JACC: HEART FAILURE VOL. 14, NO. 1, 2026

BRIEF REPORT

Rapid Titration of Heart Failure Therapies by Etiology

An Analysis of STRONG-HF

Rahul Aggarwal, MD,[a] Deepak L. Bhatt, MD, MPH, MBA,[b] Alexandre Mebazaa, MD,[c,d] Beth Davison, PhD,[c,e] Ovidiu Chioncel, MD,[f] Marco Metra, MD,[g] Piotr Ponikowski, MD,[h] Karen Sliwa, MD,[i] Christopher Edwards, BS,[e] Gad Cotter, MD[c,e]

Heart failure (HF) mortality is increasing in the United States, with nearly 1 in 4 individuals expected to develop HF during their lifetime.[1] High-intensity titration of guideline-directed medical therapy (GDMT) after HF hospitalization can reduce all-cause mortality or HF readmissions.[2]

Patients with ischemic vs nonischemic HF differ in characteristics, comorbidities, and risk profiles.[3,4] Patients with ischemic HF are often older, have worse kidney function, and experience higher mortality, which can raise concerns of their response and tolerability to therapy.[3] In this study, we assessed the efficacy and safety of high-intensity titration of GDMT among patients hospitalized with acute HF by ischemic and nonischemic HF etiologies.

What is the clinical question being addressed?
Does the effectiveness and safety of high-intensity titration of guideline-directed medical therapy for HF differ by ischemic vs nonischemic HF etiology?

What is the main finding?
Intensive GDMT titration reduced 180-day HF readmissions and was safe regardless of HF etiology.

METHODS

STUDY DESIGN. STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testing, of Heart Failure Therapies) was a multinational, open-label clinical trial that randomized patients admitted with acute HF to usual or high-intensity care and has previously been described.[2] Inclusion criteria included age of 18 to 85 years, admission for HF, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>2,500 pg/mL), and not on optimal doses of oral HF therapies (within 2 days of expected hospital discharge). Patients with intolerances to high doses of beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) were excluded.

From the [a]Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts, USA; [b]Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [c]Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France; [d]Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France; [e]Momentum Research, Durham, North Carolina, USA; [f]Emergency Institute for Cardiovascular Diseases "Prof. C.C.Iliescu," University of Medicine "Carol Davila," Bucharest, Romania; [g]Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [h]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; and the [i]Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 20, 2025; revised manuscript received July 8, 2025, accepted July 23, 2025.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2025.102615

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

eGFR = estimated glomerular filtration rate

GCMT = guideline-directed medical therapy

HF = heart failure

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

STRONG-HF was approved by the ethics review committees at each site. Patients provided written informed consent.

INTERVENTION. Patients were randomized to usual care or high-intensity care, with randomization stratified by left ventricular ejection fraction (≤40% vs >40%) and country. Usual care consisted of local practice for GDMT titration after randomization. High-intensity care consisted of an algorithm-based approach for GDMT titration. Two days before discharge, patients were prescribed at least half optimal doses of a beta-blocker, ACEI/ARB/angiotensin receptor-neprilysin inhibitor (ARNI), and mineralocorticoid receptor antagonist (MRA). Patients were expected to be on full optimal doses of therapy by the 2-week visit.

In this post hoc analysis, patients were stratified by randomized group and investigator-reported HF etiology at baseline.

OUTCOMES. The primary composite efficacy endpoint was 180-day HF readmission or all-cause death. Safety outcomes included 90-day change in estimated glomerular filtration rate (eGFR), and fatal, serious, and all adverse events.

STATISTICAL ANALYSES. Time-to-event endpoints were analyzed using Cox regression models that included HF etiology, treatment, and their interaction, and covariates prognostic of the outcome in the usual care group. Continuous outcomes were assessed using analysis of covariance, adjusting for baseline value.

RESULTS

CHARACTERISTICS AND MEDICATION USE. Among patients with HF etiology data, a total of 514 (47.8%) and 561 (52.2%) patients had ischemic etiology and nonischemic HF etiology, respectively. Patients with ischemic HF etiology had higher mean age (68.6 vs 57.8 years), were less likely female (30.7% vs 45.8%), had lower mean eGFR (57.1 vs 72.0 mL/min/1.73 m^2), and were more likely to have history of acute coronary syndrome (57.8% vs 2.5%) or percutaneous transluminal coronary intervention (28.3% vs 1.2%). Patients with ischemic etiology HF had higher rates of left ventricular ejection fraction >40% (37.0% vs 27.6%) and increased rates of recent HF hospitalizations (30.4% vs 20.9%).

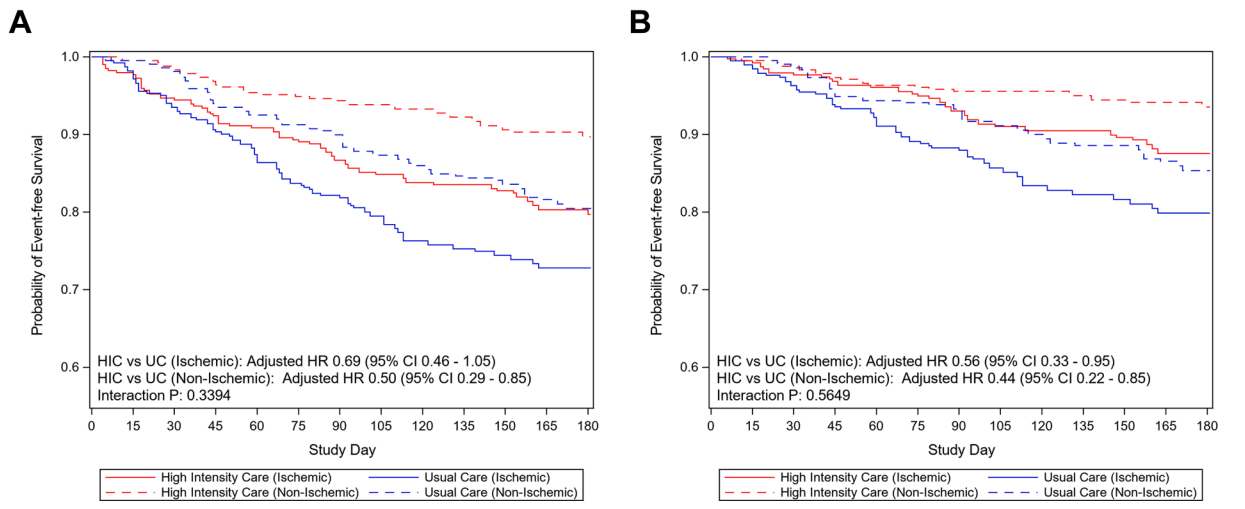
Among the ischemic etiology subgroup, patients receiving high-intensity care compared with usual care had greater 90-day increases in the use of beta blockers (86.8% vs 21.3%), ACEI/ARB/ARNI (84.6% vs 24.1%), and MRAs (58.1% vs 26.4%). Similar findings were observed among the nonischemic etiology subgroup, with greater increases in the use of beta blockers (89.1% vs 15.4%), ACEI/ARB/ARNI (89.1% vs 12.6%), and MRA (55.1% vs 16.1 %) with high-intensity vs usual care.

EFFICACY ENDPOINTS. Patients receiving high-intensity care compared with usual care had lower rates of 180-day all-cause death or HF readmission (15.3% vs 23.5%; adjusted HR [aHR]: 0.61; 95% CI: 0.44-0.85),[2] with findings consistent irrespective of HF etiology: 20.3% vs 27.2% (aHR: 0.69; 95% CI: 0.46-1.05) for ischemic and 10.3% vs 20.2% (aHR: 0.50; 95% CI: 0.29-0.85) for nonischemic ($P_{interaction}$ = 0.34) (Figure 1). Similar findings were observed when COVID deaths were excluded ($P_{interaction}$ = 0.54).

While patients with ischemic etiology HF had higher rates of 180-day HF readmission than those with nonischemic HF etiology, high-intensity care compared with usual care reduced 180-day HF readmissions irrespective of ischemic (12.5% vs 20.1%; aHR: 0.56; 95% CI: 0.33-0.95) or nonischemic (6.5% vs 14.7%; aHR: 0.44; 95% CI: 0.22-0.85) HF etiology ($P_{interaction}$ = 0.56). No treatment difference in 180-day all-cause death was observed overall or by ischemic (11.5% vs 11.6%; aHR: 0.89; 95% CI: 0.49-1.62) or nonischemic (5.7% vs 8.8%; aHR: 0.64; 95% CI: 0.30-1.38) HF etiology, although 180-day all-cause death rates were higher in the ischemic etiology compared with nonischemic etiology HF group.

SAFETY ENDPOINTS. eGFR changes at 90 days were similar between high-intensity and usual care groups, irrespective of ischemic (least square [LS] mean difference: −0.23 mL/min/1.73 m^2; 95% CI: −2.95 to 2.49 mL/min/1.73 m^2]) or nonischemic (LS mean difference: −0.03 mL/min/1.73 m^2; 95% CI: −2.55 to 2.49 mL/min/1.73 m^2) HF etiology. Among patients with ischemic HF etiology, adverse events were observed in 118 (45.4%) and 96 (37.8%) patients in the high-intensity and usual care groups, respectively, serious adverse events were observed in 50 (19.2%) and 59 (23.2%) patients, and fatal adverse events in 17 (6.5%) vs 19 (7.5%). Similar patterns were observed among patients with nonischemic etiology HF, with adverse events observed in 104 (37.0%) and 62 (22.1%) patients, serious adverse events observed in 38 (13.5%) and 33 (11.8%) patients, and fatal adverse events in 8 (2.8%) vs 13 (4.6%) patients by high-intensity vs usual care groups, respectively.

FIGURE 1 Kaplan-Meier Curves by HF Etiology for 180-Day Endpoints in STRONG-HF



Primary endpoint (all-cause death or HF readmission) (A) and HF readmission (B). HF = heart failure; HIC = high-intensity care; STRONG-HF = Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testing, of Heart Failure Therapies; UC = usual care.

DISCUSSION

In this study, we found that high-intensity GDMT titration reduced the risk of 180-day HF readmission. Although patients with ischemic etiology experienced higher overall readmission rates compared with those with nonischemic etiology, the benefit of high-intensity GDMT titration was consistent across both etiologies. Regardless of the underlying HF etiology, high-intensity care did not lead to significant differences in kidney function. Although overall adverse events were more frequent in the high-intensity care group, rates of serious and fatal events remained similar to those observed with usual care.

Evidence suggests variability in prescribing patterns based on HF etiology, with higher rates of ACEI or ARB use among patients with ischemic etiology HF.[5] Implementing a standardized, rapid GDMT titration protocol, such as the one used in this study, may help overcome these differences and improve the overall use of GDMT, leading to reduced HF outcomes.

Given the clear reduction in HF readmission risk with intensive care compared with usual care, the higher overall adverse event rate in the intensive group should not discourage rapid GDMT titration—particularly because serious and fatal adverse event rates were similar. The safety of intensive care is further supported by the lack of significant differences in kidney function.

STUDY LIMITATIONS. This was a post hoc analysis, and sodium-glucose cotransporter 2 inhibitors were not included in the intervention protocol.

CONCLUSIONS

High-intensity titration of beta blockers, ACEI/ARB/ARNIs, and MRAs within 2 weeks of HF hospitalization reduces 180-day HF readmissions and is safe irrespective of ischemic or nonischemic HF etiology.

DATA SHARING STATEMENT. 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 main article publication and should be directed to alexandre.mebazaa@aphp.fr.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Funding for the study was through a grant provided to the Heart Initiative by Roche Diagnostics International. Dr Aggarwal has received research training support from the National Heart, Lung, and Blood Institute grant 5T32HL007604; is involved in research funded by the Bristol Myers Squibb-Pfizer alliance, Novartis, Lexicon, Cleerly, and Amarin; and serves as a consultant for Lexicon. Dr Bhatt is on the advisory boards of Angiowave, Antlia Bioscience, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, E-Star Biotech, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, NirvaMed, Novo Nordisk, Repair Biotechnologies, Stasys, and Tourmaline Bio; is on the Board of Directors of the American Heart Association-New York City, Angiowave (including

stock options), Bristol Myers Squibb (including stock), DRS.LINQ (including stock options), and High Enroll (including stock); is a consultant for Alnylam, Altimmune, Broadview Ventures, Corcept Therapeutics, Corsera, GlaxoSmithKline, Hims, SERB, SFJ, Summa Therapeutics, and Worldwide Clinical Trials; is on the data monitoring committees for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research, Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute, and Rutgers University (for the NIH-funded MINT trial); has received honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (AHA lecture), Duke Clinical Research Institute, Engage Health Media, HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Philips (Becker's Webinar on AI), Population Health Research Institute, WebMD (CME steering committees), Wiley (steering committee); is the Deputy Editor for *Clinical Cardiology* and *Progress in Cardiovascular Diseases*; holds a patent for Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither he nor Brigham and Women's Hospital receive any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Alnylam, Amarin, Amgen, AstraZeneca, Atricure, Bayer, Boehringer Ingelheim, Boston Scientific, CellProthera, Cereno Scientific, Chiesi, Cleerly, CSL Behring, Faraday Pharmaceuticals, Fractyl, Idorsia, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, MiRUS, Moderna, Novartis, Novo Nordisk, Pfizer, PhaseBio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, and 89Bio; has received royalties from Elsevier (Editor, *Braunwald's Heart Disease*); and is site co-investigator for Cleerly. Dr Mebazaa has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer, and Merck Sharp & Dohme; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is co-inventor of a patent on combination therapy for patients having acute or persistent dyspnea. Drs Davison and Cotter are employees of Momentum Research, which has received grants for research from 4TEEN4 Pharmaceuticals, Corteria Pharmaceuticals, Echosens, Heart Initiative, Roche Diagnostics, Windtree Therapeutics, and XyloCor Therapeutics. Dr Chioncel has received grants from Servier. Dr Metra has received personal consulting honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and Roche Diagnostics in the past 3 years; and Speakers Bureau honoraria from Boehringer Ingelheim. Dr Ponikowski has received grants and personal fees from Amgen, Servier, Boehringer Ingelheim, Vifor Pharma, Novartis, Bayer, Cibiem, AstraZeneca, BMS, Renal Guard Solutions, Impulse Dynamics, and Abbott Vascular; and personal fees from Berlin Chemie outside of the submitted work. Dr Sliwa has received grants from Medtronic, Servier, and Amylam; and honoraria from Merck Sharp & Dohme, Novartis, and Sanofi. Mr Edwards is an employee of Momentum Research, which has received grants for research from 4TEEN4 Pharmaceuticals, Corteria Pharmaceuticals, Echosens, Heart Initiative, Roche Diagnostics, Windtree Therapeutics, and XyloCor Therapeutics.

ADDRESS FOR CORRESPONDENCE: Dr Deepak L. Bhatt, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box 1030, New York, New York 10029, USA. E-mail: Deepak.Bhatt@mountsinai.org. X handle: @DLBhattMD.

REFERENCES

1. Bozkurt B, Ahmad T, Alexander K, et al. HF STATS 2024: Heart failure epidemiology and outcomes statistics. An updated 2024 report from the Heart Failure Society of America. *J Card Fail*. 2025;31(1):66-116. https://doi.org/10.1016/j.cardfail.2024.07.001

2. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet Lond Engl*. 2022;400(10367):1938-1952. https://doi.org/10.1016/S0140-6736(22)02076-1

3. Silverdal J, Sjöland H, Bollano E, Pivodic A, Dahlström U, Fu M. Prognostic impact over time of ischaemic heart disease vs. non-ischaemic heart disease in heart failure. *ESC Heart Fail*. 2020;7(1):264-273. https://doi.org/10.1002/ehf2.12568

4. Vedin O, Lam CSP, Koh AS, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail*. 2017;10(6):e003875. https://doi.org/10.1161/CIRCHEARTFAILURE.117.003875

5. Corbalan R, Bassand JP, Illingworth L, et al. Analysis of outcomes in ischemic vs nonischemic cardiomyopathy in patients with atrial fibrillation: a report from the GARFIELD-AF Registry. *JAMA Cardiol*. 2019;4(6):526-548. https://doi.org/10.1001/jamacardio.2018.4729

KEY WORDS guideline-directed medical therapy, heart failure, ischemic, nonischemic, therapy