ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 1156–1165
doi:10.1002/ejhf.2882

RESEARCH ARTICLE

Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial

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Received 2 April 2023; revised 4 May 2023; accepted 5 May 2023; online publish-ahead-of-print 1 June 2023

Aims The aim of this study was to evaluate efficacy and safety of rapid up-titration of guideline-directed medical therapies (GDMT) in men and women hospitalized for acute heart failure (AHF).

Methods and results In STRONG-HF, AHF patients were randomized just prior to discharge to either usual care (UC) or a high-intensity care (HIC) strategy of GDMT up-titration. In these analyses, we compared the implementation, efficacy, and safety of the HIC strategy between men and women. In the randomized AHF population, 416/1078 (39%) were women. By day 90, a higher proportion of both sexes in the HIC group had been up-titrated to full doses of GDMT compared to UC. Overall, there were no differences in the primary endpoint between the sexes. The primary endpoint, 180-day heart failure readmission or death, occurred in 15.8% HIC women versus 23.5% women in the UC group (adjusted hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.40–1.13) and in 14.9% HIC men versus 23.5% UC men

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(adjusted HR 0.57, 95% CI 0.38–0.88) (adjusted interaction $p = 0.65$). There was no significant treatment-by-sex interaction in quality-of-life improvement or in adverse events, including serious or fatal adverse events.

Conclusion The results of the current analyses suggest that a rapid up-titration of GDMT immediately after an AHF hospitalization can and should be implemented similarly in men and women, as it results in reduction of 180-day all-cause death or heart failure readmission, quality-of-life improvement in both men and women with a similar safety profile.

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

Introduction

The association of biological sex with multiple aspects of heart failure (HF) risk factors, phenotype and response to treatment has been the subject of many studies.[1] There are important differences between chronic and acute HF (AHF) with regard to sex-specific aspects. While long-term outcomes have been reported to be better in women than men with chronic HF,[2–4] in AHF outcomes have been reported to be similar in men and women.[5–7]

Although some treatment response differences to guideline-directed medical therapies (GDMT) have been noted in men and women with chronic HF with preserved ejection fraction (HFpEF),[8,9] no sex-related differences in treatment effect have been found in chronic HF with reduced ejection fraction (HFrEF) patients[10–13] and, more recently, pooled analyses of sodium–glucose cotransporter 2 (SGLT2) inhibitors found no sex-related treatment effect attenuation across the left ventricular ejection fraction (LVEF) spectrum in patients with chronic HF.[14,15] Data of the interaction between treatment effects and sex in AHF are lacking. Discrepancy in GDMT use between men and women with HF has been reported,[16] however there is a lack of sex-specific analyses of treatment response to GDMT in patients hospitalized with 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 rapid up-titration of treatments before discharge from an AHF admission and during the following weeks compared with usual care (UC). Pre-specified analyses of STRONG-HF showed no difference between the sexes regarding the high-intensity care (HIC) effect on the primary endpoint of 180-day readmission for HF or all-cause death. To address the knowledge gap of sex-specific treatment response among AHF patients, we further compared the implementation, efficacy, and safety of the HIC strategy between men and women hospitalized for AHF.

Methods

The study design, randomization process and procedures of STRONG-HF have been previously described in detail.[17–19] Briefly, STRONG-HF was a multinational, multicentre, open-label, randomized, parallel-group study designed to assess the safety and efficacy of up-titration of guideline-recommended HF medical therapy on morbidity and mortality when initiated during and up-titrated early after hospitalization for AHF. Patients aged 18–85 years admitted to hospital within 72 h of screening and not treated with optimal doses of oral HF therapies were included. Exclusion criterion was clear intolerance to high doses of GDMT. Patients across the LVEF spectrum were included. Included patients were randomized within 2 days prior to anticipated discharge in a 1:1 fashion to either HIC or UC group. Randomization was stratified by LVEF and country. Due to the nature of the study, treatment allocation could not be blinded. Patients assigned to HIC were up-titrated at randomization to half optimal doses, and at 2 weeks to full doses, of medications in three classes: renin–angiotensin system inhibitor (RASI, including angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or angiotensin receptor–neprilysin inhibitor [ARNI]), beta-blocker, and mineralocorticoid receptor antagonist (MRA). HIC patients had scheduled outpatient visits at 1, 2, 3, and 6 weeks post-discharge. Both HIC and UC patients were seen at day 90 and contacted by telephone at day 180 for an assessment of vital status and occurrence of any rehospitalization, and current prescriptions of oral HFmedications. The primary cause of death and primary reason for readmission were defined by investigator report and were not adjudicated.

Protocol amendments have also been detailed elsewhere[17,19]; first, a patient contact was added at 180 days for safety and, second, the primary endpoint was changed from 90- to 180- day HF readmission or death and target enrolment increased from 900 to 1800 to increase study power. The study was approved by appropriate competent authorities and ethics committees prior to enrolment. All patients provided written informed consent. An independent data and safety monitoring board was responsible for the safety of trial participants. This study is registered at ClinicalTrials.gov, NCT03412201.

Outcomes

The primary endpoint of the trial was 180-day HF readmission or all-cause death. Secondary endpoints were change in quality of life from baseline to day 90 as measured by the EQ-5D visual analogue scale (VAS),[20] 180-day all-cause death, and 90-day HF readmission or all-cause death. Safety was evaluated by the incidence of treatment-emergent adverse events, and changes in vital signs (systolic and diastolic blood pressure, heart rate, and body weight) and local laboratory results up to 90 days.

Statistical analysis

All analyses included all patients validly randomized to the treatment group assigned at randomization. Continuous variables are presented

as mean (standard deviation) or as adjusted mean (standard error), as appropriate, and categorical variables as absolute and relative frequencies. N-terminal pro-B-type natriuretic peptide (NT-proBNP) values were log-transformed for analysis. Patients were classified by their reported sex at birth as either man or woman and compared with respect to continuous variables using ANOVA models, binary variables using chi-square tests, and ordered categorical variables using Cochran–Mantel–Haenszel chi-square tests.

To explore the time course of up-titration of oral HF medications, the percentage dose of each medication in each of three classes (RASI, beta-blocker, and MRA) relative to the drug optimal dose (see online supplementary *Table S3* in the original publication[19]) was calculated and then averaged across the three medication classes. The difference in average diuretic dose between sex at birth for those subjects in the HIC group was compared using a mixed method repeated measures model including terms for visit, sex, and visit by sex interaction.

As previously described,[14] because the primary endpoint was changed from 90- to 180-day HF readmission or death, analyses of 180-day outcomes down-weight, proportional to half its sample size, results of the initial cohort randomized before the change and include only patients enrolled at sites where the protocol change was approved. Subgroup analyses comparing treatment effects on primary and secondary efficacy endpoints by sex at birth were pre-specified. Sexes were compared with respect to clinical outcomes using Cox proportional hazards regression, and with respect to EQ-VAS change using ANCOVA (including adjustment for baseline EQ-VAS, geographic region, and baseline LVEF ≤40%/>40%). Covariates for further adjustment were selected from variables shown to be prognostic of each outcome in previous studies[5,6] using backwards selection in the UC group. Potential modification of the treatment effect by sex was examined by inclusion of a treatment-by-sex interaction term in the models. Results for the EQ-VAS are based on observed data, excluding data where no linguistically validated translation was available. To explore the impact of COVID-19 on all-cause mortality, we conducted sensitivity analyses where deaths due to COVID-19 were censored rather than counted as an event.

Treatment effects on changes in vital signs and in local laboratory values from baseline to day 90 were compared between sexes using ANCOVA models adjusted for baseline value.

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

Results

Of a total of 1078 randomized AHF patients, 416 (39%) were women. The baseline characteristics of all patients and comparisons between sexes are presented in *Table 1*. There were significantly more non-white and non-European women, compared to men. Men were more likely to have HF of ischaemic origin and more frequently had a history of acute coronary syndrome, prior coronary artery bypass surgery and percutaneous coronary intervention, compared to women. Men were also more likely than women to have a history of atrial fibrillation, to be in New York Heart Association (NYHA) class IV and to have a lower LVEF. Women were more likely than men to have a history of HF and malignancies, and to have worse baseline EQ-VAS score. There were no differences in rate of implanted devices. Compared to men, women had higher mean systolic blood pressure and heart rate, lower creatinine and liver enzyme levels, higher total cholesterol and lower potassium and sodium concentrations at screening. NT-proBNP did not differ significantly between the sexes. Other baseline signs and symptoms and laboratory findings are presented in online supplementary *Table S1*.

Medication up-titration by sex

Prior to admission, women were prescribed MRA at full optimal dose significantly more frequently than men and were chronically treated with higher loop diuretic doses (*Table 1* and online supplementary *Table S2*). Almost no men and women were prescribed full optimal doses of RASI (one woman and two men) and beta-blockers (no women and two men) prior to admission. At screening during admission, men were treated with higher loop diuretic doses. At week 2 there were no differences between the number of fully up-titrated patients ($p = 0.074$, 0.51, and 0.54 for RASI, beta-blockers and MRA, respectively) or loop diuretic doses ($p = 0.50$) between women and men in the HIC group. By day 90, most patients of both sexes in the HIC group had been up-titrated to full doses of each of the three oral HF medication classes compared to only a small number in the UC group (RASI 56.6% vs. 1.6% in women, 54.0% vs. 2.5% in men, interaction $p = 0.65$; beta-blockers 45.4% vs. 2.2% in women, 51.8% vs. 5.1% in men, interaction $p = 0.43$; MRA 83.2% vs. 44.8% in women, 84.1% vs. 47.5% in men, interaction $p = 0.73$). Dose of loop diuretics was lower in both women and men of the HIC group (total furosemide equivalence dose 54 mg furosemide equivalents in the HIC group vs. 62 mg in the UC group in women; 52 mg furosemide equivalents in the HIC group vs. 58 mg in the UC group in men, interaction $p = 0.75$). The average percentage of the optimal dose across the three GDMT classes by sex in the HIC group throughout the study visits is shown in *Figure 1*. Of note, throughout most time points men patients received less diuretics than women (online supplementary *Table S2*). However, the average difference was not significant (−3.65 [−10.95 to 3.65], $p = 0.33$).

Outcomes by sex

Day 180 results were included for 394 (95%) women and 614 (93%) men. Overall, the outcomes did not differ between the sexes, regardless of the treatment strategy (online supplementary *Table S3*). The primary endpoint (HF readmission or all-cause death at day 180) occurred in 73 (19.6% down-weighted adjusted Kaplan–Meier estimate) women and in 110 (19.2%) men (adjusted hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.62–1.21; $p = 0.41$, *Figure 2*). HF readmission by day 180 occurred in 45 (12.8%) women and in 76 (13.6%) men (adjusted HR 1.06 [95% CI 0.69–1.64], $p = 0.77$). All-cause death at day 180 occurred in 37 (9.5%) women and in 50 (9.0%) men (adjusted HR 0.99 [95% CI 0.61–1.62], $p = 0.97$) (online supplementary *Figure S1*). All-cause death or HF readmission excluding COVID-related deaths occurred in 69 (18.5%) women and 108 (18.8%) men (adjusted HR 1.01 [95% CI 0.72–1.42], $p = 0.97$). All-cause death by day 180 excluding COVID-related deaths occurred in 33 (8.3%) women and 47 (8.6%) men (adjusted HR 1.11 [95% CI 0.66–1.87], $p = 0.69$).

Table 1 Demographic and clinical characteristics of the study population by sex at birth

Parameter	Women ($n = 416$)	Men ($n = 662$)	*p*-value
Age, years	62.4 (16.73)	63.3 (11.16)	0.2767
Self-reported race			<0.0001
Black	148 (35.6%)	82 (12.4%)	
Caucasian	263 (63.2%)	569 (86.2%)	
Native American	1 (0.2%)	0	
Other[a]	3 (0.7%)	9 (1.4%)	
Pacific Islander	1 (0.2%)	0	
Geographical region			<0.0001
Europe	252 (60.6%)	545 (82.3%)	
Non-Europe	164 (39.4%)	117 (17.7%)	
NT-proBNP at screening, ng/L[b]	5936.7 (5636.2–6253.3)	6065.5 (5797.1–6346.2)	0.5494
NT-proBNP at baseline, ng/L[b]	3153.2 (2977.7–3339.0)	3242.9 (3084.1–3410.0)	0.4796
History of AF/flutter or present at screening	158 (38.0%)	325 (49.1%)	0.0004
Baseline EQ-VAS	55.9 (13.57)	60.7 (15.52)	<0.0001
Medical history			
Stroke or transient ischaemic attack	42 (10.1%)	57 (8.6%)	0.4011
Severe liver disease	2 (0.6%)	4 (0.7%)	0.8023
Psychiatric or neurological disorder	9 (2.2%)	11 (1.7%)	0.5495
Malignancies	17 (4.1%)	12 (1.8%)	0.0248
Diabetes	121 (29.1%)	192 (29.2%)	0.9740
Diabetes control method			
Insulin	30 (7.2%)	52 (7.9%)	0.6778
Diet only	79 (19.0%)	123 (18.7%)	0.9033
Oral antidiabetic agents	93 (22.4%)	141 (21.4%)	0.7103
Pulmonary embolism	4 (1.0%)	15 (2.3%)	0.1124
Acute coronary syndrome	99 (23.8%)	212 (32.1%)	0.0035
Coronary artery bypass surgery	12 (2.9%)	47 (7.1%)	0.0031
Percutaneous coronary intervention	36 (8.7%)	116 (17.5%)	<0.0001
Angina CCS class ≥2	53 (12.8%)	72 (10.9%)	0.3419
Moderate or severe COPD or asthma	8 (1.9%)	19 (2.9%)	0.3309
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	0	1 (0.2%)	0.4274
Cardiac resynchronization therapy	2 (0.5%)	4 (0.6%)	0.7895
Automatic internal cardiac defibrillator	2 (0.5%)	7 (1.1%)	0.3101
HF history			
History of HF	365 (87.7%)	551 (83.4%)	0.0496
NYHA class 1 month before hospital admission			0.0173
I	24 (6.1%)	39 (6.4%)	
II	138 (34.9%)	169 (27.9%)	
III	166 (42.0%)	249 (41.2%)	
IV	67 (17.0%)	148 (24.5%)	
Ischaemic aetiology	158 (38.1%)	356 (53.9%)	<0.0001
LVEF, %[c]	39.1 (13.40)	34.6 (11.63)	<0.0001
LVEF category			<0.0001
≤40%	250 (60.1%)	481 (72.7%)	
>40%	166 (39.9%)	181 (27.3%)	
Hospitalized for HF in the past year?	110 (26.4%)	163 (24.7%)	0.5126
No. of HF hospitalizations in the past year	0.4 (1.60)	0.3 (0.65)	0.2592
History of AF/flutter	167 (40.1%)	329 (49.8%)	0.0020
Type of AF/flutter			0.4997
Paroxysmal	43 (26.5%)	74 (22.6%)	
Permanent	91 (56.2%)	202 (61.6%)	
Persistent	28 (17.3%)	52 (15.9%)	

Table 1 (Continued)

Parameter	Women ($n = 416$)	Men ($n = 662$)	p-value
Oral HF medications taken at visit 2, pre-randomization			
ACEI/ARB/ARNI	274 (66.0%)	415 (63.0%)	0.3102
Beta-blockers	135 (32.5%)	248 (37.6%)	0.0891
MRA	395 (95.2%)	623 (94.5%)	0.6441
Loop diuretic	394 (94.9%)	635 (96.4%)	0.2586

Data are expressed as mean (standard deviation), *n* (%), or geometric mean (95% CI).
ACE, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; EQ-VAS, EQ-5D visual analogue scale; 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.
[a]Other reported races were African ($n = 2$), Europiod ($n = 2$), Latin American ($n = 1$), Berber ($n = 1$), Gipsy ($n = 1$), and not specified ($n = 5$).
[b]Values reported as >9000 ng/L were set to 9000 ng/L.
[c]Most recent value within 6 months before screening, including during the index hospitalization. Values <10% were set to 10% for analysis.

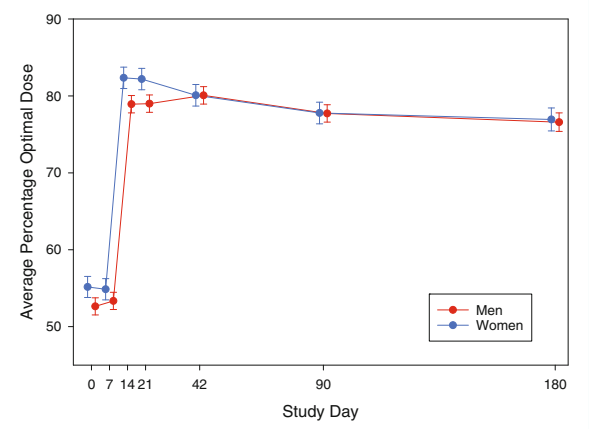

Figure 1 Average optimal dose of three oral guideline-directed medical therapies (renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists) by visit and sex in the high-intensity care group.

EQ-VAS change from baseline to day 90 was 9.43 (0.70) points in women and 8.40 (0.58) points in men (adjusted least square [LS] mean difference −1.35 [95% CI −3.25 to 0.55], $p = 0.1649$). These data are presented in online supplementary *Table S3*.

Effect of high-intensity care strategy by sex

The HIC strategy reduced the incidence of the primary endpoint in both women (30 [15.8%] in the HIC group vs. 43 [23.5%] in the UC group; adjusted HR 0.67 [95% CI 0.40–1.13]) and men (44 [14.9%] in the HIC group vs. 66 [23.5%] in the UC group; adjusted HR 0.57 [95% CI 0.38–0.88]) (*Table 2*). Sex was not a modifier of the treatment strategy effect (adjusted interaction $p = 0.65$). Kaplan–Meier curves with down-weighting of cohort 1 for the primary endpoint are shown in *Figure 3*. Additionally, we found no treatment attenuation by LVEF in both men and women when analysing the primary endpoint (online supplementary *Table S4*).

Furthermore, there was no significant effect modification by sex when analysing mortality separately: all-cause death by day 180 occurred in 17 (9.2%) women in the HIC group and in 20 (9.8%) women in the UC group (adjusted HR 0.97 [95% CI 0.46–2.06]); and in 22 (8.2%) men in the HIC group and in 28 (10.3%) men in the UC group (adjusted HR 0.69 [95% CI 0.38–1.25]) (adjusted interaction $p = 0.48$) (for Kaplan–Meier curves, see online supplementary *Figure S2*). The primary endpoint after excluding COVID-related deaths, occurred in 26 (13.6%) women in the HIC group and 43 (23.5%) women in the UC group (adjusted HR 0.56 [95% CI 0.32–0.97]); and in 43 (14.5%) men in the HIC group and in 65 (23.1%) men in the UC group (adjusted HR 0.57 [95% CI 0.37–0.87]); with no treatment modification by sex (interaction $p = 0.96$). After excluding COVID-related deaths, all-cause death by day 180 occurred in 13 (6.8%) women in the HIC group and in 20 (9.8%) women in the UC group (adjusted HR 0.69 [95% CI 0.30–1.57]); and in 20 (7.1%) men in the HIC group and in 27 (9.9%) men in the UC group (adjusted HR 0.64 [95% CI 0.34–1.20]) with no treatment modification by sex (interaction $p = 0.89$). There was no treatment-by-sex interaction when analysing HF readmission by day 180 (adjusted interaction $p = 0.90$; *Table 2*).

EQ-VAS was completed in 341/416 (82%) of women and 574/662 (87%) of men at baseline and day 90. Among women who completed the EQ-VAS at baseline and at day 90, there was a 11.50-point improvement in the HIC group versus 5.98 in the UC group (adjusted LS mean difference 5.48 [95% CI 2.71–8.25]). In men, there was a 10.28-point improvement in the HIC group versus 7.98 in the UC group (adjusted LS mean difference 2.68 [95% CI 0.54–4.81]). Again, sex was not found to modify the effect of the treatment strategy on quality of life (*Table 2*, *Figure 4*).

Safety of the treatment strategy

The incidence of treatment-emergent adverse events in men and women is summarized in online supplementary *Tables S5 and S6*. Select adverse events and serious adverse events are reported in *Table 3*. Adverse events were reported through day 90 in 93 (43.1%) women in the HIC group versus 58 (29.0%) in the UC

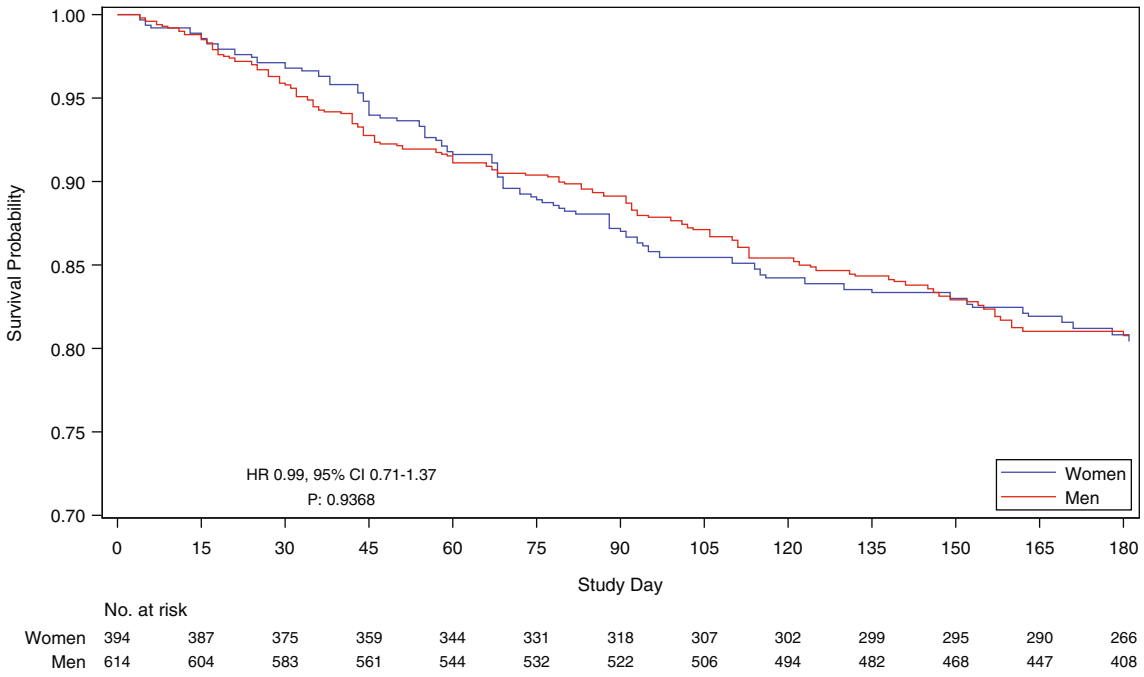

Figure 2 Unadjusted Kaplan–Meier curves for all-cause death or heart failure readmission through day 180 by sex at birth. Results in the initial cohort have been down-weighted. CI, confidence interval; HR, hazard ratio.

group. In men, 130 (39.9%) in the HIC group reported any adverse event versus 100 (29.8%) in the UC group (interaction $p = 0.52$). The most common adverse events were cardiac failure (36 [16.7%] women in the HIC group vs. 31 [15.5%] women in the UC group; 43 [13.2%] men in the HIC group vs. 42 [12.5%] men in the UC group); hypotension (9 [4.2%] vs. 1 [0.5%] in women; 18 [5.5%] vs. 1 [0.3%] in men); hyperkalaemia (3 [1.4%] vs. 0 in women; 15 [4.6%] vs. 0 in men), and renal impairment (6 [2.8%] vs. 0 in women; 8 [2.5%] vs. 1 [0.3%] in men). Any serious adverse event was reported in 37 (17.1%) HIC women versus 34 (17.0%) UC women; and in 51 (15.6%) HIC men versus 58 (17.3%) UC men (interaction $p = 0.70$). Serious adverse events included cardiac failure (14 [6.5%] vs. 21 [10.5%] in women; 24 [7.4%] vs. 26 [7.7%] in men), sudden death (3 [1.4%] vs. 5 [2.5%] in women; 2 [0.6%] vs. 5 [1.5%] in men) and viral pneumonia (4 [1.9%] vs. 0 in women; 3 [0.9%] vs. 3 [0.9%] in men). There was no significant increase of adverse event risk in either of the sexes or a significant treatment-by-sex interaction (all $p > 0.05$).

NT-proBNP decreased more in the HIC group compared to UC, similarly between the sexes (ratio of geometric mean ratios 0.73 [95% CI 0.58–0.91] in women, 0.80 [95% CI 0.67–0.96] in men, interaction $p = 0.49$). Systolic blood pressure and heart rate also decreased similarly in both sexes in the HIC group. Body weight decrease was more pronounced in women in the HIC group, although sex was not found to be a modifier of the treatment effect (interaction $p = 0.17$). Overall, there was no signal of treatment-by-sex interaction, regarding the change in vital signs from baseline to day 90 (online supplementary *Table S7*).

Discussion

In this analysis of STRONG-HF, both women and men with AHF derived benefits from a rapid up-titration of GDMT implemented immediately after an AHF hospitalization. All-cause 180-day death or HF readmission risk was reduced in both men and women in the HIC group with no significant treatment-by-sex interaction. The same was true for quality-of-life improvement. The safety of the high-intensity strategy after an AHF admission was similar in men and women. There was no evidence of relevant treatment-by-sex interaction in any outcomes or safety events.

Certain baseline sex differences of this analysis were consistent with previous HF epidemiological studies or clinical trials.[7,8,21,22] Women were more likely to have preserved LVEF, while men were more likely to have ischaemic HF aetiology, prior acute coronary syndrome, coronary artery bypass grafting or percutaneous coronary intervention, atrial fibrillation, and higher NYHA class. However, age did not differ between women and men with AHF, and baseline NT-proBNP was also similar in both sexes. Notably, the STRONG-HF population was more diverse, including more non-white and non-European female AHF patients, which could explain at least some of the deviations from prior studies, since a comparable epidemiological profile was reported in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF).[6]

Underutilization of GDMT prior to admission was similar in men and women in STRONG-HF. However, there were more women on full optimal dose of MRAs – whether this is related to the higher proportion of women with HFpEF in whom secondary TOPCAT

Table 2 Primary and secondary endpoints by sex at birth and treatment group

Endpoint	Women ($n = 416$)				Men ($n = 662$)				*p*-value (treatment-by-sex interaction)	
	High intensity care	Usual care	Unadjusted treatment effect	Adjusted treatment effect	High intensity care	Usual care	Unadjusted treatment effect	Adjusted treatment effect	Unadjusted	Adjusted
Day 90 analyses	216	200			326	336				
Day 180 analyses	203	191			303	311				
All-cause death or HF readmission by day 180[a]	30 (15.8%)	43 (23.5%)	0.67 (0.40–1.13)	0.67 (0.40–1.13)	44 (14.9%)	66 (23.5%)	0.59 (0.40–1.13)	0.57 (0.38–0.88)	0.7055	0.6474
All-cause death by day 180[b]	17 (9.2%)	20 (9.8%)	0.96 (0.49–2.02)	0.97 (0.46–2.06)	22 (8.2%)	28 (10.3%)	0.76 (0.42–1.37)	0.69 (0.38–1.25)	0.6227	0.4794
HF readmission by day 180[c]	18 (9.2%)	27 (16.5%)	0.54 (0.27–1.07)	0.52 (0.27–1.04)	29 (9.6%)	47 (17.7%)	0.51 (0.31–0.86)	0.50 (0.30–0.84)	0.9069	0.8952
All-cause death or HF readmission by day 180 (excluding COVID-related deaths)[a]	26 (13.6%)	43 (23.5%)	0.56 (0.32–0.97)	0.56 (0.32–0.97)	43 (14.5%)	65 (23.1%)	0.58 (0.38–0.89)	0.57 (0.37–0.87)	0.9093	0.9626
All-cause death (excluding COVID-related deaths) by day 180[b]	13 (6.8%)	20 (9.8%)	0.69 (0.30–1.54)	0.69 (0.30–1.57)	20 (7.1%)	27 (9.9%)	0.70 (0.38–1.31)	0.64 (0.34–1.20)	0.9594	0.8855
EQ-VAS change from baseline to visit 7[d]	11.50 (1.17)	5.98 (1.05)	5.52 (2.66–8.39)	5.48 (2.71–8.25)	10.28 (1.05)	7.98 (1.05)	2.30 (0.09–4.50)	2.68 (0.54–4.81)	0.0804	0.1167

Data presented as *n* (%) or least squares mean (standard error). Unadjusted treatment effects are the least squares mean difference between treatment groups (for change in EQ-5D) and hazard ratio (95% confidence interval) for the other endpoints. Results for patients in cohort 1 were down-weighted for day 180 analyses.

EQ-VAS, EQ-5D visual analogue scale; HF, heart failure; LS, least square; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[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]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF (≤40%/>40%), and oedema.

[d]LS mean change and LS mean difference from an ANCOVA model with baseline EQ-VAS, treatment, baseline LVEF (≤40%/>40%), region and sex at birth. Subjects from Mozambique were excluded from these analyses because of the unavailability of a linguistically validated translation of the EQ-VAS in that country (i.e. analysis includes $n = 461$ [284 men and 177 women] from the high-intensity care group and $n = 454$ [290 men and 164 women] the from the usual care group). Additional adjustment for age, haemoglobin, creatinine, cholesterol, NT-proBNP, hospitalization for HF in the previous year, oedema severity, and NYHA class.

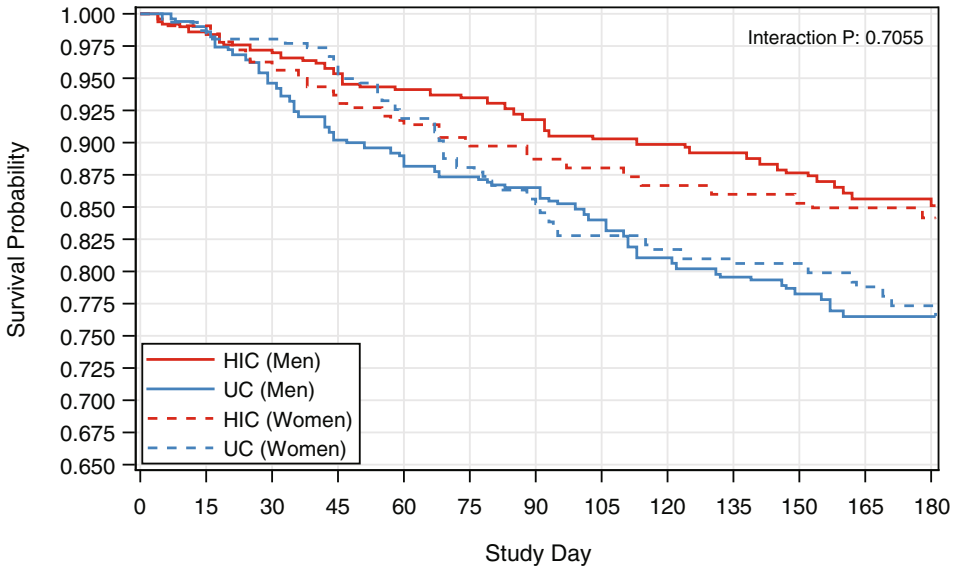

Figure 3 Unadjusted Kaplan–Meier curves for all-cause death or heart failure readmission through day 180 by sex at birth and treatment arm. Results in the initial cohort have been down-weighted. CI, confidence interval; HIC, high-intensity care; HR, hazard ratio; UC, usual care.

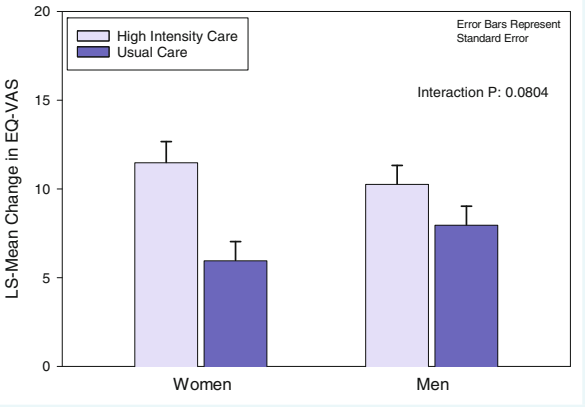

Figure 4 Change in EQ-5D visual analogue scale (EQ-VAS) from baseline to day 90 by sex at birth and treatment arm. Change at day 90 adjusted for baseline EQ-VAS, baseline LVEF (≤40%/>40%) and region. LS, least square.

analysis suggest significant benefit of MRA is unclear.[10] Interestingly, despite having a lower NYHA class, women on average received higher doses of loop diuretics at screening. This finding contradicts prior studies.[5]

Better outcomes in women have been reported in both epidemiological and clinical studies of chronic HF.[2–4,14,23] In an analysis of AHF registries, women had lower risk of 1-year mortality, even though they less often received optimal medical therapy at discharge.[16] However, there are several trials demonstrating that although women with chronic HF have better reported survival, this is not the case for AHF patients.[5–7] In a sex-specific analysis of the PROTECT trial,[5] risk-adjusted 180-day mortality was similar in men and women hospitalized for AHF. In a retrospective analysis of a multicentre registry of hospitalized AHF patients, 6-month all-cause and cardiovascular mortality rates were almost identical in men and women.[7] In the THESUS-HF, there were no differences in any of the analysed outcomes between the sexes.[6] Similarly, in our analysis the rates of 180-day HF readmission and/or all-cause death were similar between women and men with AHF, regardless of the treatment strategy.

Although significant benefit of ARNI and spironolactone has been reported in women and not men with stable HFpEF in secondary analyses,[8,9] there is substantial evidence from subgroup analyses of the pivotal randomized clinical trials indicating no sex-related treatment attenuation in HFrEF.[10–13,24,25] Sacubitril/valsartan reduced the primary outcome of death from cardiovascular causes or a first hospitalization for HF similarly in men and women in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[10] Spironolactone significantly reduced all-cause mortality in both men and women with HFrEF in the Randomized Aldactone Evaluation Study (RALES).[12] Similar results were seen with another drug of MRA class, eplerenone, which reduced hospitalization for HF or death from cardiovascular causes in both sexes in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[25] Relative risk of all-cause mortality was equally reduced in women when treated with carvedilol.[13] In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, carvedilol reduced combined risk of death or hospitalization for a cardiovascular reason or for HF in men and women with severe chronic HFrEF.[24] Furthermore, biological sex was not a treatment-effect modifier across the LVEF spectrum in pooled analyses of SGLT2 inhibitors.[14,15] While all these studies were

Table 3 Selected adverse events and serious adverse events by sex at birth and treatment

System organ class preferred term	Women		Men		Treatment-by-sex interaction *p*-value
	High intensity care (*n* = 216)	Usual care (*n* = 200)	High intensity care (*n* = 326)	Usual care (*n* = 336)	
Any adverse event	93 (43.1%)	58 (29.0%)	130 (39.9%)	100 (29.8%)	0.5267
Metabolism and nutrition disorders	6 (2.8%)	1 (0.5%)	19 (5.8%)	2 (0.6%)	0.6498
Hyperkalaemia	3 (1.4%)	0	15 (4.6%)	0	0.4368
Renal and urinary disorders	9 (4.2%)	0	11 (3.4%)	2 (0.6%)	0.9346
Renal impairment	6 (2.8%)	0	8 (2.5%)	1 (0.3%)	0.6719
Vascular disorders	13 (6.0%)	5 (2.5%)	22 (6.7%)	4 (1.2%)	0.2528
Hypotension	9 (4.2%)	1 (0.5%)	18 (5.5%)	1 (0.3%)	0.5805
Any serious adverse event	37 (17.1%)	34 (17.0%)	51 (15.6%)	58 (17.3%)	0.7047

Including events with onset date equal to or greater than date of randomization through 90 days post-randomization.

performed in patients with chronic HF, there is also evidence that treatment response does not differ between men and women hospitalized for AHF. In the Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial, ARNI reduced NT-proBNP similarly in men and women with HFrEF hospitalized for AHF.[11] Empagliflozin equally improved the primary composite outcome in men and women and found no significant treatment interaction between the sexes regardless of LVEF in the Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE).[26] In our study, rapid up-titration of GDMT after hospitalization for AHF resulted in risk reduction of 180-day all-cause death or HF readmission and improvement of quality of life in both men and women with no significant effect modification by sex. We also found no treatment attenuation related to LVEF in neither men nor women with AHF. Our findings support rapid up-titration of GDMT and HIC strategy after AHF hospitalization to improve outcomes in both sexes regardless of their LVEF.

It has recently been suggested in a post-hoc analysis of two observational HF studies that women might benefit from lower doses of ACEI or ARBs and beta-blockers than men, with maximal effects of treatment reached with 40–50% of beta-blocker and 60% of ACEI/ARB target doses.[8] However, no detrimental effects were reported with higher doses. In our cohort, the proportion of AHF patients up-titrated to full optimal doses of GDMT was very similar in men and women in the HIC arm. A higher incidence of adverse events (mostly hypotension, hyperkalaemia, and renal impairment) in the HIC group and a similar incidence of serious adverse events between the UC and HIC groups has been previously described.[19] In this sex-specific analysis, the safety profile was comparable between men and women, and we found no significant differences or treatment-by-sex interaction when analysing any, or serious adverse events.

Limitations

In addition to previously reported limitations,[19] only 39% of the included patients were women. Due to limited sample sizes, we could not properly address whether lower doses could have resulted in the same benefit in women with AHF. However, no excessive safety concerns were detected in women up-titrated to full optimal doses of GDMT.

Conclusions

An intensive treatment strategy implemented immediately after a hospitalization for AHF resulted in a reduction of 180-day all-cause death or HF readmission risk and quality-of-life improvement in both men and women. The safety of rapid up-titration of GDMT after an AHF admission was similar in men and women.

Supplementary Information

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

Funding

Funding for the study was through a grant provided to the Heart Initiative by Roche Diagnostics International. The funder had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the manuscript for publication.

Conflict of interest: 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 & non-executive director of Us2.ai. A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; 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 coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. B.D., C.E., M.B., M.N., K.T., and G.C. 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. B.D. and G.C. are directors of Heart Initiative, a non-profit organization. M.Ad. has received speaker fees from Abbott Vascular and Medtronic. O.C. 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. 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. 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. 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; consulting fees from Roche; honoraria from WebMD; and he has financial interest in The Heart Course. K.S. has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. A.A.V. has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. J.C. has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. All other authors have nothing to disclose.

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