Amended STRONG-HF study design

Cotter, Gad; Davison, Beth; Metra, Marco; Sliwa, Karen; Voors, Adriaan A.; Addad, Faouzi; Celutkiene, Jelena; Chioncel, Ovidiu; Solal, Alain Cohen; Diaz, Rafael

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2348

Publication date:
2021

RESEARCH LETTER

doi:10.1002/ejhf.2348
Online publish-ahead-of-print 4 October 2021

Amended STRONG-HF study design

Patients are not adequately treated in the vulnerable period following discharge from a hospital admission for acute heart failure (AHF).[1,2] The Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF) study (ClinicalTrials.gov NCT03412201) was designed to assess whether rapid optimization of oral heart failure therapies, using frequent visits and biomarkers to monitor congestion, within a short time following discharge from a hospitalization for AHF can improve clinical outcomes.[3] A total of 900 patients were to be randomized 1:1 to either 'high-intensity' or 'usual' care and followed for 90 days. Patients in the usual care arm are managed according to local practice. In the high-intensity care arm, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitors (ARNi), and mineralocorticoid receptor antagonists (MRA) are rapidly up-titrated to 50% optimal doses before discharge and to 100% within 2 weeks following discharge from an admission for AHF. The safety of up-titration is guided by clinical assessment of signs and symptoms of congestion and measures of congestion [N-terminal pro-B-type natriuretic peptide (NT-proBNP)] and blood potassium, blood pressure, heart rate, and renal function. The primary endpoint was initially 90-day heart failure readmission or cardiovascular (CV) death. Enrolment began in May 2018. The protocol was amended after enrolling approximately 230 patients. This amended protocol included a follow-up contact at Day 180 to evaluate longer-term safety and potential benefit and a revised primary endpoint encompassing all-cause rather than CV death.[3]

An interim futility analysis was performed when 519 patients had completed Day 90 follow-up, of whom 353 patients had completed Day 180. Conditional power calculations suggested that the study as it was designed had insufficient power to address the question of potential benefit of high-intensity care on outcomes. To increase power, the protocol was amended in January 2021 to revise the primary endpoint and increase the sample size. The management of enrolled patients remains largely unchanged.

The primary endpoint has been changed from 90-day to 180-day heart failure readmission or death, analysed using estimated 180-day event rates. The analyses of the primary endpoint will include results from both the initial cohort who were included in the interim analysis of 180-day outcomes and the cohort of patients enrolled subsequently. The interim result can be considered 'hypothesis-generating' with respect to the 180-day outcome. The primary analysis will down-weight, to half its sample size, the result in the initial cohort. The difference between groups regarding the estimated cumulative event rate of 180-day death or heart failure readmission, adjusted for randomization strata, will use a weighted average of the result in the initial cohort and subsequently enrolled patients. Sensitivity analyses will be conducted that, first, exclude the result in the initial cohort and, second, that fully weight the initial cohort result. This approach is somewhat analogous to the use of power prior distributions in Bayesian analysis, in which the prior distribution based on previous studies is discounted to degrees varying from non-informative to full borrowing of historical data.[4] Here, the primary analysis will constitute partial reliance on the initial cohort's 'historical' result, with sensitivity analyses bracketing ignoring and fully including the initial result.

Total planned enrolment has been increased from 900 to 1800 patients. With total enrolment of 1800 patients and down-weighting the initial result by half its sample size, the study will have approximately 89% power to detect a difference in event rates of 14% vs. 20% at the two-sided 0.05 significance level. A futility analysis is planned when 1300 patients have at least 90-day follow-up. Because the usual care group is seen less frequently than the high-intensity care group, the potential biases introduced through the treatment group reclassification for the safety set and the selection of a per-protocol subset are unclear. Thus, efficacy and safety analyses will be conducted in only the analysis set comprising randomized patients, excluding only patients randomized erroneously, and placing patients in their assigned treatment groups for analysis.

Secondary endpoints were revised to include the 90-day change in quality of life assessed using the EQ-5D, 180-day all-cause mortality, and the former primary endpoint of 90-day heart failure readmission or death, tested sequentially in order to maintain the alpha level. Exploratory endpoints now include 180-day and 90-day CV death; 90-day all-cause mortality; 180-day and 90-day heart failure readmission; a Finkelstein–Schoenfeld hierarchical composite endpoint comprising death, heart failure readmission, and 90-day change in EQ-VAS; 90-day changes in NT-proBNP; changes in other biomarkers; and changes in weight and signs and symptoms of congestion.

Some additional modifications to the protocol were implemented. First, real-time assessment of growth differentiation factor-15 (GDF-15) was stopped due to logistical reasons as contemporaneous measurements at many sites were not feasible. Therefore, the measurement of GDF-15 has been removed from the protocol and the study name revised to 'Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP testing, of Heart Failure therapies'. Second, due to severe limitations in screening and enrolment during the COVID-19 pandemic, the limit on the number of patients with a history or presence of atrial fibrillation or flutter has been eliminated. Third, the optimal (full) dose of spironolactone was updated from 25 to 50 mg q.d. to be consistent with the target dose included in the European Society of Cardiology (ESC) guidelines.[5,6] Finally, recommendations to consider treatment with sodium–glucose co-transporter inhibitors and intravenous ferric carboxymaltose as part of high-intensity care were added.

As of 17 August 2021, 812 total patients have been randomized in STRONG-HF. Full enrolment is expected in the first quarter of 2022, with final results available by year's end. Recently, authors have advocated the rapid and simultaneous up-titration of evidence-based heart failure therapies, but note that physicians may be hesitant to implement

such a strategy due to a lack of evidence from randomized controlled trials supporting its safety.[7] Indeed, the most recent ESC guidelines acknowledge this lack of evidence supporting such a recommendation.[6] STRONG-HF will provide needed evidence regarding the rapid up-titration of these medications in AHF patients across the spectrum of ejection fraction in a high-risk period following hospital discharge.

Funding

Funding for this study is provided by Roche Diagnostics.

Conflict of interest: G.C. is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, Windtree Therapeutics Inc., and Xylocor Therapeutics, Inc. B.D. is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, Windtree Therapeutics Inc., and Xylocor Therapeutics, Inc. A.A.V. received consultancy fees and/or research grants from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, GSK, Merck, Myokardia, Novartis, Roche Diagnostics, and Servier. J.C. received speaker and investigator fees from Novartis, Servier, Roche Diagnostics, AstraZeneca, Pfizer, Amgen, and Sanofi. A.M. received fee as member of advisory board and/or steering committee and/or research grant from Adrenomed, 4TEEN4, Novartis, Bayer, AstraZeneca, Roche, Abbott, and SphyngoTec. All other authors have nothing to disclose.

Gad Cotter[1,2], Beth Davison[1,2], Marco Metra[3], Karen Sliwa[4], Adriaan A. Voors[5], Faouzi Addad[6], Jelena Celutkiene[7], Ovidiu Chioncel[8], Alain Cohen Solal[1,9], Rafael Diaz[10], Albertino Damasceno[11], Hans-Dirk Duengen[12], Gerasimos Filippatos[13], Eva Goncalvesova[14], Imad Merai[15], Piotr Ponikowski[16], Dmitry Privalov[17], Mahmoud U. Sani[18], Koji Takagi[2], Zaur Shogenov[19], Hadiza Saidu[20], and Alexandre Mebazaa[1,21]*

[1]INSERM UMR-S 942, Paris, France; [2]Momentum Research Inc, Durham, NC, USA; [3]Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [4]Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; [5]Department of Cardiology, University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; [6]Department of Cardiology, Abderrahmen Mami University hospital, Ariana, Tunisia; [7]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [8]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine 'Carol Davila', Bucharest, Romania; [9]Department of Cardiology, Lariboisère University Hospital, Paris, France; [10]Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; [11]Eduardo Mondlane University Hospital, Maputo, Mozambique; [12]Department of Internal Medicine - Cardiology, Campus Virchow Klinikum, Charité - Universitätsmedizin Berlin, Berlin, Germany; [13]Heart Failure Unit, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [14]Department of Heart Failure and Transplantation, National Institute of Cardiovascular Diseases, Bratislava, Slovak Republic; [15]Head of Cardiac Care Unit, Moscow City Hospital, Moscow, Russia; [16]Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [17]Critical Cardiac Unit, City Clinical Hospital, Moscow, Russia; [18]Department of Medicine, Bayero University Kano, Kano, Nigeria; [19]Moscow SHI City Clinical Hospital, Moscow, Russia; [20]Murtala Muhammed Specialist Hospital/Bayero University Kano, Kano, Nigeria; and [21]Department of Anesthesiology and Critical Care Medicine, St. Louis and Lariboisère University Hospitals, Paris, France

*Email: alexandre.mebazaa@aphp.fr

References

1. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015;**12**:220–229.
2. Arrigo M, Nijst P, Rudiger A. Optimising heart failure therapies in the acute setting. *Card Fail Rev* 2018;**4**:38–42.
3. Kimmoun A, Cotter G, Davison B, Takagi K, Addad F, Celutkiene J, Chioncel O, Solal AC, Diaz R, Damasceno A, Duengen HD, Filippatos G, Goncalvesova E, Merai I, Metra M, Ponikowski P, Privalov D, Sliwa K, Sani MU, Voors AA, Shogenov Z, Mebazaa A. 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. *Eur J Heart Fail* 2019;**21**:1459–1467.
4. Ibrahim JG, Chen MH, Gwon Y, Chen F. The power prior: theory and applications. *Stat Med* 2015;**34**:3724–3749.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
7. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. *JAMA Cardiol* 2021;**6**:743–744.