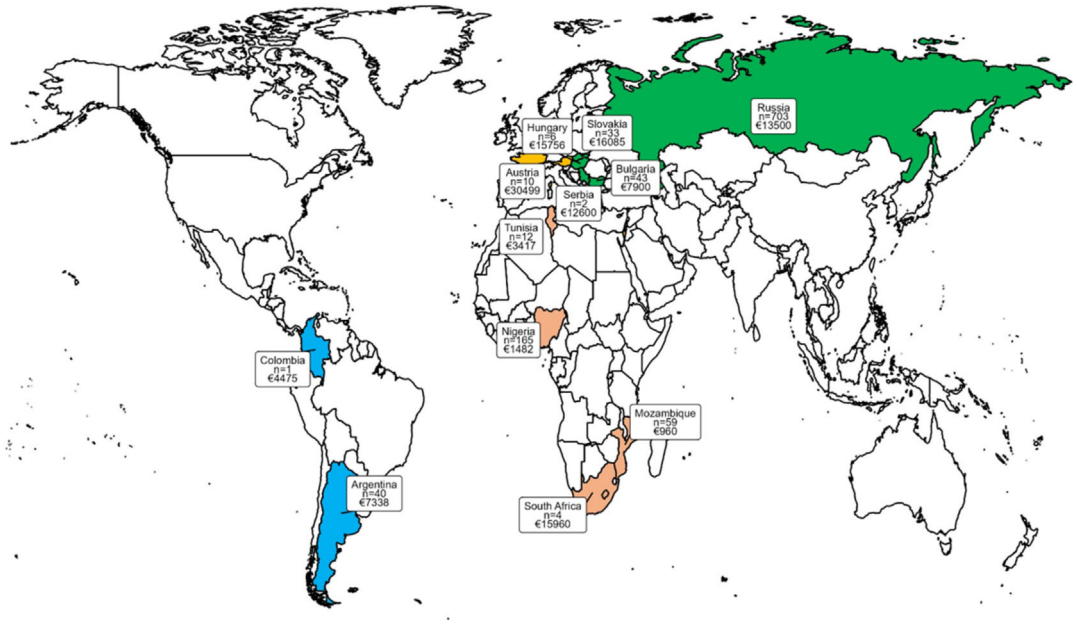
At screening, patients' SES was assessed by collecting three variables: annual household income, years of education (0, 1–4, 5–8, 9–12, 13–16 or >16 years) and medical insurance coverage (either private or national). Household income reported in local currency was converted to euros based on the conversion rate at the time of database lock (24 October 2022).[16] Each patient's income and education level relative to the median[17] or mean,[18] respectively, in 2021 in the country was calculated and categorized into tertiles (0, 1 or 2 from lowest to highest). Since the median income per country was reported in international dollars, the purchasing power parity (PPP) conversion factor was used to convert back to the local currency of the country. That median income in the local currency was then converted to euros based on the market exchange rate at the time of database lock. That value was then used in the denominator of the derivation. Participating countries, along with the median income and number of patients enrolled in each, are shown in *Figure 1*. A SES score, with possible range of 0–5, was computed as the sum of the income and education levels plus insurance coverage (0 = *no* or 1 = *yes*). Patients' baseline characteristics, outcomes (HF readmission, death and their composite) and the effect of HIC vs. UC were examined by SES scores 0–2, 3 and 4–5.

The study's primary outcome was a combined endpoint of 180-day first HF readmission or all-cause death. Other outcomes examined include 180-day all-cause death, 180-day death excluding deaths due to COVID-19 and change in EQ-VAS from randomization to day 90.

Statistical methods

We present continuous variables as either the mean (SD) or the geometric mean (95% confidence interval [CI]) for skewed variables and present absolute and relative frequencies for categorical variables. To account for missing values or non-response to any of the three components of the SES score, multiple imputation was used. Ten imputation datasets were created using Markov chain Monte Carlo procedures, which assume multivariate normal distribution, to impute the missing responses for the components of the

Figure 1 Map showing the number of patients enrolled in each of the countries that participated in the STRONG-HF trial and these countries' median incomes in 2021.



SES score by considering available baseline characteristics and medical history. The average value across the 10 datasets for a missing component was then used, which allowed an SES score to be calculated for all 1078 patients in the full analysis set.

The SES score was compared between treatment groups using a Kruskal–Wallis test. Baseline characteristics were compared across ordinal groups, including groups defined by tertiles and by grouped SES score (0/1/2, 3, and 4/5), using trend tests. The Cochran–Armitage trend test was used for binary variables, Jonckheere's trend test for continuous variables, Cochran–Mantel–Haenszel test of general association for nominal categorical variables and the Cochran–Mantel–Haenszel correlation statistic for testing whether there was a linear association between ordinal categorical variables.

Clinical outcomes through 180 days were restricted to patients enrolled at sites where a protocol amendment was approved, which allowed the collection of follow-up data to day 180. Results for patients enrolled prior to amendment of the primary endpoint from 90- to 180-day HF readmission or death were down-weighted for these analyses. Subjects from Mozambique were excluded from analyses of the EQ-VAS due to the unavailability of a linguistically validated EQ-5D translation. Cox proportional hazards models were used to examine effects for the primary endpoint and the secondary endpoint 180-day all-cause death between SES score groups. The number of events, Kaplan–Meier estimates, hazard ratios with associated 95% CI (with those in the lower SES score grouping as the reference) and Wald chi-square *P*-value are presented. A sensitivity analysis of the 180-day mortality endpoint, in which patients who died due to COVID-19 were censored at the time of death, was additionally examined. The change in EQ-VAS from baseline to Visit 7 (Day 90) by SES groups was examined using an ANCOVA model adjusted for baseline EQ-VAS, region and baseline LVEF ($\leq$40%/$>$40%). Results are presented as the least square (LS) mean change (SE) for each SES score group, the LS-mean difference and associated 95% CI (compared to those in the lower SES score grouping) and associated *P*-value for the test of whether the effect differed for any of the SES score groups. These analyses were further conducted adjusting for variables found to be prognostic of outcome. Treatment effects for these endpoints were explored to test whether the effect varied between SES score group by additionally including treatment and the treatment-by-SES score group interaction in the models both unadjusted and adjusted. Kaplan–Meier plots by treatment and SES score group are included for the primary endpoint.

We examined the administration of GDMT for patients randomized to the HIC group by SES score group. The average percentage of the optimal dose, which took the average of the percentage optimal dose of RASi, beta-blockers and MRAs was analysed, as well as the percentage of optimal dose for each of the three medication categories separately. Plots showing the mean (SE) by visit with lines for SES score grouping are presented.

All analyses were further conducted by the individual components of the SES score. Annual household income was examined by tertiles of the absolute value and, in order

to standardize values between countries, by the ratio of the patient's income relative to the individual country's median income. Education level was examined by the groups 0–8, 9–12 and >12 years as well as by tertiles of the ratio of the number of years relative to the country's mean. Since years of education was collected in ranges, the midpoint within the category was assigned for each patient with a value of 18.5 years used for those who reported >16 years.

Two-sided *P*-values of less than 0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics according to SES

The distribution of the patients according to the SES score is presented in *Table 1* and did not differ by assigned treatment strategy. The patients' characteristics according to SES score are presented in *Table 2*. Patients' characteristics according to insurance status, income level and education both raw and as compared to the country median or mean are presented in *Table S1*. In short, patients with lower SES were younger and more often women, Black and non-European. Only 5% of patients with a SES score of 4/5 were Black compared with more than 90% of Caucasian patients ($P < 0.0001$). Patients with lower SES had less frequent co-morbidities—less atrial fibrillation, diabetes and ischaemic heart disease—and less severe HF according to lower NYHA class prior to admission and lower creatinine and higher cholesterol before discharge. Patients with lower SES score had been admitted less frequently for HF in the year before the study-qualifying admission. Ejection fraction (EF) was lower in patients with lower SES score. Blood pressure and pulse just prior to discharge were higher in patients with lower SES and fewer patients with lower SES were treated with RASi but more with BB.

180-day death or heart failure readmission

The patients' clinical outcomes including 180-day death or HF readmission, all-cause death, all-cause death excluding COVID-19 deaths and 90-day changes in quality of life (QoL) by EQ-VAS according to SES score are presented in *Table 3*. These outcomes are presented according to insurance status, income level and education both raw and as compared to the country median or mean in *Table S2*. In short, no statistically significant differences in outcomes were detected although some trends were observed towards better outcomes in patients with higher SES score.

Medication up-titration in the high-intensity care group

The up-titration of GDMT therapy in patients assigned to the HIC group for all medications combined (RASi, BB and MRA) and then separately according to SES score are presented in *Figure 2*.The GDMT up-titration according to insurance sta-

Table 1 Components of the socio-economic status score by treatment

Socio-economic status indicator	Statistic	High-intensity care (*N* = 542)	Usual care (*N* = 536)	*P*	Overall (*N* = 1078)
Socio-economic status score					
0	*n* (%)	50 (9.2)	47 (8.8)	0.3298	97 (9.0)
1	*n* (%)	56 (10.3)	56 (10.4)		112 (10.4)
2	*n* (%)	102 (18.8)	114 (21.3)		216 (20.0)
3	*n* (%)	138 (25.5)	128 (23.9)		266 (24.7)
4	*n* (%)	116 (21.4)	133 (24.8)		249 (23.1)
5	*n* (%)	80 (14.8)	58 (10.8)		138 (12.8)
Annual household income, euros	Mean (SD)	12 958.2 (18 762.29)	12 161.8 (12 400.52)	0.4117	12 562.2 (15 917.73)
	Median (min, max)	12 494.6 (0, 328 600)	12 225.9 (1, 213 590)		12 375.7 (0, 328 600)
Annual household income relative to country median	Mean (SD)	1.53 (2.987)	1.39 (2.394)	0.3886	1.46 (2.708)
	Median (min, max)	1.00 (0.0, 33.4)	0.98 (0.0, 21.8)		0.99 (0.0, 33.4)
Highest education level completed					
0 years	*n* (%)	50 (9.2%)	49 (9.1%)	0.6944	99 (9.2%)
1–4 years	*n* (%)	30 (5.5%)	31 (5.8%)		61 (5.7%)
5–8 years	*n* (%)	64 (11.8%)	56 (10.4%)		120 (11.1%)
9–12 years	*n* (%)	149 (27.5%)	171 (31.9%)		320 (29.7%)
13–16 years	*n* (%)	210 (38.7%)	190 (35.4%)		400 (37.1%)
>16 years	*n* (%)	39 (7.2%)	39 (7.3%)		78 (7.2%)
Highest education level relative to country median	Mean (SD)	0.95 (0.494)	0.95 (0.489)	0.8207	0.95 (0.492)
	Median (min, max)	1.12 (0.0, 4.5)	0.92 (0.0, 3.3)		0.94 (0.0, 4.5)

Socio-economic status score is derived as the sum of the following three components: (i) covered by health insurance: No = 0, Yes = 1; (ii) tertile of income relative to country median: Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2; and (iii) tertile of years of education relative to country mean: Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2.

Table 2 Baseline characteristics by grouped socio-economic status (SES) score

Parameter	Statistic	SES score (0/1/2) (*N* = 425)	SES score (3) (*N* = 266)	SES score (4/5) (*N* = 387)	*P* Trend
Age, years	Mean (SD)	59.6 (15.15)	65.1 (12.77)	65.1 (11.44)	<0.0001
Sex					
Female	*n* (%)	192 (45.2%)	99 (37.2%)	125 (32.3%)	0.0002
Male	*n* (%)	233 (54.8%)	167 (62.8%)	262 (67.7%)	
Self-reported race					
Black	*n* (%)	183 (43.1%)	27 (10.2%)	20 (5.2%)	<0.0001
Caucasian/White	*n* (%)	238 (56.0%)	233 (87.9%)	361 (93.5%)	
Native American	*n* (%)	1 (0.2%)	0	0	
Other	*n* (%)	2 (0.5%)	5 (1.9%)	5 (1.3%)	
Pacific Islander	*n* (%)	1 (0.2%)	0	0	
Geographical region					
Europe	*n* (%)	222 (52.2%)	226 (85.0%)	349 (90.2%)	<0.0001
Non-Europe	*n* (%)	203 (47.8%)	40 (15.0%)	38 (9.8%)	
NT-proBNP at screening, ng/L	Geom. mean (95% CI)	5894.0 (5574.3, 6232.0)	6181.8 (5783.0, 6608.1)	6037.4 (5701.4, 6393.3)	0.8072
History of atrial fibrillation or atrial flutter or present at screening	*n* (%)	145 (34.1%)	126 (47.4%)	212 (54.8%)	<0.0001
Medical history					
Stroke or transient ischaemic attack	*n* (%)	29 (6.8%)	28 (10.5%)	42 (10.9%)	0.0435
Severe liver disease	*n* (%)	3 (0.8%)	0	3 (1.1%)	0.8183
Psychiatric or neurological disorder	*n* (%)	6 (1.4%)	7 (2.6%)	7 (1.8%)	0.6565
Malignancies	*n* (%)	7 (1.7%)	8 (3.0%)	14 (3.6%)	0.0803
Diabetes	*n* (%)	90 (21.2%)	83 (31.2%)	140 (36.5%)	<0.0001
Diabetes control method					
Insulin	*n* (%)	24 (5.7%)	25 (9.4%)	33 (8.6%)	0.1100
Diet only	*n* (%)	59 (13.9%)	50 (18.8%)	93 (24.2%)	0.0002
Oral antidiabetic agents	*n* (%)	64 (15.1%)	64 (24.1%)	106 (27.6%)	<0.0001
Pulmonary embolism	*n* (%)	7 (1.6%)	2 (0.8%)	10 (2.6%)	0.3541
Acute coronary syndrome	*n* (%)	75 (17.6%)	81 (30.5%)	155 (40.2%)	<0.0001
Coronary artery bypass surgery	*n* (%)	21 (4.9%)	18 (6.8%)	20 (5.2%)	0.8605
Percutaneous transluminal coronary intervention	*n* (%)	37 (8.7%)	45 (16.9%)	70 (18.1%)	0.0001
Angina Canadian Cardiovascular Society class 2 or higher	*n* (%)	54 (12.7%)	43 (16.2%)	28 (7.3%)	0.0179
Moderate or severe chronic obstructive pulmonary disease or asthma	*n* (%)	11 (2.6%)	4 (1.5%)	12 (3.1%)	0.7374
Cardiac resynchronisation therapy	*n* (%)	2 (0.5%)	1 (0.4%)	3 (0.8%)	0.6471
Automatic internal cardiac defibrillator	*n* (%)	2 (0.5%)	3 (1.1%)	4 (1.0%)	0.4469
Anaemia	*n* (%)	123 (28.9%)	75 (28.2%)	95 (24.6%)	0.1696
Heart failure history					
History of heart failure	*n* (%)	360 (84.7%)	228 (85.7%)	328 (85.0%)	0.9082
NYHA class 1-month before hospital admission					
1	*n* (%)	30 (7.6%)	20 (8.2%)	13 (3.6%)	<0.0001
2	*n* (%)	173 (43.8%)	74 (30.2%)	60 (16.7%)	
3	*n* (%)	172 (43.5%)	120 (49.0%)	123 (34.2%)	
4	*n* (%)	20 (5.1%)	31 (12.7%)	164 (45.6%)	
Ischaemic aetiology	*n* (%)	147 (34.6%)	146 (55.1%)	221 (57.4%)	<0.0001
Left ventricular ejection fraction, %	Mean (SD)	35.1 (12.44)	36.9 (11.73)	37.1 (13.06)	0.0153
Left ventricular ejection fraction category					
LVEF <=40%	*n* (%)	321 (75.5%)	168 (63.2%)	242 (62.5%)	<0.0001
LVEF >40%	*n* (%)	104 (24.5%)	98 (36.8%)	145 (37.5%)	
Hospitalized for heart failure in the past year?	*n* (%)	88 (20.7%)	52 (19.5%)	133 (34.5%)	<0.0001

(*Continues*)

Table 2 (continued)

Parameter	Statistic	SES score (0/1/2) (*N* = 425)	SES score (3) (*N* = 266)	SES score (4/5) (*N* = 387)	*P* Trend
Number of heart failure hospitalisations in the past year	Mean (SD)	0.3 (1.58)	0.3 (0.66)	0.4 (0.64)	<0.0001
History of atrial fibrillation or atrial flutter	*n* (%)	149 (35.1%)	128 (48.1%)	219 (56.7%)	<0.0001
Type of atrial fibrillation or atrial flutter					
Paroxysmal	*n* (%)	26 (17.4%)	27 (21.4%)	64 (29.8%)	0.0244
Permanent	*n* (%)	95 (63.8%)	84 (66.7%)	114 (53.0%)	
Persistent	*n* (%)	28 (18.8%)	15 (11.9%)	37 (17.2%)	
Baseline vital signs					
Systolic blood pressure at baseline, mmHg	Mean (SD)	124.6 (14.48)	121.9 (12.97)	121.6 (10.77)	0.0245
Pulse, beats/min	Mean (SD)	82.2 (11.72)	77.1 (11.37)	75.8 (11.15)	<0.0001
Respiratory rate, breaths/min	Mean (SD)	18.3 (4.32)	17.7 (2.39)	18.4 (5.98)	0.2662
Local laboratory					
Haemoglobin, g/L	Mean (SD)	135.0 (19.42)	135.6 (19.28)	138.7 (20.91)	0.0007
Lymphocytes, %	Mean (SD)	28.5 (10.61)	25.5 (9.32)	27.0 (8.97)	0.0437
White blood cells, 10^9/L	Mean (SD)	6.8 (1.99)	7.1 (1.95)	7.1 (2.09)	0.0377
Glucose, mmol/L	Mean (SD)	5.9 (1.83)	6.4 (2.91)	6.5 (2.30)	<0.0001
Creatinine, umol/L	Mean (SD)	102.6 (28.45)	108.1 (32.41)	108.9 (26.34)	<0.0001
Potassium, mmol/L	Mean (SD)	4.2 (0.45)	4.3 (0.41)	4.3 (0.46)	<0.0001
Sodium, mmol/L	Mean (SD)	139.9 (4.06)	140.4 (4.66)	140.4 (3.91)	0.0047
Urea, mmol/L	Mean (SD)	7.5 (3.39)	8.4 (3.59)	8.3 (3.48)	<0.0001
ALT, U/L	Mean (SD)	27.7 (30.37)	30.0 (48.10)	32.1 (52.19)	0.0270
Total bilirubin, umol/L	Mean (SD)	16.4 (10.48)	17.6 (11.76)	18.1 (11.85)	0.0308
Total cholesterol, mmol/L	Mean (SD)	4.4 (1.11)	4.2 (1.07)	4.1 (1.08)	<0.0001
NT-proBNP, ng/L	Geom. mean (95% CI)	3002.9 (2832.5, 3183.5)	3518.1 (3246.1, 3812.9)	3239.7 (3043.5, 3448.4)	0.0608
Oral heart failure medications taken at Visit 2: Pre-randomization					
ACE inhibitors/ARBs/ARN inhibitors	*n* (%)	265 (62.4%)	137 (51.7%)	287 (74.7%)	0.0004
Beta-blockers	*n* (%)	164 (38.6%)	125 (47.2%)	94 (24.5%)	<0.0001
Mineralocorticoid receptor antagonists	*n* (%)	407 (95.8%)	248 (93.6%)	363 (94.5%)	0.4160
Loop diuretic	*n* (%)	411 (96.7%)	254 (95.8%)	364 (94.8%)	0.1752

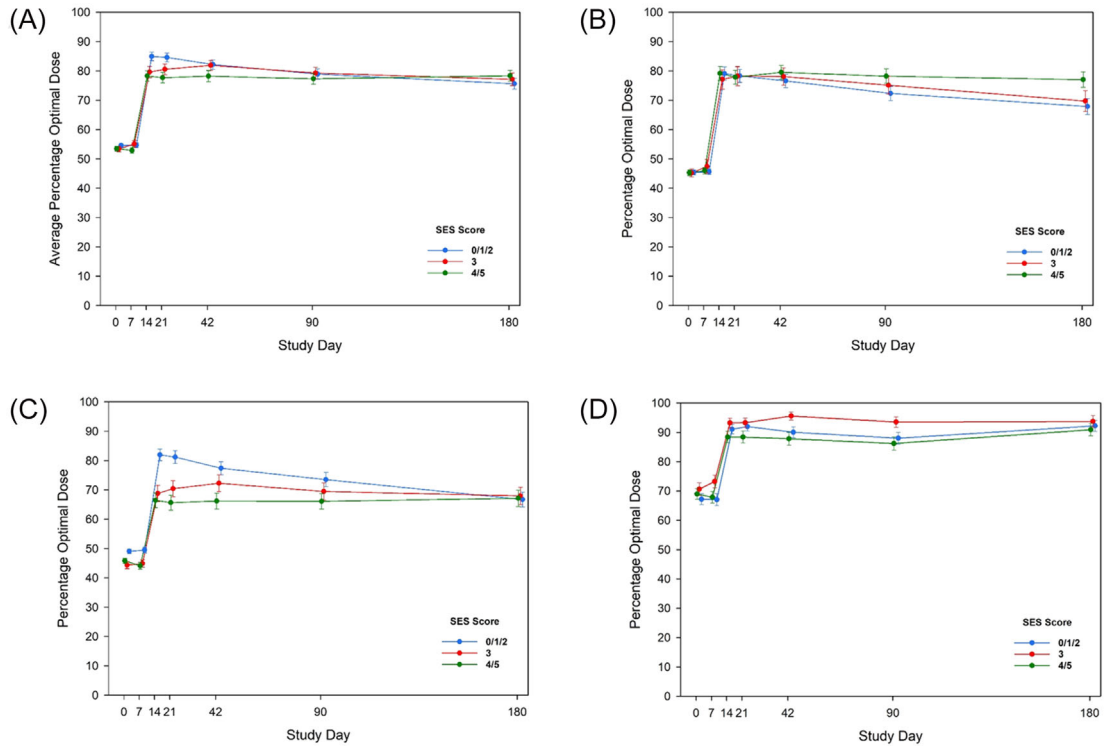
Table 3 Clinical outcomes by grouped socio-economic status (SES) score

Endpoint	*n/N* (KM%)	Unadjusted HR (95% CI)	Unadjusted *P*	Adjusted HR (95% CI)	Adjusted *P*
All-cause death or heart failure readmission by Day 180[a]			0.5519		0.4067
SES = 0/1/2	70/387 (19.7%)	[Ref]		[ref]	
SES = 3	42/252 (16.5%)	0.85 (0.55, 1.30)		0.75 (0.48, 1.16)	
SES = 4/5	71/369 (21.0%)	1.07 (0.74, 1.54)		0.85 (0.58, 1.23)	
All-cause death by Day 180[b]			0.6253		0.6184
SES = 0/1/2	36/387 (10.0%)	[Ref]		[Ref]	
SES = 3	25/252 (10.3%)	1.06 (0.60, 1.87)		0.87 (0.49, 1.54)	
SES = 4/5	26/369 (8.0%)	0.81 (0.47, 1.40)		0.76 (0.43, 1.32)	
All-cause death (excluding COVID deaths) by Day 180[b]			0.5352		0.4451
SES = 0/1/2	35/287 (9.7%)	[Ref]		[Ref]	
SES = 3	22/252 (8.9%)	0.94 (0.52, 1.71)		0.77 (0.42, 1.41)	
SES = 4/5	23/369 (7.0%)	0.73 (0.41, 1.29)		0.70 (0.39, 1.25)	

	LS-mean (SE)	LS-mean difference (95% CI)	*P*	LS-mean difference (95% CI)	*P*
EQ-VAS change from baseline to Visit 7[c]			0.0938		0.1190
SES = 0/1/2	8.56 (0.93)	[Ref]		[Ref]	
SES = 3	10.57 (1.08)	2.01 (−0.31, 4.32)		2.33 (−0.06, 4.72)	
SES = 4/5	8.19 (1.02)	−0.37 (−2.52, 1.78)		0.35 (−1.86, 2.55)	

Results restricted to subjects at sites where patients were followed to 180 days for day 180 analyses. Results for patients in Cohort 1 are down-weighted proportional to half its sample size. Data presented as *n/N* (Kaplan–Meier %) or LS-mean (standard error). Hazard ratios from Cox proportional hazards model. Subjects from Mozambique excluded from EQ-VAS analyses.
[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 and baseline LVEF (≤40/>40%). Additional adjustment for age, haemoglobin, creatinine, cholesterol, NT-proBNP, hospitalization for heart failure in the previous year, oedema severity and NYHA class.

Figure 2 Percentage of optimal doses of oral HF medications by SES score over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers and (D) percentage optimal dose of MRAs.



tus, income level and education both raw and as compared to the country median or mean are shown in *Figure S1*. In general, GDMT therapy was up-titrated in HIC regardless of SES although in patients with lower SES some quicker up-titration was observed in the first weeks after discharge, especially with respect to BB.

Treatment effect of high-intensity care vs. usual care by SES

The effect of HIC compared to UC on clinical outcomes according to SES score are presented in *Table 4* and *Figure 3*, and according to insurance status, income level and education both raw and as compared to the country median or mean are presented in *Figure S2*. No statistically significant differences in outcomes were detected although some trends were observed towards a greater treatment effect in patients with higher SES score.

Safety of high-intensity care vs. usual care by SES

Treatment emergent adverse events are described in *Table S3*. No significant differences were observed in adverse events according to treatment by SES group, although a trend towards more frequent adverse events was observed in patients with higher SES: 144 (33.9%), 82 (30.8%) and 155 (40.1%) of patients with SES score 0/1/2, 3 and 4/5, respectively, experienced an adverse event ($P = 0.073$).

Discussion

Patients enrolled in the STRONG-HF study varied substantially in region, income and education, in contrast to many previous studies that were more homogenous recruiting patients from one country or region.[5,7,8,10] Hence, there is substantial variability between patients as reflected in the baseline characteristics. In the STRONG-HF study, patients with lower SES were more likely to be women, Black and of non-European origin. Patients with lower SES had signs of less advanced disease. Despite this milder clinical presentation, patients with lower SES had numerically higher rates of death or HF readmission at 180 days and a numerically lower effect of more rapid GDMT up-titration in the HIC group, although these differences did not reach statistical significance.

Patients with AHF and lower SES were found to be more women and Black also in the ARIC registry[8] and Medicare analysis[7] recruiting exclusively in the United States, but not in the ASIAN-HF registry[5] with respect to gender as Black race

Table 4 Clinical outcomes by socio-economic status (SES) score and treatment

			Unadjusted		Adjusted	
Outcome	High-intensity care	Usual care	Treatment effect (95% CI)	Treatment-by-SES score interaction *P*	Treatment effect (95% CI)	Treatment-by-SES score interaction *P*
Primary endpoint						
All-cause death or heart failure readmission by Day 180[a]						
SES = 0/1/2	29/189 (16.6)	41/198 (22.6)	0.71 (0.42, 1.21)	0.5897	0.69 (0.40, 1.17)	0.6044
SES = 3	20/131 (14.3)	22/121 (19.0)	0.72 (0.36, 1.44)		0.72 (0.36, 1.44)	
SES = 4/5	25/286 (14.6)	46/183 (27.4)	0.50 (0.30, 0.85)		0.50 (0.29, 0.85)	
Secondary endpoints						
All-cause death by Day 180[b]						
SES = 0/1/2	17/189 (10.1)	19/198 (9.9)	1.03 (0.49, 2.14)	0.7555	0.99 (0.47, 2.08)	0.7316
SES = 3	11/131 (8.6)	14/121 (12.2)	0.68 (0.29, 1.64)		0.70 (0.29, 1.67)	
SES = 4/5	11/186 (7.0)	15/183 (9.1)	0.75 (0.33, 1.72)		0.66 (0.29, 1.52)	
EQ-VAS Change from baseline to Visit 7[c]						
SES = 0/1/2	10.33 (1.15)	6.78 (1.15)	3.55 (0.85, 6.25)	0.1216	4.01 (1.28, 6.75)	0.2955
SES = 3	10.73 (1.36)	10.24 (1.41)	0.49 (−2.95, 3.93)		1.42 (−2.03, 4.87)	
SES = 4/5	10.59 (1.22)	5.48 (1.25)	5.11 (2.33, 7.90)		4.87 (2.14, 7.61)	
Sensitivity analyses						
All-cause death (excluding COVID deaths) by Day 180[b]						
SES = 0/1/2	16/189 (9.5)	19/198 (9.9)	0.95 (0.45, 2.02)	0.5599	0.92 (0.43, 1.96)	0.4939
SES = 3	9/131 (6.9)	13/121 (11.2)	0.58 (0.22, 1.52)		0.59 (0.23, 1.54)	
SES = 4/5	8/186 (5.0)	15/183 (9.1)	0.53 (0.21, 1.32)		0.46 (0.18, 1.16)	

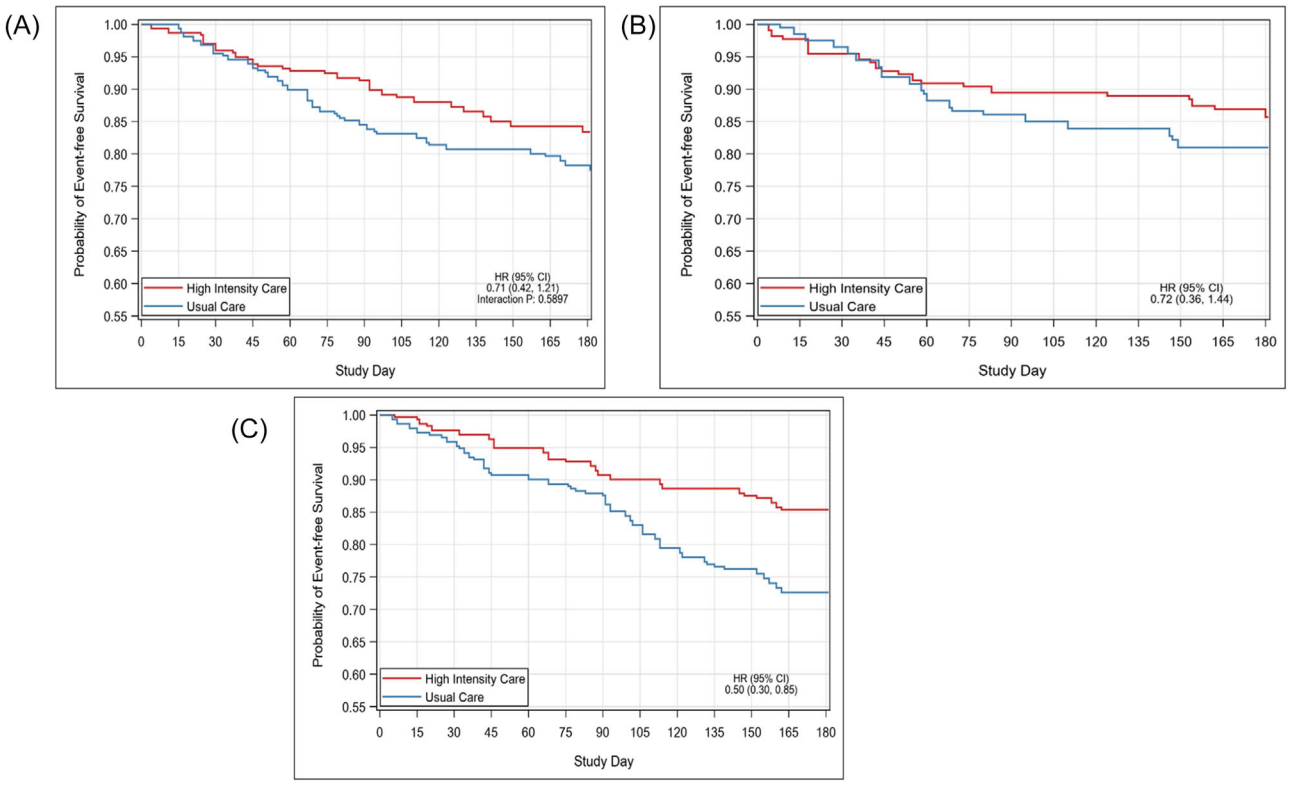
Results restricted to subjects at sites where patients were followed to 180 days for day 180 analyses. Results for patients in cohort 1 are down-weighted proportional to half its sample size. Data presented as *n*/*N* (Kaplan–Meier %) or LS-mean (standard error). Hazard ratios from Cox proportional hazards model. Subjects from Mozambique excluded from EQ-VAS analyses.

[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, and baseline LVEF (≤40/>40%). Additional adjustment for age, haemoglobin, creatinine, cholesterol, NT-proBNP, hospitalization for heart failure in the previous year, oedema severity and NYHA class.

Figure 3 Kaplan–Meier plot of primary endpoint (first heart failure readmission or death) through 180 days by treatment and SES score: (A) SES score 0/1/2, (B) SES score 3 and (C) SES score 4/5.



was not reported. To the best of our knowledge, this is the first study to show that patients with lower SES are admitted with milder AHF and less comorbidities corresponding to younger age and less advanced stage of the disease. In the ARIC study,[8] impaired renal function and rate of diabetes were more prevalent in patients with lower SES. In the ASIAN-HF registry, patients with lower SES had higher NYHA class but also higher eGFR, implying better kidney function.[5] A Danish registry found little difference in clinical characteristics according to SES.[10] It is possible that patients with lower SES may have a different 'cultural perception of severity' as compared to patients from higher SES stratum, and they may perceive differently acuity of the disease. This fact may be amplified in regions with poor access to ambulatory care, where hospitalization remains probably the unique option for diagnosis and treatment even for patients with milder signs and symptoms otherwise amenable in ambulatory care. Another reason for the less severe HF pattern at baseline in patients with lower SES in the STRONG-HF study may be a general delay in seeking care, in both the ambulatory setting[19] and in emergency facilities, leading to earlier decompensation. It is also possible that for patients of lower SES admitted with AHF, the hospital is one of the only care settings available for them.[20] Another possibility is that some of the young women who are more represented in the lower SES had peripartum cardiomyopathy, which is known to be associated with a better clinical compensatory reserve despite presenting with low EF and may have been related to milder HF at admission.[21]

The association of lower SES and worse clinical outcomes is well documented.[4–6,8,22] In agreement with this finding, we have observed in the STRONG-HF study numerically worse clinical outcomes in patients with lower SES.

Treatment of patients with AHF and lower SES has been documented in only a few studies, with contradictory results.[3,7,10] In the STRONG-HF study, patients with lower SES received less RASi but more BB and the same proportion of MRA compared to those with higher SES at the time of randomization, shortly prior to a discharge from an AHF admission. During the study, GDMT up-titration was achieved equally in patients with lower and higher SES, although the up-titration of some medications, most notably BB, was slower during the first few weeks in patients with higher SES, possibly because those patients had a more severe AHF episode. Probably for the same reason, there was a trend towards more adverse events during GDMT up-titration in the HIC in patients with higher SES.

With respect to the effectiveness of treatment interventions during and after an AHF event, there are very few studies to describe an interaction with SES. In a recent analysis,

Aguilera *et al*.[11] have observed that patients with lower SES had worse outcomes but benefited to the same degree from a combined intervention after discharge. The difference in 'cultural perception of severity' may also explain the less improvement in QoL as result of GDMT up-titration in patients with lower SES.

In the STRONG-HF study, we have observed a trend towards more benefit in patients with higher SES randomized to HIC, especially when based on education and income. Such factors as poorer general nutritional status including thiamine deficiency, undisclosed alcohol abuse and different genetic profiling—in particular in patients presenting with dilated or peripartum cardiomyopathy—might explain the slightly lower benefit in cases of lower SES, which, however, has to be confirmed in well-funded studies focusing on interplay between individual patient pathophysiology, patient-level healthcare, socio-economic determinants and environmental factors, in particular in Black patients and other non-Caucasian ethnic groups.

Limitations

The current analysis of the STRONG-HF study is limited by the size of the study. Some notable trends on associations between SES and outcomes and treatment effects of HIC vs. UC did not reach statistical significance. In addition, there was a substantial amount of missing household income data, which could have led to biased associations if the missingness was systematically associated with a higher or lower income; the imputation assumes the data were missing at random, that is, that they only depended on the other SES measures and other baseline patient characteristics. SES may be related to patient adherence to prescribed therapies; however, a lack of patient adherence data precludes further examination of this potential issue.

Conclusions

In the STRONG-HF study, patients with lower SES were more often women, Black and of non-European origin. They had markers of less severe disease at baseline, but numerically, non-statistically significantly, worse outcomes. GDMT medications were up-titrated to the same degree regardless of SES. HIC was beneficial across all SES levels, although again the benefits were numerically better in those with higher SES. More research into socio-economic factors for this population group is needed to facilitate better patient care.

Conflict of interest

A.D. works for the Faculty of Medicine, Eduardo Mondlane University (Maputo, Mozambique), which received research grants from the Heart Initiative for their participation in this study. A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4 and Windtree Therapeutics; received honoraria for lectures from Roche Diagnostics, Bayer and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4 and Adrenomed; and is co-inventor of a patent on combination therapy for patients having acute or persistent dyspnoea. G.C., B.D., C.E., M. B., M.N. and K.T. are employees of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics and XyloCor Therapeutics. G.C. and B.D. are directors of Heart Initiative, a non-profit organization. J.C. has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics and Pfizer. M.Ad has received speaker fees from Abbott Vascular and Medtronic. OC received grants from Servier. A.C.-S. has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott and Boehringer Ingelheim. R.D. has received supporting fees for coordination of STRONG-HF trial activities. G.F. has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier and Amgen. C.S.P. L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Redcardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder and non-executive director of Us2.ai. MM has received personal fees from Amgen, Livanova and Vifor Pharma as a member of executive committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences and Roche Diagnostics for participation to advisory boards or for speaking at sponsored meetings. M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. P.S.P. has received grants or research contracts from American Heart Association, Roche, Siemens, Ortho Diagnostics, Abbott, Beckman Coulter and Siemens and consulting fees from Roche; honoraria from WebMD; and he has financial interest

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Supporting information

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

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Table S1b. Baseline characteristics by tertile of annual household income in euros
Table S1c. Baseline characteristics by highest education level completed
Table S1d. Baseline characteristics by tertiles of household income relative to country median
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Table S2a. Clinical outcomes by insurance coverage
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Table S3. Adverse events by grouped SES score
Table S4. Serious adverse events by grouped SES score
Figure S1a. Percentage of optimal doses of oral HF medications by insurance coverage over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers, (D) percentage optimal dose of MRAs.
Figure S1b. Percentage of optimal doses of oral HF medications by tertiles of annual household income in euros over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers, (D) percentage optimal dose of MRAs.
Figure S1c. Percentage of optimal doses of oral HF medications by highest education level completed over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers, (D) percentage optimal dose of MRAs.
Figure S1d. Percentage of optimal doses of oral HF medications by tertiles of household income relative to country median over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers, (D) percentage optimal dose of MRAs.
Figure S1e. Percentage of optimal doses of oral HF medications by tertiles of education relative to country mean over study days in the high intensity care group: (A) average percentage optimal dose across all three medication classes, (B) percentage optimal dose of ACEi/ARB/ARNi, (C) percentage optimal dose of β-blockers, (D) percentage optimal dose of MRAs.
Figure S2a. Kaplan-Meier Curve for All-Cause Death or Heart Failure Readmission to Day 180 by Insurance Coverage and Treatment
Figure S2b. Kaplan-Meier Curve for All-Cause Death or Heart Failure Readmission to Day 180 by Tertiles of Annual Household Income in Euros and Treatment
Figure S2c. Kaplan-Meier Curve for All-Cause Death or Heart Failure Readmission to Day 180 by Highest Education Level Completed and Treatment
Figure S2d. Kaplan-Meier Curve for All-Cause Death or Heart Failure Readmission to Day 180 by Tertiles of Household Income Relative to Country Median and Treatment
Figure S2e. Kaplan-Meier Curve for All-Cause Death or Heart Failure Readmission to Day 180 by Tertiles of Education Relative to Country Mean and Treatment

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