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STUDY DESIGN

Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study

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Aims Patients admitted for acute heart failure (HF) are at high risk of readmission and death, especially in the 90 days following discharge. We aimed to assess the safety and efficacy of early optimization of oral HF therapy with beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitors (ARNi), and mineralocorticoid receptor antagonists (MRA) on 90-day clinical outcomes in patients admitted for acute HF.

Methods In a multicentre, randomized, open-label, parallel-group study, a total of 900 patients will be randomized in a 1:1 ratio to either 'usual care' or 'high-intensity care'. Patients enrolled in the usual care arm will be discharged and managed according to usual clinical practice at the site. In the high-intensity care arm, doses of oral HF medications – including a BB, ACEi or ARB, and MRA – will be up-titrated to 50% of recommended doses before discharge and to 100% of recommended doses within 2 weeks of discharge. Up-titration will be delayed if the patients develop worsening

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symptoms and signs of congestion, hyperkalaemia, hypotension, bradycardia, worsening of renal function or significant increase in N-terminal pro-B-type natriuretic peptide between visits. The primary endpoint is 90-day all-cause mortality or HF readmission.

Conclusions STRONG-HF is the first study to assess whether rapid up-titration of evidence-based guideline-recommended therapies with close follow-up in a large cohort of patients discharged from an acute HF admission is safe and can affect adverse outcomes during the first 90 days after discharge.
Clinical Trial Registration: ClinicalTrials.gov NCT03412201.

Keywords Acute heart failure • Biomarker • Cardiovascular mortality • Rehospitalization

Introduction

Acute heart failure (AHF) is a major contributor to morbidity and mortality of patients with heart failure (HF).[1] However, no new therapies have been implemented for its treatment since decades; and most therapies available for patients with HF, including beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNi) and mineralocorticoid receptor antagonists (MRA), are largely approved for patients who have HF with reduced ejection fraction (HFrEF) while the proportion of patients with AHF who have ejection fractions that are preserved (HFpEF) or mid-range (HFmrEF) is increasing.[2] Furthermore, these therapies have been investigated in patients during the chronic phase of their HF, since most of the studies performed prior to the approval of these drugs have explicitly excluded patients with recent AHF episodes.[3,4]

To complicate things further, a large part of AHF patients are, in real life, not adequately followed and are undertreated during the 'vulnerable phase', i.e. the first few months following discharge from an AHF admission and during which most of the adverse events occur.[5,6] Some retrospective analyses have identified this lack of therapy as a potential cause for the high event rate early after a hospital admission.[5,7] Recently, we and others have suggested that oral HF therapies and especially the combination of BBs and ACEi may be associated with a rapid benefit on survival when given at discharge from an AHF episode.[7,8]

Potential reasons for under-treatment after discharge include the lack of adequate randomized controlled trials on post-discharge follow-up, leading to lack of guidance. While the 2008 European Society of Cardiology (ESC) and the 2013 Joint American College of Cardiology/American Heart Association (ACC/AHA) guidelines included an *ad hoc* chapter on how and when to up-titrate oral cardiovascular medical therapies, this information is lacking in the 2016 ESC and 2017 updated ACC/AHA guidelines as is the minimum number of follow-up visits after hospital discharge.[9–12]

The ESC[11] recommends 'a follow-up plan after discharge' and that 'patients should preferably be seen by general practitioners and/or by the hospital cardiology team within a week of discharge, if feasible'. However, no indications were given for later visit(s).[11] Additionally, physicians and other caregivers may be concerned about the potential side effects commonly observed when such therapies are up-titrated, namely hypotension, worsening of kidney function, hyperkalaemia, brady-arrhythmias, and sometimes worsening of congestion. This issue is even more significant in patients with HFpEF where the use of BB, ACEi/ARBs/ARNi and MRAs is not recommended clearly in most guidelines, while patients with AHF frequently have a mid-range or preserved ejection fraction.[11,12] In a recent retrospective analysis, it might be suggested that these therapies, particularly renin–angiotensin–aldosterone system blockers and BB, are possibly effective in patients with AHF regardless of their ejection fraction.[7]

Previous single- and multicentre studies investigating early biomarker-targeted management of AHF during the post-discharge phase have had contradictory results (online supplementary *Table S1*), and hence have failed to establish a standard of care that can be recommended for the practicing physician.

Based on this lack of evidence, we designed the STRONG-HF study, a randomized, prospective clinical trial, to assess the safety and efficacy of rapid up-titration of medical therapy including BBs, ACEi/ARB or ARNi, and MRA, initiated just prior to discharge from a hospitalization for AHF, helped by close follow-up.

Methods

Overview (*Figure 1*)

The STRONG-HF study is a prospective multicentre, randomized, parallel-group trial. Eligible patients will be recruited from up to 100 centres. The study was approved in each country by local ethics committees and was registered in clinicaltrial.gov (NCT03412201) and in EudraCT (number 2018-000486-37).

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent will be required prior to starting study intervention.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the study are presented in the online supplementary *Table S2*. In short, consenting patients will those who were admitted for AHF regardless of the speciality of the initial medical contact. Then, they will be screened within 72 h of an AHF admission characterized by congestion on chest X-ray and other symptoms and signs of congestion. Patients will be screened if not optimally treated with oral HF medications, i.e. either (i) no ACEi/ARB/ARNi

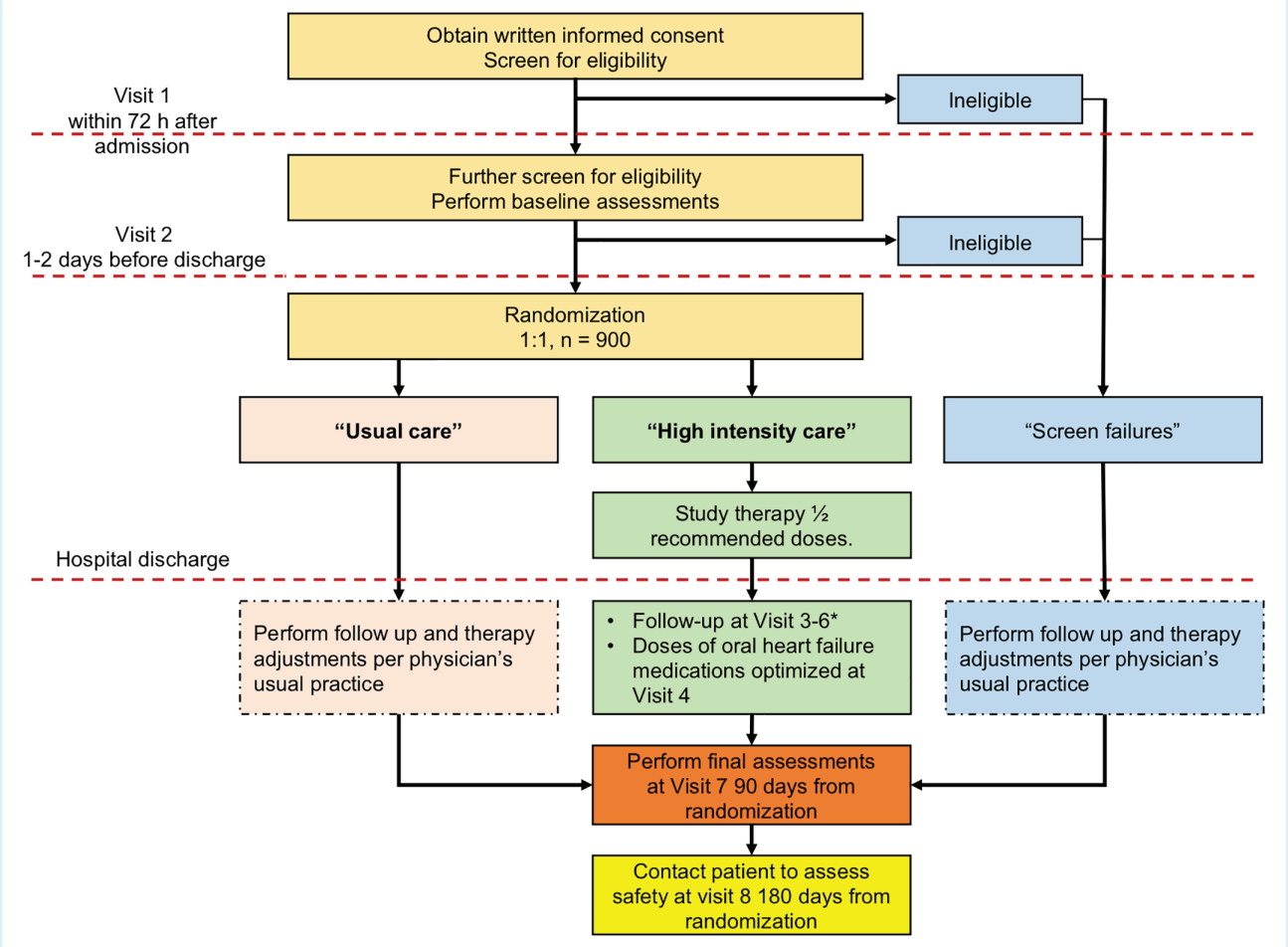

Figure 1 Overview of the study design. *Visit 3: 1 week from randomization; Visit 4: 2 weeks from randomization; visit 5: 3 weeks from randomization; visit 6: 6 weeks from randomization; additional visit(s): 1 week after any additional up-titration.

prescribed, ≤50% of the recommended dose of BB prescribed, and ≤50% of the recommended dose of MRA prescribed, or (ii) ≤50% of the recommended dose of ACEi/ARB/ARNi prescribed, no BB prescribed, and ≤50% the recommended dose of MRA prescribed. An illustration of the recommended doses of these medications is presented in *Table 1*. Furthermore, patients should have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 2500 pg/mL.

One to two days prior to discharge patients will undergo further assessment. At that time, all inclusion and exclusion criteria should be met and in addition, to ensure that the patient was acutely ill, the patient's NT-proBNP should remain > 1500 pg/mL but have decreased by more than 10% compared to screening. To ensure the safety of a rigorous up-titration of HF medications, all measures within 24 h of systolic blood pressure should be ≥ 100 mmHg, and of heart rate ≥ 60 bpm, and all measures within 24 h of serum potassium should be ≤ 5.0 mEq/L (mmol/L). Patients meeting these criteria will be randomized to the study.

Randomization and treatment before discharge

Patients meeting eligibility criteria will be randomized via an interactive web response system to one of the two study arms in a 1:1 ratio, according to a central randomization scheme stratified by left ventricular ejection fraction (≤ 40 vs. > 40%) and country. No investigator will have access to the randomization scheme during the course of the study.

For patients randomized to in the 'usual care' arm, the follow-up schedule and HF medication management will be left to the treating physician's discretion according to local practice at the site.

Just following randomization, patients assigned to the 'high-intensity care' arm will be prescribed medical therapy with BBs, ACEi (or ARB if intolerant to ACEi) or ARNi, and MRA adjusted to at least half the optimal doses. In haemodynamically stable patients, it will be recommended to increase the dose of all three classes of HF therapies ideally in the same day but, if needed, dose adjustments can span several days – for instance, BBs and MRA can be given or up-titrated in 1 day (the day before discharge) and ACEi (or ARB or ARNi) on the following day (the day of discharge).

Treatment between discharge and day 90 (*Table 2*)

In the usual care arm, patients will be followed by the patient's cardiologist and/or general physician as per usual care practiced in the country and their community.

Table 1 Optimal doses of heart failure oral medications

Medication generic name	Dose (half daily dose) at visit 2	Optimal (full) dose at visit 4
MRA		
Eplerenone	25 mg q.d.	50 mg q.d.
Spironolactone	25 mg q.d. each 2 days	25 mg q.d.
BB		
Bisoprolol	5 mg q.d.	10 mg q.d.
Carvedilol	12.5–25 mg b.i.d.[a]	25–50 mg b.i.d.[a]
Metoprolol succinate extended-release tablet	100 mg q.d.	200 mg q.d.
Nebivolol	5 mg q.d.	10 mg q.d.
ACEi		
Captopril	25 mg t.i.d.	50 mg t.i.d.
Enalapril	10 mg b.i.d.	20 mg b.i.d.
Lisinopril	17.5 mg q.d.	35 mg q.d
Ramipril	2.5 mg b.i.d. or 5 mg q.d.	5 mg b.i.d. or 10 mg q.d.
Trandolapril	2 mg q.d.	4 mg q.d.
Perindopril	4 mg q.d.	8 mg q.d.
ARB		
Candesartan	16 mg q.d.	32 mg q.d.
Valsartan	80 mg b.i.d.	160 mg b.i.d.
Losartan	75 mg q.d.	150 mg q.d.
ARNi		
Sacubitril/valsartan	49/51 mg b.i.d.	97/103 b.i.d.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist.
[a]Depending on weight.
Adapted from Wollert *et al.*[13]

Patients randomized to the high-intensity care arm will be assessed by the study team at 1, 2, 3, and 6 weeks following randomization. Safety and tolerability will be evaluated at visits 3 to 6 by full physical examination, and laboratory assessments of NT-proBNP, growth differentiation factor 15 (GDF-15), sodium, potassium, glucose, kidney function, and haemoglobin measures. Two weeks following randomization, up-titration to full optimal doses of BBs, ACEi/ARB/ARNi, and MRA should be performed given adequate safety. Based on blood withdrawn before each visit, measures of NT-proBNP will be available locally for all study patients and of GDF-15 only in few centres. Biomarker results and clinical assessments will guide the safety of up-titrations of oral HF medications. Guidance for delaying up-titrations is as follows:

- ACEi/ARB/ARNi and/or MRAs will not be up-titrated if systolic blood pressure is < 95 mmHg, serum potassium > 5.0 mmol/L, or estimated glomerular filtration rate (eGFR) is < 30 mL/min/1.73 m^2.
- If eGFR alone is < 30 mL/min/1.73 m^2, investigators are encouraged to reduce the dose of diuretics, if those are deemed high or have been recently up-titrated.
- BBs will not be up-titrated if heart rate < 55 bpm or systolic blood pressure is < 95 mmHg. If the NT-proBNP level is $> 10\%$ higher than the pre-discharge level, physicians should consider not up-titrating BBs and consider increasing diuretics.
- If GDF-15 > 2500 pg/mL, the investigator will consider correcting c-omorbidities, including diabetes or hypertension for instance, if needed. Indeed, circulating GDF-15 was suggested to reflect, in HF, inflammatory state related to various modifiable health factors including diabetes, hypertension, total cholesterol.[13] Of note, GDF-15 is increased to a similar degree in patients with HFpEF or HFrEF.
- At each visit more than 1 week following randomization, if the patient is not on maximally tolerated doses of BBs and/or ACEi/ARBs/ARNi and based on the above criteria it is deemed safe to up-titrate these medications, further up-titrations will be encouraged. Additional visits will be done at 1 week following any up-titration to assess safety and tolerability at which time full physical examination, and laboratory assessments of NT-proBNP, GDF-15, serum sodium, serum potassium and kidney function measures will be performed. The use of concomitant medications or medical procedures is left to the treating physician's discretion.

90-day visit (*Table 2*)

At 90 days from randomization all patients will be assessed during a clinic visit by physical examination and laboratory evaluation. The occurrence of any adverse events, including any rehospitalizations or death, between discharge and day 90 will be recorded. Further therapy and changes in any medication at this stage will be left to the discretion of the treating physician. Patients who failed to qualify for randomization will be contacted by phone to ascertain readmissions and death.

180-day contact

Randomized patients will be contacted by telephone 180 days following completion of the study treatment period to assess vital status, the occurrence of rehospitalizations, and current prescriptions for oral HF medications.

Table 2 Schedule of activities

	Visit 1 (screening within 72 h after admission)	Visit 2 (randomization 1–2 days before discharge)	Visit 3 (week 1[a])	Visit 4 (week 2[a])	Visit 5 (week 3[a])	Visit 6 (week 6[a])	Visit 7 (day 90[a])	Visit 8 (day 180[a,b])
Eligibility	X							
Medical history	X							
Chest X-ray[c]	X							
ECG[c]	X							
Echocardiogram[c]	X							
NT-proBNP and growth differentiation factor 15	X	X	X (high[d])	X (high)	X (high)	X (high)	X	
Local labs including haemoglobin, serum sodium, glucose, potassium and kidney function measures	X	X	X (high)	X (high)	X (high)	X (high)	X	
Physical exam including vital signs and clinical HF assessment	X	X	X (high)	X (high)	X (high)	X (high)	X	
Medications	X	X	X (high)	X (high)	X (high)	X (high)	X	X
Randomization		X						
Study therapy optimization		X (high-half[e])		X (high-full[e])	X (high-full)	X (high-full)	X	
Events including endpoints and adverse events		←	←	←	←	←	→	
EQ-5D		X					X	
Biobanking samples		X					X	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.
[a]From visit 3 to 8, number of weeks are counted after randomization.
[b]Follow-up contact to assess safety and tolerability.
[c]Non-study-related procedure expected as standard of care for acute HF and required to assess eligibility. Echocardiogram should have been performed within 6 months prior to screening.
[d]High-intensity care arm only.
[e]Following randomization, BB, ACEi (or ARB if intolerant to ACEi) or ARNi, and MRA at half recommended dose at visit 2 and at full recommended dose at visit 4. Additional visit(s): 1 week after any additional up-titration.

Primary endpoint

The study primary objective is to assess the effects of optimization of medical therapy with BBs, ACEi (or ARB if intolerant to ACEi) or ARNi and MRAs on 90-day all-cause mortality or HF readmission in patients admitted with AHF and clinical and biological signs of congestion. To address this objective, the primary endpoint is the occurrence of all-cause mortality or HF readmission through 90 days post-randomization.

Secondary endpoints

Secondary study objectives are to assess the effect of such intervention on 90-day all-cause mortality, 180-day all-cause mortality, change in quality of life as measured by the EQ-5D questionnaire, and 90-day change in NT-proBNP.[14–18] Secondary endpoints addressing these objectives are 90-day all-cause mortality; 180-day all-cause mortality; changes in EQ-5D visual analogue scale (VAS) score, and index values from baseline to day 90; and change in NT-proBNP from randomization to day 90.

Other endpoints include 90-day cardiovascular death, 90-day HF rehospitalization, and changes in other biomarkers. Changes in the primary and secondary endpoints will be examined in pre-determined subgroups including left ventricular ejection fraction ≤ 40 or $> 40\%$. Pharmacoeconomics analyses may also be performed.

Safety

Patients will be asked at each study visit regarding the occurrence of any adverse event. Non-serious adverse events with an onset from the time of signing the study informed consent to the date of visit 7 (90-day post-randomization) will be recorded for randomized patients. Serious adverse events will be recorded from signing informed consent through the date of screen failure determination for screen failures and through the date of visit 7 for randomized patients.

A data and safety monitoring board (DSMB) will meet at least semi-annually to assess safety data on each arm of the study in accordance with a DSMB charter. The medical monitor will review serious adverse events as they are reported and share information with the DSMB as described in the charter. The DSMB will provide its input to the executive committee.

Sample size calculation

Based on prior studies, a 90-day event rate of 20% for death or readmission in patients admitted for AHF and receiving usual care was assumed in this study.[19–21] With an exponential dropout of $< 1\%$, and assuming constant and proportional hazards (i.e. exponential survival), 450 patients per study arm provides approximately 80% power for the log-rank test to detect a relative risk reduction of 35% (13% vs. 20%, or a hazard ratio of 0.624) at the two-sided 0.05 significance level. Power was estimated using SAS Proc Power (SAS Institute Inc., Cary, NC, USA).

Statistical analysis

Study arms will be compared with respect to efficacy outcomes in all randomized patients with the exception of those patients who are randomized in error. Following the intent-to-treat principle, patients will be analysed according to the arm to which they were assigned at randomization. Safety outcomes will be analysed in all randomized patients, except that any patient assigned to the high-intensity care arm who fails to attend at least one post-randomization titration visit (visit 3, 4, or 5) will be included in the usual care arm for purposes of analysis.

Analysis of the primary efficacy endpoint

The time from randomization to the first HF readmission or all-cause death will be calculated in days through day 90. Patients who withdraw consent or who are lost to follow-up without an event will be censored at the last date the patient was known to be alive. The two study arms will be compared at the two-sided 5% significance level (equivalent to a one-sided 2.5% significance level) using a log-rank test stratified by randomization stratification factors (HFrEF vs. HFmrEF/HFpEF and country). Kaplan–Meier estimates of the cumulative event rates in the two groups will be given. The estimated hazards ratio and the corresponding two-sided 95% confidence interval, estimated from a Cox regression model containing randomized study arm as a predictor and stratified by HFrEF vs. HFmrEF/HFpEF and country, will be provided.

Analysis of secondary endpoints

All-cause mortality through day 90 and day 180 will be analysed similarly. Patients who withdraw consent or who are lost to follow-up without an event will be censored at the last date the patient was known to be alive.

Study arms will be compared with respect to the change from baseline to day 90 in the EQ-5D VAS score using ANCOVA with baseline EQ-VAS and randomization stratification factors as covariates. The cross-classification of the baseline by follow-up responses for each of the five health dimensions for each arm will be presented. Study arms will also be compared with respect to changes from baseline to day 90 in EQ-5D index, using the Europe value set weights.[22]

Treatment groups will be compared with respect to the change in NT-proBNP level from visit 2 (baseline) to visit 7 (day 90) using ANCOVA with the visit 2 (baseline) value and randomization stratification factors as covariates. Central laboratory measures of NT-proBNP will be log-transformed for this analysis.

Planned interim analyses

An interim futility analysis is planned when approximately 450 patients have reached 90 days of follow-up. It is not intended to stop the trial early on the basis of superior efficacy. 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 is < 0.25, the DSMB may recommend that the study be discontinued for futility. No adjustment to the final alpha level is required for this futility analysis.

Discussion

The STRONG-HF study is designed to compare the effects of a strategy including robust and prompt optimization of oral HF medications with usual care on clinical outcomes during the vulnerable phase following hospitalization for AHF.

Substantial progress in the management of chronic HF patients has been achieved with guideline-recommended medical and device treatments, especially for the HFrEF population. However, the same progress has not been achieved with regard to AHF. Despite

Table 3 Comparison of STRONG-HF and GUIDE-IT designs

	STRONG-HF	GUIDED-IT[27]
Design	Multicentre	Multicentre
Inclusion criteria		
Population	Acute HF No or sub-optimal doses of ACEi/ARB, ARNi, BB, MRA	Decompensated chronic HF
Biomarker	Admission NT-proBNP > 2500 pg/mL Randomization NT-proBNP > 1500 pg/mL	NT-proBNP > 2000 pg/mL in 30 days prior to randomization
HpEF included	Yes	No
No. of patients (planned/included)	900/ongoing	1100/894
Intervention		
Biomarker-guided arm	Care (based on high-intensity algorithm) adjusted on clinic with NT-proBNP measurements as safety	Care adjusted to achieve target level of NT-proBNP < 1000 pg/mL
Standard of care arm	Care based on guidelines	Care based on guidelines
Physician ensuring follow-up		
Biomarker-guided arm	Expert	Expert
Standard of care arm	General cardiologist/primary care physician	Expert
No. of visits planned		
Biomarker-guided arm	8	≥6
Standard of care arm	At physician discretion	6
Endpoint	All-cause mortality or HF readmission	Cardiovascular death or first HF hospitalization
Time of endpoint	3 months	12 months

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

large-scale attempts, no new therapies have been approved for those patients for many decades.[23] With a mortality rate persisting at 10% in the few months following an index hospitalization for AHF, it is understandable that attention is also focused on this vulnerable period.[24] Thus, many observational studies suggest, in stable AHF patients, benefits of in-hospital initiation of guideline-directed oral cardiovascular medical therapies.[25] Recently, in patients admitted at hospital for AHF with HFrEF, ARB–ARNi therapy has proven to be more effective than ACEi alone demonstrating the value of designing studies focused on patients with AHF.[26]

However, no pivotal study has been conducted that would result in formal practice recommendations. This is especially true for patients with HFmrEF and HFpEF where no therapy has been shown to be effective when prescribed either acutely or chronically.

As a result of this lack of evidence, the systematic early up-titration to maximal tolerated dose for each of these medications is not clearly recommended by the guidelines from either the ACC/AHA or ESC.[10–12] The STRONG-HF study will attempt to bridge this knowledge gap by testing rapid up-titration of guideline-recommended therapies as compared to usual care in patients across the range of ejection fraction (HFrEF, HFmrEF and HFpEF). Inclusion of AHF patients whatever the ejection fraction makes sense knowing that (i) to date, no other study has already tested a global strategy of early optimal follow-up and up-titration including all usually recommended oral cardiovascular medical therapies, and (ii) acute HFpEF represents at least half of AHF patients.

An important issue is the use of biomarkers to guide the implementation of therapies in patients with HF. For instance, the GUIDE-IT trial, a multicentre randomized clinical trial, aimed to demonstrate in chronic HFrEF patients the efficacy of an NT-proBNP-guided therapeutic strategy compared to a standard optimal therapeutic strategy.[27] The primary endpoint was a composite of time to first readmission for HF or cardiovascular-associated mortality at 12 months. This trial was terminated prematurely for futility after enrolling 894 patients of 1100 planned. This result was unexpected considering previous meta-analysis demonstrating that natriuretic peptide-guided therapy compared to standard care reduced all-cause mortality rates.[28] Reasons of this neutral result were particularly well addressed in the accompanying editorial.[29] First, the standard optimal care group was under the supervision of expert centres resulting in a median of 10 visits in 12 months with four dose adjustments. This is far from a pragmatic daily management of such patients.[30] Consequently, medical therapy and changes in the levels of NT-proBNP were similar between the two groups and, largely, NT-proBNP decreases reached the target goal in both the active and control arms. Second, because of safety concerns (hypotension, exacerbation of renal function), these patients with severe HF as demonstrated by a median ejection fraction ≈ 25%, whatever the arm, did not receive the full recommended drug doses in either arm as physicians were reluctant to up-titrate doses even in the interventional arm. Optimal doses were achieved in only 55% of patients for ACEi/ARB and 48% for BBs at 12 months in the interventional arm. As a result, NT-proBNP remained high in both arms.

The STRONG-HF study was designed to address these limitations (*Table 3*). Briefly, STRONG-HF will include patients with

AHF, regardless of the ejection fraction and with high NT-proBNP (> 2500 pg/mL at admission). Contrary to previously published studies, biomarkers will be used to gauge safety and tolerability but not the efficacy of prescribed doses. Thus, drugs will be up-titrated early to full doses as much as possible based on clinical tolerability and biological safety parameters. Moreover, in a pragmatic and practical way, patients included in the usual care arm will be followed by their general physicians while patients included in the high-intensity care arm will be followed closely by the hospital team specialized in HF. In parallel to mandating faster up-titration of medical therapy, we aim that patients enrolled in the high-intensity care arm will be closely followed. The number of visits is pre-specified in the high-intensity care arm while it is left to discretion of the general physician in the usual care arm as in daily life. Finally, the primary endpoint is ambitious but also pragmatic as HF-related readmission and all-cause mortality most often occur in the first few months following the index hospitalization.[7] Secondary analyses and endpoints were chosen to support the results by assessing the effect of early optimal follow-up and rapid up-titration of therapies according to HF phenotypes (left ventricular ejection fraction ≤ 40% and > 40%) and on self-assessment of quality of life of patients admitted for AHF.

The study has an important limitation. Yet, the follow-up will be different between active and control arm and hence the study compares two strategies of implementing standard of care after an AHF admission and not just different pharmacological strategies. As a result, there is a possibility that some events may be less well reported in the control arm due to reduced follow-up.

Conclusion

STRONG-HF is the first study to assess whether rapid up-titration of evidence-based guideline-recommended therapies assisted by close follow-up in a large cohort of patients discharged from an AHF admission can affect adverse outcomes during the first 90 days after discharge.

Supplementary Information

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

Table S1. Design comparisons of selected trials investigating biomarker-targeted management post-acute heart failure.

Table S2. Inclusion and exclusion criteria.

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