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# Characteristics, treatment, and outcomes of early vs. late enrollees of the STRONG-HF trial

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## ABSTRACT

**Background** The STRONG-HF trial showed that high-intensity care (HIC) consisting of rapid up-titration of guideline-directed medical therapy (GDMT) and close follow-up reduced all-cause death or heart failure (HF) readmission at 180 days compared to usual care (UC). We hypothesized that significant differences in patient characteristics, management, and outcomes over the enrolment period may exist.

**Methods** Two groups of the 1,078 patients enrolled in STRONG-HF were created according to the order of enrolment within center. The early group consisted of the first 10 patients enrolled at each center (N = 342) and the late group consisted of the following patients (N = 736).

**Results** Late enrollees were younger, had more frequently reduced ejection fraction, slightly lower NT-proBNP and creatinine levels compared with early enrollees. The primary outcome occurred less frequently in early compared to late enrollees (15% vs. 21%, aHR 0.65, 95% CI 0.42-0.99, $P = .044$). No treatment-by-enrolment interaction was seen in respect to the average percentage of optimal dose of GDMT after randomization, which was consistently higher in early and late patients randomized to HIC compared to UC. The higher use of renin-angiotensin-inhibitors in the HIC arm was more pronounced in the late enrollees both after randomization (interaction-$P = .013$) and at 90 days (interaction-$P < .001$). No interaction was observed for safety events. Patients randomized late to UC displayed a trend toward more severe outcomes (26% vs. 16%, $P = .10$), but the efficacy of HIC showed no interaction with the enrolment group (aHR 0.77, 95% CI 0.35-1.67 in early and 0.58, 95% CI 0.40-0.83 in late enrollees, adjusted interaction-$P = .51$) with similar outcomes in the HIC arm in late and early enrollees (16% vs. 13%, $P = .73$).

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**Conclusions** Late enrollees have different clinical characteristics and higher event rates compared to early enrollees. GDMT implementation in the HIC arm robustly achieved similar doses with consistent efficacy in early and late enrollees, mitigating the higher risk of adverse outcome in late enrollees.

**Trial registration** ClinicalTrials.gov Identifier: NCT03412201. (Am Heart J 2024;274:119–129.)

## Background

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-intensive care (HIC) compared with usual care (UC) in patients admitted with acute heart failure (AHF). HIC consisted of rapid up-titration of guideline-directed medical therapy (GDMT) before hospital discharge and during the following weeks combined with close follow-up.[1,2] The study showed that a HIC strategy was feasible, reduced symptoms, improved quality of life, and reduced the risk of all-cause death or heart failure readmission at 180 days compared to UC.[3]

Limited data exist on whether patient characteristics, treatment, and outcomes change over the course of a clinical trial and whether this might impact trial results. We hypothesized that significant differences in patient characteristics, management, and outcomes over the enrolment period exist.

The aim of these analyses is to describe the associations of the order of enrolment (early vs. late) at each center with patient characteristics, the ability to up-titrate GDMT, the safety of such up-titration, and its effects on outcomes.

## Methods

### Study participants, procedures, and outcomes

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 usual care. 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 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 Supplemental Table 3 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 this analysis, the study population was divided by the order of inclusion within center into 2 groups: early enrollees (first 10 patient enrolled at each center) and late enrollees (11th patient and following of each center).

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. 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 bodyweight, and local laboratory results.

### Statistical analysis

All efficacy and safety analyses included all randomized patients, except for those randomized in error. Continuous variables are presented as mean and standard deviation (SD), geometric mean (95% CI) for log-transformed, 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 early and late enrolment categories across the 2 treatment groups using the Cochran-Mantel-Haenszel mean score test while the interaction between enrolment group and treatment was examined using a test of the homogeneity of the Mann-Whitney statistic which was derived from the Somers' D statistic and its associated SE. A continuous variable, indicating the percentage of optimal dose, was calculated for

each of the three medication classes (ACEi/ARB/ARNi, Beta-blockers, and MRAs) along with an overall average percentage optimal dose across these classes. Figures depicting the percentage optimal dose over time, starting at day 0 (post-randomization), for each medication class individually, as well as the average percentage optimal dose of the 3 classes, by treatment and enrolment groups are presented.

As previously described, because the primary endpoint was changed from 90-day to 180-day death or heart failure 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. Cox regression models were used to examine the treatment effect on the primary endpoint within each enrolment group (early and late) and to test whether there was a significant interaction between the enrolment groups. The total number of events and down-weighted Kaplan-Meier estimates are presented along with unadjusted and adjusted hazard ratios (HR) and associated 95% confidence intervals. A Kaplan-Meier plot is presented for the primary endpoint with lines for each treatment/enrolment group. Covariates used for adjustment were selected from variables shown to be prognostic of each outcome in previous studies using backwards selection in the usual care group. Sensitivity analyses were conducted in which the population was restricted to just those patients at sites that enrolled greater than 10 patients, in sites that enrolled greater than 10 patients including the first 10 and up to the last 10 patients enrolled, and in sites that enrolled 20 or more patients including the first 10 and last 10 patients enrolled.

A radar plot is provided which compares early and late enrollees across eight selected baseline clinical characteristics, recognized as indicators of disease severity. The eight characteristics were standardized to z-scores and the mean z-score within each group are plotted for each characteristic.

Two-sided $P < .05$ was considered to be statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## Results

### Baseline characteristics and outcome of early and late enrollees

During the study period, 1078 patients were recruited from 87 hospitals in 14 countries (Argentina, Austria, Bulgaria, Colombia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia) and were randomly assigned to high-intensity care (HIC; n = 542) or usual care (UC; n = 536). Fifty-five of the 87 centers enrolled at least 1 patient. Twenty centers that enrolled >10 patients each accounted for 936 (87%) of the total patients enrolled (Supplementary Table 1). The distribution of patients by geographic region among these 20 centers was similar to the overall distribution of patients enrolled: Africa 24% vs. 22%, Europe 4% vs. 9%, Russia 71% vs. 65%, and South America 1% vs. 4%. Eleven sites enrolled ≥20 patients each, with a total enrolment of 806 (75%) patients, and a similar geographic distribution except for South America (Africa 25%, Europe 4%, Russia 71%, and South America 0%)."

The group of early enrollees consisted of the first 10 patients enrolled at each center (N = 342) and the late enrollees group consisted of the following patients at each center (N = 736).

Late enrollees were younger (61±14 vs. 66±12 years, $P < .001$), more symptomatic (prevalence of dyspnoea at rest: 27% vs 9%, $P < .001$), and had more severe cardiac disease compared with early enrollees: previous acute coronary syndrome (32% vs. 22%, $P < .001$) and reduced ejection fraction (71% vs. 62%, $P = .003$) were more prevalent in late enrollees. They also presented less comorbid conditions such as chronic obstructive pulmonary disease (2% vs. 5%, $P = .002$).

Vital signs were similar in both groups and small but relevant differences in laboratory parameters at baseline were observed: NT-proBNP and serum creatinine were lower in late compared to early enrollees (3,103 [2,967-3,245] vs. 3,450 [3,217-3,700] ng/L, $P = .01$ and 104±25 vs. 110±35 μmol/L, $P = .002$, respectively) (Table 1 and Figure 1).

Although some individual risk factors appeared to be lower in later enrollees while others appeared to be higher, the overall risk of the primary outcome of all-cause death or HF readmission at 180 days in the usual care group was lower (22/135, Kaplan-Meier 16.4%) among early enrollees than among later enrollees (87/367, Kaplan-Meier 25.6%; adjusted Cox regression $P = .05$, see also Table 3).

### Treatment of early and late enrollees

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 more than half of patients did not receive a beta-blocker. Before randomization, the use and dosing of ACEi/ARB/ARNi, and MRA were higher in late compared to early enrollees. Conversely, the use of beta-blocker was higher in early enrollees. No treatment-by-enrolment interaction was found (Table 2).

After randomization, the average percentage of optimal dose of GDMT was higher in the HIC compared to UC

**Table 1.** Baseline characteristics by early and late enrolment groups

| Parameter | Statistic | Enrolment Group | | *P*-value |
|---|---|---|---|---|
| | | Early enrollees (N = 342) | Late enrollees (N = 736) | |
| Demographic characteristics | | | | |
| Age, years | Mean (SD) | 66.2 (12.39) | 61.5 (13.86) | <.001 |
| Sex | | | | .18 |
| Female | n (%) | 122 (35.7%) | 294 (39.9%) | |
| Male | n (%) | 220 (64.3%) | 442 (60.1%) | |
| Self-reported Race | | | | <.001 |
| Black | n (%) | 47 (13.8%) | 183 (24.9%) | |
| Caucasian | n (%) | 286 (84.1%) | 546 (74.2%) | |
| Other | n (%) | 7 (2.1%) | 7 (0.9%) | |
| Geographical region | | | | .38 |
| Europe | n (%) | 247 (72.2%) | 550 (74.7%) | |
| Non-Europe | n (%) | 95 (27.8%) | 186 (25.3%) | |
| Heart failure history | | | | |
| History of heart failure | n (%) | 284 (83.3%) | 632 (85.9%) | .27 |
| NYHA class 1-month before admission | | | | <.001 |
| 1 | n (%) | 28 (8.8%) | 35 (5.1%) | |
| 2 | n (%) | 101 (31.6%) | 206 (30.3%) | |
| 3 | n (%) | 162 (50.6%) | 253 (37.2%) | |
| 4 | n (%) | 29 (9.1%) | 186 (27.4%) | |
| Ischaemic aetiology | n (%) | 175 (51.6%) | 339 (46.1%) | .09 |
| LVEF, % | Mean (SD) | 37.3 (12.80) | 35.8 (12.37) | .063 |
| LVEF <=40% | n (%) | 211 (61.7%) | 520 (70.7%) | .003 |
| HF admission in the past year | n (%) | 90 (26.4%) | 183 (24.9%) | .59 |
| Number of HF admission in the past year | Mean (SD) | 0.4 (0.78) | 0.3 (1.24) | .41 |
| NT-proBNP at screening, ng/L | Geom. Mean (95% CI) | 5995.7 (5624.6, 6391.4) | 6024.6 (5785.5, 6273.5) | .90 |
| Medical History | | | | |
| Acute coronary syndrome | n (%) | 74 (21.7%) | 237 (32.2%) | <.001 |
| Coronary artery bypass surgery | n (%) | 28 (8.2%) | 31 (4.2%) | .007 |
| Percutaneous coronary intervention | n (%) | 49 (14.4%) | 103 (14.0%) | .85 |
| History of atrial fibrillation or atrial flutter | n (%) | 146 (42.7%) | 337 (45.8%) | .34 |
| Stroke or transient ischaemic attack | n (%) | 36 (10.6%) | 63 (8.6%) | .29 |
| Diabetes | n (%) | 111 (32.6%) | 202 (27.6%) | .09 |
| Malignancies | n (%) | 14 (4.1%) | 15 (2.0%) | .051 |
| Moderate or severe COPD | n (%) | 16 (4.7%) | 11 (1.5%) | .002 |
| Baseline Vital Signs | | | | . |
| Systolic blood pressure, mmHg | Mean (SD) | 122.6 (12.95) | 122.9 (12.95) | .72 |
| Pulse, beats/min | Mean (SD) | 78.0 (12.29) | 79.0 (11.55) | .20 |
| Respiratory Rate, breaths/min | Mean (SD) | 17.7 (3.30) | 18.4 (5.15) | .037 |
| Baseline Laboratory values | | | | . |
| Hemoglobin, g/L | Mean (SD) | 135.1 (20.61) | 137.1 (19.67) | .12 |
| White blood cells, 10/L | Mean (SD) | 7.4 (2.28) | 6.8 (1.86) | <.001 |
| Sodium, mmol/L | Mean (SD) | 139.6 (4.62) | 140.5 (3.92) | .002 |
| Potassium, mmol/L | Mean (SD) | 4.3 (0.51) | 4.3 (0.42) | .78 |
| Urea, mmol/L | Mean (SD) | 9.0 (4.27) | 7.6 (2.98) | <.001 |
| Creatinine, $\mu$mol/L | Mean (SD) | 110.3 (34.83) | 104.3 (25.48) | .002 |
| Glucose, mmol/L | Mean (SD) | 6.8 (2.96) | 6.0 (1.91) | <.001 |
| NT-proBNP, ng/L | Geom. Mean (95% CI) | 3450.0 (3217.0, 3700.0) | 3102.8 (2966.8, 3244.9) | .01 |
| Oral heart failure medications taken before randomization | | | | |
| ACEi/ARB/ARNi | n (%) | 176 (52.1%) | 513 (69.7%) | <.001 |
| Beta-blockers | n (%) | 164 (48.5%) | 219 (29.8%) | <.001 |
| MRA | n (%) | 290 (85.8%) | 728 (98.9%) | <.001 |
| Loop diuretic | n (%) | 313 (92.6%) | 716 (97.3%) | <.001 |
| Daily dose, mg | Mean (SD) | 60.5 (51.12) | 63.7 (43.98) | .30 |

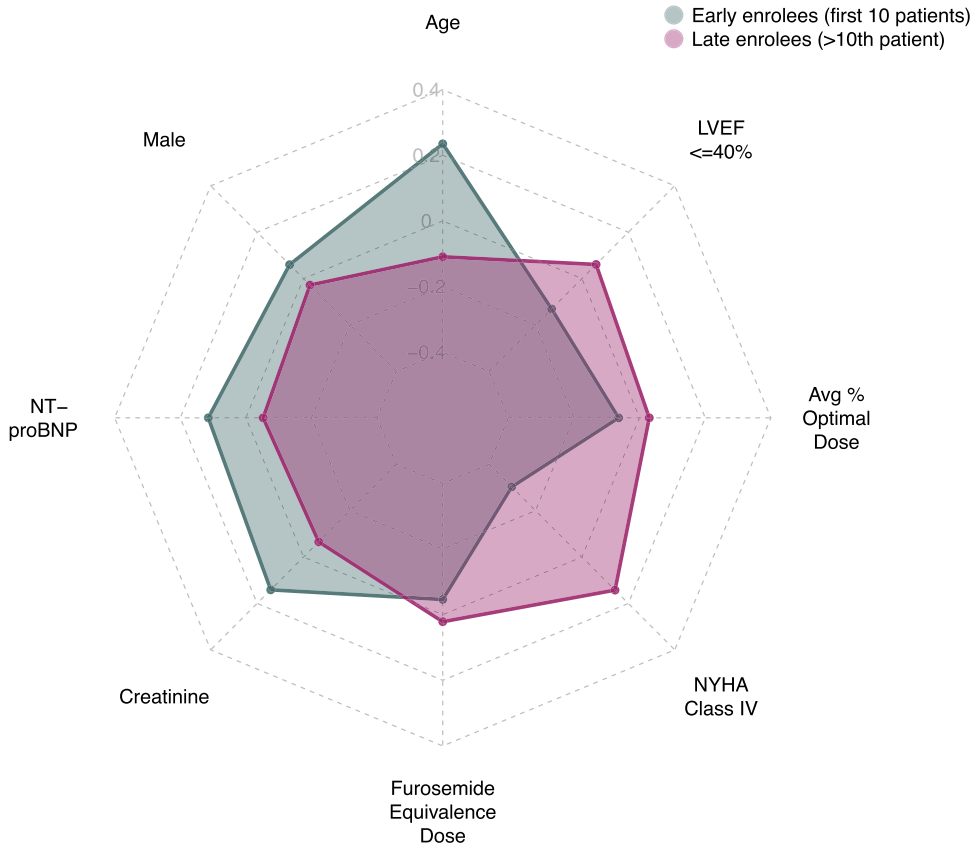
Legend: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

**Table 2.** Guideline-directed medical therapy dose relative to the optimal dose by visit, treatment arm, and enrolment group

| Treatment arm | Before randomization | | | | | | Immediately after randomization | | | | | | Day 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Early enrollees (N = 342) | | Late enrollees (N = 736) | | Early vs. Late *P* | Treatment-by-group interaction *P* | Early enrollees (N = 342) | | Late enrollees (N = 736) | | Early vs. Late *P* | Treatment-by-group interaction *P* | Early enrollees (N = 342) | | Late enrollees (N = 736) | | Early vs. Late *P* | Treatment-by-group interaction *P* |
| | HIC | UC | HIC | UC | | | HIC | UC | HIC | UC | | | HIC | UC | HIC | UC | | |
| N (data available) | 171 | 167 | 369 | 367 | | | 172 | 167 | 369 | 367 | | | 156 | 156 | 349 | 341 | | |
| **ACEi/ARB/ARNi** | | | | | .006 | .66 | | | | | .046 | .013 | | | | | .26 | <.001 |
| None | 46% | 50% | 29% | 31% | | | 4% | 45% | 1% | 32% | | | 5% | 33% | 1% | 28% | | |
| < ½ full dose | 31% | 22% | 44% | 46% | | | 29% | 26% | 16% | 44% | | | 20% | 30% | 9% | 43% | | |
| ½ - < full dose | 21% | 25% | 27% | 22% | | | 63% | 28% | 83% | 24% | | | 21% | 31% | 34% | 28% | | |
| ≥ full dose | 2.9% | 2.4% | 0.3% | 0 | | | 4% | 2% | 1% | 0% | | | 54% | 5% | 56% | 1% | | |
| **Beta-blockers** | | | | | <.001 | .29 | | | | | .013 | <.001 | | | | | <.001 | <.001 |
| None | 54% | 49% | 71% | 69% | | | 5% | 43% | 0% | 69% | | | 7% | 35% | 4% | 60% | | |
| < ½ full dose | 21% | 19% | 10% | 14% | | | 18% | 17% | 10% | 11% | | | 10% | 15% | 13% | 17% | | |
| ½ - < full dose | 24% | 32% | 18% | 17% | | | 74% | 38% | 89% | 20% | | | 30% | 42% | 36% | 21% | | |
| ≥ full dose | 0.6% | 1.2% | 0.5% | 0.3% | | | 2% | 2% | 1% | 1% | | | 53% | 8% | 48% | 2% | | |
| **MRA** | | | | | <.001 | .75 | | | | | .001 | .87 | | | | | <.001 | .77 |
| None | 16% | 12% | 0.8% | 1.1% | | | 5% | 8% | 0% | 1% | | | 10% | 14% | 4% | 3% | | |
| < ½ full dose | 0.6% | 1.2% | 0.3% | 0.3% | | | 1% | 1% | 0% | 0% | | | 1% | 3% | 0% | 0% | | |
| ½ - < full dose | 54% | 61% | 67% | 68% | | | 55% | 59% | 61% | 68% | | | 8% | 42% | 11% | 48% | | |
| ≥ full dose | 29% | 26% | 32% | 31% | | | 40% | 32% | 39% | 31% | | | 81% | 41% | 85% | 49% | | |

Legend: 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.** Radar plot of eight selected demographic, medication usage and clinical characteristics collected prior to randomization in early and late enrollees. Parameters are expressed as Z-scores, which represents how many standard deviations a particular point differs from the mean within each group. Higher Z-scores are outside, lower Z-scores inside. Avg % optimal dose indicates the "average percentage optimal dose", the average of the three GDMT drug classes, expressed as percent of the target dose. LVEF left-ventricular ejection fraction.

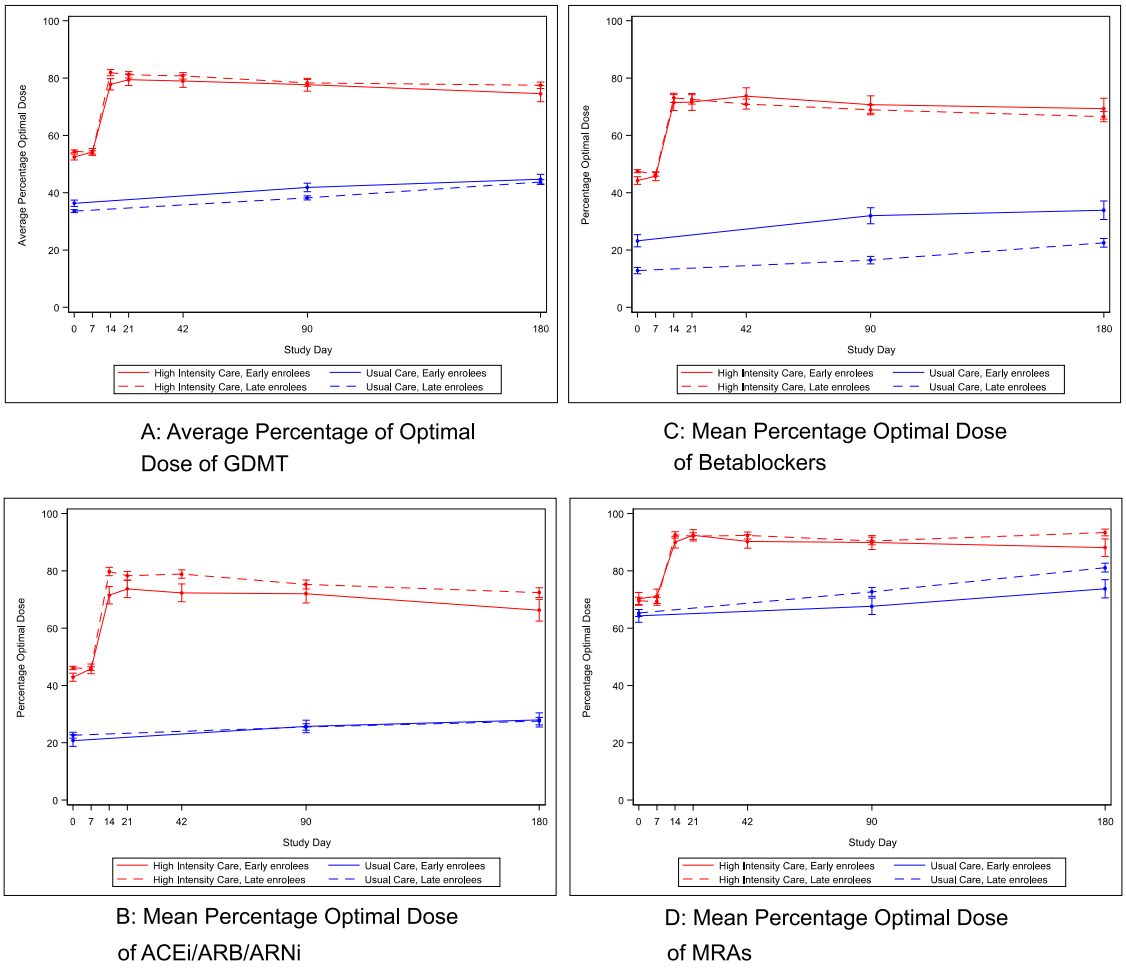



(Figure 2A). However relevant treatment-by-enrolment interactions were found for each single GDMT class. The lower betablockers use in the UC arm was more pronounced in late enrollees during the whole study period (Table 2 and Figure 2C). Conversely, higher ACEi/ARB/ARNi use in the HIC arm was more pronounced in the late enrollees both immediately after randomization (interaction $P = .013$) and at 90 days (interaction $P < .001$) (Table 2 and Figure 2B).

## Efficacy and safety of high-intensity care in older patients

The effect of HIC on the primary endpoint seemed more pronounced in late enrollees (adjusted HR 0.58, 95% CI 0.40–0.83) compared to early enrollees (adjusted HR 0.77, 95% CI 0.36–1.67), but the interaction with enrolment group was not statistically significant (adjusted interaction $P = .51$), (Table 3). However, while in the UC arm a trend toward more severe outcomes in late enrollees was observed (26% vs. 16%, $P = .09$), outcomes in the HIC were similar irrespective of the enrolment group (Figure 3). depicts the cumulative risk for all-cause death and HF readmission during the 180-day follow-up according to enrolment group and treatment arm. When restricted to sites that enrolled greater than 10 patients, the effect of HIC was similar between late (adjusted HR 0.58, 95% CI 0.40–0.83) and early enrollees (adjusted HR 0.60, 95% CI 0.23–1.59, adjusted interaction $P = .93$). Further sensitivity analyses comparing the first and last patients enrolled at sites that enrolled greater than 10 patients showed a more pronounced effect in late vs. early enrolled, though the difference was not statistically significant (Table 3). A consistent benefit favoring the HIC group was observed when dividing patients into cohorts of twenty based on the timing of enrolment within each site (interaction $P = .78$), although the estimates trended towards a greater effect of HIC for later-enrolled patients (Figure 4).

**Figure 2.** Percentage of optimal doses of GDMT by early vs. late enrollees. A, average percentage optimal dose across all three medication classes, B, percentage optimal dose of ACEi/ARB/ARNi, C, percentage optimal dose of beta-blockers, D, percentage optimal dose of MRAs. The "average percentage optimal dose" indicates the average of the 3 GDMT drug classes, expressed as percent of the target dose.




A: Average Percentage of Optimal Dose of GDMT

C: Mean Percentage Optimal Dose of Betablockers

B: Mean Percentage Optimal Dose of ACEi/ARB/ARNi

D: Mean Percentage Optimal Dose of MRAs

Proportions of adverse events (including bradycardia, hypotension, acute kidney injury and hyperkalemia), were numerically higher in patients randomized to HIC compared to UC but did not vary significantly by enrolment group (early enrollees: 50% vs 30%; late enrollees 37% vs 29%, treatment-by-enrolment interaction $P = .09$), (Supplementary Table 2). Rates of serious adverse events in the HIC compared to UC were similar across the enrolment groups: 21% vs. 16% in early enrollees, and 14% vs. 18% in late enrollees, interaction $P = .06$, (Supplementary Table 3).

## Discussion

This analysis of STRONG-HF showed that over the course of the trial small but relevant differences in patient characteristics and event rates between early and late enrollees occurred. Late enrollees, despite being younger, having less comorbidities, and lower natriuretic peptides, displayed more severe cardiac disease and lower LVEF, which translated into a higher risk of death or HF readmission. This observation carries implications for the execution of interventional clinical trials, particularly if the enrolment period is expected to last several years. Indeed, despite precise in- and exclusion criteria that are used to enrich and homogenize the study population, the duration of clinical trials may have a relevant impact on the number of events. Our data confirm the observed differences in baseline characteristics between patients enrolled early or late during the recruitment period of the ACTION-HF study.[4] We further extend prior data by showing that the observed differences in baseline characteristics translate into different incidences of

**Table 3.** Primary endpoint (all-cause mortality / HF readmission at day 180) according to enrolment group and treatment arm

| Analysis | Early enrollees | | | | Late enrollees | | | | *P*-value (Treatment-by-enrolment 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 |
| *Main analysis: all sites* | 16/137 (12.9%) | 22/135 (16.4%) | 0.77 (0.35, 1.67) | 0.77 (0.36, 1.67) | 58/369 (16.0%) | 87/367 (25.6%) | 0.59 (0.41, 0.85) | 0.58 (0.40, 0.83) | .55 | .51 |
| Sensitivity analyses | | | | | | | | | | |
| Sites enrolling >10 patients | 10/97 (10.8%) | 18/103 (17.2%) | 0.60 (0.23, 1.57) | 0.60 (0.23, 1.59) | 58/369 (16.0%) | 87/367 (25.6%) | 0.59 (0.41, 0.85) | 0.58 (0.40, 0.83) | .98 | .93 |
| Sites enrolling >10 patients with late enrollees including up to last 10 patients | 10/97 (10.8%) | 18/103 (17.2%) | 0.60 (0.23, 1.57) | 0.59 (0.22, 1.56) | 6/80 (10.4%) | 10/70 (19.7%) | 0.46 (0.16, 1.31) | 0.38 (0.13, 1.07) | .73 | .54 |
| Sites enrolling ≥ 20 patients with late enrollees including the last 10 patients | 6/50 (11.4%) | 12/60 (18.4%) | 0.58 (0.16, 2.14) | 0.60 (0.16, 2.22) | 4/56 (8.5%) | 6/54 (16.9%) | 0.53 (0.14, 1.98) | 0.40 (0.11, 1.52) | .92 | .67 |

Legend: Adjustment for baseline diastolic blood pressure, ischemic etiology, edema, and baseline NT-proBNP using Cox regression.

**Figure 3.** Unadjusted kaplan-meier curves for the primary endpoint (all-cause death or heart failure readmission) through day 180 by enrolment group (early vs. late) and treatment. HIC, high-intensity care; UC, usual care.




**Figure 4.** Treatment effect of high intensity care vs. usual care for the primary endpoint (all-cause death or heart failure readmission) through day 180 by enrolment order in sites that enrolled greater than 10 patients. HR, hazard ratio; CI, confidence interval.




the primary outcome between early and late enrollees. If outcomes of trial participants enrolled early or late are different, this may have significant implications, not only for trial design and conduct, but for decisions on premature termination of studies during interim assessments or protocol amendments mid-stream of a trial. For instance, a low early event rate may be inappropriately ascribed to treatment futility. A protocol amendment that caps recruitment in subgroups or changes the risk profile of the study population without considering potential differences between early and late enrollees may inadvertently harm the trial. Furthermore, these data support the importance of timely enrolment during a clinical trial to maintain a homogeneous study population, or consideration of statistical approaches to assess potential drifts

in risk profile over time should a study take much longer than anticipated.

Despite these differences in clinical characteristics between early and late enrollees, the present analysis confirmed the robustness of the HIC strategy in achieving GDMT up-titration compared to UC with no treatment-by-enrolment interaction between early and late patients.

Before randomization, the use of ACEi/ARB/ARNi and MRA was higher in late enrollees, while the use of betablockers was higher in early enrollees. However, randomization to HIC was associated to marked up-titration in both enrolment groups and similar achieved average percentage of optimal doses of these three medication classes irrespective of the order of inclusion. This observation is important because it suggests that when GDMT up-titration is performed following a protocol, this can be more easily achieved without a significant learning curve. The observed differences in pre-randomization use of 2 GDMT classes might be related to heterogeneity of the sites or an overall improvement in performance of the local staff with time, involving also the treatment period before study inclusion. Furthermore, a previously published sub-analysis of the EVEREST trial highlighted that the enrolment volume of the study sites might translate into differences in baseline characteristics, treatment, and outcomes. High enrolling sites had fewer sick patients, better protocol completion, and lower incidence of the primary outcome.[5] In our analysis we didn't consider the size of the enrolment site, but we might anticipate that the "late enrollees" group includes more patients from high enrolling sites, which per definition included at least 10 patients.

We also found that pre-randomization betablockers were used less often in late enrollees compared to the early group, and although up-titrated in HIC, the difference in betablocker doses between HIC and UC was less pronounced over the 90 days in early enrollees. The reasons of the differential use of betablocker between early and late patients cannot be fully explained. According to the study protocol, betablocker up-titration was discouraged when clinical or biochemical evidence of congestion was present. We might anticipate that in the more severe group of late enrollees, the proportion of patients in whom betablocker up-titration was postponed could have been higher. Pre-randomization, ACEi/ARB/ARNI were less commonly prescribed among early enrollees, and post-randomization up-titration of this medication class in HIC was somewhat less among early enrollees. Again, the difference between early and late enrollees cannot be fully explained, although it might be noted that baseline renal function was worse, on average, among early than late enrollees. The smaller between-treatment-group differences in these two medication classes among early compared to late enrollees might explain, in part, the somewhat greater effect of HIC on the primary outcome in later patients.

The third – and clinically most relevant finding of this analysis – is that the efficacy and safety of HIC was robust and consistent in early and late enrollees with a non-significant trend towards a more pronounced effect in late enrollees. The deployment of HIC mitigated the higher risk of the primary outcome observed in late enrollees randomized to UC.

### Limitations

There are several inherent limitations to these analyses, in addition to those already mentioned in the overall STRONG-HF study. First, given that subgroup analyses are performed, statistical power might be limited as the study was not specifically powered for these analyses. Second, for this analysis we defined the early and late groups according to the order of enrolment within each center. This approach allows consideration of a larger number of study sites and reduces bias by centers compared to a definition based on a given calendar date. Furthermore, by performing the analyses based on within-site enrolment order would reduce biases related to asynchronous site initiations and increase accuracy for local changes occurring over the course of the study (e.g. with increasing experience at each center)." On the other hand, the inclusion of the 10th patient occurred at different calendar dates in each center, and temporal changes including the impact of the COVID pandemic on the study sites might have heterogeneously affected the enrolment groups. Third, low enrolling sites, which included less than 10 patients, might have biased the results of the early group. In a sensitivity analysis for the primary outcome, after removal of patients from study sites including less than 10 patients, we found robust results, with similar efficacy of HIC irrespective of enrolment group.

Finally, we were only able to describe associations, and causality cannot be proven. Our analysis should be considered hypothesis generating, providing additional data on the association between order of enrolment, patient risks, management, and outcomes.

## Conclusion

In STRONG-HF, late enrollees had different clinical characteristics and higher event rates compared to early enrollees. The implementation of GDMT through a HIC strategy was robust with similar achieved doses in early and late enrollees. Deployment of HIC had a consistent efficacy in early and late enrollees, mitigating the higher risk of adverse outcome in late enrollees.

## Conflict of interest

AM 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.

BD, MB, CE, MN, KT, GC 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. BD and GC are directors of Heart Initiative, a non-profit organisation. MAd has received speaker fees from Abbott Vascular and Medtronic. JC has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. AC-S has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. OC received grants from Servier. AD 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. RD has received supporting fees for coordination of STRONG-HF trial activities. GF has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier and Amgen. CSPL 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. MP has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. PSP 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. KS has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. AAV has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. All other authors declare no competing interests.

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**Mattia Arrigo:** Conceptualization, Writing – original draft, Writing – review & editing. **Beth Davison:** Conceptualization, Supervision, Writing – review & editing. **Christopher Edwards:** Data curation, Methodology, Formal analysis. **Marianna Adamo:** Writing – review & editing. **Andrew P. Ambrosy:** Writing – review & editing. **Marianela Barros:** Writing – review & editing. **Jan Biegus:** Writing – review & editing. **Jelena Celutkiene:** Writing – review & editing. **Kamilė Čerlinskaitė-Bajorė:** Writing – review & editing. **Ovidiu Chioncel:** Writing – review & editing. **Alain Cohen-Solal:** Writing – review & editing. **Albertino Damasceno:** Writing – review & editing. **Rafael Diaz:** Writing – review & editing. **Gerasimos Filippatos:** Writing – review & editing. **Etienne Gayat:** Writing – review & editing. **Antoine Kimmoun:** Writing – review & editing. **Carolyn S.P. Lam:** Writing – review & editing. **Marco Metra:** Writing – review & editing. **Maria Novosadova:** Writing – review & editing. **Matteo Pagnesi:** Writing – review & editing. **Peter S. Pang:** Writing – review & editing. **Piotr Ponikowski:** Writing – review & editing. **Hadiza Saidu:** Writing – review & editing. **Karen Sliwa:** Writing – review & editing. **Koji Takagi:** Data curation, Methodology, Formal analysis. **Jozine M. Ter Maaten:** Writing – review & editing. **Daniela Tomasoni:** Writing – review & editing. **Adriaan A. Voors:** Writing – review & editing. **Gad Cotter:** Conceptualization, Supervision, Writing – review & editing. **Alexandre Mebazaa:** Conceptualization, Supervision, Writing – review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.04.019.

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