Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

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Summary

Background There is a paucity of evidence for dose and pace of up-titration of guideline-directed medical therapies after admission to hospital for acute heart failure.

Methods In this multinational, open-label, randomised, parallel-group trial (STRONG-HF), patients aged 18–85 years admitted to hospital with acute heart failure, not treated with full doses of guideline-directed drug treatment, were recruited from 87 hospitals in 14 countries. Before discharge, eligible patients were randomly assigned (1:1), stratified by left ventricular ejection fraction (≤40% *vs* >40%) and country, with blocks of size 30 within strata and randomly ordered sub-blocks of 2, 4, and 6, to either usual care or high-intensity care. Usual care followed usual local practice, and high-intensity care involved the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over the 2 months after discharge that closely monitored clinical status, laboratory values, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. The primary endpoint was 180-day readmission to hospital due to heart failure or all-cause death. Efficacy and safety were assessed in the intention-to-treat (ITT) population (ie, all patients validly randomly assigned to treatment). The primary endpoint was assessed in all patients enrolled at hospitals that followed up patients to day 180. Because of a protocol amendment to the primary endpoint, the results of patients enrolled on or before this amendment were down-weighted. This study is registered with ClinicalTrials.gov, NCT03412201, and is now complete.

Findings Between May 10, 2018, and Sept 23, 2022, 1641 patients were screened and 1078 were successfully randomly assigned to high-intensity care (n=542) or usual care (n=536; ITT population). Mean age was 63·0 years (SD 13·6), 416 (39%) of 1078 patients were female, 662 (61%) were male, 832 (77%) were White or Caucasian, 230 (21%) were Black, 12 (1%) were other races, one (<1%) was Native American, and one (<1%) was Pacific Islander (two [<1%] had missing data on race). The study was stopped early per the data and safety monitoring board's recommendation because of greater than expected between-group differences. As of data cutoff (Oct 13, 2022), by day 90, a higher proportion of patients in the high-intensity care group had been up-titrated to full doses of prescribed drugs (renin-angiotensin blockers 278 [55%] of 505 *vs* 11 [2%] of 497; β blockers 249 [49%] *vs* 20 [4%]; and mineralocorticoid receptor antagonists 423 [84%] *vs* 231 [46%]). By day 90, blood pressure, pulse, New York Heart Association class, bodyweight, and NT-proBNP concentration had decreased more in the high-intensity care group than in the usual care group. Heart failure readmission or all-cause death up to day 180 occurred in 74 (15·2% down-weighted adjusted Kaplan-Meier estimate) of 506 patients in the high-intensity care group and 109 (23·3%) of 502 patients in the usual care group (adjusted risk difference 8·1% [95% CI 2·9–13·2]; p=0·0021; risk ratio 0·66 [95% CI 0·50–0·86]). More adverse events by 90 days occurred in the high-intensity care group (223 [41%] of 542) than in the usual care group (158 [29%] of 536) but similar incidences of serious adverse events (88 [16%] *vs* 92 [17%]) and fatal adverse events (25 [5%] *vs* 32 [6%]) were reported in each group.

Interpretation An intensive treatment strategy of rapid up-titration of guideline-directed medication and close follow-up after an acute heart failure admission was readily accepted by patients because it reduced symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care.

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Introduction

The period starting with an admission to hospital due to acute heart failure and the couple of following months, often called the vulnerable period, is a time of increased risk of heart failure-related morbidity and death of patients with history of heart failure. Despite this substantially increased risk, few patients admitted to hospital after acute heart failure are closely followed up

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Research in context

Evidence before this study

The 2021 scientific statement of the Heart Failure Association of the European Society of Cardiology on the treatment of acute heart failure recommended early follow-up of patients after hospital admission for 2–4 weeks after discharge and initiation of recommended therapies, but the level of evidence for this recommendation is low and doses to which medications should be titrated are not clearly specified. Additionally, oral heart failure medications such as β blockers; angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors; and mineralocorticoid receptor antagonists have been shown to be beneficial for the long-term outcomes of patients with chronic stable heart failure. However, how to safely optimise oral heart failure medications during the so-called vulnerable phase after discharge from hospital after acute heart failure is unknown. Retrospective analyses and some prospective studies, which were mostly small and underpowered for significant adverse events such as readmissions and death, and registries of different strategies, have not given conclusive results. Rapid up-titration of guideline-recommended therapies, under close follow-up and monitoring, during and early after discharge from a heart failure hospital admission might affect outcomes.

Added value of this study

To our knowledge, STRONG-HF is the first prospective, randomised study to compare an intensified protocol implemented at the end of an acute heart failure admission, in which patients were either quickly up-titrated within 2 weeks of discharge to 100% doses of guideline-directed medical therapy under strict follow-up (high-intensity care), inclusive of clinical assessments, laboratory assessment, and measurement of N-terminal pro-B-type natriuretic peptide, or were followed up per local practice (usual care). The primary endpoint of heart failure readmission or all-cause mortality up to day 180 was reduced in patients assigned to the high-intensity care group. STRONG-HF intended to enrol 1800 patients; after enrolling more than 1000 patients, the data and safety monitoring board of the study recommended early termination of the study because of greater than expected between-group differences, implying that intensive follow-up with rapid up-titration of guideline-directed medical therapies are clinically significant after admission to hospital for acute heart failure.

Implications of all the available evidence

Millions of people are admitted to hospital for acute heart failure worldwide each year, with a substantial risk of rehospitalisation or death within 3–6 months of admission; therefore, the results of the STRONG-HF trial might have a substantial impact on clinical practice and, if adopted and implemented worldwide, on outcomes for patients with heart failure.

or treated with full doses of guideline-directed medical therapies.[1–7] The association of closer follow-up and quicker up-titration of treatment after an acute heart failure event has been examined in a few studies, but with mixed results.[8–15] On the basis of this paucity of evidence from prospective randomised studies, the 2021 European Society of Cardiology Heart Failure Association guidelines for the treatment of heart failure recommend follow-up of patients after an acute heart failure admission within 2–4 weeks after discharge and initiation of recommended therapies, but the level of evidence for this recommendation is low.[16] Furthermore, frequency and content of visits and the dose to which medications should be titrated during those visits are not clearly specified in these guidelines.[16]

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, randomised, prospective clinical trial, designed to assess the safety and efficacy of rapid up-titration of treatments before discharge from an acute heart failure admission and during the following weeks compared with usual care. The safety of up-titration was guided by physical examination, assessment of symptoms and signs of congestion, and laboratory assessments including N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Methods

Study design and patients

The study design has been published elsewhere.[17,18] Briefly, STRONG-HF was a multinational, multicentre, open-label, randomised, parallel-group study designed to assess the safety and efficacy of up-titration of guideline-recommended heart failure medical therapy, including β blockers, angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] if the patient was intolerant to ACE inhibitors) or angiotensin receptor-neprilysin (ARN) inhibitors, and mineralocorticoid receptor antagonists, on morbidity and mortality when initiated and up-titrated early after hospitalisation for acute heart failure.

Patients were recruited from 87 hospitals in 14 countries (Argentina, Austria, Bulgaria, Columbia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia). Patients were eligible for inclusion if they were aged 18–85 years; had been admitted to hospital within 72 h before screening for acute heart failure, defined as dyspnoea at rest and pulmonary congestion on chest x-ray, and other signs or symptoms of heart failure (eg, oedema or positive rales on auscultation); were haemodynamically stable; had elevated NT-proBNP concentrations at screening (>2500 pg/mL) and a more than 10% decrease in concentration between screening and before randomisation (but

still >1500 pg/mL); and had not been treated with optimal doses of oral heart failure therapies within 2 days before anticipated hospital discharge for acute heart failure. Patients were excluded if they had a clear intolerance to high doses of β blockers, ACE inhibitors, or ARBs. There were no inclusion criteria based on left ventricular ejection fraction (LVEF). Full eligibility criteria are in the appendix (pp 3–4).

At the time of study start-up, SGLT-2 inhibitors were either not approved for the treatment of heart failure or not widely used in many countries, and intravenous iron supplementation use was not yet recommended. Sites were encouraged to use only treatments, especially β blockers, which have been shown to improve heart failure outcomes.[16] After study start, the protocol was amended twice:[18] first, to add a patient contact at 180 days for safety (protocol amendment 1: June 11, 2019) and, second, to increase study power by changing the timing of assessment for the primary endpoint from 90 to 180 days and increasing target enrolment from 900 to 1800 (protocol amendment 2: Jan 11, 2021). The protocol is available online.[17,18] Before enrolment, the study was approved by appropriate competent authorities and all sites obtained approval from the ethics committees. All patients provided written informed consent. An independent data and safety monitoring board (DSMB) was responsible for the safety of trial participants.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to usual care or intensification of treatment with β blocker, and ACE inhibitor (or ARB) or ARN inhibitor, and a mineralocorticoid receptor antagonist (ie, high-intensity care). A central statistician generated the randomisation scheme, which was stratified by LVEF (≤40% *vs* >40%) and country, with blocks of size 30 within strata, with randomly ordered sub-blocks of size 2, 4, and 6. A central interactive web response system was used so that investigators had no knowledge of upcoming treatment assignments. Because of the nature of the interventions, the investigators and patients were not masked to treatment allocation. However, the investigators and monitors at the sites had no access to aggregate data in any stage of the study. Members of the DSMB were not masked to treatment assignment.

Procedures

Patients in the usual care group were discharged and followed up according to the local practice until day 90 after randomisation when they were seen by the study team.

For patients randomly assigned to the high-intensity care group, treatment followed an algorithm combining optimisation of oral heart failure therapies and frequent visits, including circulating NT-proBNP measures, to assess congestion. For patients in this group, the first dose adjustment occurred just after randomisation (within 2 days before anticipated hospital discharge), when patients were prescribed medical therapy with β blockers, renin-angiotensin blockers (ie, ACE inhibitors [or ARBs if intolerant to ACE inhibitors] or ARN inhibitors), and mineralocorticoid receptor antagonists adjusted to at least half the optimal doses. Doses considered to be optimal are provided in the appendix (p 5). Patients were assessed by the study team at 1, 2, 3, and 6 weeks after randomisation (ie, baseline). Additionally, at 2 weeks after randomisation, up-titration to full optimal doses of β blockers; ACE inhibitors, ARBs, or ARN inhibitors; and the mineralocorticoid receptor antagonist should have been reached if safe. An additional safety visit was done 1 week after any up-titration for patients for whom up-titration had to be delayed. Safety and tolerability were assessed at weeks 1, 2, 3, and 6 by full physical examination and laboratory

See **Online** for appendix

For the **protocol** see https://worldheartinitiative.org/

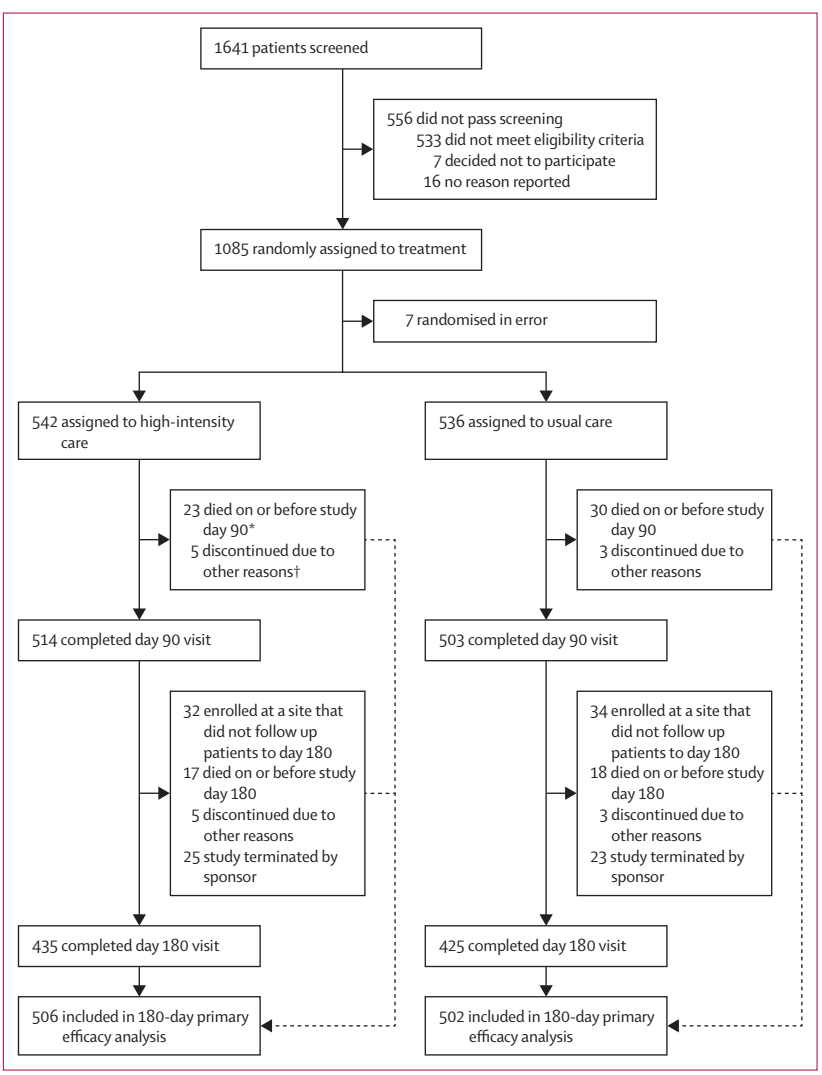

Figure 1: **Trial profile**

*One patient was at a site that did not follow up patients to day 180. †Three patients were at sites that did not follow up patients to day 180.

assessments of NT-proBNP, sodium, potassium, glucose, kidney function, and haemoglobin measures. Investigators assessed congestion by physical examination focused on heart failure signs and symptoms and NT-proBNP measurement, and increased diuretics as needed on the basis of those assessments. ACE inhibitor, ARB, or ARN inhibitor and mineralocorticoid receptor antagonist were not to be up-titrated if a patient's systolic blood pressure was less than 95 mm Hg, serum potassium concentration was more than 5·0 mmol/L, or estimated glomerular filtration rate was less than 30 mL/min per 1·73 m². β blockers were not to be up-titrated if a patient's heart rate was less than 55 beats per min or systolic blood pressure was less than 95 mm Hg. If a patient's NT-proBNP concentration at a follow-up visit was more than 10% higher than the pre-discharge concentration, physicians should have considered not up-titrating β blockers and considered increasing diuretics. In case full up-titration to optimal doses of one or all of the medications was not reached, additional visits were scheduled to implement full optimal doses. Any down-titration of one or more medications was left to the investigator's discretion. All laboratory tests were done locally. A schema describing the timing of all patient visits is in the appendix (p 21).

	High-intensity care group (n=542)	Usual care group (n=536)	Total (N=1078)
Demographics			
Age, years	62·9 (13·5)	63·0 (13·7)	63·0 (13·6)
Sex			
Female	216 (40%)	200 (37%)	416 (39%)
Male	326 (60%)	336 (63%)	662 (61%)
Self-reported race			
Black	115 (21%)	115 (21%)	230 (21%)
White or Caucasian	418 (77%)	414 (77%)	832 (77%)
Native American	1 (<1%)	0	1 (<1%)
Other*	7 (1%)	5 (1%)	12 (1%)
Pacific Islander	1 (<1%)	0	1 (<1%)
Missing	0	2 (<1%)	2 (<1%)
Systolic blood pressure at baseline, mm Hg			
Mean	123·4 (13·30)	122·2 (12·56)	122·8 (12·95)
≤Median (120 mm Hg)	267/542 (49%)	276/534 (52%)	543/1076 (50%)
>Median	275/542 (51%)	258/534 (48%)	533/1076 (49%)
NT-proBNP at screening, ng/L†	7310·4 (4991·26)	6908·3 (4326·78)	7110·7 (4675·17)
NT-proBNP at baseline, ng/L†	4120·8 (3676·59)	3929·2 (3213·36)	4025·6 (3453·98)
History of atrial fibrillation or atrial flutter or present at screening	229 (42%)	254 (47%)	483 (45%)
Geographical region			
Africa	122 (23%)	118 (22%)	240 (22%)
Eastern and western Europe	47 (9%)	47 (9%)	94 (9%)
Russia	351 (65%)	352 (66%)	703 (65%)
South America	22 (4%)	19 (4%)	41 (4%)
Clinical history			
Stroke or transient ischaemic attack	56 (10%)	43 (8%)	99 (9%)
Severe liver disease	3 (1%)	3 (1%)	6 (1%)
Psychiatric or neurological disorder	8 (1%)	12 (2%)	20 (2%)
Malignancies	18 (3%)	11 (2%)	29 (3%)
Diabetes	152 (28%)	161 (30%)	313 (29%)
Diabetes control method			
Insulin	50 (9%)	32 (6%)	82 (8%)
Diet only	102 (19%)	100 (19%)	202 (19%)
Oral antidiabetic agents	110 (20%)	124 (23%)	234 (22%)
Pulmonary embolism	13 (2%)	6 (1%)	19 (2%)
Acute coronary syndrome	166 (31%)	145 (27%)	311 (29%)
Coronary artery bypass surgery	27 (5%)	32 (6%)	59 (5%)
Percutaneous transluminal coronary intervention	80 (15%)	72 (13%)	152 (14%)
Angina Canadian Cardiovascular Society class 2 or higher	74 (14%)	51 (10%)	125 (12%)
Moderate or severe chronic obstructive pulmonary disease or asthma	14 (3%)	13 (2%)	27 (3%)
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	0	1 (<1%)	1 (<1%)
Cardiac resynchronisation therapy	3 (1%)	3 (1%)	6 (1%)
Automatic internal cardiac defibrillator	3 (1%)	6 (1%)	9 (1%)
History of heart failure	465 (86%)	451 (84%)	916 (85%)

(Table 1 continues on next page)

All patients randomly assigned to treatment and those who did not meet eligibility criteria were followed up at 90 days for the occurrence of hospital readmission or death. Adverse events were collected throughout the 90-day period for all patients randomly assigned to treatment. Events were solicited at each study visit or reported when noted by the investigator to have occurred during the follow-up period. Patients assigned to both groups were contacted by telephone at 180 days after randomisation for an assessment of vital status and occurrence of rehospitalisation, and current prescriptions of oral heart failure medications. Adverse events were coded using Medical Dictionary for Regulatory Activities (version 21.1) terminology. Primary cause of death, including death due to COVID-19, and primary reason for re-admission to hospital were selected from predefined lists in the case report form by the investigator and were not adjudicated centrally.

Outcomes

The primary endpoint of the trial (as amended on Jan 11, 2021) was 180-day heart failure readmission or all-cause death, considering only the first occurrence of these events per patient from the time of randomisation (day 0) until day 180. Secondary endpoints were change in quality of life from baseline (just before randomisation) to day 90 as measured by the EQ-5D visual analogue scale (VAS), 180-day all-cause death, and 90-day heart failure readmission or all-cause mortality.

Prespecified exploratory endpoints were 180-day cardiovascular death; 90-day cardiovascular death; 90-day all-cause death; 180-day heart failure readmission; 90-day heart failure readmission; a Finkelstein-Schoenfeld

hierarchical composite endpoint comprising death, heart failure readmission, and change in EQ-VAS from randomisation to 90 days; change in NT-proBNP from randomisation to 90 days; and change from randomisation to 90 days in bodyweight, and signs and symptoms of congestion (including dyspnoea on exertion or rest, orthopnoea, rales, jugular venous pulse, and peripheral oedema).

The predefined safety endpoint was the incidence of treatment-emergent adverse events up to 90 days. Changes from baseline in vital signs (systolic and diastolic blood pressure, heart rate, and bodyweight) at each visit and changes from baseline in local laboratory results were also used to assess safety.

Statistical analysis

We present continuous variables as mean (SD) or as adjusted mean (SE), as appropriate, and categorical variables as absolute and relative frequencies. We did all efficacy and safety analyses in the intention-to-treat (ITT) population, which included all patients who were validly randomised to the treatment group to which they were randomly assigned. Analyses of all 180-day outcomes included only patients enrolled at sites where the ethics committees approved protocol amendment 1 or 2, allowing follow-up of patients to day 180.

We compared the occurrence of primary endpoint events between treatment groups using a χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF (≤40% *vs* >40%) and geographical region (South America, Russia, Africa, and western and eastern Europe) using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. We combined countries into regions for analysis because of the sparseness of events in some countries. Because the protocol was amended on the basis of a lower than expected event rate to increase the sample size and change the primary endpoint from 90-day to 180-day death or heart failure readmission, for 180-day outcomes we down-weighted the results of the initial cohort (hereafter referred to as cohort 1; which included patients randomly assigned to treatment on or before Feb 7, 2020) in the main analysis, proportional to half its sample size.[18] The remaining patients (ie, recruited after Feb 7, 2020), are referred to as cohort 2. We present the total number of events and adjusted and down-weighted event rates in each treatment group, and both the adjusted risk difference (the absolute difference in proportions) and adjusted risk ratio [RR] for the primary endpoint. Based on simulations, with 1800 patients randomly assigned to treatment groups, we estimated the study to have approximately 89% power to detect a difference in event rates of 14% versus 20% at the two-sided 0·05 significance level.

In prespecified analyses of the primary endpoint, we assessed subgroup-by-treatment group interactions by comparing estimated treatment group risk differences between subgroups defined by age at study entry (≤65 *vs* >65 years and ≤75 *vs* >75 years), baseline LVEF (≤40% *vs* >40%), baseline systolic blood pressure (≤median *vs* >median), baseline local value of NT-proBNP (≤median *vs* >median), and history of atrial fibrillation or flutter or atrial fibrillation or flutter present at screening (yes *vs* no). In post-hoc analyses, we examined additional subgroups including baseline LVEF (<50% *vs* ≥50%), region (Europe *vs* not Europe), race (White or Caucasian *vs* not White), sex (male *vs* female), and baseline estimated glomerular filtration rate (≤median *vs* >median). We constructed a χ^2 test of the treatment-by-subgroup interaction from the unadjusted Kaplan-Meier estimates of event rate

	High-intensity care group (n=542)	Usual care group (n=536)	Total (N=1078)
(Continued from previous page)			
NYHA class 1 month before hospital admission			
I	29/508 (6%)	34/492 (7%)	63/1000 (6%)
II	147/508 (29%)	160/492 (33%)	307/1000 (31%)
III	216/508 (43%)	199/492 (40%)	415/1000 (42%)
IV	116/508 (23%)	99/492 (20%)	215/1000 (22%)
Primary cause of heart failure			
Ischaemic	260/541 (48%)	254/534 (48%)	514/1075 (48%)
Non-ischaemic	281/541 (52%)	280/534 (52%)	561/1075 (52%)
LVEF category at baseline			
≤40%	365 (67%)	366 (68%)	731 (68%)
>40%	177 (33%)	170 (32%)	347 (32%)
<50%	452/540 (84%)	460/535 (86%)	912/1075 (85%)
≥50%	88/540 (16%)	75/535 (14%)	163/1075 (15%)
LVEF at baseline, %‡	36·7 (12·57)	35·9 (12·47)	36·3 (12·52)
Hospitalised for heart failure in the past year	140 (26%)	133 (25%)	273 (25%)
Number of heart failure hospitalisations in the past year	0·3 (0·68)	0·4 (1·42)	0·3 (1·11)
History of atrial fibrillation or atrial flutter	238 (44%)	258 (48%)	496 (46%)
Type of atrial fibrillation or atrial flutter			
Paroxysmal	57/234 (24%)	60/256 (23%)	117/490 (24%)
Permanent	137/234 (59%)	156/256 (61%)	293/490 (60%)
Persistent	40/234 (17%)	40/256 (16%)	80/490 (16%)
Oral heart failure medications taken before randomisation			
ACE inhibitors	208/540 (38%)	211/534 (39%)	419/1074 (39%)
ARBs	104/540 (19%)	76/534 (14%)	180/1074 (17%)
ARN inhibitors	42/540 (8%)	48/534 (9%)	90/1074 (8%)
β blockers	184/540 (34%)	200/534 (37%)	384/1074 (36%)
Mineralocorticoid receptor antagonists	509/540 (94%)	510/534 (96%)	1019/1074 (95%)
Loop diuretic	520/540 (96%)	509/534 (95%)	1029/1074 (96%)

Data are n (%), n/N (%), or mean (SD). ACE=angiotensin converting enzyme. ARBs=angiotensin receptor blockers. ARN=angiotensin receptor-neprilysin. LVEF=left ventricular ejection fraction. N-proBNP= N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association. *Other reported races were African (n=2), Europoid (n=2), Latin American (n=1), Berber (n=1), Gipsy (n=1), and not specified (n=5). †Values reported as greater than 9000 ng/L were set to 9000 ng/L. ‡Most recent value within 6 months before screening, including during the index hospitalisation. Values below 10% were set to 10% for analysis.

Table 1: **Demographic and clinical characteristics of the study population**

differences and associated SEs in each level of a subgroup factor. Event rates from cohort 1 were down-weighted in these subgroup analyses.

Secondary endpoints were to be tested sequentially. For the prespecified main analysis of the EQ-VAS, we used only observed data and excluded patients for whom no linguistically validated EQ-5D translation was available. We compared treatment groups using ANCOVA, with fixed terms for treatment, LVEF (≤40 *vs* >40%), geographical region, and baseline value. We analysed the secondary, prespecified exploratory, and sensitivity 180-day clinical outcomes similarly to the primary endpoint. For 90-day outcomes, patients enrolled at all sites were included and the results of cohort 1 were not down-weighted.

We calculated the Finkelstein-Schoenfeld hierarchal composite endpoint by comparing each patient with every other patient within randomisation strata with respect to a hierarchy of outcomes: time to death up to day 90, number of heart failure readmissions up to day 90, and categorised change in EQ-5D VAS from baseline to day 90. We present the treatment effect as the Mann-Whitney odds adjusted for LVEF (≤40% *vs* >40%) and geographical region using Mantel-Haenzsel weights. We compared treatment groups using the van Elteren's test, stratified by LVEF (≤40% *vs* >40%) and geographical region, using modified ridit scores.

We did prespecified sensitivity analyses of the primary endpoint in which the results in cohort 1 were fully weighted according to its sample size and in which results in cohort 1 were discarded thus including only results in cohort 2. We also did a prespecified sensitivity analysis to assess the effect of COVID-19 on the result, in which we censored the time to event in patients who died due to COVID-19 without a previous hospitalisation due to heart failure on the date of death due to COVID-19. To assess the effect of investigator experience on the findings, we did a prespecified sensitivity analysis of the primary endpoint only including patients at sites that enrolled more than ten patients. We did a prespecified sensitivity analysis of the change in EQ-VAS from baseline to day 90 in which a missing value due to death was set to 0 ("the worst health you can imagine") and then remaining missing values were multiply imputed; estimates and tests of treatment effect were then combined over the imputation datasets using Rubin's algorithm. We did post-hoc exploratory analyses to assess all-cause death or all-cause readmission to hospital at 180 days, including COVID-19-related events and excluding COVID-19-related events. In these analyses, we used the same methods as for the primary endpoint, with the same adjustment for LVEF and geographical region and with results in cohort 1 down-weighted.

We compared treatment groups with respect to changes in vital signs and in local laboratory values from baseline to day 90 using ANCOVA models with fixed terms for treatment, LVEF (≤40% *vs* >40%), geographical region, and baseline value; we present least square mean (SE) for each treatment group along with the estimated adjusted mean treatment group difference (95% CI). Local measurements of NT-proBNP greater than the upper reporting limit for the assay used were set to the upper reporting limit; values were log-transformed for analysis. Geometric means with associated 95% CIs at each visit, and adjusted ratios of follow-up to baseline geometric means are presented in each treatment group, along with the treatment group ratio of these ratios. We compared the treatment groups with respect to ordered categorical measures of heart failure signs and symptom severity using van Elteren's tests, stratified by LVEF (≤40% *vs* >40%), geographical region, and baseline value; we present treatment effects as Mann-Whitney odds stratified by LVEF (≤40% *vs* >40%), geographical region, and baseline value.

As stated in the protocol, the DSMB could recommend that the study be discontinued for futility at either of two planned interim futility analyses if the estimated conditional power for the primary endpoint—assuming that the treatment effect assumed for the sample size in the protocol applies to the remainder of the study—was

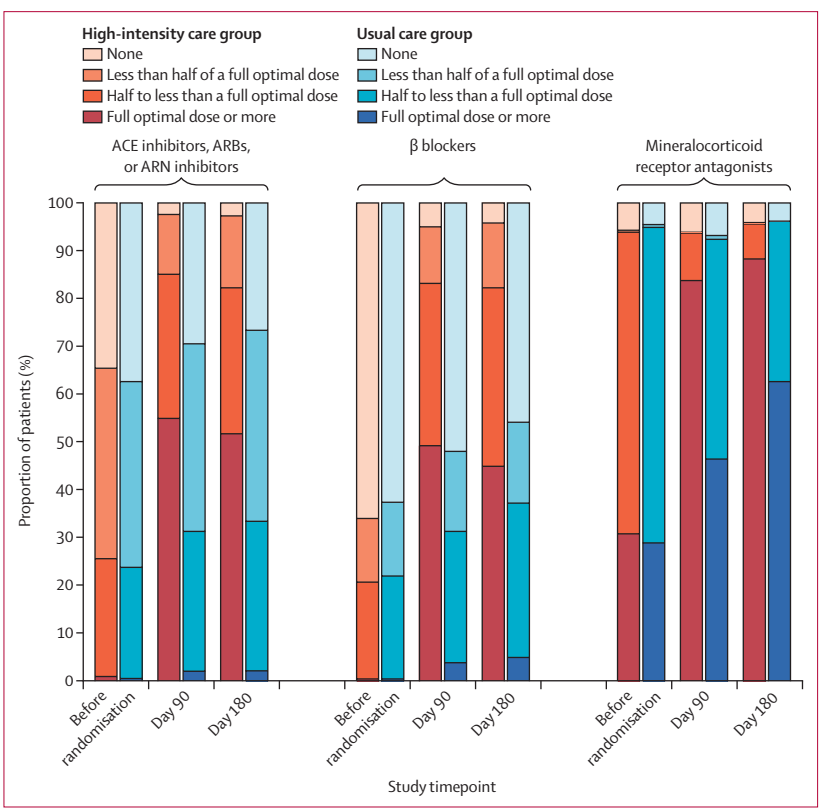

Figure 2: **Oral guideline-directed medical therapies for heart failure prescribed, in high-intensity care and usual care groups by visit**

Full optimal doses for each treatment are given in the appendix (p 5). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARN=angiotensin receptor-neprilysin.

less than 0·25. No adjustment to the final α level was required for these futility analyses. After a planned interim futility analysis, when approximately 500 patients had 90-day follow-up data, the study was amended to revise the primary endpoint and increase the sample size to increase power to assess the outcome differences between the two treatment groups. It was not intended to stop the trial early for superior efficacy. However, after reviewing a second interim futility analysis presented at a planned safety evaluation when approximately 1000 patients had 90-day follow-up data, the DSMB recommended stopping the trial because of the larger than expected risk reduction of the primary endpoint in the high-intensity care group, which remained highly significant in sensitivity analyses, and without safety concerns. Patients who had not completed the trial at the time the trial was terminated were brought in for a final study visit. These and any other censored follow-up times were included in the Kaplan-Meier estimates of cumulative risks.

Two-sided p values of less than 0.05 were considered to be statistically significant. We did all analyses using SAS (version 9.4). This study is registered at ClinicalTrials.gov, NCT03412201.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Between May 10, 2018, and Sept 23, 2022, 1641 patients were screened and 1085 were randomly assigned to treatment. Seven individuals were randomly assigned in error, such that 1078 patients were validly assigned to high-intensity care (n=542) or usual care (n=536; ITT population). 1008 patients (n=506 high intensity care and n=502 usual care) were at sites that followed-up patients to day 180 (figure 1). The study was terminated on Sept 23, 2022, following the recommendation of the DSMB who, due to a larger than expected difference in risk of the primary endpoint between the groups based on an analysis when 1069 total patients had been randomly assigned, believed withholding the intensive treatment strategy from both current and future study patients to be unethical.

At the time of study termination, a final visit had been completed for all but 112 (10%) of 1078 patients randomly assigned to treatment. For these 112 patients, final follow-up visits were completed within 3 weeks (by Oct 13, 2022 [data cutoff]) after the study was terminated. Baseline characteristics of the ITT population are shown in table 1; enrolment by country and site is included in the appendix (p 2). Mean age was 63·0 years (SD 13·6), 416 (39%) of 1078 patients were female, 662 (61%) were male, 832 (77%) were White, 230 (21%) were Black, 12 (1%) were other races, one (<1%) was Native American,

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	p value
Vital signs				
Systolic blood pressure, mm Hg				
Baseline	123·4 (13·30)	122·2 (12·56)	..	..
Day 90	119·0 (15·93)	123·8 (15·29)	..	..
Adjusted mean change	−3·7 (0·92)	1·6 (0·94)	−5·4 (−7·2 to −3·5)*	<0·0001
Diastolic blood pressure, mm Hg				
Baseline	76·7 (10·22)	75·9 (8·71)	..	..
Day 90	74·0 (10·41)	75·9 (10·14)	..	..
Adjusted mean change	−2·4 (0·59)	−0·07 (0·61)	−2·3 (−3·5 to −1·1)*	0·0001
Heart rate, beats per min				
Baseline	78·5 (11·78)	78·8 (11·82)	..	..
Day 90	71·3 (13·30)	77·3 (12·61)	..	..
Adjusted mean change	−7·8 (0·77)	−2·0 (0·79)	−5·8 (−7·3 to −4·3)*	<0·0001
Respiratory rate, breaths per min				
Baseline	18·0 (2·43)	18·3 (6·13)	..	..
Day 90	17·2 (2·41)	17·7 (2·59)	..	..
Adjusted mean change	−2·1 (0·14)	−1·7 (0·15)	−0·4 (−0·7 to −0·1)*	0·0028
Bodyweight, kg				
Baseline	81·02 (20·39)	81·63 (20·58)	..	..
Day 90	80·23 (20·55)	81·87 (20·19)	..	..
Adjusted mean change	−1·78 (0·282)	−0·42 (0·290)	−1·36 (−1·91 to −0·80)*	<0·0001
Signs and symptoms of heart failure				
Peripheral oedema†				
Baseline	..	..	..	..
None	309/542 (57%)	297/534 (56%)	..	..
1+	197/542 (36%)	201/534 (38%)	..	..
2+	33/542 (6%)	31/534 (6%)	..	..
3+	3/542 (1%)	5/534 (1%)	..	..
Day 90	..	..	1·30 (1·17 to 1·44)‡	0·0002
None	384/491 (78%)	315/483 (65%)	..	..
1+	91/491 (19%)	130/483 (27%)	..	..
2+	15/491 (3%)	33/483 (7%)	..	..
3+	1/491 (<1%)	5/483 (1%)	..	..
Jugular venous pressure, cm				
Baseline	..	..	..	..
<6	422/507 (83%)	411/488 (84%)	..	..
6–10	79/507 (16%)	74/488 (15%)	..	..
>10	6/507 (1%)	3/488 (1%)	..	..
Day 90	..	..	1·13 (1·05 to 1·21)‡	0·015
<6	420/453 (93%)	378/429 (88%)	..	..
6–10	31/453 (7%)	40/429 (9%)	..	..
>10	2/453 (<1%)	11/429 (3%)	..	..

(Table 2 continues on next page)

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	p value
(Continued from previous page)				
Rales, proportion of lung field or fields§				
Baseline	..	..	..	..
None	458/542 (85%)	457/534 (86%)	..	..
<1/3	71/542 (13%)	69/534 (13%)	..	..
1/3 to 2/3	12/542 (2%)	8/534 (2%)	..	..
>2/3	1/542 (<1%)	0/534 (0%)	..	..
Day 90	..	..	1·07 (1·00 to 1·15)‡	0·073
None	454/490 (93%)	421/479 (88%)	..	..
<1/3	33/490 (7%)	57/479 (12%)	..	..
1/3 to 2/3	3/490 (1%)	1/479 (<1%)	..	..
>2/3	0/490 (0%)	0/479 (0%)	..	..
NYHA class				
Baseline	..	..	..	..
I	34/542 (6%)	28/534 (5%)	..	..
II	315/542 (58%)	326/534 (61%)	..	..
III	188/542 (35%)	177/534 (33%)	..	..
IV	5/542 (1%)	3/534 (1%)	..	..
Day 90	..	..	1·36 (1·22 to 1·53)‡	<0·0001
I	116/495 (23%)	76/488 (16%)	..	..
II	297/495 (60%)	288/488 (59%)	..	..
III	77/495 (16%)	107/488 (22%)	..	..
IV	5/495 (1%)	17/488 (4%)	..	..
Local laboratory measurements				
Haemoglobin, g/L				
Baseline	136·3 (20·3)	136·6 (19·7)	..	..
Day 90	132·2 (17·2)	133·4 (17·3)	..	..
Adjusted mean change	−4·92 (0·84)	−3·96 (0·86)	−0·96 (−2·61 to 0·70)*	0·26
White blood cells, 10^9 per L				
Baseline	6·90 (1·95)	7·08 (2·08)	..	..
Day 90	6·89 (1·80)	7·03 (2·06)	..	..
Adjusted mean change	−0·04 (0·108)	0·04 (0·111)	−0·08 (−0·29 to 0·14)*	0·48
Lymphocytes, %				
Baseline	27·23 (9·94)	27·24 (9·67)	..	..
Day 90	28·05 (8·71)	27·46 (9·19)	..	..
Adjusted mean change	0·86 (0·504)	0·25 (0·512)	0·61 (−0·37 to 1·59)*	0·22
Glucose, mmol/L				
Baseline	6·21 (2·47)	6·27 (2·17)	..	..
Day 90	6·34 (2·47)	6·34 (2·65)	..	..
Adjusted mean change	0·11 (0·138)	0·07 (0·141)	0·04 (−0·24 to 0·31)*	0·78
Sodium, mmol/L				
Baseline	140·14 (4·03)	140·30 (4·30)	..	..
Day 90	140·50 (4·28)	140·25 (4·26)	..	..
Adjusted mean change	−0·69 (0·239)	−1·03 (0·245)	0·34 (−0·13 to 0·80)*	0·15

(Table 2 continues on next page)

and one (<1%) was Pacific Islander (two participants had missing data on race). Cohort 1 comprised 380 patients who were included in day 180 analyses.

A higher proportion of patients in the high-intensity care group were up-titrated to higher doses of treatments for heart failure than those in the usual care group (figure 2). By day 90, most patients in the high-intensity care group but only a small number assigned to usual care were up-titrated to full doses of each of the three oral heart failure medication classes (renin-angiotensin blockers 278 [55%] of 505 *vs* 11 [2%] of 497; β blockers 249 [49%] *vs* 20 [4%]; mineralocorticoid receptor antagonists 423 [84%] *vs* 231 [46%]). The doses of medication and their up-titration did not differ by LVEF (appendix pp 10–14). However, up-titration in the high-intensity care group was achieved by using more early outpatient clinic visits than in the usual care group. During the first 90 days of the study, patients in the high-intensity care group had a mean of 4·8 visits (SD 1·0) versus 1·0 visits (0·3) in the usual care group. SGLT-2 inhibitors and intravenous iron supplementation use were only captured in the last years of the study (between Jan 25, 2021 and Oct 13, 2022; after approval and recommendation for heart failure). SGLT2 inhibitors were reported to have been prescribed at day 90 in 48 (10%) of 505 patients in the high-intensity care group and 27 (5%) of 497 in the usual care group. Use of intravenous iron during the index hospitalisation was reported for five (1%) patients in the high-intensity care group and none in the usual care group.

At day 90, treatment groups differed significantly with respect to changes from randomisation in some measures expected to be associated with increased dose of drugs, such as systolic blood pressure, pulse, and bodyweight (table 2). Bodyweight decreased more among patients in the high-intensity care group than in the usual care group, and most signs of congestion improved more in the high-intensity care group than in the usual care group, as did New York Heart Association (NYHA) class (table 2), despite lower adjusted mean total daily dose of oral loop diuretics dose at day 90 (50·8 mg furosemide equivalents in the high-intensity care group *vs* 57·2 mg furosemide equivalents in the usual care group [p=0·038]). The reduction in NT-proBNP was greater in the high-intensity care group than in the usual care group (adjusted geometric mean ratios of NT-proBNP concentration at day 90 to baseline were 0·436 high-intensity care *vs* 0·564 usual care; p=0·0003; table 2).

The primary endpoint at 180 days was observed in 74 (15·2% down-weighted adjusted Kaplan-Meier estimate) of 506 patients in the high-intensity care group and 109 (23·3%) of 502 patients in the usual care group. The risk of the primary endpoint, 180-day heart failure readmission or all-cause death, was lower in the high-intensity care group than in the usual care group

(table 3). The adjusted risk was 8·1% (95% CI 2·9–13·2; p=0·0021) lower in the high-intensity care group than in the usual care group, which corresponds to an adjusted RR of 0·66 (95% CI 0·50–0·86). Adjusted Kaplan-Meier curves with down-weighting of cohort 1 for the primary endpoint are shown in figure 3. Analyses of the primary endpoint by subgroups of interest are shown in figure 4. The benefits of high-intensity care were consistent across all subgroups examined.

Sensitivity analyses of the primary endpoint in which the results of cohort 1 were either fully weighted according to its sample size or discarded (ie, including only results of cohort 2) showed similar effects (risk differences of 7·3% [95% CI 2·4–12·1] when cohort 1 was fully weighted and 9·4% [3·1–15·6] when cohort 1 was discarded). Treatment effects estimated in sensitivity analyses of the primary endpoint in which we censored deaths due to COVID-19 (adjusted risk difference 8·9% [95% CI 3·9–14·0]) and in sites enrolling more than ten patients (adjusted risk difference 9·0% [95% CI 3·6–14·4]), down-weighting results in cohort 1, were somewhat larger than the 8·1% estimated in the primary analysis.

Post-hoc exploratory analyses showed that the risks of 180-day all-cause death or all-cause readmission (adjusted risk difference 7·1% [95% CI 1·6–12·5]; adjusted RR 0·73 [95% CI 0·57–0·93]) and all-cause death or all-cause readmission excluding COVID-19-related events (adjusted risk difference 8·2% [95% CI 3·0–13·4]; adjusted RR 0·66 [95% CI 0·51–0·86]) were also lower in the high-intensity care group than in the usual care group.

Results for secondary endpoints are shown in table 3. The adjusted mean change from baseline to day 90 in EQ-5D VAS was 3·49 (95% CI 1·74–5·24; p<0·0001) points higher in favour of the high-intensity care group. A prespecified sensitivity analysis of the change in EQ-5D VAS in which deaths were assigned the worst possible value (0) and then remaining missing values multiply imputed showed a similar difference (adjusted mean difference 3·98 [95% CI 1·51–6·45; p=0·0016]). Results for other secondary endpoints and exploratory endpoints are shown in tables 2 and 3.

The incidence of treatment-emergent adverse events is summarised in the appendix (pp 15–17). Adverse events up to day 90 were observed in 223 (41%) of 542 patients in the high-intensity care group and 158 (29%) of 536 in the usual care group. The most commonly observed adverse events were cardiac failure in 79 (15%) of 542 patients in the high-intensity care group and 73 (14%) of 536 patients in the usual care group, hypotension (27 (5%) *vs* two [<1%]), hyperkalaemia (18 [3%] *vs* 0), and renal impairment (14 [3%] *vs* one [<1%]). Serious adverse events were observed in 88 (16%) patients in the high-intensity care group and 92 (17%) patients in the usual care group (appendix pp 18–19). Reported serious adverse events included cardiac failure (38 [(7%] of 542 patients in the high-intensity care group and 47 [9%] of 536 patients in the usual care group), sudden death (five [1%] *vs* ten [2%]), and viral pneumonia (seven [1%] *vs* three [1%]). Fatal serious adverse events were observed in 25 (5%) versus 32 (6%) patients (appendix p 20). Fatal serious adverse events included cardiac failure (seven [1%] *vs* ten [2%]), sudden death (five [1%] *vs* 11 [2%]), COVID-19 (four [1%] *vs* 0), cerebrovascular accident (three [1%] *vs* one [<1%]), and

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	p value
(Continued from previous page)				
Potassium, mmol/L				
Baseline	4·27 (0·455)	4·26 (0·442)	..	..
Day 90	4·60 (0·471)	4·45 (0·504)	..	..
Adjusted mean change	0·32 (0·030)	0·17 (0·031)	0·15 (0·09 to 0·21)*	<0·0001
Urea, mmol/L				
Baseline	8·11 (3·59)	7·96 (3·40)	..	..
Day 90	7·84 (3·83)	7·93 (4·01)	..	..
Adjusted mean change	0·10 (0·223)	0·37 (0·229)	–0·27 (–0·71 to 0·18)*	0·24
eGFR, ml/min per 1·73 m²				
Baseline	61·92 (19·92)	62·89 (21·83)	..	..
Day 90	62·13 (21·54)	63·01 (21·71)	..	..
Adjusted mean change	1·50 (0·94)	1·85 (0·97)	–0·35 (–2·22 to 1·52)*	0·71
Uric acid, µmol/L				
Baseline	437·58 (124·98)	444·69 (126·93)	..	..
Day 90	399·67 (103·76)	409·83 (111·13)	..	..
Adjusted mean change	–63·15 (8·036)	–51·60 (8·314)	–11·55 (–25·69 to 2·58)*	0·11
Aspartate aminotransferase, U/L				
Baseline	26·5 (13·54)	26·8 (17·08)	..	..
Day 90	25·2 (32·47)	27·5 (32·41)	..	..
Adjusted mean change	–4·79 (2·477)	–2·70 (2·490)	–2·08 (–6·30 to 2·14)*	0·33
Alanine aminotransferase, U/L				
Baseline	30·9 (49·30)	28·8 (37·30)	..	..
Day 90	23·9 (34·87)	24·7 (26·06)	..	..
Adjusted mean change	–9·73 (2·363)	–9·09 (2·388)	–0·64 (–4·67 to 3·39)*	0·75
Total bilirubin, µmol/L				
Baseline	17·61 (11·99)	16·97 (10·59)	..	..
Day 90	14·25 (8·92)	15·68 (11·72)	..	..
Adjusted mean change	–4·87 (0·778)	–3·18 (0·783)	–1·69 (–2·99 to –0·39)*	0·011
Total cholesterol, mmol/L				
Baseline	4·21 (1·09)	4·24 (1·10)	..	..
Day 90	4·41 (1·04)	4·45 (1·18)	..	..
Adjusted mean change	0·17 (0·087)	0·17 (0·088)	–0·002 (–0·14 to 0·13)*	0·98

(Table 2 continues on next page)

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	p value
(Continued from previous page)				
NT-proBNP, pg/mL¶				
Baseline	3258·4 (3087·5 to 3438·8)	3159·2 (2995·4 to 3332·0)	..	..
Day 90	1356·6 (1223·1 to 1504·6)	1729·5 (1559·6 to 1917·9)	..	..
Adjusted ratio of geometric means	0·436	0·564	0·77 (0·67 to 0·89)¶	0·0003

Data are n (%), n/N (%), mean (SD), adjusted mean change (SE), or geometric mean change with 95% CI (shown for NT-proBNP), unless otherwise indicated. eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association. *Least square means (SEs) and mean difference (95% CI) estimated based on an ANCOVA model with fixed terms for treatment, LVEF (≤40% *vs* >40%), geographical region, and baseline value. †Primary oedema scale: 0: complete absence of skin indentation with mild digital pressure in all dependent areas; 1+: indentation of skin that resolved over 10–15 s; 2+: indentation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); and 3+: large areas of indentation easily produced and slow to resolve (>30 s). ‡Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% *vs* >40%), geographical region, and baseline value; p value from van Elteren's test stratified by LVEF (≤40% *vs* >40%), geographical region, and baseline value; a Mann-Whitney odds value of >1·0 favours high-intensity care. §None: no rales after clearing with cough; rales <1/3: moist or dry rales heard in lower third of one or both lung fields that persist after cough; 1/3 to 2/3: moist or dry rales heard throughout the lower half to two-thirds of one or both lung fields; and >2/3: moist or dry rales heard throughout both lung fields. ¶Geometric mean (95% CI) presented at each visit; adjusted ratio of geometric means represents the ratio of the post-baseline value over the baseline value from an ANCOVA model of the log-transformed NT-proBNP with fixed terms for treatment, LVEF (≤40% *vs* >40%), geographical region, and baseline log-transformed NT-proBNP value. Treatment effect represents the ratio of the ratios in the two treatment groups adjusted for the specified covariates.

Table 2: **Vital signs, signs and symptoms of heart failure, and laboratory measures (exploratory outcomes)**

pulmonary embolism (one [<1%] *vs* three [1%]). Cardiovascular adverse events were similar between the two groups. In addition to cardiac failure, the most commonly reported cardiovascular adverse events were atrial fibrillation (four [1%] *vs* three [1%]), tachycardia (0 *vs* five [1%]), and bradycardia (four [1%] *vs* two [<1%]). Other than cardiac failure, the most commonly reported cardiovascular serious adverse events were atrial fibrillation (two [<1%] *vs* two [<1%]) and ventricular tachycardia (one [<1%] *vs* two [<1%]).

Discussion

Although many oral therapies are available for patients with chronic heart failure,[16] their fast implementation during or early after admission to hospital for acute heart failure (especially β blockers; ACE inhibitors, ARBs, or ARN inhibitors; and mineralocorticoid receptor antagonists) is not supported by robust evidence. STRONG-HF was designed to test whether rapid up-titration of treatments after an admission for acute heart failure was safe and could alter the prognosis of these patients in the vulnerable early post-discharge period. The STRONG-HF study shows that most patients admitted for acute heart failure and not treated with optimal doses of oral heart failure therapies can be rapidly and safely up-titrated to recommended doses of drugs within a few weeks after discharge, with frequent visits comprising clinical and laboratory assessments, including NT-proBNP, to ensure the safety of such up-titration and indicate the need for additional visits. This high-intensity strategy was safe and associated with a reduced risk of death or being readmitted for heart failure at 180 days after an acute heart failure episode.

In the high-intensity care group, almost all patients received recommended medications, including at least half of patients receiving full recommended doses of renin-angiotensin-aldosterone system (RAAS) inhibitors (ie, ACE inhibitor, ARB, or ARN inhibitor), β blocker, and mineralocorticoid receptor antagonist by day 90. These therapies were up-titrated before discharge and in the few weeks after discharge, with some visits where only patient safety was assessed. In the usual care group, although half of patients received β blockers and two-thirds received RAAS inhibitors, only a very small minority received 100% of recommended doses by day 90 or day 180. The proportion of patients who received guideline-recommended therapies for heart failure in the usual care group, and the proportion receiving 100% of recommended doses and above are largely similar to those seen in the CHAMP-HF registry,[4] despite the fact that patients enrolled in STRONG-HF had a high proportion of preserved ejection fraction and were selected because they were not maximally treated before randomisation. Thus, patients enrolled in this study and randomly assigned to usual care were largely treated with the same medications and same doses as those in a real-life registry. As a result of these differences in implementation of treatments, the high-intensity care group had lower mean blood pressure, heart rate, NYHA class, signs and symptoms of congestion, bodyweight, and NT-proBNP concentrations at day 90 than did those in the usual care group. However, an increased incidence of adverse events was noted in the high-intensity care group compared with the usual care group, most commonly those related to blood pressure decrease, hyperkalaemia and renal impairment. This increase in adverse events can also be explained by the higher frequency of follow-up, which might have created a bias towards higher adverse event detection and reporting in the high-intensity care group than in the usual care group. Nonetheless, a strategy in which patients are more aggressively up-titrated might lead to an increase in the known adverse events typical of treatment. Importantly, this increase in adverse events did not translate into an increase in serious adverse events nor fatal adverse events and, importantly, no increase in cardiovascular adverse events or serious adverse events.

The high-intensity care strategy, with rapid up-titration of guideline-recommended therapies for heart failure, was associated with a substantial decrease in the rate of readmission for heart failure or all-cause death at day 180—the study's primary endpoint—compared with usual care. This finding was more pronounced in prespecified sensitivity analyses excluding deaths due to COVID-19 and only including sites enrolling more than

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	Adjusted risk ratio (95% CI)	p value
Primary endpoint					
All-cause death or heart failure readmission by day 180*	74/506 (15·2%)	109/502 (23·3%)	8·1 (2·9 to 13·2)	0·66 (0·50 to 0·86)	0·0021
Secondary endpoints					
Change from baseline to day 90 in EQ-5D VAS†	10·72 (0·88)	7·22 (0·90)	3·49 (1·74 to 5·24)	NA	<0·0001
All-cause death by day 180*	39/506 (8·5%)	48/502 (10·0%)	1·6 (–2·3 to 5·4)	0·84 (0·56 to 1·26)	0·42
All-cause death or heart failure readmission by day 90*	55 (10·4%)	72 (13·8%)	3·4 (–0·4 to 7·3)	0·73 (0·53 to 1·02)	0·081
Prespecified exploratory endpoints					
Cardiovascular death by day 180*	32/506 (6·9%)	44/502 (9·3%)	2·4 (–1·2 to 6·1)	0·74 (0·47 to 1·16)	0·19
Cardiovascular death by day 90*	17 (3·3%)	28 (5·4%)	2·1 (–0·3 to 4·6)	0·60 (0·33 to 1·09)	0·086
All-cause death by day 90*	23 (4·3%)	30 (5·7%)	1·4 (–1·2 to 4·0)	0·76 (0·45 to 1·29)	0·28
Heart failure readmission by day 180*	47/506 (9·5%)	74/502 (17·1%)	7·6 (3·0 to 12·1)	0·56 (0·38 to 0·81)	0·0011
Heart failure readmission by day 90*	36 (6·9%)	48 (9·5%)	2·5 (–0·8 to 5·8)	0·67 (0·43 to 1·04)	0·13
Finkelstein-Schoenfeld hierarchical composite‡	..	..	1·28 (1·13 to 1·46)	NA	0·0002
Proportion of comparisons where group is superior§	40·4%	29·4%	..	..	..
Proportion of comparisons where groups are tied	30·2%	NA	..	..	..
Sensitivity analyses					
All-cause death or heart failure readmission by day 180, excluding COVID-19 deaths*	69/506 (14·1%)	108/502 (23·0%)	8·9 (3·9 to 14·0)	0·61 (0·46 to 0·82)	0·0005
All-cause death by day 180, excluding COVID-19 deaths*	33/506 (7·1%)	47/502 (9·8%)	2·7 (–1·0 to 6·4)	0·72 (0·47 to 1·12)	0·15

Data are n (adjusted Kaplan-Meier %), n/N (down-weighted adjusted Kaplan-Meier %), or mean (SD), unless otherwise stated. For 180-day outcomes, results for patients in cohort 1 are down-weighted proportional to half its sample size. For 90-day outcomes, cohort 1 is fully weighted. LVEF=left ventricular ejection fraction. NA=not applicable. VAS=visual analogue scale. *Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% *vs* >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group. Treatment effect is the adjusted risk difference between treatment groups. †Analysis of change in EQ-5D VAS is based on available data and excludes patients from Mozambique because of the unavailability of a linguistically validated translation of the EQ-5D VAS in that country (ie, analysis includes n=461 from the high-intensity care group and n=454 the from usual care group). Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF (≤40% *vs* >40%), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups. ‡Treatment effect is the Mann-Whitney odds adjusted for LVEF (≤40% *vs* >40%) and geographical region, using Mantel-Haenzsel weights. p value calculated from van Elteren's test stratified by LVEF (≤40% *vs* >40%) and geographical region, using modified ridit scores. A Mann-Whitney odds value of >1·0 favours high-intensity care. §Proportion of 78 666 total pairwise patient comparisons within strata where outcome in given treatment group is superior.

Table 3: **Primary, secondary, and exploratory analyses**

ten patients. Moreover, patients' symptoms, signs of congestion, and NT-proBNP concentrations, as well as functional NYHA class and quality of life measured with the EQ-5D VAS, were significantly improved in the high-intensity care group compared with the usual care group, suggesting additional benefit. However, these results should be interpreted with caution because the study was open label and so patients might have been biased to report greater improvements if they knew they were in the high-intensity care group.

Although the numerical adjusted RRs for both heart failure readmission and all-cause death favoured the high-intensity care group, the effect on heart failure readmission by 180 days was nominally significant while that for all-cause death by 180 days was not; and all-cause death was not significant even after excluding deaths due to COVID-19. Nonetheless, the fact that both heart failure readmission and all-cause death trended in the same direction adds to the evidence that intensive follow-up coupled with rapid up-titration of treatment is beneficial after admission to hospital for acute heart failure.

The high-intensity care strategy required an average of approximately five visits within 3 months after discharge, compared with an average of one visit during this period with usual care. The effect of more intense management (ie, more visits) early after admission to hospital for an acute heart failure by itself (ie, without up-titration) has been examined in four previous reasonably sized and powered prospective randomised studies.[8,19–21] In all these studies, no effect was seen for intensified follow-up alone on endpoints of readmission or death. Therefore, without rapid up-titration to maximally tolerated doses, additional early follow-up visits alone do not seem to affect patient outcomes.[8,19–21] Furthermore, adjustment of loop diuretic dose does not seem to explain the strategy's effect, because the dose of loop diuretics administered to patients before randomisation was similar between the high-intensity and usual care groups, but at day 90 patients in the high-intensity care group were treated with lower doses of loop diuretics than were patients in the usual care group, and despite this fact patients in the high-intensity care group still had greater bodyweight loss and decongestion. Hence, the reduction in the rates of death or heart failure readmission observed in the study in the high-intensity care group were most likely not related to

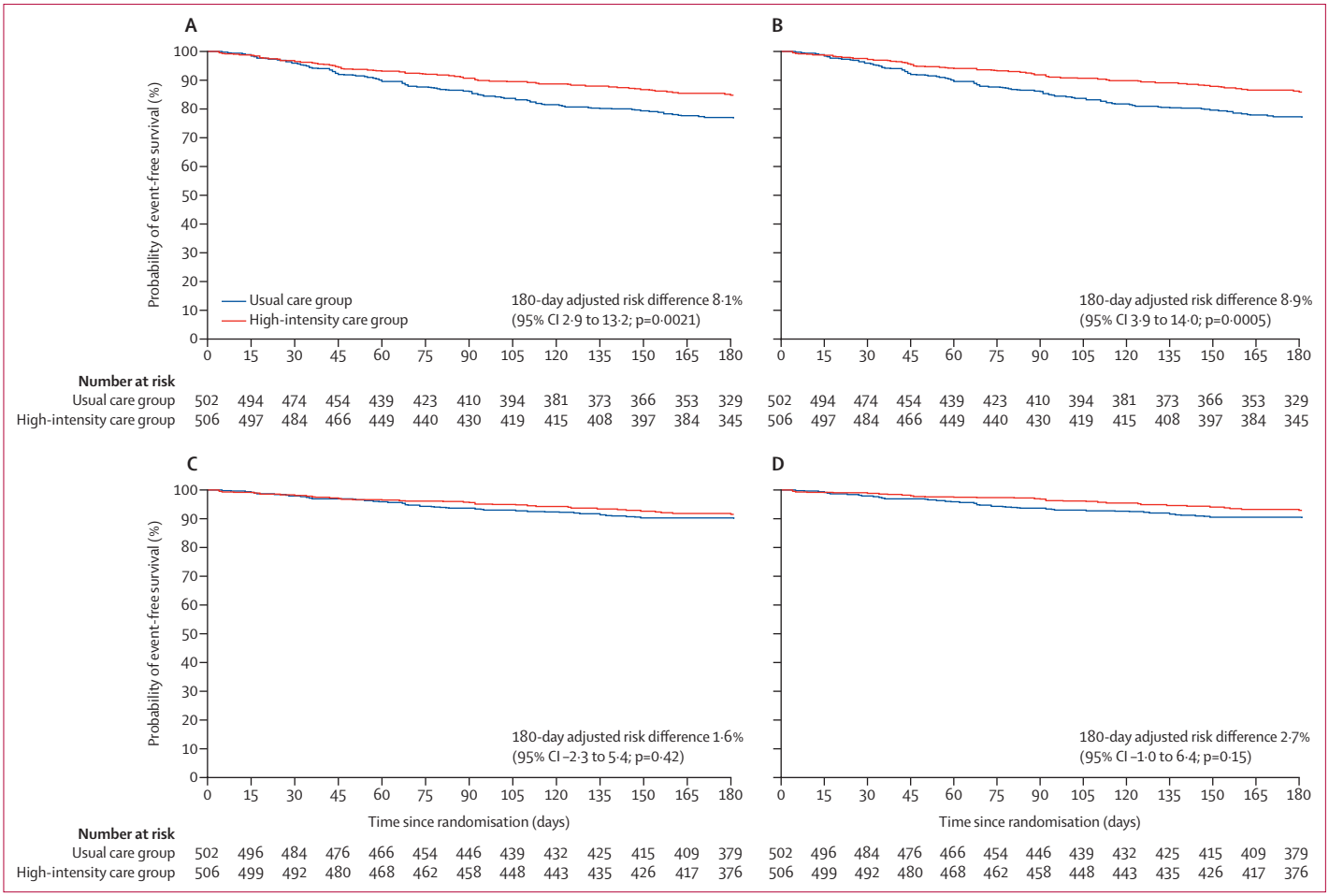

Figure 3: **Adjusted Kaplan-Meier estimates of cumulative event-free survival with down-weighting of cohort 1 for all-cause death or heart failure readmission (A), all-cause death or heart failure excluding deaths due to COVID-19 (B), all-cause mortality (C), and all-cause mortality excluding deaths due to COVID-19 (D), from randomisation up to day 180**
Adjusted 180-day risk differences are given. Analyses excluding COVID-19-related deaths were prespecified sensitivity analyses.

either closer follow-up or more up-titration of loop diuretics, but were related to rapid up-titration in a safe manner. The continued separation of the survival curves well after drug optimisation period (ie, up to day 90) further suggests that it was the guideline-directed medication that drove the effect.

STRONG-HF included patients across the spectrum of LVEFs, including reduced, mildly reduced, or preserved LVEF, similarly to those seen in other acute heart failure registries[14,15] and in recent acute heart failure trials.[22,23] Furthermore, in those studies, β blockers, RAAS inhibitors, and mineralocorticoid receptor antagonists were administered to most patients who had acute heart failure at the time of hospital discharge, regardless of LVEF. These therapies might be associated with improved post-discharge outcomes in all patients with acute heart failure with reduced or preserved LVEF.[24] Therefore, in the present study, patients were enrolled regardless of their baseline ejection fraction. Subgroup analysis results suggest that the intervention was at least as effective in patients with higher ejection fraction (>40% or ≥50%) as in those with reduced or mildly reduced ejection fraction (≤40% or <50%). This finding is of importance especially because β blockers, which have the least evidence of efficacy in patients with heart failure with preserved ejection fraction, were numerically up-titrated the most in the current study. Interestingly, the proportion of patients treated with mineralocorticoid receptor antagonists in this study is higher than previously observed in other acute heart failure studies.[23]

The results of our analysis contrast with those of a previous attempt to guide heart failure therapy with NT-proBNP and clinical assessments.[12] In the GUIDE-IT study,[12] patients in the NT-proBNP-guided therapy intensification and control groups received very similar care during the study including similar doses of guideline-recommended therapies, and hence differing outcomes are unlikely when therapies are similar in both groups, an issue that was avoided in STRONG-HF.

In STRONG-HF, the effect of early up-titration of drugs on clinical outcomes started to become apparent after 30–60 days and increased thereafter. This finding agrees with other publications showing early benefit of guideline-recommended therapies on outcomes.[25–32]

For the pre-discharge period, the 2021 European Society of Cardiology Heart Failure Association guidelines provide two separate recommendations, based on low-level evidence, for initiation or up-titration of drugs and planning a 7–14-day post-discharge follow-up visit.[16] In the STRONG-HF trial, we found that a combined strategy including rapid up-titration coupled with a more intensified early safety follow-up visit was safe and associated with improved outcomes. The results of the STRONG-HF trial could inform future guidelines and provide evidence-based guidance to tailor intensification of medical care and to provide an optimal approach for patients admitted to hospital for acute heart failure.

Most treatments that were used as part of the high-intensity care strategy in the STRONG-HF study are widely available, and, for the most part, they are generic drugs. Hence, the implementation of the results of the STRONG-HF study could be easily and rapidly achieved globally, and not restricted in countries and regions where newer expensive medications are not widely available.

This study has several limitations. First, the study was amended to change the primary endpoint from 90-day to 180-day death or heart failure readmission and to increase target enrolment, based on a low event rate. Sensitivity analysis shows that even if the cohort enrolled before the amendment was removed from the analysis, the study result was unchanged. Second, the study was stopped early by the DSMB. This was done due to the DSMB's assessment that because of the large treatment effect and significance of the results it was no longer ethical to randomly assign and treat patients in the usual care group. Thus, the power to detect differences in risks for secondary and exploratory endpoints is reduced; however, even with full enrolment, the trial was not powered to detect a difference in the risk of all-cause death up to day 180. Third, the study was unblinded, which might have affected the perceptions of the study team. However, the main separation in the rate of all-cause death and heart failure readmission occurred between day 90 and day 180, a period when no patients in either group were seen by members of the study team. The effect of the open-label nature of the study might have been more pronounced on the EQ-5D, because patients might have expected the intensive strategy to improve their status. Fourth, the causes of readmissions were not adjudicated and were based on the investigator's determination. However, the effect size on 180-day all-cause death or all-cause readmission (post-hoc analysis) was similar to that on 180-day all-cause death or heart failure readmission. Finally, because the study was designed and executed mostly before SGLT2 inhibitors were approved or available for the treatment of heart failure, and these medications were implemented only late in the study, they were not prescribed to most patients.

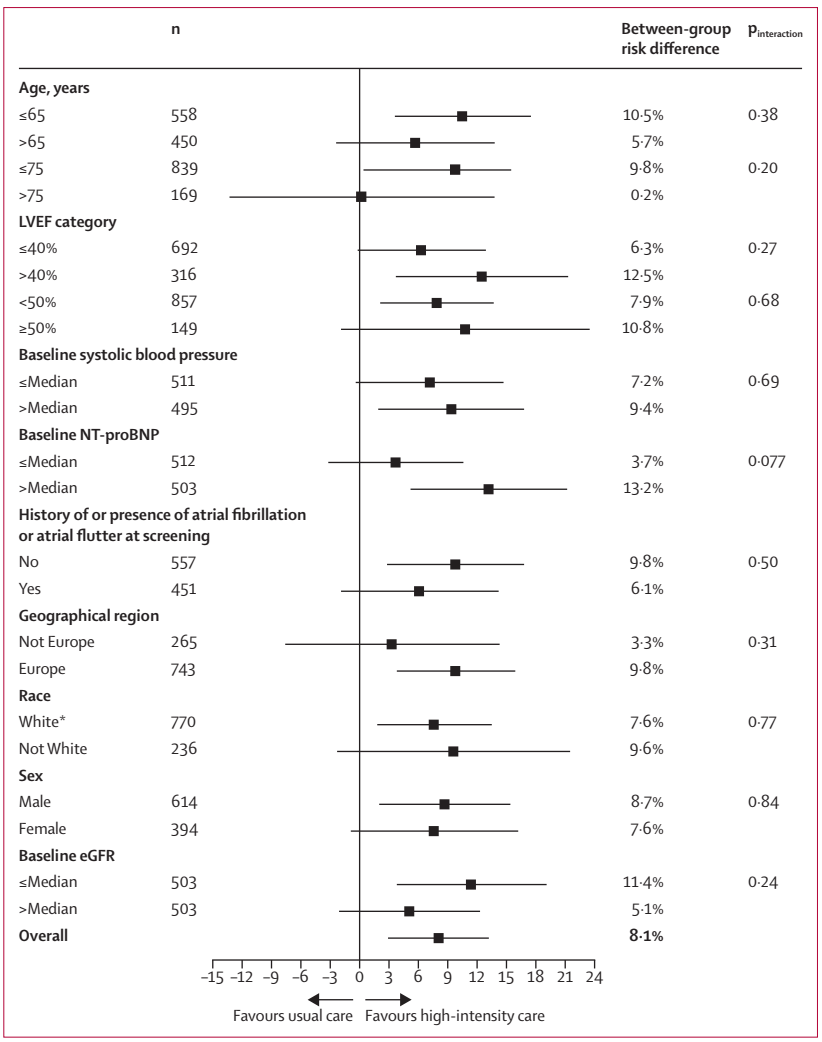

Figure 4: **Prespecified and post-hoc subgroup analysis of primary endpoint (difference in 180-day risk of all-cause death or heart failure readmission)**
Median systolic blood pressure was 120 mm Hg, median NT-proBNP concentration was 2859 pg/mL, and median eGFR was 59·40 mL/min per 1·7 3m². eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. *Includes self-reported White or Caucasian.

Rapid up-titration of guideline-recommended therapies under close follow-up and monitoring, during and early after discharge from a heart failure hospital admission is safe and results in a reduction of heart failure readmissions or all-cause deaths and improves patients' quality of life within 180 days.

Contributors
AM, BD, and GC were responsible for study conceptualisation and overall supervision. GC, BD, CE, and KT were responsible for data curation, formal analysis, data validation, and visualisation. AM and GC acquired funding for the study. AM, GC, MN, RD, KS, and AD were responsible for trial coordination. AM, BD, and GC were responsible for development of study methods. AM, GC, and MN were responsible for

project administration. AM, BD, and GC wrote the original manuscript draft. All authors critically reviewed the manuscript. AM, GC, BD, CE, and KT accessed and verified the underlying study data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

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 and GC are directors of Heart Initiative, a non-profit organisation. BD, CE, MN, KT, and 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. OC serves on an advisory board for Boehringer Ingelheim. KS has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. AC-S has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. 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, and Amgen. MM has received personal fees since January, 2021, from Actelion, Amgen, Livanova, and Vifor Pharma as a member of executive or data monitoring committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Novartis for participation in advisory boards or for speaking at sponsored meetings. AAV has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. 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. 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. JC has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. All other authors declare no competing interests.

Data sharing

Individual participant data required to reach aims in an approved proposal, after de-identification, will be made available to investigators whose proposed use of the data has been approved by the study's Executive Committee. Proposals may be submitted up to 36 months after Article publication and should be directed to alexandre.mebazaa@aphp.fr.

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