Circulation: Heart Failure

ORIGINAL ARTICLE

Guideline-Directed Medical Therapy Use in the STRONG-HF Trial

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BACKGROUND: Assessment of medication changes in heart failure trials and registries is complex and may not capture the entirety of care. A comprehensive and standardized method is needed. We used different methods to assess the use of guideline-directed medical therapies (GDMT) and verified the association between GDMT intensity score with the STRONG-HF trial (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing of Heart Failure Therapies) clinical outcomes.

METHODS: We used data from the STRONG-HF trial to examine the baseline GDMT use for all randomized patients by applying the GDMT intensity score and evaluated its change over time. We also examined their basic adherence, indication-corrected adherence, and dose-corrected adherence, and the association with clinical outcomes up to 180 days.

RESULTS: At 90 days, triple therapy indication-corrected use increased from 4.5% to 36% in the usual care group, and from 5.2% to 93.5% in the high-intensity care group ($P<0.001$ between the 2 groups). Triple therapy dose-corrected use increased from 4.5% to 20.5% in the usual care group, and from 3.3% to 77.4% in the high-intensity care group ($P<0.001$). The GDMT intensity score at baseline was <6 in 358 (33%) patients, 6 to 7 in 329 (31%) patients, and >7 in 386 (36%) patients. At 90 days, 88.4% of patients in the high-intensity arm achieved a score >7 versus 14.3% in the usual care arm ($P<0.0001$). The GDMT intensity score was correlated with clinical outcomes at 180 days.

CONCLUSIONS: The GDMT intensity score provides a comprehensive description of medication use by means of standardized measurements and is linked to clinical outcomes. Future studies should consider utilizing this as a trial end point.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03412201.

Key Words: clinical trial ■ guideline directed medical therapy ■ heart failure

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The STRONG-HF trial (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies)[1] revealed a reduction in all-cause death or heart failure (HF) readmission with the rapid up-titration of guideline-directed medical therapies (GDMT) in the 90 days following hospitalization when compared to usual care (UC). In clinical practice, the STRONG-HF trial highlights the importance to promptly act in optimizing therapies during this window of vulnerability that follows hospitalization due to HF.[2,3]

The STRONG-HF trial enrolled participants with a range of ejection fractions (EFs), various noncardiac comorbidities[4] and low baseline GDMT use as assessed by several methods. Older methods, such as simple counts, or achievement of >50% of the target daily dose have been used but may under-represent

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WHAT IS NEW?

- The guideline-directed medical therapies intensity score provides more granularity in the evaluation of heart failure medical therapy use than conventional methods (eg, simple medication counts). This study highlights its potential to serve as a standardized tool in the design and interpretation of clinical trials and in guiding treatment strategies in clinical practice.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Rapid up-titration of guideline-directed medical therapies following heart failure hospitalization, resulting in a higher guideline-directed medical therapies intensity score, is directly linked to lower all-cause mortality and heart failure readmission, underscoring the importance of early and aggressive guideline-directed medical therapies up-titration for improving patient outcomes.

Nonstandard Abbreviations and Acronyms

ACEi	angiotensin-converting enzyme inhibitor
EF	ejection fraction
GDMT	guideline-directed medical therapies
HFC	Heart Failure Collaboratory
HF	heart failure
HIC	high-intensity care
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RASi	renin-angiotensin system inhibitor
STRONG-HF	Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing of Heart Failure Therapies
UC	usual care

the totality of care related to medications.[5,6] As HF treatments evolve, it becomes crucial in clinical trials to assess the use of these medications with more precision. This led to the adoption and subsequent modification of the Heart Failure Collaboratory (HFC) treatment score, which aggregates medications into a single unit.[7] Modifications of this have added newer medications and refined the calculations to ensure more granularity and accuracy can be obtained.[8,9] Several of these assessments have highlighted that the HFC score can better reflect the totality of care,[10] especially since there are a greater number of choices in both number and dose of medications.

We assessed the investigators' adherence to the prescription of GDMT in the STRONG-HF trial by applying a GDMT intensity score, modified from the HFC score to reflect the protocol-driven dosing algorithm, and evaluated its change over time. We also examined the investigators' basic adherence, indication-corrected adherence, and dose-corrected adherence.

METHODS

Study Design and Setting

Details and primary results of the STRONG-HF trial have been published.[1] Briefly, patients assigned to the UC group received routine follow-up according to local practice with a follow-up visit at day 90. Patients assigned to the high-intensity care (HIC) group had their first dose adjustment to half target doses immediately after randomization, within 2 days prior to anticipated discharge. They were assessed at 1, 2, 3, and 6 weeks and at day 90. At 2 weeks, target doses[11] of key medications were meant to be achieved if deemed safe. Up-titration could be delayed if not deemed safe per protocol. Safety was assessed through physical examination and evaluation of NT-proBNP (N-terminal pro-B-type natriuretic peptide),[12] sodium, potassium, glucose, kidney function and hemoglobin. Renin-angiotensin system inhibitors (RASi) and mineralocorticoid receptor antagonists (MRAs) were not up-titrated if there are safety concerns: systolic blood pressure <95 mm Hg, potassium >5 mmol/L or estimated glomerular filtration rate <30 mL/min per 1.73 m^2. Similarly, β-blockers were not up-titrated if systolic blood pressure <95[13] or heart rate <55 beats per minute. Volume status was assessed clinically and with biomarkers. Clinicians were instructed to consider not up-titrating β-blockers and consider increasing diuretics if there was a >10% increase in NT-proBNP compared to the predischarge value. Additional visits were conducted 1 week following any further up-titrations. Both groups were assessed at 180 days after randomization for recurrence of hospitalization, current prescription of GDMT and clinical outcomes.

The study was approved by local ethics committees, and all patients enrolled provided written informed consent. The data that support the findings of this study are available within the article and its supplemental files. Data and materials of the STRONG-HF trial have been previously made publicly available and can be accessed at DOI: 10.1016/S0140-6736(22)02076-1. Individual participant data required to reach the 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 should be directed to alexandre.mebazaa@aphp.fr.

Participants

The STRONG-HF trial included 1078 patients between 18 and 85 years of age who were admitted to the hospital due to acute HF and not on optimal doses of GDMT. Patients included were either being prescribed before randomization: (1) ≤ half the optimal dose of RASi, ≤ half the optimal dose of MRA, and no β-blockers; or (2) RASi, ≤ half the optimal dose of β-blockers, and ≤ half the optimal dose of MRA. The trial population was recruited from 13 countries in Europe, South America, the Middle East, and Africa. These patients, stratified by left ventricular EF

(≤40% versus >40%) and country, were randomized (1:1) to receive HIC or UC. Based on EF, participants are described as HF with reduced EF (EF <40%), HF with mid-range EF (EF 40–49%), or HF with preserved EF (EF ≥50%) .

Variables

Medication Assessment

The use and dose of GDMT, including β-blocker, RASi, and MRA, were assessed at 1 week before admission, at screening (within 72 hours following admission), and at all remaining study visits. Sodium-glucose cotransporter-2 inhibitors were not included in guidelines at the time of study start.

In general, 3 definitions of physician adherence to guidelines were used to evaluate medication use and its change over time. Basic adherence is evaluated by whether patients were prescribed medication. Indication-corrected adherence includes patients who were prescribed the medication and those who were appropriately not prescribed the medication for specific reasons. For instance, a patient whose EF is above 40% and does not have other indications for β-blockers is appropriately not prescribed this medication. We modified these definitions to reflect physician adherence to the STRONG-HF protocol. As such, appropriateness is determined by whether doses were appropriately not prescribed or up-titrated based on safety indicators such as EF, potassium level (>5.0 mmol/L), renal function (estimated glomerular filtration rate <30 mL/min per 1.73 m^2), and other reported adverse reactions (Table S1). Dose-corrected adherence is evaluated by whether a patient has achieved ≥50% of the target dose specified by the protocol (Table S2), unless contraindicated by the presence of a safety indicator. It is important to note that these definitions are to evaluate the compliance of the physician in prescribing medication and not that of the patient in taking them.

A GDMT intensity score was derived using the Modified HFC treatment score. For each medication class, the total daily dose was assigned a value from 0.5 to 5.0. For the HFC score, angiotensin-converting enzyme inhibitors (ACEi) and β-blocker doses are assigned a value of 0.5 to 5, and angiotensin II receptor blockers, angiotensin receptor/neprilysin inhibitors, and MRA doses a value of 0.5 to 4, with increasing doses up to the target level. For this analysis, medications in each class not included in the HFC treatment score were included as a score of 0.5. These values were then summed to calculate the GDMT intensity score (Table S3).

We also computed the average percentage of optimal doses prescribed across the 3 GDMT classes for each patient, which has been used as a measure of GDMT use in several STRONG-HF analyses.[14]

Study End Points

The study's primary end point was the composite of first HF rehospitalization or all-cause death at day 180. Secondary end points were changes in the EQ-5D visual analog scale score from baseline to day 90, 180-day all-cause death, and the composite of first HF rehospitalization or all-cause death at day 90.

Statistical Methods

Continuous variables are presented as the mean and SD or geometric mean and 95% confidence interval for log-transformed variables. Absolute and relative frequencies are presented for categorical variables. Baseline patient characteristics are presented by the GDMT intensity score by tertiles just before randomization, and groups were compared using Jonckheere's trend test for continuous variables, Cochran-Armitage trend test for binary variables, Cochran-Mantel-Haenszel general association for categorical variables, and Cochran-Mantel-Haenszel nonzero correlation for ordinal variables. Visit 2, just before randomization, is considered as baseline for these analyses.

χ^2 tests were used to compare HIC and UC groups with respect to the proportions of patients for whom the various adherence measures were met at each visit. The GDMT intensity score at day 90, an ordinal variable, was compared between treatment groups using a win odds stratified by geographic region and left ventricular EF ≤40% versus >40%, and adjusted for baseline GDMT intensity score using the method described by Kanaguchi and Koch[15] and implemented using the R package sanon[16] where observed values within strata at each visit were compared.

The correlation between the GDMT intensity score and the average percentage of optimal dose was computed using a mixed model approach, which accounts for the repeated nature of the measurements, as proposed by Hamlett, Ryan, and Wilfinger.[17]

The association of prescribed doses with the study's primary composite outcome was examined in Cox regression models, first including the GDMT intensity score categorized as ≤7, 7.5 to 10 or ≥11 as a time-dependent covariate, and then including the GDMT score at week 2 as a continuous variable modeled using a restricted cubic spline with 3 knots. For the latter model, patients who had an event or were censored before day 14 were excluded. In models including all participants, the doses of medications prescribed just after randomization in the UC group were assumed not to change until the next recorded medication use at day 90. As in the main analyses,[1] these models included only patients enrolled at sites that followed patients to day 180, and down-weighted results of patients enrolled before implementation of a protocol amendment modifying the primary end point. Models were adjusted for covariates found to be predictive of the outcome in the UC group: baseline diastolic blood pressure, ischemic heart disease, edema severity, and NT-proBNP.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute) and R, version 4.2.3 (R Core Team). Two-sided $P<0.05$ was considered statistically significant.

RESULTS

Trial Cohort Participant Characteristics

A total of 1078 patients were randomized; 67% of participants had an EF ≤40%, and the remainder, >40% (18% HF with mid-range EF and 15% HF with preserved EF). Most participants were male (60% in HIC and 63% in UC arms, respectively) and White (77% in both arms). Just before randomization (within 2 days before anticipated discharge), of the 1074 patients with medication data available, 66 participants were on no or 1 GDMT medication, 994 participants were on 2, and 15 were on 3 GDMT medications (Table 1). The total GDMT score was <5 in 357 (33.4%) patients, between 5 and 5.5 in 354 (33.1%) patients, and >5.5 in 357 (33.4%) patients.

Table 1. Patient Characteristics According to the Baseline GDMT Use Before Randomization (Within 2 Days Before Anticipated Discharge)

Parameter	Statistic	Total GDMT score, <5 (N=357)	Total GDMT score, 5–5.5 (N=354)	Total GDMT score, >5.5 (N=357)	Trend *P* value
Age, y	Mean (SD)	59.7 (15.47)	64.6 (12.10)	64.7 (12.40)	<0.0001
Sex					0.0016
Female	n (%)	168 (47.1)	119 (33.6)	127 (35.6)	
Male	n (%)	189 (52.9)	235 (66.4)	230 (64.4)	
Self-reported Race					<0.0001
Black	n (%)	129 (36.1)	44 (12.4)	56 (15.7)	
White	n (%)	219 (61.3)	305 (86.2)	300 (84.3)	
Native American	n (%)	1 (0.3)	0	0	
Other	n (%)	7 (2.0)	5 (1.4)	0	
Pacific Islander	n (%)	1 (0.3)	0	0	
Geographic Region					<0.0001
Europe	n (%)	207 (58.0)	300 (84.7)	285 (79.8)	
Non-Europe	n (%)	150 (42.0)	54 (15.3)	72 (20.2)	
NT-proBNP at screening, ng/L	Geom. mean (95% CI)	6059.5 (5699.9–6441.8)	6171.2 (5803.0–6562.8)	5833.3 (5514.5–6170.6)	0.3420
History of atrial fibrillation or atrial flutter or present at screening	n (%)	132 (37.0)	179 (50.6)	168 (47.1)	0.0067
Medical history					
Stroke or transient ischemic attack	n (%)	40 (11.2)	33 (9.3)	26 (7.3)	0.0690
Severe liver disease	n (%)	1 (0.3)	2 (0.7)	3 (1.0)	0.3363
Psychiatric or neurological disorder	n (%)	8 (2.3)	6 (1.7)	6 (1.7)	0.5738
Malignancies	n (%)	12 (3.4)	10 (2.8)	7 (2.0)	0.2500
Diabetes	n (%)	96 (27.0)	117 (33.1)	100 (28.1)	0.7421
Diabetes control method					
Insulin	n (%)	27 (7.6)	29 (8.2)	26 (7.3)	0.8882
Diet only	n (%)	54 (15.2)	72 (20.4)	76 (21.3)	0.0355
Oral antidiabetic agents	n (%)	72 (20.2)	81 (22.9)	81 (22.7)	0.4269
Pulmonary embolism	n (%)	7 (2.0)	7 (2.0)	5 (1.4)	0.5712
Acute coronary syndrome	n (%)	100 (28.0)	103 (29.1)	107 (30.0)	0.5638
Coronary artery bypass surgery	n (%)	22 (6.2)	18 (5.1)	19 (5.3)	0.6233
Percutaneous transluminal coronary intervention	n (%)	58 (16.2)	44 (12.5)	49 (13.7)	0.3339
Angina Canadian Cardiovascular Society class 2 or higher	n (%)	37 (10.4)	35 (9.9)	53 (14.9)	0.0624
Moderate or severe chronic obstructive pulmonary disease or asthma	n (%)	13 (3.6)	7 (2.0)	7 (2.0)	0.1526
Sustained ventricular arrhythmia (with syncopal episodes in past 3 mo)	n (%)	1 (0.3)	0	0	0.6685
Cardiac resynchronization therapy	n (%)	1 (0.3)	3 (0.8)	2 (0.6)	0.8064
Automatic internal cardiac defibrillator	n (%)	4 (1.1)	1 (0.3)	4 (1.1)	0.9999
Anemia	n (%)	101 (28.3)	91 (25.7)	98 (27.5)	0.8007
Heart failure history					
History of heart failure	n (%)	310 (86.8)	320 (90.4)	278 (77.9)	0.0008
NYHA class 1-month before hospital admission					0.1116
1	n (%)	15 (4.5)	5 (1.5)	42 (12.7)	
2	n (%)	108 (32.7)	91 (27.6)	103 (31.1)	
3	n (%)	152 (46.1)	146 (44.2)	117 (35.3)	
4	n (%)	55 (16.7)	88 (26.7)	69 (20.8)	

(*Continued*)

Table 1. Continued

Parameter	Statistic	Total GDMT score, <5 (N=357)	Total GDMT score, 5–5.5 (N=354)	Total GDMT score, >5.5 (N=357)	Trend *P* value
Ischemic cause	n (%)	159 (44.8)	186 (52.5)	167 (46.8)	0.5975
Left ventricular ejection fraction, %	Mean (SD)	36.5 (12.53)	36.5 (12.60)	35.9 (12.42)	0.7500
Left ventricular ejection fraction category					0.2614
LVEF ≤40%	n (%)	250 (70.0)	240 (67.8)	236 (66.1)	
LVEF >40%	n (%)	107 (30.0)	114 (32.2)	121 (33.9)	
Hospitalized for heart failure in the past year?	n (%)	100 (28.0)	101 (28.5)	70 (19.6)	0.0099
No. of heart failure hospitalizations in the past year	Mean (SD)	0.4 (1.72)	0.4 (0.65)	0.2 (0.59)	0.0117
History of atrial fibrillation or atrial flutter	n (%)	134 (37.5)	185 (52.3)	174 (48.7)	0.0027
Type of atrial fibrillation or atrial flutter					0.0103
Paroxysmal	n (%)	42 (31.6)	33 (18.1)	42 (24.4)	
Permanent	n (%)	79 (59.4)	116 (63.7)	95 (55.2)	
Persistent	n (%)	12 (9.0)	33 (18.1)	35 (20.3)	
Baseline vital signs					
Systolic blood pressure at baseline, mm Hg	Mean (SD)	122.7 (13.83)	123.8 (12.30)	122.1 (12.46)	0.9855
Pulse, beats per minute	Mean (SD)	80.4 (11.97)	77.5 (11.15)	77.7 (11.88)	0.0007
Respiratory rate, breaths/min	Mean (SD)	18.3 (4.92)	18.2 (4.66)	18.1 (4.39)	0.0593
Local laboratory					
Hemoglobin, g/L	Mean (SD)	132.8 (18.41)	137.8 (19.85)	138.8 (20.99)	0.0002
Lymphocytes, %	Mean (SD)	27.1 (10.31)	27.4 (10.16)	27.3 (8.90)	0.6741
White blood cells, 10^9/L	Mean (SD)	6.8 (2.03)	7.1 (2.02)	7.0 (2.00)	0.1359
Glucose, mmol/L	Mean (SD)	6.2 (2.54)	6.1 (1.96)	6.5 (2.41)	0.0011
Creatinine, μmol/L	Mean (SD)	104.2 (31.29)	108.6 (26.69)	106.2 (28.65)	0.1123
Potassium, mmol/L	Mean (SD)	4.2 (0.45)	4.3 (0.44)	4.3 (0.42)	<0.0001
Sodium, mmol/L	Mean (SD)	139.3 (4.10)	140.4 (4.24)	141.0 (3.95)	<0.0001
Urea, mmol/L	Mean (SD)	7.9 (3.66)	8.3 (3.41)	8.0 (3.43)	0.2171
ALT, U/l	Mean (SD)	22.9 (18.02)	29.4 (28.29)	37.1 (67.23)	<0.0001
Total bilirubin, μmol/L	Mean (SD)	16.2 (9.65)	17.4 (10.50)	18.5 (13.63)	0.0983
Total cholesterol, mmol/L	Mean (SD)	4.1 (1.05)	4.2 (1.10)	4.3 (1.13)	0.2279
NT-proBNP, ng/L	Geom. Mean (95% CI)	3170.2 (2969.9, 3384.1)	3281.2 (3069.1, 3508.0)	3162.9 (2961.6, 3377.9)	0.9997
Oral heart failure medications taken at visit 2: prerandomization					
ACE inhibitors/ARBs/ARN inhibitors	n (%)	260 (72.8%)	226 (63.8%)	203 (56.9%)	<0.0001
β-Blockers	n (%)	84 (23.5%)	130 (36.7%)	169 (47.3%)	<0.0001
Mineralocorticoid receptor antagonists	n (%)	311 (87.1%)	353 (99.7%)	354 (99.2%)	<0.0001
Loop diuretic	n (%)	341 (95.5%)	338 (95.5%)	345 (96.6%)	0.4513
Furosemide equivalence dose, mg	Mean (SD)	67.3 (46.19)	55.2 (42.31)	65.0 (48.67)	0.0234

Jonckheere trend test for continuous variables, Cochron-Armitage trend test for binary variables, CMH general association for categorical variables, and CMH non-zero correlation for ordinal variables. ACE indicates angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; CMH, Cochran-Mantel-Haenszel; GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

Basic Adherence

In the UC group, 47.8% of patients were on a RASi agent, 31.2% were on a β-blocker, and 47.6% were on an MRA 1 week before admission (Table 2). These increased to 73.4%, 54.2%, and 96.2% at day 180, respectively. For the HIC group, 54% were receiving RASi, 28.4% were on a β-blocker and 44.0% were on an MRA 1 week before admission. The basic adherence increased to 97.3%, 95.8%, and 95.8% at day 180, respectively. Adherence to triple therapy was 0.4% in the UC group and 0.2% in the HIC group 1 week before admission; at 180 days, triple therapy use increased to 25.8% in the UC group and to 91.5% in the HIC group (Table 2).

Table 2. Adherence by Treatment Group and Visit

	Basic adherence		Indication-corrected adherence		Dose-corrected adherence	
Parameter	HIC	UC	HIC	UC	HIC	UC
ACE inhibitors/ARBs/ARNi						
1-week before admission	270 (54.0%)	233 (47.8%)	…	…	…	…
Visit 1 (screening)	350 (64.6%)	329 (61.6%)	377 (69.6%)	351 (65.7%)	196 (36.2%)	182 (34.1%)
Visit 2 (pre-Rand)	354 (65.6%)	335 (62.7%)	371 (68.7%)	353 (66.1%)	202 (37.4%)	177 (33.2%)
Visit 2 (post-Rand)	533 (98.5%)*	343 (64.2%)	534 (98.7%)*	359 (67.2%)	385 (71.2%)*	188 (35.2%)
Visit 3 (day 7)	518 (98.9%)	…	522 (99.6%)	…	394 (75.2%)	…
Visit 4 (day 14)	509 (98.8%)	…	513 (99.6%)	…	470 (91.3%)	…
Visit 5 (day 21)	507 (98.6%)	…	510 (99.2%)	…	458 (89.1%)	…
Visit 6 (day 42)	495 (99.0%)	…	497 (99.4%)	…	451 (90.2%)	…
Visit 7 (day 90)	493 (97.6%)*	351 (70.6%)	496 (98.2%)*	374 (75.3%)	440 (87.1%)*	220 (44.3%)
Visit 8 (day 180)	389 (97.3%)*	287 (73.4%)	…	…	…	…
β-Blockers						
1-week before admission	142 (28.4%)	152 (31.2%)	…	…	…	…
Visit 1 (screening)	175 (32.3%)	193 (36.1%)	176 (32.5%)	195 (36.5%)	95 (17.5%)	97 (18.2%)
Visit 2 (pre-Rand)	184 (34.1%)	200 (37.5%)	186 (34.4%)	201 (37.6%)	114 (21.1%)	119 (22.3%)
Visit 2 (post-Rand)	531 (98.2%)*	210 (39.3%)	531 (98.2%)*	211 (39.5%)	465 (86.0%)*	143 (26.8%)
Visit 3 (day 7)	510 (97.3%)	…	519 (99.0%)	…	465 (88.7%)	…
Visit 4 (day 14)	499 (96.9%)	…	508 (98.6%)	…	483 (93.8%)	…
Visit 5 (day 21)	495 (96.3%)	…	507 (98.6%)	…	474 (92.2%)	…
Visit 6 (day 42)	479 (95.8%)	…	488 (97.6%)	…	459 (91.8%)	…
Visit 7 (day 90)	480 (95.0%)*	239 (48.1%)	489 (96.8%)*	312 (62.8%)	445 (88.1%)*	249 (50.1%)
Visit 8 (day 180)	383 (95.8%)*	212 (54.2%)	…	…	…	…
Mineralocorticoid receptor antagonists						
1-week before admission	220 (44.0%)	232 (47.6%)	…	…	…	…
Visit 1 (screening)	494 (91.1%)†	504 (94.4%)	503 (92.8%)	508 (95.1%)	501 (92.4%)	507 (94.9%)
Visit 2 (pre-Rand)	509 (94.3%)	510 (95.5%)	513 (95.0%)	510 (95.5%)	511 (94.6%)	508 (95.1%)
Visit 2 (post-Rand)	532 (98.3%)	517 (96.8%)	533 (98.5%)	517 (96.8%)	532 (98.3%)	516 (96.6%)
Visit 3 (day 7)	508 (96.9%)	…	518 (98.9%)	…	518 (98.9%)	…
Visit 4 (day 14)	498 (96.7%)	…	509 (98.8%)	…	509 (98.8%)	…
Visit 5 (day 21)	494 (96.1%)	…	504 (98.1%)	…	504 (98.1%)	…
Visit 6 (day 42)	475 (95.0%)	…	487 (97.4%)	…	487 (97.4%)	…
Visit 7 (day 90)	474 (93.9%)	463 (93.2%)	488 (96.6%)	475 (95.6%)	488 (96.6%)	473 (95.0%)
Visit 8 (day 180)	383 (95.8%)	376 (96.2%)	…	…	…	…
Triple therapy						
1-week before admission	1 (0.2%)	2 (0.4%)	…	…	…	…
Visit 1 (screening)	1 (0.2%)	1 (0.2%)	28 (5.2%)	24 (4.5%)	18 (3.3%)	9 (1.7%)
Visit 2 (pre-Rand)	10 (1.9%)	5 (0.9%)	28 (5.2%)	24 (4.5%)	14 (2.6%)	14 (2.6%)
Visit 2 (post-Rand)	517 (95.6%)*	20 (3.7%)	519 (95.9%)*	37 (6.9%)	337 (62.3%)*	24 (4.5%)
Visit 3 (day 7)	491 (93.7%)	…	511 (97.5%)	…	355 (67.7%)	…
Visit 4 (day 14)	480 (93.2%)	…	501 (97.3%)	…	439 (85.2%)	…
Visit 5 (day 21)	475 (92.4%)	…	495 (96.3%)	…	422 (82.1%)	…
Visit 6 (day 42)	457 (91.4%)	…	475 (95.0%)	…	413 (82.6%)	…
Visit 7 (day 90)	456 (90.3%)*	87 (17.5%)	472 (93.5%)*	179 (36.0%)	391 (77.4%)*	102 (20.5%)
Visit 8 (day 180)	366 (91.5%)*	101 (25.8%)	…	…	…	…

1: Basic adherence defined as being prescribed the medication. 2: Indication-corrected adherence defined as being prescribed the medication or having one of the following contraindications (ACE inhibitors/ARBs/ARNi: SBP <95 mm Hg, eGFR <30 mL/min per 1.73 m^2, or serum K >5.0 mmol/L; β-blockers: HR <55 beats per minute, SBP <95 mm Hg, NT-proBNP >1.10× V2 (pre-Rand) value; MRA: SBP <95 mm Hg, eGFR <30 mL/min per 1.73 m^2, or serum K >5.0 mmol/L). Not derived at the following visits because laboratory and vital data not collected: 1 week before admission, visit 8 (day 180). 3: Dose-corrected adherence defined as total daily dose ≥50% of the target dose or having one of the following contraindications (ACE inhibitors/ARBs/ARNi: SBP <95 mm Hg, eGFR <30 mL/min per 1.73 m^2, or serum K >5.0 mmol/L; β-blockers: HR <55 beats per minute, SBP <95 mm Hg, NT-proBNP >1.10× V2 (pre-Rand) value; MRA: SBP <95 mm Hg, eGFR <30 mL/min per 1.73 m^2, or serum K >5.0 mmol/L). Not derived at the following visits because laboratory and vital data not collected: 1 week before admission, visit 8 (day 180). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HIC, high-intensity care; K, potassium; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Rand, randomization; SBP, systolic blood pressure; and UC, usual care.

*P<0.0001.

†P<0.05.

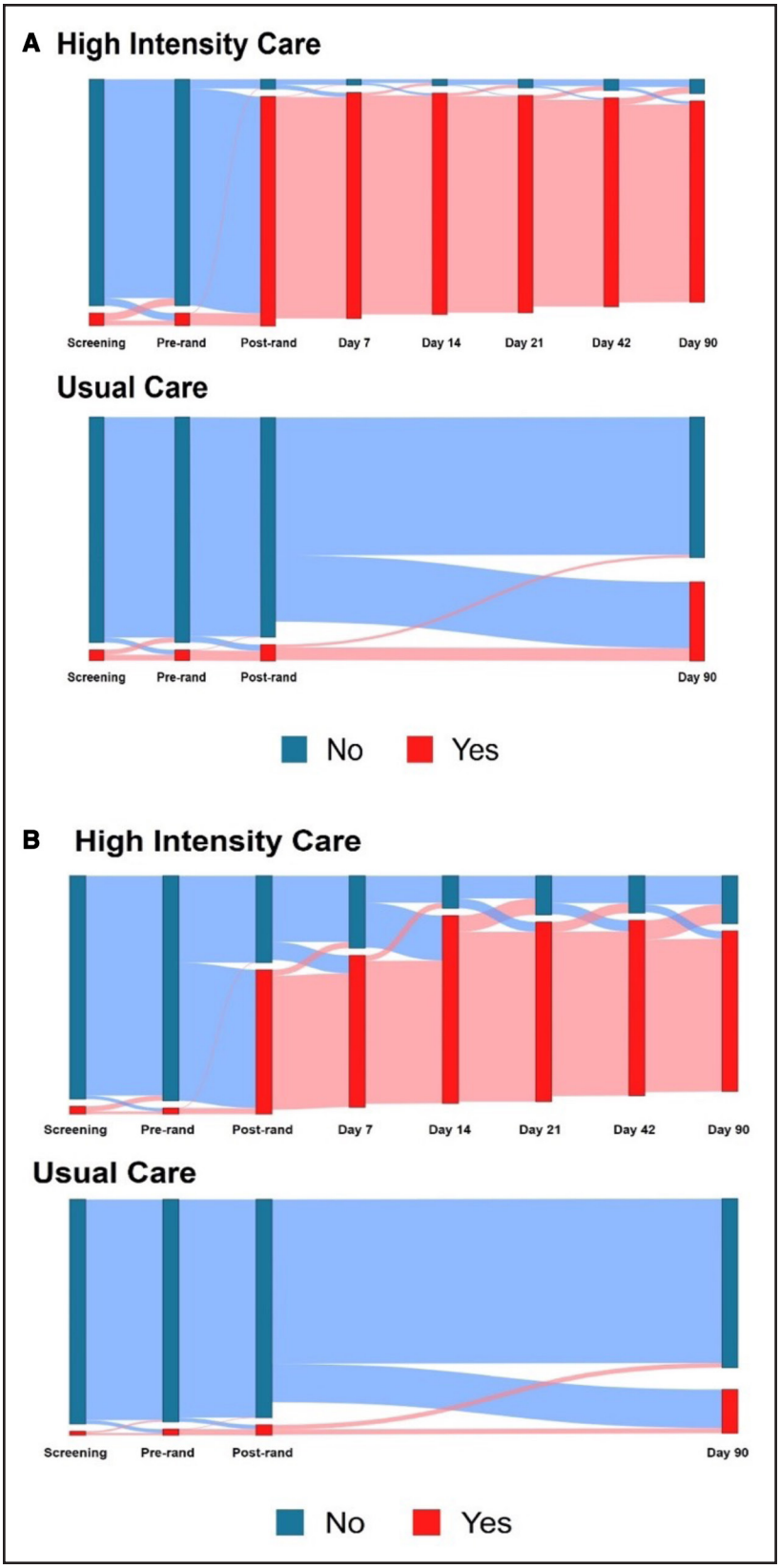

Figure 1. Sankey plot of triple therapy use.
A, Triple therapy usage for indication-corrected adherence by treatment and visit. **B**, Triple therapy usage for dose-corrected adherence by treatment and visit. rand indicates randomization.

Indication-Corrected Adherence

Per protocol, GDMT were not to be up-titrated in the presence of a protocol-defined safety contraindication. Indication-corrected adherence was not assessed either before admission or at 180 days, as no laboratory values were taken at these visits. At screening, 65.7% of patients in the UC arm were appropriately receiving an

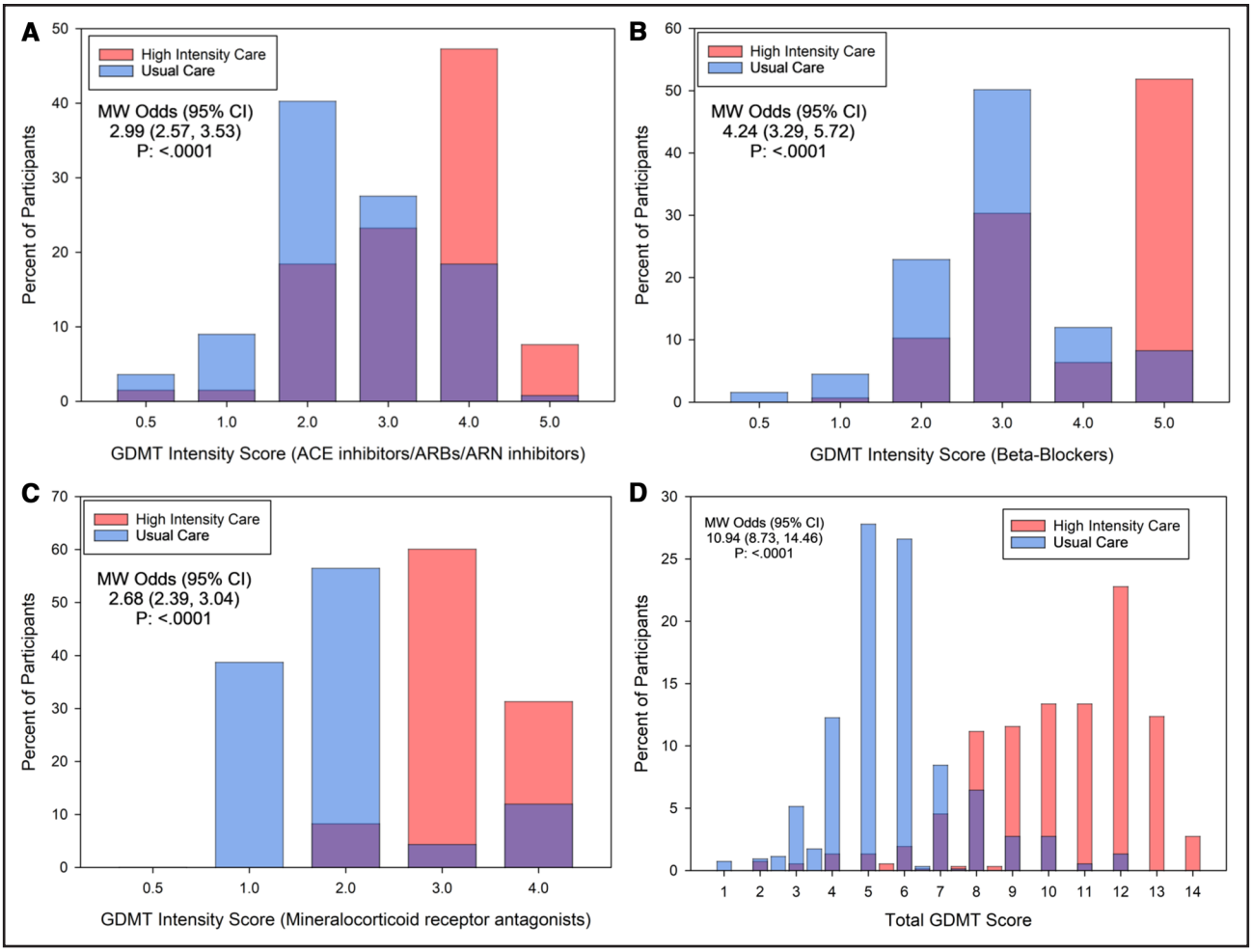

Figure 2. GDMT intensity score assessment.
A, GDMT intensity score by ACE inhibitors/ARBs/ARN inhibitors treatment group at day 90. **B**, GDMT intensity score by β-blockers treatment group at day 90. **C**, GDMT intensity score by mineralocorticoid receptor antagonists treatment group at day 90. **D**, Total GDMT score by treatment group at day 90. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARN, angiotensin receptor/neprilysin; GDMT, guideline-directed medical therapy; and MW, Mann-Whitney *U* test.

ACEi, 36.5% a β-blocker, and 95.1% an MRA. These increased to 75.3%, 62.8%, and 95.6%, respectively, at day 90.

In the HIC group, more patients were appropriately receiving ACEi at baseline (69.5%) and this increased to 98.2% at day 90. The indication-corrected use of β-blockers and MRAs at screening was similar to the UC group, 32.5% and 92.8%, respectively. At day 90, the use of β-blockers increased to 96.8%, and MRA use to 96.6%. Triple therapy indication-corrected use increased from 4.5% to 36% in the UC group and from 5.2% to 93.5% in the HIC group (Table 2).

Dose-Corrected Adherence

For patients prescribed medication at ≥50% of the target dose, the dose-corrected adherence was 34.1% for ACEi, 18.2% for β-blockers, and 94.9% for MRAs in the UC group at screening and increased to 44.3%, 50.1%, and 95.1%, respectively at day 90. For the HIC group at baseline, the dose-corrected adherence was similar at 36.2% for ACEi , 17.5% for β-blockers, and 92.4% for MRAs. These increased to 87.1%, 88.1%, and 93.2%, respectively. Figure 1 illustrates the rate of target dose achieved for therapies.

GDMT Intensity Score

Just after randomization, a GDMT score <6 was calculated in 358 (33%) patients, 6 to 7 in 329 (31%) patients and >7 in 386 (36%) patients. At day 90, the GDMT evolution is depicted in Figure 2, with 88.4% having >7 in the HIC group versus 14.3% in the UC group (P<0.0001). In addition, 50.4% of patients in the HIC arm had a score between >7 and 11 (versus 12.9% in the UC arm), and 38% of patients in the HIC arm had a score >11 (versus 1.4% of patients achieved this in the UC group; Table S4 and Figure 3).

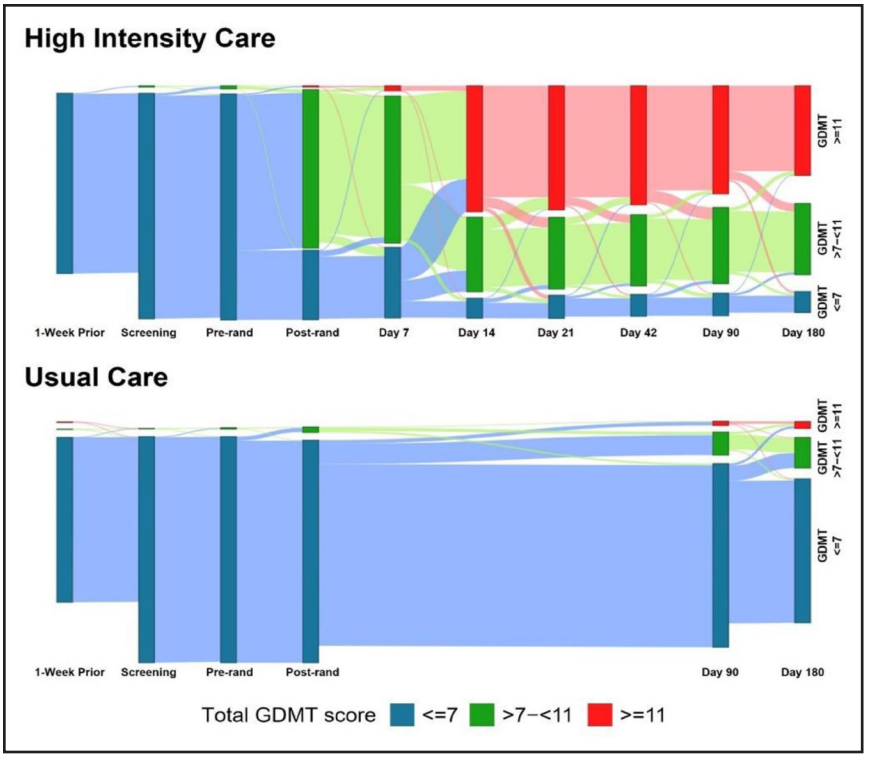

Figure 3. Sankey plot of guideline-directed medical therapy (GDMT) intensity score by treatment and visit. rand indicates randomization.

The GDMT intensity score correlated well (r=0.95) with the average percentage of optimal dose (Figure S1). Differences arise from the use in STRONG-HF of medications whose doses were weighted less in the HFC.

Outcomes

The primary outcome included HF hospitalization and all-cause mortality. GDMT intensity score is presented in tertiles (≤7, >7–11, and ≥11) to evaluate its relationship to the study's primary end point. In all patients, when considering GDMT score as a time-dependent covariate, those in the lower 2 tertiles had a higher probability of an event, with an adjusted hazard ratio of 2.34 (95% CI, 1.55–3.54) in the lowest tertile and 1.43 (95% CI, 0.86–2.38) in the middle tertile, compared with those in the highest tertile, with an overall P value of <0.0001 (Figure 4A). In the HIC patients, the adjusted hazard ratios were 2.72 (95% CI, 1.43–5.19) and 1.68 (95% CI, 0.99–2.85) in the lowest and middle tertiles, respectively, compared with those in the highest tertile, with an overall P value of 0.0086 (Figure 4B).

The association of continuous GDMT score at week 2 (when patients in HIC were to be on full doses) with the primary outcome was not statistically significantly nonlinear (P=0.356; Figure 5A). The adjusted hazard ratio was 0.90 (95% CI, 0.86–0.95) per 1-point increase in the GDMT score (P<0.001) in all patients. In the HIC arm, the adjusted hazard ratio was 0.91 (95% CI, 0.82–1.01; P=0.088) per 1-point increase (Figure 5B).

DISCUSSION

A thorough understanding of baseline GDMT use and its change over time is crucial in the design and interpretation of clinical trials.[10] The assessment of medication use should go beyond simple dichotomous descriptions and assess the totality of medication-associated care. In this analysis, we identify 3 key findings from the STRONG-HF trial. First, the use of an aggregate score, such as the modified HFC score, provides a more granular and complete description of care and provides insight as to the clinical outcome differences seen in this trial. A greater separation of the medication use than seen with simple medication counts is noted between the 2 arms of the trial, and the score is linked to the primary end point. Second, when accounting for either indication or dose, the medication use by describing both the numerator and denominator allows for a better assessment of appropriate care. This is important not just for quality improvement initiatives but also for comparisons of trials on medication optimization. For instance, 36.1% of patients in the UC arm were on a β-blocker using the basic adherence definition, whereas this proportion was only 18.2% when using the dose-corrected definition. As such, the enhanced definitions of adherence are better indicators of GDMT use. Third, and perhaps most importantly, the modified HFC score as an aggregate is likely not just a mechanism to assess quality of care but can serve as a primary outcome for clinical trials testing innovative implementation optimization strategies.

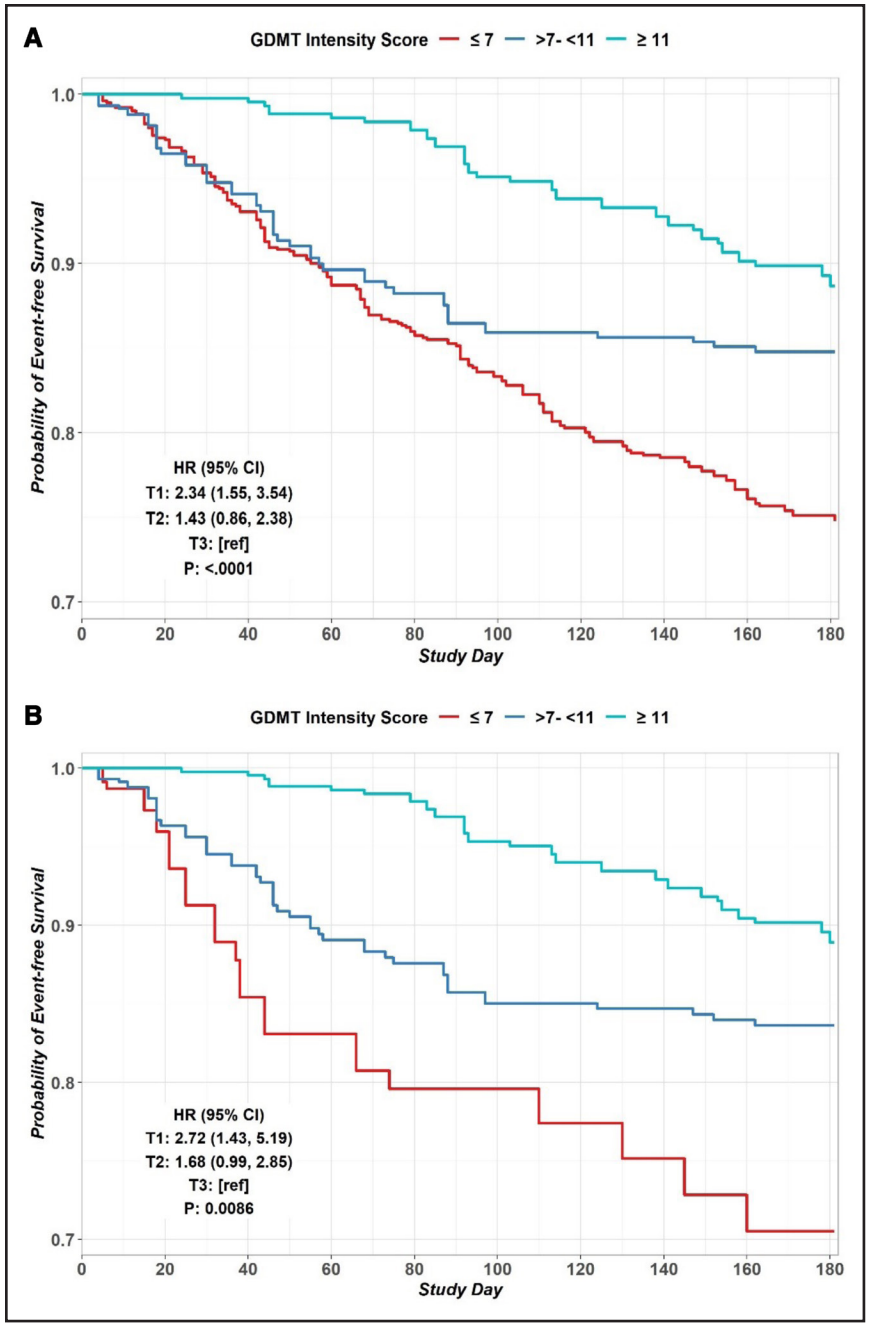

Figure 4. Time-dependent Kaplan-Meier curves for all-cause mortality or HF-readmission through day 180 by GDMT intensity score groups.
A, All patients. **B**, High-intensity care patients only. GDMT indicates guideline-directed medical therapy; HR, hazard ratio; T1, tertile 1; T2, tertile 2; and T3, tertile 3.

The STRONG-HF trial enrolled patients on suboptimal GDMT at baseline, with less than a third of patients on β-blockers. We observed a larger numerical increase in therapy use at day 90 in the HIC arm, irrespective of the definition of adherence used. This again demonstrates the completeness of GDMT optimization in the HIC arm. The current secondary analysis further establishes that the GDMT intensity score is a predictor of clinical end points: mortality and HF hospitalization (Figure 4). Unsurprisingly, patients with the highest score tertile (>11) had a lower event rate than those with lower scores (≤7 or between 7 and 11), consistent with previous studies.[3,9] The GDMT intensity score provides a simple, precise, and comprehensive assessment of medical therapy for HF. Moreover, its standardized use would be a valuable tool in clinical trials. It allows objective comparison between study populations and detects whether a novel therapy provides incremental benefits.[3] We also followed the temporal evolution of this score (Figure 4). As expected, the highest score tertile was reached by more patients in the HIC arm, and this was achieved earlier in the follow-up period. It is interesting to note that the score does not make a distinction between achieving more classes of medications versus escalating selected ones. It is unclear if there is more or less benefit to being on small doses of all 4 GDMT classes versus being on optimal doses of a few.

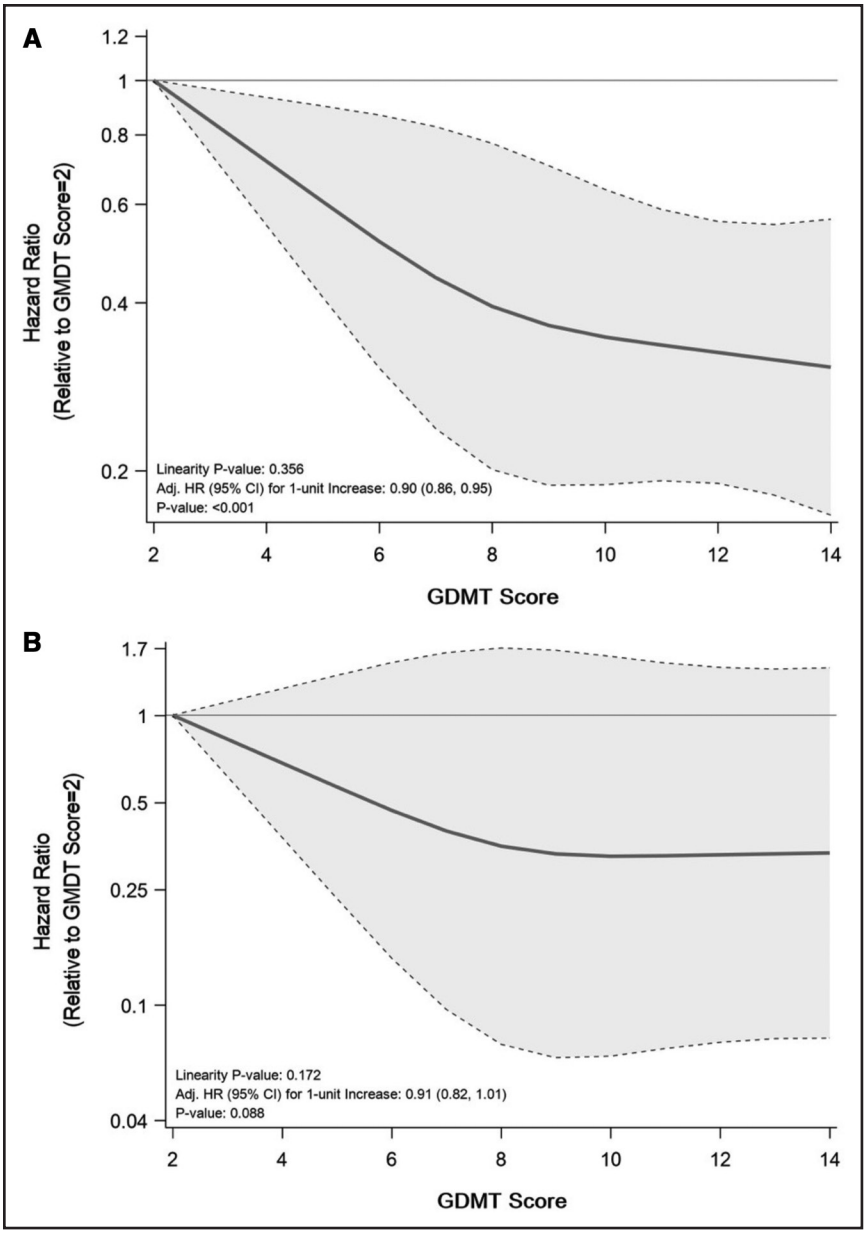

Figure 5. Adjusted hazard ratio relative to minimum observed GDMT score (2) in relationship to increasing GDMT intensity score at week 2. **A**, All patients. **B**, High-intensity care patients only. Adj. HR indicates adjusted hazard ratio; and GDMT, guideline-directed medical therapy.

For clinicians, the findings of this further reinforce the necessity to achieve rapid medication up-titration, as conceptualized through the GDMT score. Each point increase in score is associated with a 10% decrease in the hazard of death or HF-readmission within as early as 180 days.

Other methods with similar objectives have been described. For instance, the average percentage optimal dose illustrates the degree of optimal medication use by calculating the mean percentage of one's medication use compared with its target dose.[14] The Kansas City Medical Optimization score[18] is another example of using the average optimal dose to assess different medication use as a whole. While these methods objectively quantify medication use, the scoring systems derived from the Heart Failure Collaboratory Medical Therapy Score are based on a consensus developed by clinicians and patients. More recently, sodium-glucose cotransporter-2 inhibitor use has been included in these calculations.[8,19] Several scoring systems can coexist and serve different purposes when providing clinical care or supporting quality improvement efforts. How these are assessed, their linkage to outcomes, and their utility in practice should be considered carefully.

STUDY LIMITATIONS

First, indication-corrected adherence and dose-corrected adherence were not assessed at 1 week before admission. These data could not be derived due to the absence of vital signs and blood work measurements at that time. Second, several challenges arise

when assessing indication-corrected adherence. It is impractical to account for all the reasons why a patient is not on a certain therapy, and misclassification can occur. Third, as with all post hoc observational studies, the associations established are not causal and are hypothesis-generating. Although adjusted for important covariates, this can still be subject to residual confounding. We also acknowledge the lack of data with regards to sodium-glucose cotransporter-2 use in this study and assessment of this now widely used guideline-directed pillar therapy would be valuable in such an analysis.

CONCLUSIONS

The STRONG-HF trial highlights the importance of rapidly titrating GDMT in the period following HF hospitalization. Medication assessment in clinical trials is complex and should be performed with more vigorous tools. The GDMT intensity score is a standardized measure to evaluate the trajectory of GDMT up-titration and is associated with 180-day clinical outcomes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figure S1

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